Neurocognition and Emotional Processing In Bipolar Offspring

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Faculty of Medical Sciences
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To

Anita, Akhilesh, Daksh, Advay

& Kirti

With all my love and appreciation

Declaration

I declare that the thesis entitled ‘Neurocognition and Emotion Processing in Bipolar Offspring’ is entirely my own work.

The research was carried out from August 2006 to June 2013 at Newcastle University. All activities in this thesis are original unless acknowledged in the text or by reference.

The thesis has not been previously submitted at this University or any other University.

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Abstract

Background/aims: Recent evidence suggests that the psychosocial function for patients with Bipolar Disorder (BD) may not always be as favorable as originally proposed by Emil Kraeplin. This dysfunction has been statistically associated with neurocognitive measures (on tasks assessing working memory, learning and executive function) and emotional processing (on tasks assessing facial emotion labeling). Studies of Offspring of Bipolar Parents (OBP) in comparison with Offspring of Healthy Controls (OHC) demonstrate elevated risk for development of BD and limited evidence of impairment in neurocognitive function and emotional processing. The identification of an endophenotype for BD could help in early identification of BD, institution of early appropriate intervention and thereby perhaps limit this psychosocial dysfunction.

The aims included the recruitment of a matched sample of OBP and OHC and investigation of neurocognitive function and facial emotion labelling in these two groups. The hypotheses were: OBP will show impairment in the domains of memory, learning and executive function, OBP will demonstrate more errors on facial emotion labeling tasks and the deficits in facial emotion labelling will not be related to impairments demonstrated on the domains of memory, learning and executive function. Results: OBP showed deficits in IQ, spatial working memory, visual and auditory working memory as compared to OHC. OBP also made more errors on tasks of facial emotion labeling; particularly on 'fearful faces' in comparison to OHC. The novel finding from this project was the lack of significant association between the reported neurocognitive deficits and facial emotion labeling deficits in OBP. Conclusion: The study identified deficits in neurocognitive function and facial emotion labeling in OBP which appear to be independent. These deficits met some criteria for being considered an endophenotype for BD. The study was limited by a small sample size, lack of blinding and low specificity of these deficits for BD. Further longitudinal research to study the evolution of these deficits would be the next step in confirmation of these deficits as a potential candidate endophenotype for BD. In addition research should focus on factors that might contribute to these deficits such as severity of parental BD ('nature') and family environment ('nurture').

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AACAP:	American Academy of Child and Adolescent Psychiatry
ACC:	Anterior Cingulate Cortex
ACTT:	Auditory Consonant Trigram Test
ADHD:	Attention Deficit Hyperactivity Disorder
ALN:	Anterior Limbic Network
ANCOVA:	Analysis of Covariance
ANOVA:	Analysis of Variance
APA:	American Psychiatric Association
ASD:	Autism Spectrum Disorder
BD:	Bipolar Disorder
BDI:	Bipolar I Disorder
BDIn:	Beck Depression Inventory
BDII:	Bipolar II Disorder
BDNF:	Beta Brain-Derived Neurotrophic growth Factor
BD NOS:	Bipolar Disorder Not Otherwise Specified
BPD:	Parental Bipolar Disorder
CANTAB:	Cambridge Automated Neuropsychological Test Assessment Battery
CD:	Conduct Disorder
CDI:	Children's Depression Inventory
CDRS:	Children's Depression Rating Scale
CGAS:	Children's Global Assessment Scale
CMHT:	Community Mental Health Team
COMT:	Catechol-O-Methyl-Transferase
COWAT:	Controlled Oral Word Association Test
CPT:	Continuous Performance Task
CVLT-C:	California Verbal Learning Test-Children's version
DALY:	Disability Adjusted Life Year
DANVA2:	Diagnostic Analysis of Non Verbal Accuracy 2
D-KEFS:	Delis-Kaplan Executive Function System
DICA:	Diagnostic Interview for Children and Adolescents

DLPFC:	Dorso Lateral Pre Frontal Cortex
DMDD:	Disruptive Mood Dysregulation Disorder
DSM-IV:	Diagnostic and Statistical Manual-IVth edition
DSM-5:	Diagnostic and Statistical Manual-5th edition
DTI:	Deep Tensor Imaging
EOI:	Expression of Interest
FA:	Fractional Anisotropy
fMRI:	functional Magnetic Resonance Imaging
FSIQ:	Full Scale IQ
GAD:	Generalised Anxiety Disorder
GAF:	Global Assessment of Functioning
GXE:	Genes and Environment
GP:	General Practitioner
GSK3-B:	Glycogen Synthase Kinase 3
GWAS:	Genome Wide Association Studies
HC:	Healthy Controls
IED:	Intradimensional/Extradimensional shift
IFG:	Inferior Frontal Gyrus
IFOF:	Inferior Fronto-Occipital Fasciculus
ILF:	Inferior Longitudinal Fasciculus
K-SADS-PL:	Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version
MANOVA:	Multivariate Analysis of Variance
MAOA:	Monoamine Oxidase A
MASC:	Manifest Anxiety Scale for Children
MDD:	Major Depressive Disorder
MEG:	MagnetoEncephaloGraphy
MOT:	Motor Screening Test
MRI:	Magnetic Resonance Imaging
MS:	Motor Screening
NART:	National Adult Reading Test
NEPSY:	A Developmental NEuroPSYchological Assessment
NEPSYII:	A Developmental NEuroPSYchological Assessment

NHS:	National Health Service
NIMH-ChEFS:	National Institute of Mental Health Child Emotional Faces Picture Set
NLD:	Nonverbal Learning Disability
NPBD:	Narrow Phenotype Bipolar Disorder
OBP:	Offspring of Bipolar Parents
ODD:	Oppositional Defiant Disorder
OHC:	Offspring of Healthy Controls
OSP:	Offspring of Schizophrenic Parent
PAL:	Paired Associates Learning
PBD:	Paediatric Bipolar Disorder (defined as onset<18 years)
PDD:	Pervasive Developmental Disorder
PFC:	Pre Frontal Cortex
PIQ:	Performance IQ
PRM:	Pattern Recognition Memory
RAVLT:	Rey Auditory Verbal Learning Test
SCID:	Structured Clinical Interview for DSM-IV
SCID-I/P:	Structured Clinical Interview for DSM-IV TR Axis I Disorders-Patient Edition
SES:	Socio Economic Status
SLF:	Superior Longitudinal Fasciculus
SMD:	Severe Mood Dysregulation
SMS:	Spatial Memory Span
SOC:	Stockings of Cambridge
SOC MM:	Stockings of Cambridge Minimum Moves
SOC TMITT:	Stockings of Cambridge Total Mean Initial Thinking Time
SPAN:	Span of Apprehension task
SRM:	Spatial Recognition Memory
SRS:	Social Responsiveness Scale
SWM:	Spatial Working Memory
SWM: BET:	Spatial Working Memory: Between Errors Total
SWM: WET:	Spatial Working Memory: Within Errors Total
TeaCh:	Test of everyday attention of Children

TMT-A/B:	Trail Making Test-A and B
TOVA:	Test of Variables of Attention
TPH2:	Tryptophan Hydroxylase 2
VIQ:	Verbal IQ
VLPFC:	VentroLateral PreFrontal Cortex
WASH-U-KSADS:	Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia
WAIS-R:	Wechsler Adult Intelligence Scale–Revised
WASI 4:	Wechsler Abbreviated Scale for Intelligence 4
WCST:	Wisconsin Card Sorting Test
WISC:	Wechsler Intelligence Scale for Children
WM:	White Matter
YMRS:	Young Mania Rating Scale

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Chapter 1: Introduction

In his original clinical descriptions of mental health disorders, Emil Kraeplin described what was later referred to as the Kraepelinian dichotomy (Kraeplin 1896). This dichotomy reclassified what was previously considered the unitary concept of psychosis in mental health. The Kraepelinian dichotomy was based not on any particular symptoms differentiating the two conditions of manic depression and dementia praecox but instead on a specific pattern of symptoms. Manic depression [Bipolar Disorder (BD)] differed from dementia praecox (schizophrenia) on the basis of the former being an episodic disorder with apparent return to full premorbid level of functioning during an inter-episodic period. This meant that unlike schizophrenia; BD was considered to have a more benign course and better functional outcome. However, data from the past few decades indicates this not to be the case. Patients with BD often have increasing frequency and number of episodes with illness progression as well as poor functional recovery. This in turn has implications for the individual, their family and the wider society.

Chapter 1 ('Introduction') is an introductory chapter and outlines the structure of this thesis. Chapter 2 ('Bipolar disorder') provides an overview of the history of BD and describes how over the past century the understanding of this condition has changed. It describes the clinical features, types of BD and epidemiology of BD. It also discusses the proposed changes to the diagnostic categories in the context of the new classificatory systems of DSM-5. The chapter discusses psychosocial (dys)function seen in BD and special reference is made to the economic cost of patients with BD in the UK context. The chapter then focusses on an overview of the research investigating neurocognitive function and facial emotion labelling in BD. It then moves on to consider the concept of early onset BD (particularly in young people under the age eighteen years). These cases of early onset BD are referred to as Paediatric Bipolar Disorder (PBD) in this project. The chapter then explores why identification of potential candidate

endophenotypes such as neurocognitive function and facial emotion labelling are important to a better understanding of BD.

Chapter 3 ('Neurocognitive function') discusses the concept of intelligence and neurocognitive function. In this chapter, research studies of adults with BD who were assessed during affective episodes of BD and adults investigated during periods of euthymia are included. The chapter then critically appraises the studies that have assessed neurocognition in PBD and the few studies that have evaluated young people 'at risk' for BD. Chapter 4 ('Facial emotion labeling') provides a review of selected studies that have assessed adults and adolescents with BD and also adolescents 'at risk' for BD on their ability to label facial emotion correctly. Subjects 'at risk' for BD in this project refers not only to Offspring of Bipolar Parents (OBP) but also siblings of subjects with BD.

Chapter 5 ('Neurocognition and Facial Emotion Labelling') provides an overview of the few studies that have jointly assessed neurocognitive function and facial emotion labelling in adults and youth with BD. It also explores the rationale for investigating both neurocognition and facial emotion labeling in combination to further advance the understanding of BD and the search for a potential endophenotype for BD. The studies that have been included in chapters 3, 4 and 5 were selected after a systematic search was conducted from a range of electronic databases, including The Cochrane Library, EMBASE, PsycINFO, OVID and PubMED with the search terms 'bipolar disorder, offspring, at risk, first degree relatives, neurospsychology, neurocognitive, facial emotion labelling, face emotion recognition'. Studies in the 'at risk' group were included if they included at least some subjects in the under 18 age range. Certain key studies have been reported in more detail as they have significantly contributed to the understanding of neurocognitive function and facial emotion labelling in BD. The methodology, results and consideration of the limitations of these studies has informed the development of this project. These aspects are discussed in greater detail in chapter 6.

Chapter 6 ('Project development') describes the factors considered during the development of the battery of tasks, selected to investigate neurocognitive function and facial emotion labelling in this project. It outlines the statistical plan of analysis. This is followed by chapter 7 'Aims and Hypotheses' which describes the aims and hypotheses of this project. In Chapter 8 ('COMPIC - Project Protocol') the details of the project methodology including recruitment strategy, inclusion and exclusion criteria, and data analysis are presented. Chapter 9 ('COMPIC - Participants') describes the characteristics of the participants recruited. It also presents a discussion regarding the recruitment strategy as well as psychopathology found in OBP and OHC.

Chapter 10 ('COMPIC - neurocognitive function') reports the following for each of the neurocognitive tests used in the project: administration of the test, the specific measures studied from each test, mixed models used for analyses and the results of the test. This is followed by a discussion of the key findings from the neurocognitive test battery. Chapter 11 ('COMPIC - facial emotion labelling') outlines the administration of the test used to assess facial emotion labelling. The specific aspects of facial emotion labelling measures used in the project, the mixed models used for analyses of these measures and the results of the facial emotion labelling test are then presented. This is followed by a discussion of the findings. Chapter 12 ('Discussion') is an overarching discussion of the project and includes consideration of the strengths and limitations of this thesis. It also considers some of the clinical and educational implications of the research findings. In the final section recommendations are made including the development of new directions for future research.

Chapter 2: Bipolar disorder

2.1 Introduction:

Over the past century considerable progress has been made in the understanding of BD. More recently, research teams have started to gain a better understanding of the burden of psychosocial dysfunction in BD. This affects not only the individual who has developed BD but also has significant economic costs to the healthcare systems. All of these factors contribute to the burden of care that patients with BD pose to society as a whole and highlight the need for early identification of BD. Early identification of BD could employ endophenotypes for BD. This chapter will present an overview of how neurocognitive function and facial emotion labeling in BD might be considered endophenotypes for the disorder. The evidence base for the association of these potential endophenotypes for BD with the above mentioned pattern of psychosocial dysfunction is presented. The chapter then moves on to the concept of PBD and considers why the identification of endophenotypes such as neurocognitive function and facial emotion labelling could be key to improving understanding of BD.

2.2 History

BD is defined as an episodic mood disorder characterised by episodes of low mood (depression) and elevated mood (mania or hypomania) usually interspersed with periods of remission (Goodwin and Jamison 1990). Although the disorder had been described by the ancient Greeks and Egyptians it was first categorised as an illness by Falret who in 1851 and 1854 described it as ‘folie circulaire’ (circular madness) (Angst and Sellaro 2000). The term manic-depressive insanity was coined by Emil Kraepelin in the late 19th century to differentiate mood disorders from dementia precox which was later referred to as schizophrenia. Karl Leonhard further classified mood disorders into unipolar disorder and bipolar disorder (Leonhard 1957).

The Kraepelinian dichotomy highlighted the 'cyclical' course of BD in contrast to the 'chronic' course of schizophrenia (Fischer and Carpenter 2009). Kraepelin believed that schizophrenia had a deteriorating course in which mental function continuously (although perhaps erratically) declined, while manic-depressive patients experienced a course of illness which was intermittent. These patients were reported to be relatively symptom-free during the intervals which separated acute episodes. However, more recent studies (Atre-Vaidya et al. 1998; Martinez-Aran et al. 2002; Sanchez-Moreno et al. 2009) indicate that patients with BD may not experience this so-called 'good psychosocial outcome' but may instead pose a significant burden on the health economics of the nation (Das Gupta and Guest 2002).

2.3 Current classification: DSM-IV and ICD-10

BD presents with alternation between episodes of elevated mood (mania or hypomania), low mood (depression) and/or mixed episodes. Manic and depressive episodes may be associated with psychotic symptoms that can be mood congruent or incongruent. Hypomania is, by definition not associated with any psychotic features. Most patients with bipolar disorder have periods of inter-episodic remission. The 2 internationally recognised classifications of mental health disorders are the Diagnostic and Statistical Manual-IV (DSM-IV) (American Psychiatric Association 1994) and Chapter V (F00-F99) of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (World Health Organisation 1992). Both of these classificatory systems do rely very much on a categorical classificatory system and have been criticised for the lack of a dimensional approach in classifying mental health disorders. Further, the 2 classificatory systems differ in their nomenclature of BD.

In ICD-10, BD is classified as F31.xx bipolar affective disorder with no separation into Bipolar I Disorder (BDI) and Bipolar II Disorder (BDII) as in DSM-IV (the relevance of which will be discussed further below in section 2.4). For DSM-IV a single manic/mixed episode achieves the diagnostic threshold for

BD whereas in the ICD-10 to meet the diagnostic threshold, an individual must have had at least 2 mood episodes one of which must have been a manic/ hypomanic/mixed episode. A single manic episode in the WHO ICD-10 receives the diagnosis of F30.xx manic episode. These differences in criteria within the classificatory systems makes comparisons between research studies difficult.

2.4 Bipolar types: I, II and NOS

DSM-IV provides definitions of different sub-types of BD (American Psychiatric Association 1994). BDI (as defined within the DSM-IV) is closest to the description of BD conceptualised by Kraeplin as the 'classic manic depressive disorder presentation'. To meet the diagnostic threshold for BDI according to the DSM-IV a patient must have had at least one manic episode (symptoms including either elevated or irritable mood, lasting at least 7 days or less if patient is hospitalised) with associated significant psychosocial impairment. In contrast for a diagnosis of BDII a patient must have had had at least one hypomanic episode (symptoms lasting at least 4 days) with some degree of psychosocial impairment but no association with any psychotic features. Subjects with BDII often present with fewer elevations of mood but persistent and/or frequent depressive episodes (Judd et al. 2003). BDII is often under recognised and/or misdiagnosed as recurrent depressive disorder as the hypomanic symptoms are often not reported by patients (Judd et al. 2003).

The current DSM-IV classification criteria differentiate BDI and BDII as distinct disorders. Certainly in terms of the above mentioned clinical features these disorders appear distinct. Further some authors have postulated that due to the absence of psychotic features, lower degree of psychosocial impairment and neurocognitive impairment BDII is considered a less severe form of BD when compared with BDI (Torrent et al. 2006; Simonsen et al. 2008). Recent studies have reported that subjects with BDI had significantly more verbal memory deficits than subjects with BDII which might explain the overall poor psychosocial function in BDI vs BDII (Hsiao et al. 2009; Aminoff et al. 2013). However, other authors have reported that the degree of neurocognitive

dysfunction in BDII is more than in BDI perhaps as a result of more frequent depressive episodes (as part of the clinical presentation) in BDII (Summers et al. 2006). Other authors have stated that the degree of psychosocial dysfunction in BDI and BDII is comparable when other factors such as age at onset, depressive symptoms controlled for (Judd et al. 2005; Wingo et al. 2010). Despite controversies regarding whether BDI and BDII are distinct and separate disorders with regards to psychosocial function and severity of clinical features they do appear to be distinct conditions.

The final diagnostic subgroup is Bipolar Disorder Not Otherwise Specified (BD NOS). This diagnostic category is utilised by exclusion to classify individuals who have mood episodes that either do not have enough symptoms and/or the symptoms do not last the requisite duration (as discussed above in this section). There has been a dramatic increase in the rates of diagnosis of PBD; in particular of the BD NOS subtype (see section 2.7). This marked increase has prompted some groups in USA to operationalise criteria for diagnosis of BD NOS. The American Academy of Child and Adolescent Psychiatry (AACAP) guidelines suggest that the BD NOS diagnosis be used for youths with either (a) manic symptoms of insufficient duration (i.e., lasting less than four days) or (b) youths with “chronic manic-like symptoms which constitute baseline functioning” (McClellan et al. 2007). The Pittsburgh group has developed the Course and Outcome of Bipolar Youth (COBY) study and have further operationalised the definition of BD NOS. Their definition requires that symptoms must be evident for a minimum of 4 hours in a day on a minimum of 4 separate lifetime days (Axelson et al. 2006; Sala et al. 2009).

2.5 Proposed changes: DSM-5

The DSM-5 has proposed significant changes in diagnostic categories for BD (American Psychiatric Association 2013). The DSM-IV was largely a categorical classificatory system. In the DSM-5 a this approach has been supplemented with the dimensional aspects of disorders to adopt a ‘mixed categorical-dimensional’ approach (Wittchen et al. 2011). The changes as taken from the

most recent version of DSM-5 will now be presented. The first major change is in the core diagnostic criterion for manic and hypomanic episodes: changes in activity and energy are needed in addition to mood changes. The second change is that the DSM-IV diagnosis of BDI, mixed episode (requiring that the individual simultaneously meet full criteria for both mania and major depressive episode) has been removed. Instead, a new specifier, “with mixed features,” has been added that can be applied to episodes of mania or hypomania when depressive features are present, and to episodes of depression in the context of major depressive disorder or bipolar disorder when features of mania/ hypomania are present. However, it is unclear how clinicians will deal with the possibility of diagnosing major depression with mixed features and how this may impact the bipolar–unipolar dichotomy and diagnostic reliability (Vieta and Valenti 2013).

Thirdly, DSM-5 allows the specification of particular conditions for other specified bipolar and related disorder, including categorization for individuals with a past history of a major depressive disorder who meet all criteria for hypomania except the duration criterion (i.e., at least 4 consecutive days). Fourthly, given the significant levels of anxiety symptoms seen in subjects with BD, the chapter on bipolar and related disorders and the chapter on depressive disorders in DSM-5 now have a specifier for anxious distress. This specifier is intended to identify patients with anxiety symptoms that are not part of the bipolar diagnostic criteria. Fifthly, DSM-5 contains a new depressive disorder: Disruptive Mood Dysregulation Disorder (DMDD) which has been included to address concerns about potential over-diagnosis and over-treatment of PBD. It is to be considered as a diagnosis for children up to age 18 years who exhibit persistent irritability and frequent episodes of extreme behavioural dyscontrol. The condition was originally conceived by Leibenluft and colleagues as Severe Mood Dysregulation (SMD) (Leibenluft et al. 2003; Leibenluft 2011). The concept was to be used to describe youth with non-episodic irritability but not fulfill criteria for mania.

The DSM-5 is a significant change, particularly with its approach to a mixed categorical-dimensional approach in classifying mental health disorders. The proposed changes with reference to BD and the introduction of DMDD will require further critique, research and perhaps as Stringaris suggests 'tough love' which it deserves (Stringaris 2013).

2.6 Epidemiology

The peak age for diagnosis of BD has been thought to be the third decade of life with an equal male:female ratio (Goodwin and Jamison 1990). However, more recently, the age at which studies report onset of bipolar symptoms and the age at which BD is now being diagnosed is in the second decade of life (Moreno et al. 2007; Post et al. 2008). This will be discussed in more detail in section 2.7. The prevalence of BD in the adult population was previously estimated to range from 0.3% (Weissman et al. 1996) to 1.6% (Kessler et al. 1994). However, recent studies that take into account the *bipolar spectrum* (bipolar spectrum defined as including the following conditions: BDI, BDII and subthreshold BD symptoms) suggest that the prevalence may in fact be as high as 5-6% (Angst and Gamma 2002; Hirschfeld et al. 2003; Judd and Akiskal 2003; Merikangas et al. 2011). Souery and Mendlewicz have stated that 'this would make bipolar disorders one of the most frequent disorders in psychiatry' (Souery and Mendlewicz 2003).

2.7 Paediatric bipolar disorder

As presented in chapter 1 the term PBD in this project refers to cases of BD occurring before the age of 18 years. There has been considerable debate about the existence of PBD particularly in the last 2 decades of the 20th century (Leibenluft et al. 2003; Healy 2006; Parens et al. 2010). However over the past decade there has been increasing validation of the diagnosis of this disorder (Geller and Luby 1997; Nottelmann et al. 2001; Geller et al. 2004; Geller et al. 2008; Youngstrom et al. 2008).

There are a number of questions that continue to persist regarding the concept of PBD. The first is whether and how frequently manifestations of mania and sub-syndromal mania are present in preadolescents (Merikangas et al. 2010; Leibenluft 2011). The second factor is whether there are any differences in clinical manifestations of BD by age (Youngstrom et al. 2008; Papolos et al. 2009) and whether there should be modifications of the criteria required for diagnosis such as the numbers of symptoms for age as has been suggested for depression (Luby et al. 2003). The fact that some researchers in the field refer to a category of preadolescent/prepubertal subtype of PBD suggests that subjects in this subtype may perhaps manifest the condition differently from adults. There are some researchers who suggest that the subjects with this subtype have PBD characterised by less discrete episodes and greater irritability and volatility (Mick et al. 2005; Wozniak et al. 2005). Other studies suggest that subjects with this subtype of PBD have more mixed episodes with less complete remissions and more mood shifts compared to adults (Findling et al. 2001; Axelson et al. 2006). There still remains considerable 'mystery and uncertainty' regarding the clinical presentation of PBD.

A third factor is whether developmental modifications should be made for the symptoms of mania (Geller et al. 2002). For example, grandiosity is a core feature of mania across the life cycle but the specific behaviours that a subject with PBD might display may well be different from an adult subject with BD perhaps as a consequence of differences in setting and opportunity (Youngstrom et al. 2009). Clinical descriptions of what might constitute grandiosity across the developmental age range before the age of 18 years might be a step forward. The fourth issue is whether comorbidities vary as a function of age (Carlson and Meyer 2006). Children with mania often also meet criteria for ADHD thereby posing the question whether the apparent comorbidity is a function of the base rate of ADHD (Galanter and Leibenluft 2008; Youngstrom et al. 2010) versus reflecting shared symptoms (Biederman et al. 1998) or perhaps a developmental subtype of BD (Tillman and Geller 2006). The fifth issue is about how to define the mood disturbance that is an essential part of mania/hypomania. DSM-IV states that either elevation/irritability can be a

core symptom but some experts in the field, including the NICE guidelines have recommended that elevation of mood alone should be used for the diagnosis of PBD (NICE 2006). The sixth and last issue is how to define an episode as significant number of cases of PBD present as BD NOS (discussed in section 2.4) with having the same symptoms as in a manic episode but of much shorter duration lasting a few hours (usually >4 hours) to days (Findling et al. 2001; Birmaher et al. 2006) (see section 2.4).

The prevalence of PBD has been reported to vary between 0.1% and 2% (Kessler et al. 1994; Lewisohn et al. 1995; Costello et al. 1996; Weissman et al. 1996; Johnson et al. 2000; Stringaris et al. 2010). In their UK based study, Stringaris and colleagues conducted a cross-sectional survey of 5,326 subjects in the age range of 8-19-year-olds from the general population using information from both parents and youth (Stringaris et al. 2010). Measures used in the study were the Developmental and Well-Being Assessment for BD symptomatology and the impact scale of the Strengths and Difficulties Questionnaire to assess social impairment. Only 7 individuals (0.1%) met definite or probable DSM-IV criteria for BDI or BDII. The prevalence of BD NOS, however, was 10-fold higher. Parent-youth agreement was very low: kappa = .02, $p > .05$ for BD NOS with 1.1% by parent report and 1.5% by youth report. The authors reported that after adjusting for a dimensional measure of general psychopathology, self-reported (but not parent-reported) BD NOS remained associated with overall social impairment. This was a well designed study using measures with high rates of acceptability but did not include any measures that confirmed the diagnoses using clinical assessments. The reported rates of diagnosis of BD in children and adolescents in USA has increased dramatically over the past decade (Moreno et al. 2007). In this study the authors using diagnostic data reported to insurance providers over a 10 year study period, identified a 75% increase in rate of diagnosis of BD amongst outpatients and 67% increase amongst inpatients in young people under 18 years.

Researchers have also studied the rates of early onset of symptoms from large scale studies using the retrospective recall of onset of symptoms amongst adult

patients with BD. These studies had reported that 1 in 5 adults with BD had evidence of illness (using structured interviews) before age 19 (Carlson et al. 1977; Joyce 1984). More recently, Post and colleagues reported findings from the Bipolar collaborative network which included European sites (Netherlands and Germany) and 4 sites in USA (Post et al. 2008). In the study, onset of symptoms of BD was ascertained by retrospective recall [subjective recall obtained from patients and data from the Structured Clinical Interview for DSM-IV (First et al. 2002) were highly correlated at r=0.8]. Within this study, 61% of the US sample in comparison with 30% of European sample reported onset of symptoms prior to age 19 years. The very early onset (in childhood age range: although not defined by the authors but perhaps meant to imply prepubertal onset) also showed a significant transatlantic divide with 22% of the US sample vs only 2% of the European sample. These studies are limited by the retrospective nature of the design. However, despite these limitations it is of interest to note that over the past 3 decades studies have reported rates of onset of symptoms of BD in the teenage years (Moreno et al. 2007; Stringaris et al. 2010).

Notwithstanding the controversies that remain regarding the presentation, epidemiology and clinical features in PBD (Youngstrom et al. 2006) the rates of diagnosis of BD in under 18s in USA have increased by 4000% between 1995 and 2005 (Moreno et al. 2007). What remains unclear is whether these high rates are due to better identification of PBD, increased incidence or over diagnosis of PBD (Chang 2009).

2.8 Psychosocial function and burden

Psychosocial function and functional outcome are the terms used to describe various fundamental, different but often related aspects of daily living such as social interaction, community participation, recreation, independent living and employment (Sanchez-Moreno et al. 2009). In their recent review, Sanchez-Moreno and colleagues, reported that adult subjects with BD showed

considerable impairment in psychosocial function. The factors that appeared to demonstrate significant association with this impairment were subsyndromal symptoms together with neurocognitive impairment (Sanchez-Moreno et al. 2009). Other studies have indicated that subsyndromal mood symptoms per se are related to the psychosocial dysfunction seen in subjects with BD (Kauer-Sant'Anna et al. 2009; Rosa et al. 2009; Sanchez-Moreno et al. 2009). Some other recent studies have demonstrated that several neurocognitive functions appear to be independent, equal and even primary correlates of impairment in psychosocial function (Zarate et al. 2000; Altshuler et al. 2008; Mur et al. 2009) or predictors of functional outcome in longitudinal studies (Martino et al. 2009; Bonnin et al. 2010). The problem with the interpretation of these findings is that the studies have used different assessment measures and focussed on different aspects of functioning, neurocognition and symptomatology. The study samples have included heterogenous populations of patients ranging from euthymic to symptomatic, and from first episode to chronic presentations. This heterogeneity makes comparisons across studies problematic (Simonsen et al. 2010).

In a recent well designed study, Lahera and colleagues assessed 39 adults with BD (euthymic) fulfilling DSM-IV-TR criteria for BDI or BDII (Lahera et al. 2012). Subjects were divided in two groups: high (n = 19) and low (n = 20) global functioning. Participants completed tasks assessing verbal and nonverbal social cognition (Faux pas test and Facial Emotion Recognition test), sustained attention and executive function. Subjects in the low-functioning group showed a significant impairment in both verbal and nonverbal measurements of social cognition compared with the high-functioning group. Globally, both bipolar groups showed a significant impairment in facial emotion recognition compared with a similar sample of healthy volunteers. The authors suggest that based on the results from their study, social cognition may play a significant role in the clinical-functional gap of subjects with BD. More recently, a meta analysis conducted by Depp and colleagues, assessed the degree to which neurocognitive impairment might contribute to pyschosocial dysfunction in BD, has reported that the degree of correlation between neurocognitive dysfunction

and psychosocial function in the 44 pooled studies was modest ranging in 0.2 to 0.33 (Depp et al. 2012). This explained only 10% of the variance in everyday functioning in adults with BD. In summary, the contribution made by neurocognitive impairment to psychosocial impairment in BD remains unclear.

It has been proposed that the psychosocial impairment experienced by subjects with BD contributes to the overall economic burden of BD. BD has been described as one of the most costly and debilitating of psychiatric disorders (Bryant-Comstock et al. 2002; Judd and Akiskal 2003; Hong et al. 2011). Using the concept of Disability Adjusted Life Years (DALYs) the World Heath Organisation has ranked BD as seventh among the worldwide causes of non-fatal disease burden (WHO 2001). More recently, Merikangas and colleagues reported that bipolar spectrum disorders have higher DALYs than major neurological conditions or cancer (Merikangas et al. 2011). These high rates of economic costs and disability, however, would appear to be at odds with the aforementioned Kraepelinian description of manic depression (presented in section 2.2).

2.9 Economic cost to UK

Das Gupta and Guest assessed the direct and indirect economic costs attributable to BD in the UK NHS health system in comparison with other mental health disorders in particular with schizophrenia (Das Gupta and Guest 2002). The total costs reported in this study to UK society based on 1999/2000 figures, was £2 billion of which the majority (86%) of annual societal costs (£1770 million annually) were defined as indirect costs including excess unemployment, absenteeism and suicide. The annual direct costs to the NHS attributed to BD was £198.7 million. This comprised about 10% of the annual cost to the NHS. In this study of all the patient groups studied by age, subjects with PBD had the longest mean length of hospital admission at 92 days. This would have had a impact on the lives of affected young people and their families due to the high level of impairment and incapacity. However, due to the low numbers (<0.5% of total number of annual admissions) this figure did not directly impact on overall annual NHS costs.

2.10 Cost comparison with schizophrenia

In the same study (presented in section 2.9) the authors reported the annual costs attributable to schizophrenia as £3.7 billion in comparison to £2 billion reported for BD (Das Gupta and Guest 2002). The costs for BD imply that in spite of similar (if not increased) prevalence of BD (compared to schizophrenia) the burden to UK society is lower for BD on a case-by-case basis compared with schizophrenia. Although the study used robust statistical techniques it does require replication especially since a decade has elapsed since publication of this study.

2.11 Genetics

Family, adoption and twin studies indicate that BD is a highly heritable disorder (Roybal et al. 2012). Craddock and Jones reported that the rates of concordance in monozygotic twins range from 56-80%, while in family studies an 80% rate of heritability was reported (Craddock and Jones 1999). More recent studies report that the heritability evident in twin studies may be even higher than previously thought: 89% in a recent hospital register study of 67 twin pairs in the UK (McGuffin et al. 2003) and 93% in a population register study of 19 124 same-sex twin pairs in Finland (Kieseppa et al. 2004). Although these high rates of heritability could be considered as convincing indicators of the importance of genetic factors affecting BD susceptibility, the rates of monozygotic concordance are less than 100% which indicates that genetic vulnerability alone may not be the full story (Craddock and Sklar 2013). The Genes and Environment (GXE) interaction requires detailed examination for BD.

Based on findings from their meta-analysis, Lapalme and colleagues found that OBP are 4 times more likely to develop an affective illness in comparison with OHC (Lapalme et al. 1997). Indeed other studies have reported that the rates of bipolar spectrum disorder in OBP range from 14-50% (DelBello and Geller 2001; Chang et al. 2003). Additionally, family studies suggest that PBD is

associated with a greater genetic load for BD than for adult onset BD (Todd 2002; Mick and Faraone 2009).

In common with most other mental health disorders, studies of repeated linkage and Genome Wide Association Studies (GWAS) have reported no single gene as responsible in the pathogenesis of BD (Craddock and Sklar 2013). GWAS in BD have generated some important findings that show the potential involvement of cell migration, calcium, and sodium channel genes such as CACNA1C, NCAN, and ANK3 (Van Rheenen and Rossell 2013). Data for these genes though has been ambivalent even for the CACNA1C gene which has been considered to demonstrate the strongest statistical association with the disorder (Sklar et al. 2008). The other genes that have attracted a lot of interest in the development of BD include Catechol-O-MethylTransferase (COMT), Glycogen Synthase Kinase 3 Beta (GSK3-B), Brain-Derived Neurotrophic growth Factor (BDNF), Monoamine Oxidase A (MAOA), dopamine transporter (G72/G30) and the serotonin transporter (SLC 6A4), Tryptophan Hydroxylase 2 (TPH2) (Roybal et al. 2012; Van Rheenen and Rossell 2013) It is interesting, however, that the most commonly implicated genes in this polygenic pattern of inheritance for adult BD [COMT, GSK3-B, BDNF, MAOA), dopamine transporter (G72/G30) and the serotonin transporter (SLC 6A4)] have not all been linked within the genetic studies in PBD (Roybal et al. 2012). However this lack of overlap requires replication.

The significant impairment in psychosocial function and high economic costs reported in BD (described in sections 2.8, 2.9 and 2.10) as well as the high heritability of BD (described in section 2.11) lend support to early recognition, diagnosis and implementation of appropriate management particularly in subjects ‘at risk’ to develop BD. One way to facilitate this approach would be to identify a reliable endophenotype for BD which might assist the recognition of individuals who are ‘at risk’ for developing BD (Olvet et al. 2013). The concept of endophenotypes will be presented in the next section (section 2.12).

2.12 Endophenotypes

The term ‘endophenotype’ was coined by John and Lewis when studying the factors influencing the evolution of grasshoppers (John and Lewis 1966). The authors stated that the geographical distribution of grasshoppers was a consequence of some features not yet apparent in their external phenotype (‘exophenotype’) but rather due to an ‘endophenotype‘ which was microscopic and internal. Gottesman and Shields adapted the term ‘endophenotype’ to use in psychiatry as an internal phenotype discoverable by ‘microscopic examination or biochemical test’ (Gottesman and Shields 1973). The term is well suited for use in the field of mental health to fill the gap between available descriptors and the gene/disease processes (Gottesman and Gould 2003). Endophenotypes provide a means for identifying the ‘downstream’ traits or facets of clinical phenotypes and the ‘upstream’ consequences of genes. In theory, endophenotypes should assist in the identification of the underlying genetic mechanism in hypothesised polygenic systems conferring vulnerability for a particular disorder (Gottesman and Gould 2003). Gottesman and Gould have suggested that the identification of an intermediate phenotype or ‘endophenotype’ may be useful for the investigation of the causal chain of aetiology: including the links between genes, environment and final disease behavioral phenotype.

Gershon and Goldin proposed 4 criteria for a putative endophenotype (Gershon and Goldin 1986). Subsequently, Leboyer and colleagues suggested a fifth criteria for diseases that display complex inheritance patterns (Leboyer et al. 1998). Gottesman and Gould have summarised these criteria and they are presented next (Gottesman and Gould 2003):

Criterion 1: The endophenotype is associated with illness in the population.
Criterion 2: The endophenotype is heritable.
Criterion 3: The endophenotype is primarily state-independent (manifests in an individual whether or not illness is active).
Criterion 4: Within families, endophenotype and illness co-segregate.

Criterion 5: The endophenotype found in affected family members is found in non-affected family members at a higher rate than in the general population.

2.13 Importance of identifying endophenotypes

Recent studies have attempted to understand the *process of being bipolar* by examining measures such as neuropsychological function, facial emotion processing, genetics, inflammatory markers and neuroimaging (Frey et al. 2013). As discussed in section 2.8, some studies have reported aspects of neurocognitive function have a statistical association with psychosocial and occupational dysfunction seen in BD (Zarate et al. 2000; Altshuler et al. 2008; Mur et al. 2009; Sanchez-Moreno et al. 2009). More recently, there has been considerable interest in studying facial emotion labeling in subjects with BD (discussed in chapter 4). Lahera and colleagues demonstrated that deficits in social cognition might contribute to the functional difficulties in BD (Lahera et al. 2012). These neurocognitive deficits and emotional processing deficits might be potential endophenotypes for BD. If confirmed, such endophenotypes may aid early detection of BD, improve prognosis for the individual through earlier access to appropriate treatment and perhaps as a consequence reduce the societal economic burden of BD. However to date, most studies investigating neurocognitive and facial emotion labelling deficits have investigated young patients (age<18 years) and adults who have an established BD. This approach, has the limitation that any identified deficits in neurocognition and facial emotion labeling may simply be part of or a consequence of either the disorder or the medications used to treat BD.

As presented in section 2.12 the 5 criteria for a marker to be considered a putative endophenotype are:

Criterion 1: The endophenotype is associated with illness in the population.

Criterion 2: The endophenotype is heritable.

Criterion 3: The endophenotype is primarily state-independent (manifests in an individual whether or not illness is active).

Criterion 4: Within families, endophenotype and illness co-segregate.

Criterion 5: The endophenotype found in affected family members is found in non-affected family members at a higher rate than in the general population.

As regards the first 3 criteria for a marker being considered endophenotypes for BD the most consistent neurocognitive findings have been verbal memory, executive function and sustained attention deficits (Bora et al. 2009). Further studies assessing facial emotion processing have demonstrated that patients with BD make more errors recognising facial affect than HC with some studies implicating fear as a particular facial affect that is not identified correctly (Rocca et al. 2009). There have been few studies assessing whether neurocognition (chapter 3.9) and emotion processing deficits (chapter 4.6) occur more frequently in subjects 'at risk' for BD as compared to general population. Fewer studies have assessed these functional domains in a developmentally appropriately population where confounding factors such as comorbid mental health/neurodevelopmental disorders and pharmacological treatment for the same have been considered.

2.14 Endophenotype: 'at risk' studies

One appropriate strategy to address the identified shortcomings in previous research (section 2.13) would be to study a population of individuals known to be at a high risk to develop BD but who have not yet developed the disorder (Henin et al. 2005). BD is highly familial (discussed in section 2.11). The examination of an 'at risk' group could provide a methodology for identifying possible endophenotype(s) for mood disorders (Klimes-Dougan et al. 2006). OBP provide an 'ideal' group for studying early manifestations of risk (Henin et al. 2005). A better understanding of the disruptions in neurocognitive processing (Klimes-Dougan et al. 2006; Maziade et al. 2009; Diwadkar et al. 2011; Deveci et al. 2013) and facial emotion processing (Brotman et al. 2008; Brotman et al. 2008; Whitney et al. 2013) in this high risk group has been described as 'a step towards elucidating the pathogenesis for mood disorders and perhaps lead to identification of endophenotypes for Bipolar Disorder' (Klimes-Dougan et al. 2006).

2.15 Psychopathology in offspring of bipolar parents

Lapalme and colleagues in their meta analysis reported that OBP were 2.5 times more likely to develop a psychiatric disorder and 4 times more likely to develop an affective disorder in their lifetime in comparison with OHC (Lapalme et al. 1997). Studies assessing for a DSM-IV Axis I Disorder in OBP (of at least school age) report rates varying from 52% (Birmaher et al. 2009) to 71.4% (Duffy et al. 2007). The range of conditions include Attention Deficit Hyperactivity Disorder (ADHD), mood disorders (depression and BD), anxiety disorders and subsyndromal features of anxiety. A recent European study from Madrid also reported that 50% of OBP fulfilled the diagnostic criteria for at least one DMS-IV Axis I disorder with attention-deficit/hyperactivity disorder (30%), anxiety disorders (14%) and affective disorders (10%) as the most frequent (Garcia-Amador et al. 2012). After controlling for having more than one sibling in the study, the odds ratio for OBP receiving at least one axis I disorder was 15.02 (when a biological parent had bipolar disorder with a lifetime history of psychotic symptoms) and 3.34 (when one parent had bipolar II disorder).

Vandeleur and colleagues have also reported that, in Switzerland, rates of mood and anxiety disorders were elevated among OBP (34.5% any mood disorder; 42.5% any anxiety disorder) compared to controls (12.6% any mood disorder; 22.8% any anxiety disorder) (Vandeleur et al. 2012). Moreover, recurrent Major Depressive Disorder (MDD) was more frequent among OBP (7.9%) than controls (1.6%). Parental concordance for bipolar spectrum disorders was associated with a further elevation in the rates of mood disorders in offspring (64.3% for both parents versus 27.2% for one parent). The data suggests that psychopathology in OBP both affective and non-affective disorders is quite frequent.

With specific reference to the risk of developing BD in OBP, data from North America suggests that the risk may vary considerably from 3-27% (DelBello and Geller 2001; Duffy et al. 2011). In a recent Dutch bipolar offspring study, data is reported on 140 OBP from 86 families (BDI and BDII) followed from

adolescence into adulthood to a mean age of 28 years (Mesman et al. 2013). Although 70% of the sample developed an Axis I DSM-IV disorder the rates of developing a lifetime bipolar spectrum disorder as 13% (BDI: 3%, BDII: 8%, schizoaffective disorder, bipolar type:1% and cyclothymia: 1%). The important message here appears to be that although the risk for developing bipolar disorder was higher in OBP than OHC, a significant (larger proportion) of OBP did not develop BD.

The high rates of mental health and neurodevelopmental disorders (predominantly ADHD) seen in OBP are an important consideration when designing a study seeking to identify a potential endophenotype for BD. These disorders (and the pharmacological treatment for the same) can contribute to neurocognitive and facial emotion labeling deficits identified. The study of OBP who do not meet the criteria for a currently recognised disorder and are not receiving any pharmacological treatment, would provide a next step for the further investigation of previously identified neurocognitive and facial emotion labelling deficits.

2.16 Summary

BD is a highly prevalent and heritable disorder with considerable impact on the individual, their family, the health care services and wider society (Hong et al. 2011). The identification of a potential endophenotype may be helpful in both the understanding of the aetiology of BD and the earlier identification of BD. It would also assist in the characterisation of and address some of the controversies around very early onset BD. Proposed endophenotypes for BD include deficits in neurocognitive function and facial emotion processing. Most studies that have investigated these domains have assessed adults with BD. A smaller number of studies have included adolescents with BD. Little research (as will be discussed in the next chapters) has tested those who are at an increased genetic risk for development of BD. Neurocognitive function and facial emotion processing have not been assessed in combination in ‘at risk’ or ‘high risk’ studies as far as this author is aware.

'If our brains were so simple that we could understand them, we would be so simple that we could not'

Anonymous taken from ***(Lezak 1995)***

Chapter 3: Neurocognitive function

'Cognitive abilities (and disabilities) are functional properties of the individual that are not directly observed but instead are inferred from.... behavior....

All behavior (including neuropsychological test performances) is mutiply determined: a patient's failure on a test of abstract reasoning may not be due to a specific impairment in conceptual thinking but to attention disorder, verbal disability, or inability to discriminate the stimuli of the test instead'

*(Sivan and Benton **1999**)*

3.1 Introduction

This chapter first defines neurocognitive function and the domains of function assessed in this project. It then discusses the progression of evidence for neurocognitive deficits in BD starting with the studies that initially assessed these domains in adults in affective episodes of BD and then in euthymic adults with BD. The chapter then progresses to studies that have assessed neurocognition in PBD and the few studies that have done the same in OBP.

3.2 Neurocognitive function

'Neurocognitive function is an applied science concerned with the behavioural expression of brain dysfunction. Neurocognitive assessments allow the examination of the brain by the study of behaviours that rely on the integrity of the brain.' (Lezak 1995)

3.3 Neurocognitive domains

For this project the domains considered as part of an individual's neurocognitive function include:

a. Attention
b. Sustained attention (Concentration)
c. Working Memory
d. Learning
e. Executive function

3.4 What about intelligence?

'General intelligence is as valid as the "strength of soil" concept is for plant growers. It is not wrong but archaic'

(Das 1989)

Intelligence was originally attributed to a single function (Lezak 1995). Early investigators treated intelligence as if it were a unitary variable which, like physical strength, increased at a regular rate in the course of normal childhood development (Binet and Simon 1908; Terman 1916). As refinements in testing and data-handling techniques have afforded greater precision and control over observations of cognitive ability, it has become evident that the behaviour measured by 'intelligence' tests involves specific cognitive functions (Feinberg and Farah 2003).

An early finding was that the summation scores (i.e. IQ scores) on standard intelligence tests did not bear a predictably direct relationship to the size of brain lesions (Maher 1963). Brain lesions produce impairments in a broad range of cognitive functions, however these functions may be affected in different ways. Abilities most directly served by the lesion may be destroyed; associated or dependent abilities may be depressed (Lezak 1995). In sum,

neuropsychological studies have not found a general cognitive or intellectual function, but rather many discrete ones that work so smoothly in the brain that cognition is experienced as a single seamless attribute (Lezak 1995). For those individuals who have already developed brain lesions, this concept of intelligence would, seem to justify the practice of using premorbid measure of 'intelligence' as a best indicator of premorbid function against which to compare current activities, observations and detailed cognitive test performances (Lezak 1995).

3.4.1 IQ and composite scores: the reification of *g*

'The term IQ is bound to the myths that intelligence is unitary, fixed and predetermined.... As long as the term IQ is used, these myths will complicate efforts to communicate the meaning of test results and classification decisions.

(Reschly 1981)

'IQ' refers to a derived score used in many test batteries designed to measure a hypothesised general ability, intelligence. Because of the multiplicity of cognitive functions assessed in these batteries, IQ scores on their own are not useful in describing neurocognitive test performance (Lezak 1995). Spearman noted that correlations between pairs of tests form a 'positive manifold' in which some portion of the variance in each test could be attributed to a universal general factor, ***'g'***, common to all intelligent activities (Spearman 1927). This concept of ***g*** has, however, been very controversial. Early psychometric evidence against ***g*** (Thomson 1919) (showing that intercorrelations among tests could produce hierarchies without invoking a general factor making ***g*** extraordinarily improbable) disciples of ***g*** (Jensen 1969) have argued that it has stood like 'a rock of Gibraltar'. Spearman conceived of ***g*** as a marker for innate mental energic capacity, a view that according to Evans and Waites (Evans and Waites 1981), Spearman supported by appeals to contemporary neurophysiology. However, other researchers have argued that there is no single brain location

for ***g*** (Dennis et al. 2009). This evidence does not lend support to the universal general factor ***g***.

3.4.2 IQ as a covariate in neurocognitive studies

As discussed in the previous section (3.4.1) when assessing neurocognition in individuals with a significant disorder such as BD, it might be appropriate to covary cognitive scores with a measure of premorbid intelligence e.g. National Adult Reading Test (NART) (Nelson and O'Connell 1978). However, when studying those who are 'at risk' for BD (particularly unaffected OBP with no psychopathology) covarying current neurocognitive domain scores with scores of IQ is a complex issue. Firstly, for these subjects, as they are unaffected i.e. have yet to develop the illness, premorbid IQ scores cannot be used. Further, in statistical analyses, a covariate is a cause of the outcome. The covariate (in this case IQ), however, should not be an outcome of the dependent (in this case scores on cognitive tests) or independent variable (Dennis et al. 2009). However, as discussed in previous section (3.4.1), IQ is derived from the multiplicity of cognitive domains. Thus by making it an covariate would violate the assumptions for it be a 'true covariate' in a statistical tool such as ANCOVA. To elaborate, it is possible that neurocognitive deficits contribute to scores of overall lowered FSIQ scores and by controlling for IQ, studies might remove potentially relevant genetic variance from the outcomes (Doyle et al. 2009; Deveci et al. 2013).

3.5 Significance of neurocognitive dysfunction

The significance of the neurocognitive deficits that have been identified in patients with BD, (discussed next in section 3.6) and the impact on psychosocial and occupational function have only recently been studied. Some studies of symptomatically improved adult patients with BD have reported a statistical association between specific neurocognitive deficits and dysfunction in psychosocial and functional outcome (Atre-Vaidya et al. 1998; Martinez-Aran et al. 2002; Goswami et al. 2006; Altshuler et al. 2008; Martino et al. 2009; Mur

et al. 2009; Sanchez-Moreno et al. 2009; Bonnin et al. 2010) and quality of life (Thompson et al. 2000). Further studies have identified that this association is at least partially related to the poor rate of inter episode functional recovery seen in a high proportion of patients with BD (Atre-Vaidya et al. 1998; Martinez-Aran et al. 2002) as well residual subsyndromal symptoms (Kauer-Sant'Anna et al. 2009; Rosa et al. 2009; Sanchez-Moreno et al. 2009).

A recent well designed prospective study has demonstrated that improvement in neurocognitive function was related to occupational recovery in BD (Bearden et al. 2011). This study included 79 adult patients with BDI who had previously been employed. All patients demonstrated symptomatic recovery (clinical euthymia for at least 6 weeks). They underwent assessments of neurocognitive function and occupational functioning every 3 months for at least 9 months. Factor analysis was applied to reduce the initial set of neurocognitive variables to five domains: episodic memory, working memory/attention, executive function, visual scanning, and speed of processing. At the time of symptomatic recovery, 4 of 5 neurocognitive domains were significant predictors of occupational recovery and the fifth, executive function, showed a trend in the same direction. For those patients who had not occupationally recovered at end point, longitudinal analyses revealed that changes between baseline and the three-month follow-up time point in most cognitive domains were highly significant predictors of occupational recovery at three months. These findings indicate that better neurocognitive function in multiple domains and improvement in these domains over time are strongly predictive of subsequent occupational recovery. Treatments that target cognitive deficit may therefore have the potential for improving long-term occupational functioning in BD.

In a recent meta-analysis which included 22 studies with a pool of 1344 patients the mean Pearson correlation between neurocognitive ability and psychosocial functioning was r = 0.27 (95% CI: 0.22–0.31) and was significant for all cognitive domains with little variability across cognitive domains (Depp et al. 2012). The degree of correlation is similar to that seen in schizophrenia (Fett et al. 2011). The authors conclude that ‘cognitive abilities account for a significant,

albeit moderate, proportion of variation in everyday (psychosocial) functioning' and 'that cognitive deficits represent a target for functional rehabilitation in bipolar disorder, yet do not support a specific pathway from individual elements of cognitive impairment to functional disability' (Depp et al. 2012). Despite this assertion, there does appear to be a body of evidence suggesting a statistical association between neurocognitive deficits and psychosocial and occupational deficits seen in BD.

3.6 Studies in adults

3.6.1 Studies in mood episodes

Neurocognitive impairment occurring during an affective episode of BD has been well documented (Clark et al. 2001; Murphy et al. 2001; Martinez-Aran et al. 2004). This would confirm criterion 1 to be considered an endophenotype for BD (chapter 2.13). Acutely affectively ill patients have been shown to demonstrate dysfunction in virtually all cognitive domains, such as attention, executive function, learning, memory and psychomotor speed (Martinez-Aran et al. 2000; Bearden et al. 2001; Quraishi and Frangou 2002). *The prominent dysfunction is seen in the domains of sustained attention, verbal memory and executive function.* Although, these studies have all demonstrated findings that are relevant both from a clinical and a research perspective, they have all by design been conducted when patients have been in an affective episode. Therefore the question posed by these studies is: *'is the pattern of neurocognitive impairment a risk factor for Bipolar Disorder or a consequence of the affective episodes'*?

3.6.2 Studies in euthymia

To clarify whether neurocognitive impairment in BD is state or trait dependent, studies assessing neuropsychological status in euthymic subjects have been undertaken. Neurocognitive dysfunction in adult euthymic patients of BD has been well documented (van Gorp et al. 1998; Ferrier et al. 1999; Rubinsztein et

al. 2000; El-Badri et al. 2001; Ferrier and Thompson 2002; Goswami et al. 2006). Virtually all cognitive domains have been implicated in this dysfunction. *However, the most commonly implicated domains are: sustained attention, verbal memory and executive function* (Robinson and Ferrier 2005).

Recent meta-analyses have attempted to pool data from several studies (Torres et al. 2007) and also contrast findings between BDI and BDII (Bora et al. 2011). In the first meta-analysis, data from 39 studies was included which evaluated a total of 948 patients and 1128 controls with minimal variation across studies in age range, gender and education (Torres et al. 2007). This meta-analysis demonstrated generalised cognitive dysfunction in most neurocognitive domains with effect sizes in the moderate-large range. In a second more recent meta analysis, 11 studies were included with a pooled data set of 444 BDI patients and 285 BDII patients who were well matched for age, gender and duration of illness and education (Bora et al. 2011).

The authors concluded that BDII is associated with similar cognitive deficits as have been reported in BDI. However, in the same meta analysis, verbal memory, visual memory, and semantic categorization deficits seem to be more specifically associated with BDI. Importantly, although these studies seem to indicate that cognitive impairment in BD is not just a state variable but in all probability a trait variable it does not help clarify whether: '*the neurocognitive impairment is responsible for, a result of or a trait variable of bipolar disorder"*? So although these studies have furthered our quest of endophenotypes for BD, the issue of whether specific neurocognitive impairment is a potential endophenotype for BD cannot be answered by these studies.

3.6.3 Aetiology of neurocognitive deficits

Studies of euthymic adults with BD have suggested that the neurocognitive impairments particularly in the domains of sustained attention, verbal memory and executive function may reflect frontal lobe damage or disruption of fronto-subcortical or mesolimbic circuitry (Ferrier et al. 1999; Strakowski et al. 2000;

Ferrier et al. 2001). Martinez-Aran and colleagues (Martinez-Aran et al. 2004) in their analysis have stated that studies have shown that cognitive functioning in bipolar disorder is affected by number of episodes (Kessing 1998; van Gorp et al. 1998; Ferrier and Thompson 2002), especially of the manic type (Morice 1990; Altshuler 1993; van Gorp et al. 1998; Zubieta et al. 2001; Cavanagh et al. 2002; Clark et al. 2002), as well as chronicity, defined as the duration of illness (van Gorp et al. 1998; Clark et al. 2002). Subclinical symptoms, particularly sub threshold depression, may also be a risk factor for neurocognitive deficits (Kessing 1998; Fava 1999; Martinez-Aran et al. 2000). However, this approach still fails to ascertain whether cognitive impairment precedes illness onset or is a part of the phenotype of BD.

3.7 Studies in paediatric bipolar disorder

Studies focussing on children and adolescents with BD have reported that subjects with PBD show impairment on tests of attentional set-shifting, visuospatial memory and executive functioning (McClure et al. 2003; DelBello et al. 2004; Dickstein et al. 2004; Doyle et al. 2005; McClure et al. 2005; McClure et al. 2005; Rich et al. 2005; Pavuluri et al. 2006).

In a key study, Dickstein and colleagues recruited participants to a National Institute of Mental Health (NIH) study (Dickstein et al. 2004). Twenty-one subjects with PBD aged 6 to 17 were matched with an equal number of control subjects for age and gender. The test subjects all met DSM-IV criteria for BD. Eighteen subjects met full duration criteria for BD (i.e. more than 4 days) whereas 3 met criteria for BD NOS (duration of episode between 1 and 3 days). The exclusion criteria included IQ<70, presence of autism spectrum disorder or severe pervasive developmental disorder, psychosis, unstable medical illness (i.e. unstable asthma), other medical illness (multiple sclerosis, thyroid disease), pregnancy and substance abuse within 2 months of initial evaluation. Following a telephone screening patients who met diagnostic criteria were invited to NIMH with a primary caregiver for a more detailed evaluation. This included the Kiddie Schedule for Affective Disorders Present and Lifetime Version (K-SADS-PL)

(Kaufman et al. 1997), ratings on the Young Mania Rating Scale (YMRS) (Young et al. 1978), the Children's Depression Rating Scale (CDRS) (Poznanski and Mokros 1995), Children's Depression Inventory (CDI) (Kovacs 1992) and Global Assessment of Functioning Scale (GAF) (Jones et al. 1995). The neuropsychological tests battery consisted of CANTAB subtests: Motor Screening (MS), Pattern Recognition Memory (PRM), Spatial Memory Span (SMS), Spatial Recognition Memory (SRM), Spatial Working Memory (SWM), Stockings of Cambridge (SOC) and Intradimensional/Extradimensional (IED) shift (Cambridge Cognition Ltd.).

The authors stated that the mood ratings in the test group (assessed by using YMRS and CDRS) demonstrated heterogeneity. YMRS ratings below 12 were defined as euthymic, between 12 and 25 as hypomanic and more than 25 as manic (authors quote Youngstrom, personal communication, March 2002). CDRS ratings >40 were considered as indicative of depression. This (relatively high) threshold score (CDRS>40) is usually used as an indication of moderate depression requiring treatment in children in clinical trials (Emslie et al. 2002). Of the 21 subjects with PBD, 13 were euthymic. Eight met criteria for hypomania at the time of neurocognitive assessment. All the patients were on at least one medication at the time of testing. The PBD group performed significantly worse on the following CANTAB subtests: pattern recognition memory, spatial span and intradimensional and extradimensional shift. The authors hypothesised that these findings indicated VentroLateral PreFrontal Cortex (VLPFC) dysfunction.

Although the study was well designed there were a number of limitations. The test group included a wide developmental age range (6-17 years). There was no separation of cases of BDI, BDII and BDNOS within the PBD group which introduced an element of heterogeneity into the group. Furthermore, a subgroup of the PBD group were not euthymic at the time of assessment and all patients were on at least 1 psychotropic medication with at least 50% on 4 or more psychotropic medications. The majority of patients studied had mental health co-morbidities eg. ADHD. The lack of euthymia at time of testing, psychotropic

medication (Torrent et al. 2011) and comorbid conditions may have contributed to the neurocognitive deficits identified.

To date, most studies reporting neurocognitive function in PBD have been cross sectional in design. Little can therefore, be extrapolated from them to understand the developmental trajectory of these deficits (Pavuluri et al. 2009). To address this issue, Pavuluri and colleagues conducted a 3 year longitudinal follow up study of 26 subjects with PBD and 17 Healthy Controls (HC) matched for age, gender, race and estimated premorbid intellectual functioning (Pavuluri et al. 2009). The PBD group were all treated according to a standard treatment algorithm described in detail in the paper. The subjects completed a rigorous neurocognitive assessment battery assessing executive function, attention, working memory, verbal memory, visual memory, motor skills and visuospatial perception.

At baseline the PBD group performed significantly worse in each of the six broad domains under study in comparison with the HC group. Interestingly, after 3 years there was improvement in some of these domains in the PBD group whilst other neurocognitive domains (executive function and verbal memory) still showed significant decline. On executive function children in both groups demonstrated improvement during the study period but the HC group showed significantly more improvement than the PBD group ($F_{1,41}$=5.5, $p<0.05$). As regards verbal memory function, the performance of PBD group appeared to decline over the study period ($F_{1,41}$= 5.5, $p<0.05$). The baseline findings were in keeping with previous studies (reported at the start of this section). The reported executive dysfunction, may implicate prefrontal cortex which in typical development matures in later adolescence (at about the age of 15-16 years) (Luna and Sweeney 2001; Casey et al. 2005). Furthermore the verbal memory impairment which is probably the most consistent finding reported in cross sectional studies of PBD (Doyle et al. 2005; Glahn et al. 2005; McClure et al. 2005; Pavuluri et al. 2006) may implicate altered integration of frontal (particularly ventral prefrontal areas) and mesial temporal systems. Both these proposed hypotheses have been investigated in recent neuroimaging studies

(Botteron et al. 1995; Chang et al. 2004; Rich et al. 2006; Gogtay et al. 2007) but further work is needed to replicate these findings.

In another study, Schenkel and colleagues sought to investigate neurocognitive functioning in unmedicated PBD with both BDI (n=27; M;F::14:13) and BDII (n=19; M:F::7:12) and matched HC (n=33; M;F::19:14) (Schenkel et al. 2012). The authors hypothesized that subjects with BDI would show more severe and widespread cognitive dysfunction, displaying greater deficits on tasks of attention, executive function, working memory, visual memory, and verbal learning and memory compared to subjects with BDII and HC. The subjects were all either manic/hypomanic or in a mixed episode and medication free for at least a week prior to assessment. The groups were matched on age, sex, parental socioeconomic status, and IQ (WASI 2) (Wechsler 1999). In the BD groups there was significant levels of comorbid conditions. Subjects in BDI group had ADHD (56%), GAD (7%), ODD (15%) and Social Phobia (4%) and subjects in BDII group had ADHD (21%), GAD (11%), ODD (11%).

The neurocognitive battery consisted of the Trail Making Test (Lezak et al. 2004), the Digit Span subtest from the Weschler Memory Scale–Third Edition (Wechsler 1997), and the California Verbal Learning Test–Child Version (Delis et al. 1987). The computerized neurocognitive test battery was compiled from the University of Pennsylvania Computerized Neuropsychological Battery (Gur et al. 2001) and Cogtest (Ventura et al. 2008). The Penn battery included the Continuous Performance Test, the Conditional Exclusion Test, and the Visual Object Learning Test. The Cogtest battery included the Set Shifting Test, the Controlled Oral Word Association Test, and the Spatial Span Test. This would indicate a well designed and age appropriate neurocognitive battery was employed by the authors as part of assessment. Standardized test scores were combined to form domain composites for attention, executive functioning, working memory, visual memory, and verbal learning and memory. Internal consistencies of the scores comprising each neurocognitive domain were calculated using Cronbach's α.

The authors developed a 3 (group) × 5 (neurocognitive domain) mixed model multivariate analyses of variance (MANOVA), with Greenhouse–Geisser correction to assess for group differences between the BD and healthy comparison groups on the five neurocognitive composites (along with follow-up post hoc pairwise comparisons to assess for group differences between the subjects in the BDI, BDII and HC groups. Analyses were repeated with the presence of any comorbid DSM–IV axis I diagnosis (including ADHD) included as a covariate. Fisher's *p* was used to compare rates of ADHD diagnoses between the two BD groups because Fisher's *p* is less influenced by imbalanced cells or small sample sizes than the chi-square statistic. A 3 (group) × 5 (cognitive domain) MANOVA post hoc analysis was done to examine group differences on each of the neurocognitive domains among healthy comparison subjects and BD youth with and without comorbid ADHD. Finally, associations between performance on the each of the neurocognitive domains and level of symptomatology were analyzed separately for each of the two BD groups using Pearson Correlation Coefficients. The statistical technique employed by the authors was robust and suitable for analysis.

The authors concluded that both BDI and BDII patients displayed significant neurocognitive impairments compared to matched HC, with the most notable deficits in verbal learning and memory which were observed in both the BD groups. Additionally, BDI paediatric patients display more widespread and severe cognitive dysfunction, along with greater ADHD comorbidity compared to those with BDII. Although a well designed study, it did have its limitations which included all subjects being in a mood episode at the time of assessment (which can have a direct impact on neurocognitive function), high levels of comorbidity including ADHD (another confounding variable). Its major strengths did lie in assessment of unmedicated subjects, homogeneity of bipolar groups, and robust statistical analysis.

In their review of the neurocognitive profile of PBD, Kyte and colleagues have stated that the findings mirror the clinical manifestations of the disorder (i.e. impaired attention, poor decision making, impulsivity etc) (Kyte et al. 2006). Based on the limited research data available the authors highlighted potentially

greater similarities than differences in the neurocognitive findings between childhood onset, adolescent onset and adult onset BD. In a recent meta-analysis Joseph and colleagues compared studies involving individuals with PBD and HC (Joseph et al. 2008). They reported the largest differences were observed for measures of verbal memory (d = 0.77). Moderate differences were found in the areas of attention (d = 0.62), executive functioning (d = 0.62), working memory (d = 0.60), visual memory (d = 0.51), visual perceptual skills (d = 0.48), and verbal fluency (d = 0.45). Small differences were found for measures of reading (d = 0.40), motor speed (d = 0.33), and FSIQ (d = 0.32).

To date most studies that have assessed neurocognitive function in PBD have done so (by design) after the onset of BD. This has meant that in common with studies of adult subjects investigators have been unable to tease apart the effects of pharmacological treatment and bipolar symptomatology on neurocognitive performance (Meyer et al. 2004). These research studies cannot answer the question: '*is the neurocognitive impairment responsible for, a result of it or a trait variable of bipolar disorder'?*

3.8 Neurodevelopmental antecedents

In this section, the literature has been restricted to the early presentations of those subjects who later developed BD. Retrospective case control studies suggest that BD may, in fact, have neurodevelopmental antecedents (Savitz et al. 2005). Crow and colleagues reported that adults who subsequently presented with affective psychosis, displayed an excess of premorbid motor and intellectual deficits compared with controls from the same birth cohort (Crow et al. 1994). van Os and colleagues reported that children who eventually developed affective disorders were delayed in reaching motor-development milestones, and suffered from twice as many speech abnormalities as their peers (van Os et al. 1997). Sigurdsson and colleagues reported an increased prevalence of delayed language, social and motor development in a group of adolescents with BD or affective psychosis (Sigurdsson et al. 1999).

Meyer and colleagues compared groups of adolescents who were offspring of bipolar or unipolar mothers with adolescents who had no family history of psychiatric illness (Meyer et al. 2004). FSIQ measures did not discriminate the three groups. They did, however, report that adolescents who later developed BD as young adults had significantly higher rates of attentional and behavioural problems. Additionally, 67% of the individuals who went onto develop bipolar disorder as an adult, displayed executive deficits as measured by the Wisconsin Card Sorting Test (WCST) in adolescence.

In contrast, some studies that have assessed neurocognitive function in subjects prior to onset of BD have not reported any deficits (Savitz et al. 2005). In a related study, Quakenbush and colleagues analyzed the premorbid school functioning of a cohort of adolescent subjects with BD (Quakenbush et al. 1996). It is important to highlight that neurocognitive function and academic ability are different variables. For this study, premorbid school functioning was defined in terms of academic achievements, work habits and peer relationships in a sample of 44 bipolar youth. Ratings were made by experienced special needs teachers and retrospective review of Ontario School Records. The authors reported that 85% of the sample demonstrated 'good-to-excellent' premorbid academic achievement (Quakenbush et al. 1996). The literature on neurodevelopmental antecedents for BD does appear to be unclear.

3.9 Studies in offspring of bipolar parents

Children and adolescent OBP are at high genetic risk for development of BD (Chang et al. 2003). When this project was being developed, there had been few well designed published studies that had explored neurocognitive function in child and adolescent OBP in a systematic manner (Kestenbaum 1979; Waters et al. 1981; Winters et al. 1981; Decina et al. 1983; McDonough-Ryan et al. 2002). In fact, most of these studies presented cross sectional IQ scores (with the study by Waters and colleagues presenting a retrospective analysis) as measures of neurocognitive function. As has been discussed in sections 3.1 and 3.2, IQ scores by themselves convey little about specific neurocognitive

deficits. There was no published study that had conducted a comprehensive assessment of neurocognitive function in OBP. During the course of this project, 4 studies have been published in peer reviewed journals (Klimes-Dougan et al. 2006; Maziade et al. 2009; Diwadkar et al. 2011; Deveci et al. 2013). These studies will be discussed later in this section.

In the 1970s, Kestenbaum attempted to investigate possible predictors for BD in a clinical descriptive study of a small sample of 13 OBP (Kestenbaum 1979). He used the technique suggested by Kaufman (Kaufman 1979). This technique predicted that a discrepancy in VIQ to PIQ scores (in either direction) equal to or greater than 15 points, would be expected in less than 13% of the general population. Using this, Kestenbaum reported that 6 of 13 OBP when assessed using the WISC (Wechsler 1974) had 'verbal achievement significantly greater than performance, with considerable subtest scatter'. For the remaining 7 OBP: 3 children did not 'follow' the pattern described above and 4 children received no psychological assessments. However, the actual FSIQ, VIQ and PIQ scores were not reported by the author. By design, the study was a case series report with no healthy control arm. Another limitation was that the recruited sample was from higher socioeconomic classes. This bias may have contributed to the finding of VIQ higher than PIQ.

Waters and colleagues identified 23 adult patients with BD from consecutive admissions for manic depression to the Royal Ottawa Hospital (Canada) between 1976 and 1978 who all had one or more offspring over the age of 15 years (Waters et al. 1981). Seventeen of the adult patients with BD agreed to participate and 58 OBP were identified as suitable for study. The aim was to compare IQ scores for those offspring who had already developed psychopathology with those who had not. The researchers were able to retrieve IQ scores (from school records) on 38 offspring as close to their 10^{th} birthday as possible. The mean IQ of the sample was 109.7$\pm$10.4 (range 88-143) which was comparable to the mean IQ score of 110 for children in 5^{th} grade in Ottawa. There was a non significant trend for OBP who had developed psychopathology (n=3) (IQ 110.7$\pm$10.7) to have a higher IQ than those who had remained well

(n=9) (IQ 108.7±10.3). For these 12 subjects only VIQ and PIQ mean IQ scores are shown in table 3.1.

Table 3.1 IQ scores in OBP (Waters et al. 1981)

	OBP with psychopathology (n=3)	OBP with no psychopathology (n=9)
PIQ	**108.3**	**110.7**
VIQ	**103.3**	**104.2**

Based on this small dataset the authors concluded that their findings did not support Kestenbaum's hypothesis (Kestenbaum 1979). However, the small sample size does not allow these conclusions to be made. They did not find higher VIQ scores in the OBP with an identified mental health disorder. In fact both groups (OBP with and without an identified mental health disorder) had a lower VIQ than PIQ. The authors reported several limitations to the study. The IQ tests were not all administered at the same age or grade level for the subjects and a number of different tests (not specified by the authors) were used to assess IQ.

Winters and colleagues assessed cognitive and attentional deficits in children vulnerable to psychopathology (Winters et al. 1981). They recruited offspring of parents with schizophrenia (OSP), unipolar and bipolar depression and healthy controls as part of the Stony Brook High Risk Study. DSM II criteria were used to make the diagnoses of schizophrenia and depression (unipolar and bipolar). The sample included 49 OBP who were assessed using the WISC (version not specified by the authors). In addition, Word Communication based on Cohen and Cahmi's work (Cohen and Cahmi 1967) was employed. This required a subject to take the role of the speaker and provide a single one word clue that would allow a listener to determine which of two words was referent. 20 word pairs were presented to the subject and the sum of the 20 trials was the measure reported by the authors.

The subjects were also assessed using the Object Sorting Test, devised by Bruner and colleagues (Bruner et al. 1966). This task consisted of an array of 42 drawings of simple objects such as an apple, a fish etc. The child was shown the array, then requested to select a group of pictures that were alike in some way, and then asked to give the reason for their choice. Ten trials were administered. Each sort was scored into one of the following categories: superordinate, complexive, thematic and vague. Superordinate sorts were based on a common feature shared by each member of a group. Complex responses, like superordinate responses were based on realistic relationships among all items, although no single attribute applied to all members of the group. Thematic responses most often included only two items that were related by a functional interaction (e.g. 'Rabbits eat carrots') or were responses that were linked on the basis of a narrative theme. Vague responses were those that specified a common attribute that was either over generalised or contained loose associations to the items. This object sorting test appeared to have features in common with a measure of executive function although as before this was not specified by the authors.

To assess distractibility the subjects were presented with digits from the digit span test (Wechsler 1955). In the distraction condition, the 1 second interval between each pair of relevant digits was filled by an opposite-gender voice saying an irrelevant digit. Credit was given only for recalling the digits in the order in which they were presented. Although the authors do not state it; this test probably assessed attention and verbal working memory. Finally a visual search task was also included in the test battery. The children were required to scan a series of letters from the English alphabet until they encountered the target letter 'G' from amongst other letters. This task is an assessment of sustained attention.

The main focus of this study by Winters and colleagues was the comparison of OSP with healthy controls. For this reason the findings of OBP were not discussed in detail. The authors reported no differences in VIQ and PIQ in OBP compared to OHC. They also stated that 'children of bipolar parents did not

typically differ from controls and were thus less 'deviant' than children of patients with unipolar depression and schizophrenia'. The sample size indicates that the study was adequately powered to assess possible neurocognitive dysfunction in all 3 groups although the authors do not report power calculations as part of the methods or results. Further, although the neurocognitive battery consisted of measures of IQ, attention, concentration, and some executive domains, there were no assessments of learning or memory.

Kestenbaum's group also published the results of 2 important studies with overlapping data sets. In the first study, Kron and colleagues utilised the Kaufman method (Kaufman 1979) to elaborate on the findings originally reported by Kestenbaum (Kron et al. 1982). They reported that 39% of the OBP group (12 out of 31 OBP, as compared to 2 of 18 OHC) had a VIQ to PIQ discrepancy of more than 15 points. An important factor was that the OBP recruited to this study had parents with both BDI (n=11) and BDII (n=7). The differences between clinical presentations and neurocognitive deficits between BDI and BDII have previously been discussed in chapter 2.4. Whether this difference is of relevance to the neurocognitive profile of the OBP is unclear.

In a further publication from the same group, Decina and colleagues tested OBP (M:F::14:17; age range: 7 to 14 years) of 18 parents meeting the Research Diagnostic Criteria (RDC) for BD in comparison with 18 OHC (Decina et al. 1983). Parental BD was confirmed by the Schedule for Affective Disorders and Schizophrenia (SADS) interview (Spitzer et al. 1978). This study included some of the OBP sample previously reported by Kron (Kron et al. 1982). Therefore as before 11 of the bipolar parent probands had BDI and 7 had BDII. The children were tested on the WISC-R (Wechsler 1974) but no other measures of specific neurocognitive domains were undertaken. ANOVA was used to analyse differences between OBP and OHC. The authors performed 2 analyses as part of 'a robust statistical plan'. First data on VIQ, PIQ was analysed using ANOVA with each child as an independent observation. In the next analysis they used each family as a unit of analysis by averaging IQ values of sibling sets.

The authors reported that children of bipolar probands manifested an atypical WISC-R profile, with VIQ significantly higher than PIQ. Twelve (39%) OBP vs 2 (11%) OHC had discrepancies of 15 points or more on VIQ than PIQ ($p<0.05$). The VIQ in OBP did not differ from OHC but PIQ was significantly lower than OHC ($p<0.05$). In contrast when the family was used as a unit of analysis there was no discrepancy between VIQ and PIQ ($p=0.16$). The latter finding may be more relevant as it attempted to control for the sibling sets nested in families. The authors did attempt to investigate the difference between bipolar probands' type of illness: BDI vs BDII. Offspring of parents with BDI showed a larger but non-significant discrepancy between VIQ and PIQ (10.6 points) compared to offspring of parents with BDII (4.4 points).

The authors themselves acknowledged the limitation of the small sample size of the offspring of parents with BDI and BDII, this highlighting the importance of studying a homogenous 'at risk' population. Other limitations include the lack of any other neurocognitive tests and the use of the ANOVA in a sample that included more than one offspring per family thereby violating the underlying assumption of the ANOVA which requires that each observation is independent of each other. However, the statistical plan of analysis did include some attempt to control for the nested data. A mixed models analysis would have been the appropriate statistical tool (discussed further in chapter 6.4.3). Apart from these limitations, the authors reported that of the 31 OBP; 16 had a formal psychiatric diagnosis (including depression+ADHD, anxiety, conduct and other disorders that could not be classified using DSM-IIIR criteria). Furthermore 7 of the remaining 15 had prominent subsyndromal psychiatric symptomatology. The high levels of psychopathology reported in the OBP group in this study are in keeping with the findings of other studies but could have contributed to the IQ discrepancies.

McDonough-Ryan and colleagues studied 28 OBP with at least one parent who had BDI (McDonough-Ryan et al. 2002). The aim of the study was to investigate whether OBP displayed a profile similar to that seen in individuals with a Nonverbal Learning Disability (NLD). NLD is defined as a triad of academic,

cognitive and socioemotional deficits (Rourke 1989; Rourke 1995). Individuals with NLD are also reported to show better developed language than visual-perception abilities. The academic difficulties are recognised as a direct result of underlying cognitive difficulties and are characterised by a weakness in mental arithmetic. Individuals with NLD are also described as having impaired social perceptual, social judgement and social interaction skills. But these problems are usually not attributed to underlying neurocognitive deficits (Rourke 1989; Rourke 1995). A control group of 24 demographically matched OHC (free of psychopathology) were also assessed. Recruiting offspring free from psychopathology is a unique strength of this study. However, the authors do not state if these numbers allowed the study to be adequately powered or not.

The parental diagnoses were confirmed by a psychiatrist using the Structured Clinical Interview for DSM-IV (SCID) (First et al. 1995). The authors explicitly excluded children with a history of head trauma, any medical condition with CNS involvement and children with mental retardation. The authors carefully excluded these conditions as they could have contributed to lowered IQ scores. The tests used to estimate cognitive ability were the WISC-III (Wechsler 1991), The Wide Range Achievement Test 3 (WRAT3) (Wilkinson 1993) and The Grooved Pegboard Test (Knight and Norwood 1980). In the WISC-III subtests 1-10 were administered and standard scores for FSIQ, VIQ and PIQ were calculated. A VIQ-PIQ split score was calculated for each child and compared to discrepancy norms for his or her age (Sattler 1998). The WRAT3 assessed arithmetic deficiency, and the Grooved Pegboard Test was used to evaluate fine motor coordination as well as a measure of psychomotor deficits.

Table 3.2 Group differences on IQ scores (McDonough-Ryan et al)

Variable	OBP	OHC	t	p-value
WISC-III				
VIQ	108.7±17.8	110.7±15.5	-0.43	0.7
PIQ	96.3±16.6	105.2±17.9	-1.8	0.07
FSIQ	104.9±13.4	111.8±16.2	-1.6	0.1

Although the authors found no significant difference between OBP and OHC on FSIQ, VIQ and PIQ, there was a greater frequency of a significant VIQ>PIQ split among OBP (n=11; 39%) vs OHC (n=1) (Fischer's exact test, p=0.02). In addition the OBP performed poorly on measures of academic achievement. The authors concluded that the VIQ>PIQ split may be an indication of right hemisphere dysfunction. The authors also hypothesised an alternate explanation for this VIQ>PIQ discrepancy that it *'may reflect deficiencies in novel problem solving or fluid abilities, each of which is an aspect of executive functioning'.* In their discussion the authors recommended that *'additional prospective studies which incorporate a comprehensive neuropsychological assessment to characterise and dissociate cognitive strengths and weaknesses among children of parents with bipolar disorder are necessary..'* (McDonough-Ryan et al. 2002).

The assessments focussed mainly on intellectual estimates and psychomotor performance to address the research question which prompted the authors to design the study. However, as regards neurocognitive function there were no measures to assess learning, memory and executive function. The authors did not state whether or not OBP and OHC were from multiplex families. Other 'at risk' studies have recruited more than one offspring from the same family so it would be likely that multiple OBP were recruited from at least some families of individual bipolar probands. As discussed before, this is important information because of the implication for data analysis.

The next 4 studies presented were published after the start of this project.

Klimes-Dougan and colleagues published a study which examined neurocognitive functioning in adolescent offspring of mothers with unipolar depression and BD in comparison with a HC group (Klimes-Dougan et al. 2006). This study was part of an ongoing longitudinal project at the National Institute of Mental Health which initially started in 1979 (Radke-Yarrow et al. 1998). Subjects returned for assessments approximately every 3 years. The focus of this study was to report findings from a neurocognitive assessment

battery conducted at the 4th assessment. These time scales are important as parental diagnostic grouping, child ADHD symptoms and IQ were based on assessments completed at the 3rd assessment. Psychopathology in parents was assessed at initial interview using the Schedule for Affective Disorders and Schizophrenia: Lifetime version (SADS-L) (Spitzer et al. 1978) and also at the 3rd interview using the Structured Clinical Interview for DSM III-R (SCID) and SADS-L (Radke-Yarrow et al. 1998). The BD mothers were included in the analysis if they had additional co-morbid conditions including anxiety disorder or substance use. Any children with IQ<86 were excluded from analysis. No explanation was given for this exclusion. Most studies would include OBP with IQ scores of more than or equal to 70. It is unclear what impact this exclusion would have had on the results.

For the unipolar depression group: 42 families participated with 72 offspring (age: 16±2.6 years). The bipolar group consisted of 26 families with 43 OBP (age 15.1±2.5 years) and the HC group consisted of 30 families with 50 OHC (age: 15.3±2.7 years). The assessment battery consisted of: Executive function [Wisconsin Card Sorting Test (WCST) (Heaton et al. 1993) & Trail Making Test (Parts A and B) (Lezak et al. 2004)]; Memory [California Verbal Learning Task for Children (CVLT-C) (Delis et al. 1987) & Rey-Osterrieth Complex Figure Test (Lezak 1995)]; Attention [Continuous Performance Task (CPT) (Halperin 1991)] and IQ [Wechsler Intelligence Scale for Children- Revised (WISC-R) (Wechsler 1974)].

The statistical analyses were conducted using multilevel analyses (random effects regression) to model both individual and family level effects. These analyses were appropriate for this dataset. Age, gender, symptoms of ADHD, IQ, symptoms of depression and mania were used as covariates in the analysis. The OBP and OHC groups were matched on age, gender and mania symptom count. The ADHD symptom count was higher in the OBP group (4.8±3.8) in comparison with OHC group (2.7±2.4) ($t(85) = 3.47$, $p < .001$). The OBP group (2.6±3.1) in comparison with the OHC group (1.5±2.3) had significantly higher depression symptom count ($t(85) = 2.04$, $p < .05$). FSIQ scores in OBP

(112.5±15.6) were significantly lower ($F(1,162) = 8.89$, $p < .004$) than those seen in the OHC group (121.4±13.7) but it is important to note that both groups had IQ scores in the above average range.

The study also reported significant differences between OBP and OHC on some of the neurocognitive tasks. The OBP performed significantly worse than OHC on the Wisconsin Card Sorting Test (WCST): executive function factor score [$t(80)=3.35$, $p=0.001$], perseverative errors number [$t(80)=3.05$, $p=0.003$], perseverative responses number [$t(80)=3.30$, $p<0.002$], total errors number [$t(80)=3.77$, $p=0.0003$], conceptual level responses [$t(80)=-3.08$, $p<0.003$] and categories completed ($Z=-2.76$, $p<0.006$). On the CVLT, OBP performed statistically worse compared to the OHC on the following aspects: long free recall [$t(82)=-2.21$, $p=0.03$] and perseverations trials 1 to 5 [$t(82)=2.25$, $p<0.03$]. Further the OBP group performed worse in comparison with the OHC group on the Rey-Osterieth recall organisation ($Z=2.97$, $p<0.003$) and CPT dyscontrol domain ($Z=2.66$, $p<0.008$). These deficits remained significant even after adjustment for IQ, depression and manic symptoms. The authors concluded that OBP demonstrated lower FSIQ, together with deficits in aspects of attention, spatial memory and executive function.

In this study, IQ scores showed a positive correlation with nearly all of the cognitive variables (and IQ scores were lower in OBP vs OHC). For this reason, the authors decided to use IQ as a covariate in the multilevel analysis. Using IQ scores as a covariate in this multilevel analysis is an incorrect technique and the reasons for the same have been previously presented in section 3.4.2. Given that the subjects in the OBP group had considerable psychopathology, a better approach would have been if the authors had covaried neurocognitive test scores with scores of a premorbid measure of IQ. It is important to recruit a sample of OBP who are ‘at risk’ for BD but have not yet developed any psychopathology as this psychopathology may impact on neurocognitive function. The study included only OBP where the bipolar proband was the mother. Other limitations identified by the authors included the use of multiple comparisons and the lack of representativeness of the sample (drawn from an

affluent, high achieving , Caucasian population). Furthermore the OBP sample consisted of offspring of bipolar probands with both BDI and BDII. However, these are the first findings from a large cross sectional study of OBP to have studied a broad range of relevant neurocognitive domains.

The next study to assess cognitive function in OBP was by Maziade and colleagues (Maziade et al. 2009). The authors assessed neurocognitive function in OBP, OSP and OHC by targeting multigenerational families 'densely affected' by schizophrenia or BD. 'Densely affected' families were defined by the authors as those with at least one first degree relative affected with the same disorder as the proband and if there were at least 4 other affected individuals with the same disorder. OSP (n=22; age=17.2±4.16; M:F::9:13) and OBP (n=23; age=17.45±4.54; M:F::14:9) were older than in the previous studies presented in this thesis. All the offspring were assessed on neurocognitive tests before age 23 years. The authors reported high rates of lifetime psychopathology (including anxiety and communication disorders) in both OSP and OBP groups. Only 36.4% of OSP subjects and 39.1% of OBP subjects were symptom-free at the time of the study. Unfortunately, the authors did not report the rates of psychopathology in OHC.

A strength of this study was that the authors used appropriate statistical techniques including the use of multilevel modelling for the sample which included family sibships nested in the group. To compensate for the multiple tests done, the authors set their criterion for detecting a significant overall F test for ANCOVA at p=0.005 whilst p between 0.05 and 0.005 was interpreted as a possible tendency. Further the analyses were performed with and without those offspring with significant psychopathology, although children with language and learning disorder were not excluded as the authors did not consider these neurodevelopmental disorders as equivalent to behaviour disorders. However, the individuals with neurodevelopmental disorders are likely to have associated neurocognitive deficits which may in turn have contributed to the findings (Ellison et al. 2007).

The FSIQ in OBP (94.1±8.1) was significantly lower (p= 2E-04; effect size= -0.99) than in the OHC group (108.3±9.4). The subjects in the OBP group performed worse than the subjects in the OHC group on the sustained attention tasks (CPT-hit standard error block change p= 0.007), verbal episodic memory (CVLT total recall p= 0.0005), CVLT delayed recall (p= 0.0002), visual episodic memory (Rey immediate recall p= 0.006, Rey delayed recall p= 0.001), executive function (WCST total errors p= 0.0005, letter fluency test p= 0.0003, total number of problems solved in minimum moves p= 0.001). In summary, the OBP when compared with OHC displayed deficits in FSIQ, attention, verbal and visual memory as well as executive function.

The limitations of this study included the small sample size in this which may have resulted in Type II errors. Furthermore, the findings reported by the authors were found in a sample of 'densely affected' individuals. Whether the same findings would be found in most families of BD which are not so 'densely affected' by BD is not certain. Although the authors had stringent inclusion criteria and the BD status of bipolar proband was rigorously assessed, the BD status of the proband included both BDI and/or BD II. The possible limitation of heterogeneity of these disorders in parental proband has been discussed before (see chapter 2.4).

Maziade and colleagues then published another study where they compared neurocognitive function in young nonaffected offspring of a parent affected by Schizophrenia or BD (age 17.1±4.1 years; OSP n= 25; OBP n=35), nonaffected adult relatives, and the patients, ie, the adult proband affected by schizophrenia or BD (Maziade et al. 2011). They also had a young persons HC group (n=76; age 16.9±4 years). The offspring sample was composed of 40 families of which 23 comprised a single subject, 14 families comprised 2 siblings, and 3 families comprised 3 siblings. The exclusion criteria included the presence of a DSM-IV psychotic disorder, BD or major depression, and brain and metabolic disorders known to cause neuropsychological impairments. Of the 60 offspring (OSP and OBP), 37% had an DSM-IV Axis I nonpsychotic diagnosis. The distribution was

as follow: anxiety-like disorder 17%, substance abuse 5%, attention-deficit hyperactivity disorder 8%, and learning and language disorder 7%.

Based on findings from their previous published work (Maziade et al. 2009) the authors focussed on tasks assessing visual (Rey Complex Figure Test) (Meyers and Meyers 1995) and verbal episodic memory (CVLT) (Delis et al. 1987). For statistical analyses, the average raw scores on the neurocognitive tests were compared for each of the experimental groups (young offspring, nonaffected adult relatives, and patients) to the appropriate control group by means of analyses of covariance (ANCOVAs). Age and gender were selected as covariates in all their statistical analyses. To account for the nonindependence of observations within the same sibship, a multilevel regression analysis was applied in OBP.

For the offspring, episodic memory showed the largest effect size (verbal episodic memory: −0.84, $P_{ANCOVA} = 0.0001$ and −0.95, $P_{ANCOVA} < 0.0001$ on the CVLT total recall and delayed recall; visual episodic memory: −0.86, $P_{ANCOVA} = 0.0001$ and −0.92, $P_{ANCOVA} < 0.0001$) were significantly lower than in OHC. OSP and OBP showed very similar deficits both on verbal episodic memory (respectively, ES = −0.70, $P_{ANCOVA} < 0.05$ and ES = −0.88, $P_{ANCOVA} < 0.05$) and visual episodic memory (respectively, ES = −0.84, $P_{ANCOVA} < 0.05$ and ES = −0.88, $P_{ANCOVA} < 0.05$). These findings imply that in this larger sample the authors have replicated their previous findings of verbal and visual memory impairment in OBP. However, the performance of OBP, interestingly did not differ from that of OSP in these families ‘densely affected’ by schizophrenia and BD.

A unique strength of this study is that it is a longitudinal follow-up study of a large number of densely affected individuals with BD and schizophrenia, and their unaffected adult and youth relatives. The design also allowed the authors to test cognitive functioning cross-sectionally, using a generational paradigm to study the young offspring unaffected by schizophrenia or BD vs the adult family members who were either affected or unaffected by the same disorder. There

are limitations to this study. Firstly the differences in the proportions of siblings, offspring, or parents in the different subsamples may have biased the results. Also, as before, the dense familial loading of the sample studied, may affect the generalization of the results to other patients with BD and their relatives.

In a recent study by Diwadkar and colleagues, subjects were recruited across 2 US sites: University of Pittsburgh and Wayne State University, USA. The authors assessed attention and working memory in OBP (age 14.0±2.4 years, M:F::13:10) OSP (age 14.5±2.7 years, M:F::22:14) and OHC (age 14.9±2.7 years, M:F::25:16) (Diwadkar et al. 2011). The groups were matched on age. The participants in the OBP group (101.5±12.9) did not differ from the participants in the OHC group (101±18.2) on FSIQ. 50% of OBP sample displayed at least one DSM-IV disorder which included ADHD in 4 cases, social phobia in 2 cases, specific phobia in 1 case, adjustment disorder in 1 case, major depressive disorder in full remission in 3 cases, PTSD in 1 case, GAD in 1 case and enuresis in 2 cases.

Working memory was assessed using a spatial memory paradigm (www.cogtest.com) that had been shown to discriminate between OSP and OHC in a previous study by the same research group (Diwadkar et al. 2001). Sustained attention was assessed using the CPT. All analyses were conducted using general linear model framework in SPSS. ANCOVA was used to assess independent main effects of group (OBP vs OSP vs OHC). Age, FSIQ and presence of ADHD (only) were modeled as covariates. OBP did not differ from OHC on tasks of working memory (although OSP were significantly worse as compared to both other groups). On sustained attention the OBP performed worse compared with OHC but OSP were no worse than OHC using a one-tailed Dunn Sidak test. These deficits in OBP, the authors hypothesised might indicate cortico-striatal network involvement. Further, the authors suggested that although working memory utilises frontal lobe function it relies more specifically on the dorsal prefrontal areas. These statements appear valid based on the literature.

The limitations of the study by Diwadkar and colleagues include as with all studies published to date, limited sample size and presence of high rates of psychopathology (seen in 50% of the sample in the OBP). Further, the inclusion of bipolar proband with both BDI and BDII may have confounded the findings. The test battery comprised of measures of IQ , attention and working memory. Building on the literature a more comprehensive battery would have included measures of learning and executive function.

Finally in this section, details from the most recent study by Deveci and colleagues that investigated neurocognitive function in young offspring of adults with BDI in eastern Turkey will be presented (Deveci et al. 2013). 30 OBP (age: 12.32±2.77 years; M:F::15:15) and 37 OHC (age: 12.48±2.58 years; M:F:: 18:19) participated. The diagnosis of BDI in parents was confirmed using the Turkish version of the Structured Clinical Interview for DSMIV Axis I Disorders, Patient Edition (SCID-I). OHC were chosen from children of parents who were referred to outpatient clinics other than neurology and psychiatry. The parents of the healthy controls were evaluated using the SCID-I nonpatient version in order to exclude psychotic disorders and BD. Parents with any neurological diseases or those having a family history (first-degree relatives) of schizophrenia, BD, or schizoaffective disorder were also excluded. The participants in the OBP and OHC groups were matched for age, sex, IQ, and years of education. Offspring having a lifetime diagnosis of substance use disorder, ADHD, CD, mood or psychotic disorder, learning disability (IQ < 70), serious head trauma, seizures, or any other organic mental disorder that could have impacted on neurocognitive function were excluded.

The authors used Kent E-G-Y Test and the Porteus Maze Test for the assessment of IQ. The neurocognitive battery included the Rey Auditory Verbal Learning Test (RAVLT) as measure of verbal learning, Auditory Consonant Trigram Test (ACTT) as a measure of verbal working memory, Controlled Oral Word Association Test (COWAT) as a measure of an aspect of executive function: verbal fluency, digit span test which assessed attention and verbal working memory, Trail Making Test (TMT-A/B) which assessed attention and aspects of executive function: set shifting, WCST which was used to assess

aspect of executive function: cognitive flexibility, Stroop Test used to assess another main aspect of executive function: selective attention and Test of Variables of Attention (TOVA) used to assess sustained attention.

Deveci and colleagues assessed normality distribution of test scores using Kolmogorov–Smirnov and Shapiro–Wilk tests where appropriate. The relations between test scores were tested with the Mann–Whitney U test and independent samples t-test. The authors reported that the OBP in comparison with OHC displayed deficits on divided attention, information processing, and working memory (ACTT; p=0.027) as well as psychomotor (attention) speed and focused attention (TMT-A; p=0.034). In addition, short-term memory and learning functions were impaired regardless of the recall ability (RAVLT: total learning score, p=0.009; delayed recall score, p=0.005; recognition percent correct score, p=0.02). There were no significant differences between the OBP and OHC groups in terms of sustained attention as assessed with the TOVA; verbal attention as assessed with the digit span forward; executive functions and alternating attention (set shifting) as assessed with the TMT-B, WCST, and Stroop Test; and phonemic verbal fluency as assessed with the COWAT.

The strengths of the study lie in the homogeneity of bipolar proband diagnosis (BDI), comprehensive neurocognitive assessment battery including a very detailed assessment of executive function, offspring that were ‘at risk’ for BD but did not at the time of assessment have a recognised disorder and who were also not on any psychotropic medication. There were limitations to this study. Although the authors state that they excluded offspring with a lifetime diagnosis of substance use disorder, ADHD, CD, mood or psychotic disorder, learning disability (IQ < 70), serious head trauma, seizures, or any other organic mental disorder they do not explain how this was done. Studies often use semi structured interviews such as KSADS-PL, WASH-U-KSADS for this. Further, the authors used an unusual method of IQ assessment and do not explain why they specifically used this assessment. In addition, the authors do not specify whether more than one offspring was recruited from each family. Given the data from previous studies this would be highly likely. If this were the case, use of the t-test would be inappropriate. Whether this would have influenced the results is

unknown. Lastly, the authors acknowledge that by matching OBP and OHC for IQ they might have resulted in the compensation of slight cognitive deficits thereby minimising the group differences.

3.10 Summary

This chapter has considered the neurocognitive deficits (particularly in attention, working memory, learning and executive function) reported in adults and young people with BD. It is possible that deficits in these domains of neurocognitive function may be a potential candidate endophenotype for BD. The next step would be to investigate whether a particular pattern of neurocognitive dysfunction occurs at an increasing frequency in unaffected relatives (including offspring) of bipolar probands. The chapter has presented the limited evidence base that has attempted to study neurocognitive deficits in OBP. Most early studies investigated IQ in OBP (in comparison with OHC and OSP). All studies have been limited by a variety of factors including limited sample size (with the inevitable impact on power and effect sizes); use of appropriate statistics for multiplex families; the bipolar parent group having BDI and BDII (differing disorders and possible effects of this heterogeneity on neurocognitive profile in offspring) and significant psychopathology in OBP sometimes requiring medication. These factors are likely to impact on neurocognitive findings.

The next step should be to assess OBP free of psychopathology (and therefore medication free) so that the impact of neurodevelopmental disorders and mental health disorders seen in OBP can be minimised. Further the bipolar proband in the study should have a homogenous type of BD: BDI or BDII to reduce the impact of heterogeneity. This method of recruitment would reduce the impact of confounding variables found in published data so far. Data should be analysed using mixed effects modelling to control for more than one offspring per family participating in the study. This will allow the investigation of the contribution made to the variance of neurocognitive function by the bipolar status of parent.

Chapter 4: Facial emotion labelling

"Emotion triumphs over the hunger drive! A person may never attempt sexual contact because of the interference of fear or disgust, or may never be able to complete a sexual act. Emotion triumphs over the sex drive! And despair can overwhelm even the will to live, motivating a suicide. Emotions triumph over the will to live!"

Paul Ekman

4.1 Introduction

This chapter 'Facial emotion labelling in Bipolar Disorder' will provide a review of selected studies that have assessed facial emotion processing with specific reference to facial emotion labelling in adults and adolescents with BD. It will then discuss the studies of adolescents 'at risk' for BD and outline the proposed neural substrates for facial emotion labelling difficulties.

4.2 Overview

The ability to process and identify facial emotions is an essential component of human communication and social interaction (Rocca et al. 2009). Furthermore, being able to discriminate accurately between different facially expressed emotions is thought to be critical in the context of social behaviour (Venn et al. 2004). The perception of these facial expressions is believed to occur independently from identification of faces (Bruce and Young 1986). Six universal emotions have been identified: happiness, sadness, anger, fear, disgust and surprise each of which appears to have a partially separable neural circuitry (Ekman and Friesen 1971; Gosselin and Kirouac 1995). Neuroimaging provides further evidence for partially separate neural substrates for processing of different facial expressions (Venn et al. 2004). The most compelling evidence for this comes from double dissociation studies in patients with neurological

disorders where the ability to recognise one emotion facially is preserved whilst the ability to identify another may be lost. Impairments in the ability to recognise fear (facially) appears to be affected in patients with disorders affecting the amygdala (Adolphs et al. 1994).

The neural substrates implicated in facial emotion processing include ventromedial prefrontal area, inferior temporal and occipital gyrus and subcortical structures including amygdala, ventral striatum, hippocampal formation and dorsomedial nucleus of thalamus (Kohler et al. 2003; Lawrence et al. 2004). The amygdala is reported to be particularly important for the recognition of negative emotions such as fear (Adolphs 2001).

4.3 Why study facial emotion labelling

Facial emotion labelling has been studied extensively in typically developing children (Thomas et al. 2007) as well as in neurodevelopmental disorders such as autism (Dawson et al. 2005; Harms et al. 2010). In children with Autism/ASD the ability to process facial emotions has been shown to be impaired compared with typically developing youth matched for age and ability (Dawson et al. 2005).

Bruce and Young have reported that adults with BD have difficulty regulating affect (Bruce and Young 1986). Similar difficulties have been identified in young people with BD (Dickstein et al. 2009). These findings would suggest that affective dysregulation appears across the lifespan in BD. These deficits are not limited to affective episodes in BD. Difficulty with affective modulation has been identified even during euthymic states, suggesting that disturbances in emotional processing capacity may be a factor in the development of BD (Yurgelun-Todd et al. 2000). It has been proposed that the difficulty in regulation of affect and interpretation of emotion could co-exist in BD, either with one causing the other or by operating through similar brain areas (George et al. 1998). Patients with BD (PBD and adults with BD) and individuals at risk for BD (including OBP) also have difficulty identifying and labelling facial emotion

correctly. These deficits in facial emotion labeling may help explain the psychosocial dysfunction seen in BD (previously discussed in chapter 2.8). There is also some preliminary data from studies assessing youth at risk for BD suggesting that ability to identify facial emotion may be a putative endophenotype for BD (Brotman et al. 2008; Brotman et al. 2008; Whitney et al. 2013). This is discussed further in section 4.6.

4.4 Studies in adults

Adult patients with BDI had worse overall performance on tests assessing their ability to identify facial emotion during a manic episode (Lembke and Ketter 2002; Getz et al. 2003). Lembke and Ketter also reported that adult patients with BDI made significant errors in recognising fear and disgust in particular (Lembke and Ketter 2002). Venn and colleagues studied euthymic adult patients with BD and reported that BD patients were less accurate at identifying facial emotion correctly (Venn et al. 2004). In their study, subjects demonstrated a trend to correctly identify fear but this was not statistically significant .

In the first imaging study on facial affect perception in adult patients with BD, Yurgelun-Todd and colleagues hypothesised that functional deficits of the DLPFC would explain altered responses to facial stimuli (Yurgelun-Todd et al. 2000). The authors chose to evaluate happy and fearful faces in BD. Ten of the 14 patients were able to correctly identify fear which was not in keeping with the finding reported by previous studies (Lembke and Ketter 2002; Venn et al. 2004). There was reduced activation on fMRI in the right prefrontal area and increased activation on fMRI in the left amygdalar region in patients with BD suggesting changes in fronto-limbic circuitry that might perhaps underlie fearful affect recognition. In the absence of data on cognitive parameters such as attention and concentration commenting on the significance of these findings is difficult. Attentional difficulties are often seen in BD (both during episodes and in euthymia). These difficulties can limit the subjects' ability to focus on the facial emotion labeling task thereby becoming a confounding variable. Although these

studies are limited by the absence of neurocognitive measures, they were designed to be preliminary investigations and have furthered the evidence base.

4.5 Studies in paediatric bipolar disorder

Some studies have investigated the ability to identify facial emotions in subjects with PBD. McClure and colleagues in their brief report presented findings from 11 subjects with PBD (82% were also comorbid for ADHD), 10 children with anxiety disorder and 25 HC (all groups matched on age and IQ) on their ability to correctly identify and label facial emotion (McClure et al. 2003). The authors used the Diagnostic Analysis of Non Verbal Accuracy 2 (DANVA 2) (Nowicki and Duke 1994). This instrument is regularly used to assess facial emotions. It has stimuli that include both 'high and low' intensity as well as 'child and adult' faces (discussed later in chapter 6.3.5). Unfortunately, the authors do not report whether the subjects with PBD were euthymic at the time of assessment nor whether the subjects had BDI or BDII.

Several deficits were reported in the PBD group. The first was that subjects with PBD made more errors in identification of 'high and low intensity' facial emotions compared to children in both HC and anxious groups ($F=5.96$, $df=2, 43$, $p<0.01$; $eta^2=0.22$). Secondly, subjects in the PBD group made more errors in identification of facial emotions of a 'low intensity' in comparison with both groups ($F=3.82$, $df=2, 42$, $p<0.05$; $eta^2=0.15$). Thirdly, subjects in the PBD group made more errors identifying facial emotion when presented with 'child' faces than both of the other groups. Fourthly 82% of the subjects in the PBD group over identified faces as angry. In contrast, this type of error was not seen in the other 2 groups.

The study was designed to be a brief report but was limited by the small sample sizes in all 3 groups. Further limitations included lack of clarity regarding whether the subjects in the PBD groups were euthymic or not at time of assessment. All subjects with PBD were on medication which may have contributed to the findings. Further the high rates of ADHD in the subjects with PBD may have contributed to the results, either as a direct consequence of

ADHD on the ability to correctly identify facial emotion and/or as part of a general cognitive deficit (Yuill and Lyon 2007).

In a further study published by the same group, McClure and colleagues have studied the ability to correctly identify facial emotion using the DANVA (McClure et al. 2005). The participants included 40 subjects with Narrow Phenotype Bipolar Disorder (NPBD) (BDI n=32 and BDII n=8) and 22 HC subjects with no family history of psychiatric disorder. NPBD refers to BD where diagnosis of hypo/mania requires elevation of mood (irritability on its own is not a core mood disturbance). This study included subjects from the previous brief report published by the same group (McClure et al. 2003). Both groups were matched for age (NPBD group 12.9±2.7 years, HC group 13.5±2 years; p=0.32) and FSIQ (NPBD group 107.4±13.7, HC group 117±12; p=0.24). Gender was used as a covariate in the analysis. 83% of the BD group met criteria for an additional DSM-IV Axis I disorder mainly anxiety disorder (current 58%; lifetime 65%), ADHD (current 58%, lifetime 70%) and oppositional defiant disorder (current 35%, lifetime 40%). Only 15% of the NPBD group were not receiving psychotropic medication at the time of the study with the remainder (85%) on one or more medications: atypical antipsychotics (55%), lithium (24%), anticonvulsants (73%), antidepressants (30%) and stimulant medication (30%).

Facial emotion labelling was assessed using the DANVA. Post hoc Mann-Whitney U tests of discriminability scores for each emotion within each DANVA subtest indicated that subjects in the NPBD group vs HC group were less sensitive to happiness ($z=-2.07$, $p=0.04$) and anger ($z=-2.78$, $p<0.01$) on child faces and to sadness ($z=-3.62$, $p<0.001$) and anger ($z=-2.43$, $p=0.02$) on adult faces. Not all subjects with NPBD were euthymic at the time of assessment. The authors then appropriately conducted a within group (NPBD) analysis and found the groups not too differ. There are limitations to this study which include a small sample size, extensive co-morbidity and most subjects in NPBD group being on medication. The latter two findings could have impacted on and therefore contributed to the facial emotion labelling findings. Furthermore, the

study included subjects with both BDI (n=32) and BD II (n=8) in their study. This heterogeneity could also have had an impact on their findings.

Guyer and colleagues assessed facial emotion labelling in 4 groups of children with psychopathology: youth with anxiety and/or MDD (n=44); ADHD and/or Conduct Disorder (CD) (n=35); NPBD (n=42; both BDI and BDII) and SMD (n=39) (Guyer et al. 2007). Diagnoses for anxiety/MDD/NPBD and SMD were confirmed using Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) (Kaufman et al. 1997). An additional K-SADS-PL supplemental module, designed in collaboration with Joan Kaufman, (author of K-SADS-PL) was used to determined SMD diagnosis. ADHD diagnoses were confirmed by Diagnostic Interview for Children and Adolescents (DICA-R) (Reich 2000), and adolescent-, parent-, and teacher-reported information obtained from the Child Behaviour Checklist (Achenbach 1991), Youth Self-Report (Achenbach 1991), Life History of Aggression (Coccaro et al. 1997), Conners' Rating Scale (Conners 1989), and Barratt Impulsiveness Scale (Barratt 1965). The authors used well validated assessments to confirm diagnoses and co-morbid conditions.

The DANVA 2 was utilised to assess facial emotion labelling deficits. To increase power, the high and low intensity stimuli were combined. The authors covaried on parameters that were significantly different across groups such as age and IQ. A 5 (group) x 2 (face-age) x 4 (emotion) repeated measures analysis of covariance of errors tested the main effects of group, face-age and emotion and group by face-age and group by emotion interactions was employed by the authors to increase power.

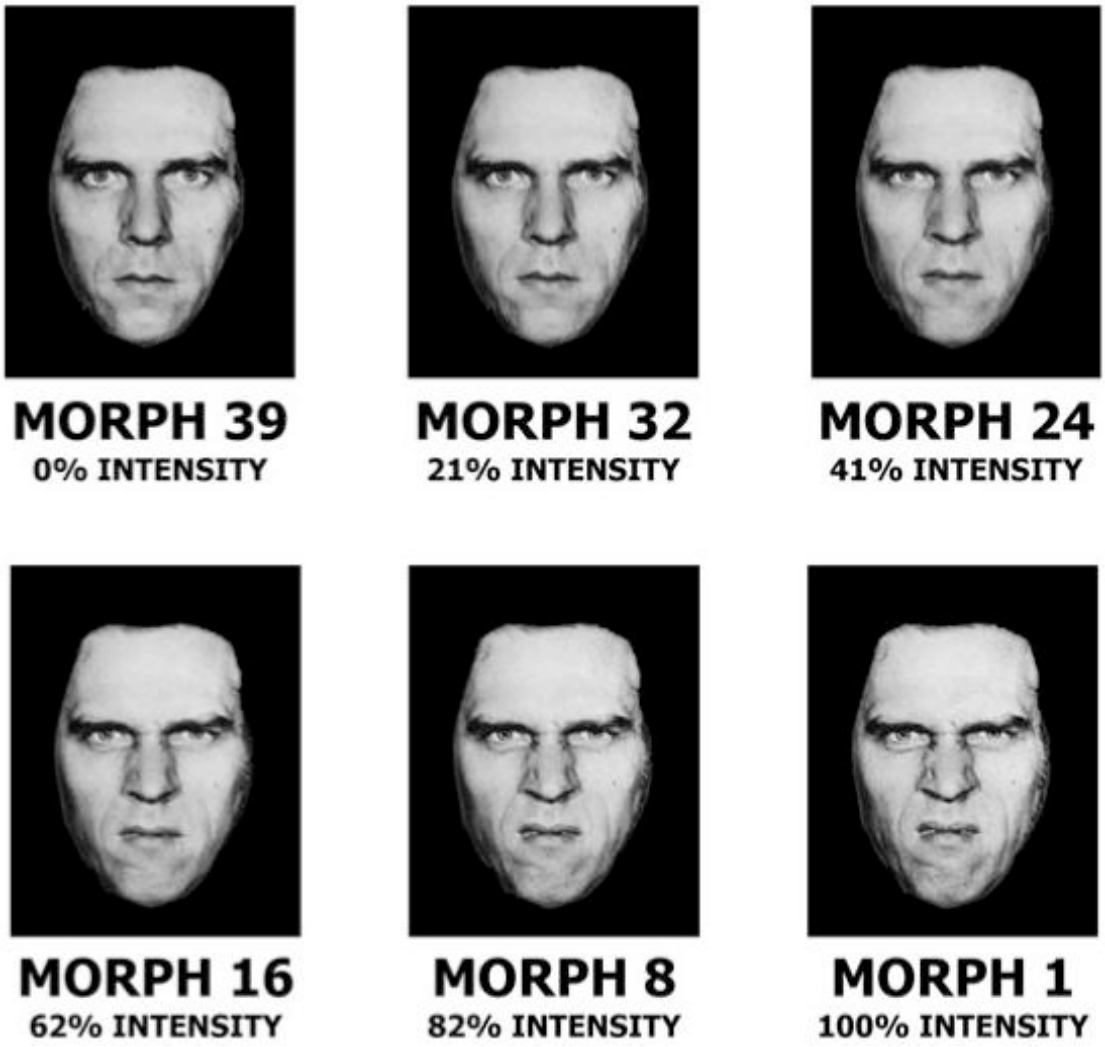
The NPBD group made more errors on the DANVA 2 than HC and all other groups (each p value<0.01) except SMD. Increasing age and higher IQ were associated with fewer errors. Not all subjects with NPBD were euthymic at the time of assessment and so a within group analysis comparing euthymic subjects of NPBD were compared to symptomatic subjects of NPBD. No statistically significant difference was found between these 2 groups.

Unmedicated NPBD subjects (Mean 1.84±0.18) made slightly more errors than medicated NPBD subjects (Mean 1.22±0.09) F(1,36)=9.23, p=0.04. These findings are interesting as they replicate previous findings reported by the NIH group with regards to NPBD (McClure et al. 2003; McClure et al. 2005). Interestingly, in this study subjects with ADHD and anxiety did not differ from HC on DANVA tasks. This is in keeping with some of the previous published work assessing facial emotion labelling in youth with ADHD (Cadesky et al. 2000). However, it is not in keeping with some previously published work (Pelc et al. 2006; Yuill and Lyon 2007). The finding of euthymic NPBD subjects not differing from symptomatic NPBD subjects is also interesting and suggests that lack of ability to label facial emotion could in fact be a putative endophenotype (as is unaffected by mood state).

Most NPBD subjects in this study were receiving psychotropic medication. However, in a sub analysis the unmedicated subjects appeared to make slightly more errors on the DANVA tasks than the medicated subjects. This may have been due to better control of symptoms whilst on medication allowing subjects to better focus on the assessment and improve accuracy of labelling. Further, high levels of comorbidity in NPBD group (as seen in previous samples recruited by the NIH group) with 69% having anxiety and 59% having ADHD. There were group differences on age, IQ, gender and ethnicity (which authors attempted to covary for statistically). An alternative strategy would have been to match the groups on as many parameters as possible.

In a further publication by the NIH group Rich and colleagues compared face emotion labelling using the emotional expression multimorph task in 39 subjects with NPBD (both BDI and BDII) (age 13.99±2.63 years, 53.8% male, FSIQ 110.08±14.15), 31 subjects with SMD (age 12.29±2.12 years, 61.3% male, FSIQ 102.7±14.36) and 36 subjects in the HC group (age 14.34±2.28 years, 55.6% male, FSIQ 115.61±14.21) (Rich et al. 2008). Diagnoses were confirmed using the same semi-structured assessments described for the previous study (Guyer et al. 2007). Twenty-five (64%) of the subjects in the NPBD group had previously been included in the McClure et al (2005) study discussed above.

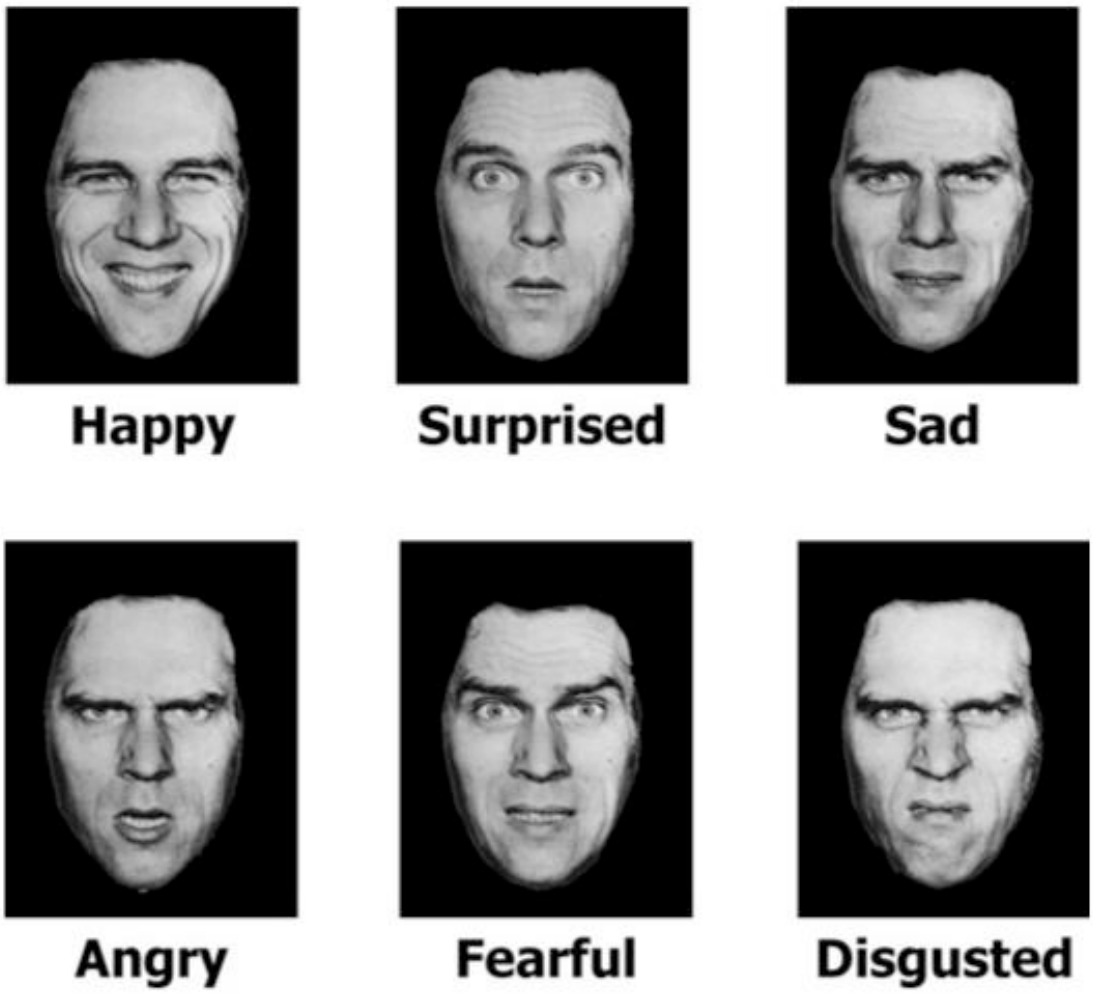
Figure 4.1 Multimorph emotion of disgust by intensity. (Rich et al. 2008)



The emotional expression multimorph task is a variation of a task by Blair and colleagues (Blair et al. 2001). Face stimuli for the task were taken from the valid and reliable pictures of facial affect (Ekman and Friesen 1976). Morphing of the facial stimuli was achieved by gradual blending created by a continua of 39 images from neutral (0% intensity) to the prototypical emotional expression (100% intensity). Morphing from 0% to 100% intensity has the advantage that the subject being assessed can stop the morph at any stage allowing the researchers to detect the intensity needed to identify facial emotion rather than use the 'high-low' intensity paradigm used in other assessments such as DANVA. However, the disadvantage of the multimorph task is that it only utilises

adult faces as stimuli. The importance of having child faces as stimuli is discussed in chapter 6.3.5.

Figure 4.2 Multimorph face emotions: 6 emotions (Rich et al. 2008)



The authors used age, IQ and gender as covariates in the analysis. Gender was included as studies in school children have shown gender differences in school age children (De Sonneville et al. 2002). The 3 groups under study differed on age and IQ scores. This is the first study from the group where authors confirm that 92.3% of sample (n=36) had BDI. However, 66.7% of the NPBD had co-morbid diagnoses as reported in previous studies including ADHD (46.2%), ODD (23.1%), GAD (15.4%), separation anxiety (15.4%), social phobia (20.5%) . Further, 82.1% of the subjects in the NPBD group were on medication (average 2.88±1.16 medications including anticonvulsants (64.1%), atypical

antipsychotics (51.3%), lithium (35.9%), stimulants (35.9%) and antidepressants (23.1%). Of the subjects in the NPBD group 48.7% were euthymic at the time of testing.

The NPBD and SMD groups displayed face processing deficits and required significantly greater intensity of emotional expression before first response and before correctly identifying facial expression compared to HC group. With reference to particular emotions, subjects in the NPBD and SMD group required significantly greater face emotion intensity before correctly labeling the expression for disgusted ($F(2, 98) = 8.85$, $p<0.001$), surprised ($F(2, 98) = 5.73$, $p=0.004$), fearful ($F(2, 98) = 4.36$, $p=0.02$) and happy ($F(2, 98) = 8.05$, $p=0.001$) faces compared to HC group. Subjects in the NPBD and SMD groups, however, did not differ from each other. This latter finding is a similar one to previous reports by their group using DANVA 2 when patients with BD made more errors on low intensity faces (Guyer et al. 2007). Furthermore, the groups made more errors identifying disgust, surprise, fearful and happy faces but not angry or sad faces. The limitations of this study include high rates of mental health and neurodevelopmental comorbid conditions in both NPBD and SMD groups which could have contributed to the facial emotion labeling deficits thereby making it difficult to consider these deficits as a putative endophenotype for BD.

4.6 Studies in offspring of bipolar parents

In the first of 3 studies assessing facial emotion labelling in subjects ‘at risk’ for BD, Brotman and colleagues assessed youth with a family history of BD on the DANVA 2 (Nowicki and Carton 1993) with a hypothesis that the youth with a family history of BD would have facial emotion processing deficits similar to that in subjects with PBD (Brotman et al. 2008). The study included participants from a previous study (McClure et al. 2005) discussed previously in section 4.5. The ‘at risk’ subjects in this study were siblings of those with NPBD (BDI and BD II) (n=14) and OBP (BD I and BD II) (n=10). All adults were screened using the SCID I/P (First et al. 2002) and youth were screened using K-SADS-PL

(Kaufman et al. 1997). Any 'at risk' subjects with a current or past history of mood disorders were excluded from the analysis; however youth with ADHD were included in the study. IQ was measured using the Wechsler Abbreviated Scale for Intelligence 4 (WASI 4) (Wechsler 1999). The subjects in the NPBD group had their mood states confirmed using the YMRS (Young et al. 1978) and CDRS (Poznanski et al. 1984). Exclusion criteria included IQ<70, Pervasive Developmental Disorder (PDD), unstable medical illness or substance abuse within the past 2 months. The subjects in the NPBD group were on medication but subjects in the 'at risk' and HC groups were all medication free. The subjects in both NPBD and 'at risk' group displayed high rates of psychopathology and this is shown in Table 4.1.

Table 4.1 Group characteristics (Brotman et al. 2008)

Characteristic	NPBD n (%)	at-risk' n (%)	Control n (%)
Total	52	24	78
Male	26 (50)	17 (70.8)	38 (48.7)
Any axis I disorder	52 (100)	8 (38.1)	0
BD I	41 (78.8)	0	
Anxiety disorder	35 (67.3)	5 (23.8)	
ADHD	28 (53.8)	2 (9.5)	
ODD	16 (30.8)	0	
CD	0	1 (4.8)	
Mood state			
Euthymic	34 (65.4)	24 (100)	
Depressed	3 (5.8)	0	
Hypomanic, manic or mixed	15 (28.8)	0	

The primary analyses were done using ANOVA to assess group differences in age and IQ. Chi-square tests were used to assess group differences in sex

distribution. Age and IQ were included as covariates in the analysis. As the data included observations that were non-independent (with more than one child per family) the authors used linear mixed modelling approach as a secondary statistical technique. The use of linear mixed modelling is appropriate; however data could have been analysed in its entirety using the mixed modelling rather than use ANOVA to assess group differences.

The authors reported that subjects in the NPBD and 'at risk' for BD groups made statistically significantly more errors than subjects in the HC group when identifying emotion on child and adult faces on DANVA shown in table 4.2. The 'at risk' subjects also made more errors on recognising child and adult face stimuli than controls. In a sub analysis in the 'at risk' group, a t test revealed no differences in the number of errors on DANVA between OBP (n=10) and siblings of NPBD (n=14).

Table 4.2 Findings from DANVA (Brotman et al. 2008)

	NPBD	at-risk'	Control			
	Mean (SD)	Mean (SD)	Mean (SD)	F	df	p
Age	13.3 (2.85)	11.45 (3.98)	14.43 (2.28)	10.82	2, 151	<0.01
IQ	106.85 (13.36)	115.54 (15.81)	109.81 (15.13)	2.89	2, 151	0.06
DANVA errors						
Child faces	3.80 (2.11)	3.67(2.2)	2.2 (2.15)	9.79	2, 150	<0.01
Adult faces	5.55 (2.39)	5.42(2.5)	3.82 (2.45)	8.84	2, 150	<0.01

Interestingly this is one of the few recent studies that did not report any difference on IQ between subjects in NPBD, 'at risk' for BD and HC groups. This is the first published study to assess facial emotion processing in subjects 'at risk' for BD (including OBP). The limitations of this study include: the small size of the 'at risk' sample (n=24) [of which OBP sample was even smaller (n=10)], the bipolar probands (NPBD, adults with BD) included both BDI and BDII and inclusion of individuals with anxiety, ADHD and CD. The lack of clarity regarding

differences between genetic risks for offspring and siblings of bipolar probands are discussed in chapter 6.3.3.

Brotman and colleagues published another study that utilised the the Emotional Expression Multimorph Task (Blair et al. 2001) (described previously in section 4.5) to assess ability to label facial emotion (Brotman et al. 2008). The authors assessed 37 patients with NPBD (age 14.16±2.92 years, 45.9% male, FSIQ 108.41±14.05, 45.9% euthymic), 25 unaffected children 'at risk' for BD (age 12.15±3.05 years, 72% male, FSIQ 113.83±12.15, 100% euthymic), and 36 typically developing youths (HC group: age 14.34±2.28 years, 55.6% male, FSIQ 115.61±14.21) on the Emotional Expression Multimorph Task. The screening methodology, inclusion and exclusion criteria were the same as employed in the previous study (Brotman et al. 2008). The groups appeared to include participants from the previous study (although this is not made explicit by the authors). The subjects had high rates (28%) of psychopathology in the 'at risk' for BD group: GAD 8%, separation anxiety 16%, social phobia 8%, ADHD 12% and CD 4%). None of the subjects in the 'at risk' for BD group were on any psychotropic medication.

Pearson correlations revealed that IQ was related to task performance across the entire group for first response ($r=.19$, $p=.05$) and at a trend level for first correct response ($r=.18$, $p=.09$). When these correlations were examined within each group, subjects in the NPBD group and HC group did not show a significant relationship between number of morphs required and IQ (all p's>.44). However, 'at-risk' youths demonstrated a significant correlation between first response and IQ ($r=.52$, $p=.01$) and between first correct response and IQ ($r=.56$, $p<.01$). Repeated measures ANCOVA, with age and IQ included as covariates, revealed a significant main effect of group for the first response point [$F(2, 92)=5.53$, $p\leq.01$], with both subjects in the NPBD group ($p\leq.01$) and 'at-risk' for BD group ($p\leq.03$) requiring higher emotional intensity before responding than subjects in the HC group. Similarly, repeated measures ANCOVA for first correct response point revealed a significant main effect of group [$F(2,88)=6.44$, $p\leq.01$). Compared to subjects in the HC group, subjects in

both NPBD group (p≤.01) and 'at-risk' group (p≤.05), required higher emotional intensity before correctly identifying the emotion being displayed. The performance of subjects in the 'at-risk' for BD group and NPBD group did not differ (p's>0.28). For both analyses, the group-by-emotion interaction was not significant (for number of morphs, p=0.56; for number of morphs until correct, p=0.16), indicating that face emotion type did not moderate group differences. This would imply that there was no specificity for subjects to make errors in labeling specific facial emotions on the Emotional Expression Multimorph Test.

There are limitations to this work. The sample sizes were relatively small which as before highlights the difficulties of recruiting to such projects. In addition, using the NPBD criterion (which are more stringent than DSM-IV-TR BD criteria), made these findings less generalisable. Given the controversies and issues with regards to diagnosis of PBD (discussed in chapter 2.7) it was however prudent to use NPBD criteria. In addition, as before the groups under study combined BDI and BDII probands probably to aid recruitment and increase power. Further, the Ekman faces used in this paradigm were not specifically developed for use in paediatric populations. The authors did not use any child faces as stimuli (which are present in the DANVA 2). In the previous study (Brotman et al. 2008) the authors have demonstrated impairment on child faces but this could not be investigated in this study.

Further, it was possible that the increased number of morphs needed for BD and at-risk youths was due an overall slower performance or conservative response bias, as opposed to an emotion identification dysfunction. Had the authors included neurocognitive measures it may have been possible to separate these issues. In addition, NPBD patients were all medicated and were not all euthymic. Although the authors excluded those 'at-risk' youths with a history of a mood disorder (but included those with other psychopathology) because a depressive episode could be the first presentation of BD. All these factors could have contributed to facial affect recognition difficulties rather than ascribing the findings to the 'at risk' for BD status.

In the most recent study, the Stanford group, aimed to investigate differences in socio-emotional processing and functioning in OBP and OHC (Whitney et al. 2013). Interestingly all the participants in the OBP group (n=24) consisted of subjects who themselves had past/current major depressive disorder, or if they had ADHD and also had moderate mood symptoms (YMRS>12 or CDRS>30 on the day of assessment). The authors do not explain why they used this particular subject group in the study. The OHC group (n=27) had no personal/ family history of mental health disorder. Parental BD was confirmed using SCID (First et al. 1996). Psychopathology in young persons was assessed using the structure of the WASH U KSADS (Geller et al. 1996) for assessment of mood disorder symptoms and the KSADS-PL (Kaufman et al. 1997) for non-mood disorders symptoms. The WASI (Wechsler 1999) was used to assess FSIQ. The neuropsychiatric measures included the Social Responsiveness Scale (SRS) (Constantino et al. 2003) completed by parents, DANVA (Nowicki and Duke 1994) and the affect recognition and ToM subtests of NEPSY II (Korkman et al. 2007).

OBP and OHC did not differ on statistical analyses on the scores of affect recognition (NEPSY II) as well as child and adult faces on DANVA. There was a lack of difference between OBP and OHC on the DANVA. The authors reported that the rates of errors in OBP did not differ from previous NIH studies (Brotman et al. 2008; Brotman et al. 2008). The rates of errors in OHC group in their study, however, were higher than in the previous studies by the NIH group. There are several limitations in this study including a small sample size, heterogeneity of disorders in OBP group who all had psychopathology (and concomitant psychopharmacological treatment)

Based on the studies discussed so far it can be proposed that the ability to identify facial emotion could be considered a putative endophenotype. Face emotion labelling deficits meet 3 of the 5 criteria to be a potential endophenotype for BD. These are now presented in comparison with the criteria for an endophenotype previously presented in chapter 2.12.

Criteria 1: association with illness in the population (Yurgelun-Todd et al. 2000; Lembke and Ketter 2002; Getz et al. 2003; McClure et al. 2003; Venn et al. 2004; McClure et al. 2005; Guyer et al. 2007; Brotman et al. 2008; Brotman et al. 2008; Rich et al. 2008)

Criteria 3: state-independence (Yurgelun-Todd et al. 2000; McClure et al. 2003; Venn et al. 2004; McClure et al. 2005; Guyer et al. 2007; Brotman et al. 2008; Brotman et al. 2008; Rich et al. 2008)

Criteria 5: presence in non-affected family members at higher rate than in general population (Brotman et al. 2008; Brotman et al. 2008; Whitney et al. 2013).

Studies are still needed to establish whether impairments in facial emotion processing satisfy the remaining two criteria (criteria 2 and 4) to become an established endophenotype for BD. The neural correlates of these deficits should be explored, with a particular emphasis on examining amygdala hyperactivity.

4.7 Summary

Facial emotion processing has been studied over the past 2 decades in mood disorders. Facial emotion labelling deficits have been demonstrated in both adults and adolescents with BD (with varying degrees of euthymia). There have been studies that have implicated deficits in recognising ‘fear’ implicating involvement of the amygdala. However, other studies have not demonstrated any specificity for deficits related to a particular affect. Some studies (NIH group) have investigated facial emotion labelling in youth ‘at risk’ for BD. Although these studies have identified facial emotion labelling deficits as an potential endophenotype for BD, the studies have had limitations. The next step would be a study which investigates facial emotion labelling deficits as a candidate endophenotype. Such a study should recruit a homogenous sample of OBP (not OBP and sibs of BD probands: reasons for the same discussed in chapter 6.3.3) of parent probands with BDI to compare their ability to label facial

emotion in comparison with OHC. The OBP group should consist of subjects who are free of psychopathology and not be receiving pharmacological treatment, both of which could impact on participants performance on tasks assessing facial emotion labelling. The facial emotion labelling task should consist of a test paradigm which includes both child and adult faces, each at low and high intensity.

Chapter 5: Neurocognition and facial emotion labelling

5.1 Introduction

Chapters 3 and 4 have discussed deficits in neurocognition and facial emotion labelling in BD. Few studies have assessed whether these deficits are independent or whether the cognitive deficits contribute to the face emotion labelling deficits. This chapter will discuss the limited number of studies that have assessed both neurocognitive function and facial emotion labelling in BD. It will also discuss reasons why these domains should be assessed together in the same sample of OBP to further the search for an endophenotype for BD.

5.2 Studies in adults

There have been few studies that have jointly assessed neurocognitive status and facial emotion processing in adults with BD (Addington and Addington 1998; Summers et al. 2006). Addington and Addington designed their study to test the hypothesis that deficits in facial recognition in schizophrenia are a stable trait (Addington and Addington 1998). They did this by assessing the schizophrenia subjects at different stages of the illness: during a period of acute relapse and hospitalization and after 3 months during a period of relative remission. The second hypothesis was that deficits in facial affect recognition would be associated with deficits in visual attention tasks. This hypothesis was tested by comparing, at the out-patient phase, the performance of individuals with schizophrenia on tasks of visual attention and facial emotion labelling with the performances of a non-psychiatric control group and a psychiatric comparison group (BD) on the same tasks. To address the question of a differential deficit, this study also utilized a facial recognition task and a non-facial cognitive task that measured right-hemisphere functioning.

The sample consisted of 40 individuals with schizophrenia at hospitalisation and then 3 months later during an out-patient phase (relative remission). At this second phase they also assessed the performance of these patients with a group of adult patients with BD (n=40; M:F::10:30) and a HC group. The diagnoses of schizophrenia and BD were confirmed using the structure of Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al. 1990).

The neurocognitive tasks included a measure of attention: CPT (Nuechterlain 1991) and the Forced-Choice Span of Apprehension Task (SPAN) (Asarnow and Nuechterlain 1992). The CPT is a measure of visual sustained attention (Nuechterlain 1991). The task involved monitoring a quasi-random series of stimuli (numbers) as they were presented briefly one at a time, in a continuous sequence, and pressing a response button each time that a predesignated stimulus occurred (target number 0). The SPAN measures the efficiency of early iconic memory and read-out stages of visual information processing relatively independently of active short-term memory (Asarnow et al. 1991). The SPAN was assessed using Version 4 of the UCLA SPAN (Asarnow and Nuechterlain 1992). The measure presented arrays of 3 or 12 letters that contain either a `T' or an `F'. Responses were scored to obtain the number of correct detections per array size. The authors were mainly interested in the SPAN 12, since they considered that this had a higher processing load than the SPAN 3. The authors also used the Rey Osterrieth memory for design task (Rey 1942) to assess the amount of visual information retained over time. Facial affect recognition tasks consisted of a discrimination task and an identification task using images developed by Ekman and Friesen (Ekman and Friesen 1976). The authors employed the Test of Facial Recognition (Benton et al. 1978) (a measure of visuospatial perception) to exclude whether the difficulties lay in face perception in general or whether these were specific to facial affect recognition.

The subjects in the BD group did not differ from subjects in the HC group on SPAN and the CPT. The subjects in the BD group did, however, perform more poorly on the facial discrimination task when compared to subjects in the HC group ($p<0.01$) but not as poorly as subjects in the schizophrenia group.

Subjects in the BD group performed as poorly as subjects in the schizophrenia group on the Rey recall and significantly worse than subjects in the HC group ($p<0.001$). Regression analysis was used to investigate any possible association between the cognitive profile and facial emotion labeling tasks. For subjects in the BD group there was a small association between the CPT and the facial identification task and between the SPAN and the facial discrimination task. Similarly there was an association with both facial identification and discrimination tasks and the Rey recall tasks. This is shown in Table 5.1.

Table 5.1 Correlations: facial affect and cognition (Addington and Addington 1998)

Measure	Facial affect identification	Facial affect discrimination	Facial recognition
Facial affect identification	1.00		
Facial affect discrimination	0.27		1.00
Facial recognition	0.46**	0.01	1.00
CPT	0.37*	0.13	0.16
SPAN 12	0.30	0.34*	0.16
Rey recall	0.33*	0.13	0.37*

This was the first study to combine the assessment of cognition and facial emotion processing in BD. It was, however, limited by a restricted neurocognitive battery assessing attention, sustained attention, visual recall and visuospatial processing but no executive measures. In addition all the subjects in the BD group were on medication (neuroleptics=12; Lithium=33; antidepressants=4) which may have contributed to some of the cognitive deficit findings. Furthermore, all the subjects in the BD group had an extensive history of hospitalisation and been recruited from a tertiary referral centre. This indicates that the subjects had a severe form of BD questioning how much these findings can be extrapolated to the majority of subjects with BD who may not have disorders that are as severe as the disorders experienced by the subjects in this project.

In another study which jointly assessed neurocognitive function and facial emotion processing in subjects with BD, Summers and colleagues examined the relationship between depression and impairment in cognition and emotion processing (Summers et al. 2006). Differences between BD subgroups were investigated by assessing 36 BD [25 BDI (M:F::10:15) and 11 BDII (M:F::3:8)] patients using a cognitive battery and a facial emotion recognition task. In this study 34 of the 36 patients were on medication (unclear for how long) and medication history was unavailable for another 2. All patients had their diagnoses confirmed using the SCID (First et al. 1996) with 9 patients in a depressive episode at the time of assessment with no information available regarding the affective episode status of 6 patients at the time of the assessment.

The neurocognitive assessment battery consisted of current measure of FSIQ (including VIQ and PIQ) using the WAIS-R (Wechsler 1981) as well as measures of premorbid IQ using the NART (Nelson and O'Connell 1978). A difference in scores of more than 20 points was taken as indicative of significant intellectual decline. Verbal and visual memory were assessed using the Recognition Memory Tests (Warrington 1984); the Paired Associates Learning Test (Warrington 1996); the Rey–Osterreich Complex Figure Test (Rey 1964) and the Doors and People Test: Shapes subtest (Baddeley et al. 1994). Attention and concentration were measured with the Trail-Making Test A of the Army Individual Test Battery (Army 1944). Naming ability was assessed with the Graded Naming Test (McKenna and Warrington 1983). Executive functions were evaluated with the Modified Wisconsin Card Sorting Test Nelson (Nelson 1976); the Stroop Colour–Word Test (Trenerry et al. 1989); the Controlled Oral Word Association (or Verbal Fluency) Test (Benton 1968); the Hayling Sentence Completion Task (Burgess and Shallice 1997); SWM and IED from the CANTAB (Sahakian and Owen 1992); and the Trail-Making Test B of the Army Individual Test Battery (Army 1944). A variation of the emotional expression multimorph task (Ekman and Friesen 1976) was administered (these have been previously discussed in chapter 4.5) to assess facial emotion processing. This was a

comprehensive battery of assessments given it was designed as an exploratory study to assess neurocognition and facial emotion labelling in BD.

The most common cognitive impairment identified was a selective executive dysfunction and the next most common was impairment in memory. Selective impairments in memory or naming were much less frequent. There was a trend for more patients to be impaired in executive function than in memory (McNemar's exact test, p=0·077) and impairment in memory was seen more frequently than abnormalities in naming (McNemar's exact test, p=0·035). To assess the effects of depressive symptomatology on neuropsychological performance the authors assessed for differences in test performance between the 15 subjects with BD who had normal Beck Depression Inventory (BDIn) scores (0–9) and the 13 subjects with BD who had residual depressive symptoms. When the BD group was considered as a whole, the scores of only two of the 10 cognitive measures in which they were impaired correlated with BDIn score [Shapes Test score (r=–0·401, p=0·034) and spatial working memory error score (r=0·431, p=0·040)]. Poorer performance of subjects in BDII group with respect to subjects in BDI patients was related to BDIn score only in the Shapes Test. The number of previous depressive episodes was negatively correlated with performance on the spatial working memory test (ρ=0·337, p=0·085) and positively correlated with composite cognitive score (ρ=0·326, p=0·07).

On the emotion processing task the subjects in the BD group underperformed with respect to controls in accuracy on the expression of surprise (t_{80}=2·327, p=0·024). Sensitivity scores did not differ between patients and controls. There were no significant differences in either accuracy or sensitivity scores between subjects in BDI and BDII subgroups. To study the relationship between cognition and facial emotion processing the authors correlated scores on recognition of surprise with scores on visual recognition memory (Spearman's ρ=0·361, p=0·039). Patients with elevated BDIn scores underperformed with respect to controls on sensitivity to happiness (t_{37}=1·93, p=0·062). These patients also underperformed with respect to euthymic patients on sensitivity to

anger (t_{25}=2·21, p=0·037). Sensitivity to happiness and anger was correlated with performance on verbal recall (happiness and PALT1 ρ=–0·417, p=0·014; PALT2 ρ=–0·469, p=0·005; anger and PALT2 ρ=–0·575, p<0·001). Differences in verbal recall performance accounted for underperformance on anger sensitivity in patients with elevated BDIn scores with respect to those with normal BDIn scores (difference in mean anger sensitivity score, controlling for the effect of verbal recall performance).

These findings indicate that cognitive impairment and isolated facial emotion processing deficit (surprise) were seen in subjects with BD compared with HC. These deficits were largely unrelated to depressive symptoms. This study also provided evidence that cognitive deficits were more severe and pervasive in subjects with BDII, suggesting that recurrent depressive episodes, rather than mania, may have a more detrimental and lasting effect on neurocognition. This also lends credence to the fact that BDI and BDII are separate disorders with differing clinical presentations and neurocognitive profiles, emphasising the need to study homogenous groups.

The limitations of this study include: the small sample size which may not have been large enough to reveal differences between the two subgroups (BDI and BDII) in emotion processing, the effects of psychotropic medication on cognitive performance and facial emotion processing and multiple statistical tests were conducted without any post-hoc correction.

5.3 Studies in paediatric bipolar disorder and offspring of bipolar parents

The criteria for an endophenotype (see chapter 2.12) are:
Criterion 1: The endophenotype is associated with illness in the population.
Criterion 2: The endophenotype is heritable.
Criterion 3: The endophenotype is primarily state-independent (manifests in an individual whether or not illness is active).
Criterion 4: Within families, endophenotype and illness co-segregate.

Criterion 5: The endophenotype found in affected family members is found in non-affected family members at a higher rate than in the general population.

The 2 studies discussed in section 5.2 meet criteria 1 and 3 for a candidate endophenotype. There are no studies that have attempted to assess neurocognition and facial emotion labelling in PBD and/or youth 'at risk' for BD (which includes) OBP compared with a general population sample. A study of this design would address other criteria for facial emotion labelling deficits to be considered an endophenotype for BD.

5.4 Joint assessment

Studies have suggested that deficits in neurocognition and facial emotion labelling may be distinct endophenotypes for BD (chapters 3 and 4). Alternatively, it could be that the identified neurocognitive deficits and emotion-processing deficits in BD represent a latent vulnerability associated with a (yet to be identified) endophenotype for BD, the impact of which may manifest under conditions of environmental stress (Green et al. 2007). This may be due to an underlying brain deficit e.g. neural connectivity that manifests in the form of neurocognitive deficits and/or face emotion labelling deficits. Further, as discussed in section 5.2, these deficits could contribute to each other or indeed be part of a more fundamental underlying deficit. There is therefore, a need for further studies to jointly assess neurocognition and facial emotion labeling in OBP. This could establish whether one or both types of deficits are present in OBP and what is the relationship between them in order to identify potential candidate endophenotypes for BD. These will now be discussed in more detail.

5.4.1 Impact on each other

Neurocognitive function (attention, sustained attention, memory, learning and executive function) all have the potential to impact on the ability to recognise and discriminate between facial emotions (Addington and Addington 1998; Summers et al. 2006; Rocca et al. 2009). Perceptual skills including acuity for

identifying and distinguishing emotions from others, and regulatory skills that facilitate the initiation and management of emotional responses, are vital for adaptive social interaction (Van Rheenen and Rossell 2013). The studies presented in section 5.2 indicate that, specific attentional, visuopatial and memory impairments can all impact on and therefore contribute to facial affect labeling deficits especially in test paradigms which are time limited. In a recent study, subjects with BD exhibited impairments in the recruitment of 'top-down' brain networks and as such were unable to engage, to the same extent as matched HC, essential prefrontal processing needed to evaluate emotional salience of disgust stimuli (Lagopoulos and Malhi 2011). Therefore, without combining neurocognitive assessments with tasks that assess emotional processing it is difficult to conclude whether a deficit in the latter is a specific deficit or as a result of subjects struggling to attend to it.

5.4.2 Neural basis

It could also be that neurocognitive impairments and facial emotion labeling deficits are due to deficits in the same underlying neural substrates (Addington and Addington 1998). Identifying these underlying neural substrates would help advance the understanding of the development and aetiology of BD. The most commonly seen deficits in BD have been in the domains of sustained attention, working memory and executive function. The connections between the temporal lobe, dorsolateral and ventrolateral prefrontal cortex abnormalities along with their connections to the subcortical structures (amygdala, hippocampus and thalamus) have been implicated as neural substrates for the above mentioned cognitive impairment in BD.

The most common structural abnormalities reported in BD have been increased lateral ventricular volumes and higher rates of White Matter (WM) hyperintensities (Hallahan et al. 2011). Decreases in volume of the medial temporal lobes or cerebellum have been reported in some, but not all, structural MRI studies in patients with BD (Ferrier and Thompson 2002). Some studies have observed significantly larger amygdala (but not hippocampal) volumes in

prospectively verified euthymic adult patients with bipolar disorder, compared with patients with schizophrenia and normal subjects (Altshuler et al. 2000). On the other hand some studies have reported smaller amygdala volumes in adults with BD (Rosso et al. 2007) as well as in PBD (Blumberg et al. 2005). The MRI studies have indicated also that patients with BD have somewhat larger lateral and third ventricles than controls . This latter finding has been interpreted as an indirect expression of a reduction in the volume of thalamus or hypothalamus, which are located at the sides of the ventricles (Videbech 1997). Cerebral white matter lesions localised in the frontal lobes and the basal ganglia have been seen in BD possibly indicating a defective basal ganglia—frontal circuit (Videbech 1997), and have been shown to be associated with poor outcome (Moore et al. 2001).

An interesting approach to better understanding the white matter changes seen so commonly in BD has been to use Deep Tensor Imaging (DTI) as it allows a more sensitive exploration of WM microstructure than conventional structural MRI (Vederine et al. 2011). The main outcome measured by DTI is fractional anisotropy (FA), an indicator of the myelination and coherence of WM tracts. In their meta-analysis, Vederine and colleagues propose that the key connections implicated in the pathophysiology of BD are the arcuate fasciculus, considered to be part of the superior longitudinal fasciculus (SLF), the inferior fronto-occipital fasciculus (IFOF), the inferior longitudinal fasciculus (ILF) and the posterior thalamic radiations (Vederine et al. 2011). ILF connects the anterior temporal lobe and amygdala with the occipital cortex. IFOF connects the orbito-frontal cortex with the occipital lobe. Both ILF and IFOF seem to serve in the identification of face emotion (Philippi et al. 2009). Decreased performance on tasks assessing facial emotion labelling have been suggested to be putative endophenotypes for BD (Brotman et al. 2008; Brotman et al. 2008). SLF connects the frontal lobe with parieto-temporal regions and may help explain the aetiology of neurocognitive deficits in BD.

Several of the limbic and prefrontal regions involved in these cognitive domains overlap areas hypothesized to mediate emotional regulation (Strakowski et al. 2005). Executive function, for example, has been localized to portions of the

PFC, which also mediates performance of attention, working memory, and Stroop tasks (Adler et al. 2006). The pattern of attention deficits in patients with bipolar disorder is most consistent with dysfunction in the orbitofrontal cortex, DLPFC, subcortical and medial temporal structures, and portions of the posterior parietal cortex (Strakowski et al. 2004). Deficits in working memory similarly suggest abnormalities in the orbitofrontal cortex, DLPFC, ACC, striatum, thalamus, and medial temporal structures (Adler et al. 2004). The pattern of cognitive deficits in bipolar disorder suggests dysfunction within a cerebello-striatal-prefrontal neural circuit (Haznedar et al. 2005).

Researchers have posited that the spectrum of affective and cognitive symptomatology see in BD represents dysfunction within a single extended network (Strakowski et al. 2005). This network called the anterior limbic network (ALN) includes prefrontal regions, subcortical structures, such as the thalamus, striatum, amygdala, and the midline cerebellum. Prefrontal-striatal-thalamic circuits compose a core aspect of the ALN, and interactions among these structures may be involved in the regulation of socioemotional behaviors (Strakowski et al. 2005). Some investigators have suggested that the abnormal processing of emotional stimuli in patients with bipolar disorder results from impaired feedback between these dysfunctional prefrontal regions and the amygdala (Drevets 1999).

5.5 Summary

Neurocognitive function and facial emotion labelling deficits appear to exist in patients with BD across the lifespan as well as those ‘at risk’ for BD. This would suggest that they may be potential endophenotypes for BD. Given the fact that they can both represent a functional outcome of a common neural substrate (eg dysfunction in the ALN; WM changes in the ILF, SLF and IFOF) and potentially interact to impact on each other may help explain the pathophysiology of BD. Any study that is seeking to study neurocognitive function and facial emotion labelling as endophenotypes for BD need to assess both in their study.

Chapter 6: Project development

6.1 Introduction

This chapter outlines the development of this project (including the role of the author) and then proceeds to discuss the factors influencing the choice of the tests that constituted the assessment battery and schedule. It also outlines the thinking behind the statistical plan of analysis.

6.2 Development

This thesis has outlined and discussed economic costs and psychosocial dysfunction due to BD worldwide (see chapter 2.8) and more specifically in the UK (see chapters 2.9 and 2.10). The association between this economic and psychosocial burden and deficits in neurocognition and emotional processing highlights the need for identification of endophenotypes (see chapter 2.13). Earlier identification of BD, could increase the likelihood of earlier diagnosis and access to treatment and hopefully reduce the impact of BD and the development of co-morbidities. The thesis has also presented the current evidence for neurocognitive (dys)function (chapter 3.9) and facial emotion labelling deficits (chapter 4.6) as candidate endophenotypes for BD. It has also presented the key findings from the limited number of studies that have attempted to study aspects of neurocognition and emotion processing together in patients with BD (chapter 5.2). There have been no published studies to date that have studied these in an 'at risk' OBP population (chapter 5.3).

The development of this project started in February 2006 and initially consisted of a literature review that identified the above gaps in knowledge. This was followed by a presentation by the author to the supervisory team. A decision was made to register the study as a PhD project and start to develop the assessment battery.

6.3 Factors influencing choice of tests

The evidence base of studies (prior to development of project protocol) assessing neurocognitive function and facial emotion labelling in OBP were characterised by several limitations:

6.3.1 Age range

OBP studies have included age ranges up to and including age 20. There are advantages in recruitment of older offspring. They are developmentally a less diverse group as brain maturation and consequent neurocognitive development can continue till late adolescence (Luna et al. 2004). However, the older the OBP range the higher the rate of psychopathology in the group (Singh et al. 2007). On balance a decision was made to recruit younger offspring as recruiting older OBP would make it harder to control for high rates of psychopathology (and the pharmacological treatment for the same). A decision was made to recruit subjects in the age range of 6-14 years. The project wished to strike a balance between likelihood of success for recruitment, wide developmental age range as well as homogeneity of BD subtype in the parent with BD.

6.3.2 Heterogeneity in diagnosis of bipolar probands

Most studies of ‘at risk’ for BD (including OBP) have included bipolar probands with BDI and BDII disorders. BDI and BDII have been considered as different disorders by some investigators with perhaps differing neurocognitive profiles (Summers et al. 2006; Torrent et al. 2006; Simonsen et al. 2008; Hsiao et al. 2009; Schenkel et al. 2012; Aminoff et al. 2013). The disorders appear to be heterogenous in their clinical presentation (previously presented in chapter 2.4). Although the NIH group published their studies of facial affect processing (Brotman et al. 2008; Brotman et al. 2008) after the start of this project it is noteworthy that their ‘at risk’ for bipolar youth consisted of OBP and siblings of bipolar probands with both BDI and BDII. The most recent study from eastern Turkey recruited a homogenous sample of offspring of parents with BDI who

completed a neurocognitive assessment battery (Deveci et al. 2013). For this project it was decided to study a more homogenous cohort to reduce confounding variables: offspring of bipolar probands who had BDI.

6.3.3 'At risk' subjects: offspring versus siblings

Studies that have assessed subjects 'at risk' for BD have included both offspring and siblings of bipolar probands collectively also referred to as First Degree Relatives (FDR). It is unclear whether the lifetime rates of illness in FDR of bipolar probands vary according to type of relative (parent, offspring, or sibling) (Craddock and Jones 1999). Gershon and colleagues initially reported that the risk in sibs could be greater than that in offspring (Gershon et al. 1975). In a later study, however, led by Gershon the difference was reported to be reversed with the risk being greater in offspring (Gershon et al. 1982). Perhaps, because of small sample sizes or because there appears to be no consistent difference between risks in offspring and siblings studies have reported only the pooled estimate of risk for all types of FDR (Craddock and Jones 1999). Studies of 'at risk' subjects have benefitted by recruiting both offspring and siblings, thereby increasing sample sizes. However, given the lack of a clear difference between the risks for offspring and siblings, on balance a decision was made to recruit only offspring of parents with bipolar I disorder, a strategy which was felt would increase homogeneity further.

6.3.4 Neurocognitive tests

At the start of this project there were few studies (Kestenbaum 1979; Waters et al. 1981; Winters et al. 1981; Kron et al. 1982; Decina et al. 1983; McDonough-Ryan et al. 2002) that had attempted to assess neurocognitive (mainly intellectual) functioning in OBP. The limited evidence base combined with studies that had assessed neurocognitive function in PBD (Dickstein et al. 2004) were used to inform the choice of tasks within the neurocognitive assessment battery. A critical appraisal of the nature and severity of neurocognitive deficits reported in adult subjects with BD further informed the

assessment battery. Given the lack of published data of neurocognitive deficits and face emotion labelling deficits in subjects 'at risk' for BD at the time of the start of this project, it was decided that the neurocognitive assessment battery should be broad based and exploratory in nature using tasks that were appropriate for a developmentally younger age group (OBP and OHC).

Best practice to complete such a detailed neurocognitive assessment should include assessment of: IQ, attention and concentration (visual and verbal), working memory (visual and verbal), learning (visual and verbal), executive function (verbal fluency and strategy formation) (Fennell 2000). The project focussed on an extensive assessment of attention and concentration as deficits in these domains have been reported in previous studies of euthymic adults with BD. Further if there were attentional deficits, these should been taken into account when analysing the data from tests assessing working memory, learning, executive function and facial emotion labelling as attentional deficits can contribute to all the 'higher order' neurocognitive deficits.

The author conducted an extensive review of available comprehensive neurocognitive assessment batteries that were well validated for use in the target age range. Unfortunately, most conventional neurocognitive assessment batteries [eg. A Developmental NEuroPSYchological Assessment: NEPSY (Korkman et al. 1997); Delis-Kaplan Executive Function System: D-KEFS (Delis et al. 2001)] were not normed and validated for the wide age range included in this project. Further, given the need to assess a broad range of neurocognitive domains as well as the exploratory nature of the project, some of the established batteries such as D-KEFS did not focus on all the domains.

The author decided to explore the use of Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition Ltd.). The CANTAB has been used with success to assess neurocognitive function in adults with BD (Sweeney et al. 2000; Clark et al. 2002; Badcock et al. 2005; Olley et al. 2005; McKirdy et al. 2009) and PBD (Dickstein et al. 2004). It also has the advantage that the computerised nature of the tests and the touch screen used in the

assessment process are likely to assist young subjects to attend to the tasks and continue to engage and motivate them in the assessment (Luciana 2003). A further advantage is the achievement of standardized administrations and automated response recording, difficult to accomplish by hand (Falconer et al. 2010; Fried et al. 2012). For example, response times can be recorded with millisecond precision, increasing the sensitivity of the test (Luciana 2003). Furthermore, CANTAB can be utilised to assess neurocognitive function in children ages 5 years and upwards (Luciana and Nelson 2002). Luciana and Nelson proposed this after their study assessing the ease of use of CANTAB in typically developing 4-12 years old. The authors inferred this on the basis that children aged 5 and older possessed the necessary stamina and were able to use the size of screen (used in the CANTAB) in comparison with the size of their hand at this age (Luciana and Nelson 2002).

The psychometric properties of the CANTAB include:

1. **Reliability.** In 4–12-year-old children, internal consistency coefficients are uniformly high, ranging from 0.73 for a measure of reaction time latency to . 95 for performance on the self-ordered search task. (Luciana, unpublished data).

2. **Construct validity.** Most research has focussed on the localisation of executive function in the frontal area. Using the Paired Associates Learning (PAL) children's performance on the task has been informative as to the course of PFC maturation. First, 4–12 year old children are able to complete the easiest (2- and 3-item search) trials in a manner that is not statistically distinct from adult performance, verifying that executive skill is present by the age of 4 years (Luciana 2003). However, when the task is administered entirely, it is evident that the most difficult (6- and 8-item search) trials are not performed by children (even at the age of 12 years) at the adult levels of task performance on these items in terms of error scores or strategy use. This would indicate that the construct validity of the CANTAB is valid and it does not appear to have a low ceiling effect.

The CANTAB is limited by an expensive liscence to use the computerised software. It is designed to run on particular versions of the Microsoft Windows Operating System, which are upgraded every several years. Thus, implementation of the battery in clinical settings will require practitioners to upgrade their software periodically in order to stay abreast of technological and scientific advances which can be cumbersome and expensive. The CANTAB requires a clinician to individually supervise each testing session and pace each subtest so cannot be considered as a replacement for a clinician. Further, most of the CANTAB battery is exclusively nonverbal in its response requirements and in the nature of stimulus presentation, limiting the conclusions that can be drawn from subtest performance. In addition, there is limited flexibility in altering the structure and order of tests. As an example, for a subject to move to the next level/task in the battery they must have completed (successfully/ unsuccessfully), a certain number of levels. Studies have reported that in younger subjects (such as in this project) can at times be frustrating (Luciana and Nelson 1998). A final limitation of the CANTAB, with special reference to this project, was the fact that it would not be suitable to assess all the neurocognitive domains that required assessment. In some instances, this was due to the complexity of the CANTAB task in relation to the younger age range of target group (6-10) (eg sustained attention tasks). On the other hand, given the largely non-verbal nature of the CANTAB, it could not assess visual aspects of neurocognition. For these domains, well validated tasks with good psychometric properties and acceptability in the target age range were selected. These will be presented next. Details of the task administration will be presented in chapter 10.

1. **Wechsler Abbreviated Scale for Intelligence 4 (WASI 4)** (Wechsler 1999). This measure is used to assess intellectual function in 6-16 year olds. The format of the subtests is similar to their counterparts in the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler 1997) and the Wechsler Intelligence Scale for Children – Third Edition (WISC-III) (Wechsler 1991) although the actual content differs. This measure was chosen to obtain summary scores for FSIQ, VIQ and PIQ. At the subtest level the reliability

coefficients for WASI range from 0.86 to 0.93 for vocabulary, from 0.81 to 0.91 for similarities, from 0.84 to 0.93 for Block Design and from 0.86 to 0.96 for Matrix Reasoning. The average reliability coefficients across the ages were from 0.92 to 0.95 for both VIQ and PIQ and from 0.95 to 0.97 for FSIQ 4 (Wechsler 1999).

2. **Motor Screening Test (MOT)** (CANTAB) (Cambridge Cognition Ltd.). It was selected to act as a training procedure to ensure that subjects could point accurately and to provide a measure of both speed and accuracy that provides an index of the subjects' motor skills.

3. **Choice Reaction Time (CRT)** (CANTAB) (Cambridge Cognition Ltd.). This was employed to assess visual attention.

4. **Test for Everyday Attention in Children (TEA-Ch): Score! Sustained Attention** (Manly et al. 1999). The benefit of using this test is that the task does very little to 'grab' the child's attention. It is therefore a good test of the child's ability to *self*-sustain his or her own attention.

5. **Digit Span** (Lezak et al. 2004) Forward Digit Span has been extensively used to assess verbal attention. Reversed Digit Span was employed to assess verbal working memory. This is because the task required the individual to not only hold the information presented to them verbally but also manipulate it using a rule requiring reversal.

6. **Spatial Working Memory (SWM)** (CANTAB) (Cambridge Cognition Ltd.) was employed to assess visual working memory. This task required the subject to retain spatial information and to manipulate remembered items in working memory. It is a self-ordered task, which also assessed heuristic strategy.

7. **California Verbal Learning Test-Children's Version (CVLT-C)** (Delis et al. 1987). The CVLT-C incorporated a strategic (Executive) component in that subjects can use semantic organisation of the list to aid performance. Thus

this test was more useful than other list learning tasks such as the Rey Auditory Verbal Learning Test to assess verbal learning.

8. **Paired Associates Learning (PAL) (CANTAB)** (Cambridge Cognition Ltd.) was used to assess visual learning. This test is a form of delayed response procedure which tested 2 different aspects of the ability to form visuo-spatial associations: the number of patterns placed correctly on the first presentation of each trial gives an index of 'list memory' and the number of repeat, reminder presentations needed for subject to learn all the associations provides a measure of 'list learning'.

9. **Category Naming Test (CNT)** was used a measure of verbal fluency (executive function). In the first 2 presentations the subject was asked to generate words from a particular category in an allocated time. In the third presentation the subject was given 2 categories and asked to generate words alternating between the categories. It was therefore also a measure of set shifting in the third presentation.

10. **Stockings of Cambridge (SOC) (CANTAB)** (Cambridge Cognition Ltd.) was employed as a measure of visual planning (executive function).

6.3.5 Facial emotion labelling test

At the time that the project protocol was being developed there was published data regarding tasks suitable for assessment of facial emotion labelling in children (Nowicki and Mitchell 1998). There was however, no published data using these tasks to assess facial emotion labelling in OBP. In addition, the studies that had assessed facial emotion labelling in adults with BD had utilised the Ekman Faces paradigm (Ekman and Friesen 1976). Upon reviewing the literature, the following factors influenced the choice of a task that would assess facial emotion labelling in children and young people:

1. the task was suitable for use with children and young people,

2. child faces and adult faces were included as stimuli (to make sure the subjects could label facial emotion in stimuli across the life span) and

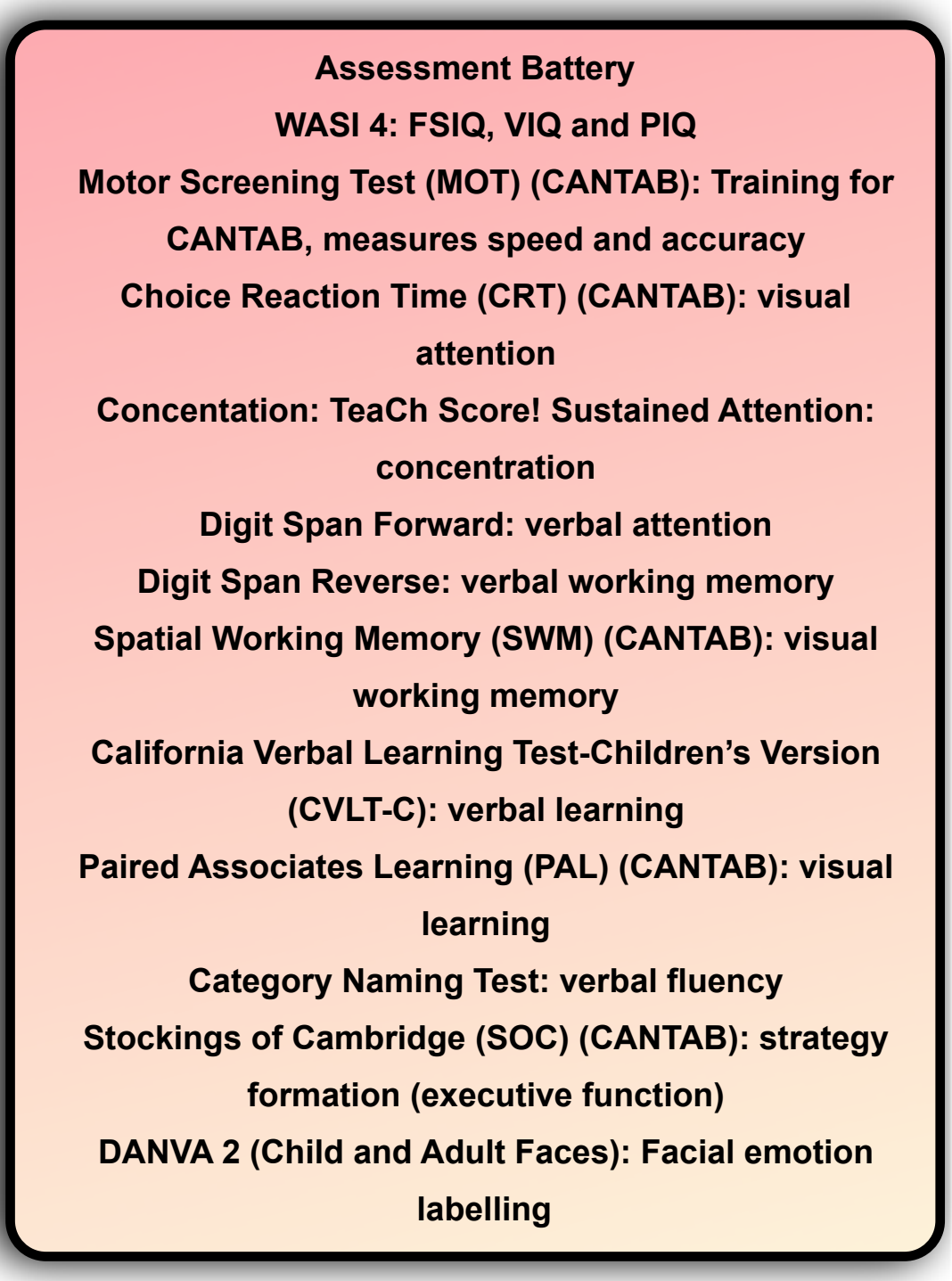
3. the task stimuli be presented at variable intensity (to ascertain whether subjects could label and identify facial emotions at lower intensity which would be more in keeping with more subtle social interaction) (Schepman et al. 2012). Intensity of emotion refers to the degree of complexity or ambiguity of the various stimuli in communicating a particular emotion (Boni et al. 2001).

In the research literature, the most commonly used stimuli for assessing facial emotion labelling have been the Ekman faces (Ekman and Friesen 1976). However, this assessment exclusively used adult faces as stimuli and was not developed for use with children and young people. For these reasons, the decision was made to use the Diagnostic Analysis of Nonverbal Behavior (DANVA 2) (Nowicki 2001). This measure has been used in studies with children (including children in the preschool age range) (Nowicki and Mitchell 1998), includes both child and adult faces as stimuli and has stimuli at high and low intensity. The limitation of the DANVA 2 is the absence of any stimuli that assess subjects' response to a neutral emotional stimulus.

Studies using the DANVA 2 in children and adults indicate that, the DANVA2-AF (Adult Faces) has a coefficient alpha of 0.78 (Baum et al. 1996). The DANVA2-CF (Child Faces) has been shown to have coefficient alphas ranging from 0.69 to 0.81 (Nowicki 2001). Scores on the DANVA2-AF and the DANVA2-CF have not been found to be related to IQ scores or tests of general cognitive ability in adolescents (Baum et al. 1996). However, given the lack of any published data at the time of project development a decision was made to use FSIQ scores as a covariate in the statistical analysis in the facial emotion labelling scores. Further, most studies that have been published after the start of the project in subjects 'at risk' for BD, have included IQ as a covariate in the statistical plan of analysis to compare scores of facial emotion labelling between OBP and OHC (Brotman et al. 2008; Brotman et al. 2008).

The assessment battery comprising tasks assessing neurocognitive function and facial emotion labelling developed for this project are shown in Figure 6.1.

Figure 6.1 Assessment Battery



6.3.6 Sample size

One limitation that all the early published studies of OBP had in common was the limited sample size under study (Kestenbaum 1979; Waters et al. 1981; Winters et al. 1981; Kron et al. 1982; Decina et al. 1983; McDonough-Ryan et al. 2002). Despite the likelihood that most adults with BD will be known to adult mental health services, there are several potential problems with recruitment of OBP. These include the need for all potential participants needing to be identified through clinicians responsible for the treatment of the adult proband with BD. Clinicians may not know about the offspring or be reluctant to raise the topic with the adult bipolar proband. This could be due to the proband being unwell. Lastly and perhaps most importantly, the bipolar proband may themselves be reluctant to discuss such projects with their offspring and family members. This could be due to changing family relationships, little consistent contact with offspring and perhaps the perceived stigma of mental illness.

6.3.7 Statistical analysis

Whilst critically appraising the literature it became clear that most studies had not clarified whether or not more than 1 OBP had been recruited from the same family into the research study (multiplex families: data nested within families). The data collected had then been usually analysed using ANOVA, ANCOVA and MANOVA. If multiplex families are included (Klimes-Dougan et al. 2006; Brotman et al. 2008; Brotman et al. 2008) (both published after project had started) this would mean that the OBP would be nested within some families. The data for these subjects would not be independent this violating the basic assumptions of the ANOVA (Gur et al. 2007). Appropriate statistical analyses for multiplex families will be discussed in section 6.4.3.

6.4 Statistical plan of analysis

6.4.1 Power calculation

At the start of this project the author was able to identify the study carried out by NIH group in which CANTAB had been used to assess neurocognitive function in PBD (Dickstein et al. 2004). A power calculation was carried out using the data from this study. If this study is powered at 80% level (with alpha=0.05 (two-tailed)) to detect group differences in neurocognitive function, a sample size in each group of 28 would yield a minimum detectable effect size of d=0.53.

6.4.2 Excluding offspring with psychopathology

Studies have reported rates of psychopathology in OBP varying from 50-74% (Duffy et al. 2007; Birmaher et al. 2009; Garcia-Amador et al. 2012; Vandeleur et al. 2012). Some studies have investigated neurocognitive function and facial emotion processing in OBP (Klimes-Dougan et al. 2006; Brotman et al. 2008; Brotman et al. 2008; Maziade et al. 2009; Diwadkar et al. 2011; Maziade et al. 2011; Deveci et al. 2013). In some of these studies the OBP with identified mood disorders were excluded but most studies reported samples with considerable psychopathology which included neurodevelopmental disorders such as ADHD and ASD as well as mental health disorders such as anxiety and mood disorders. These disorders along with their associated pharmacological treatments can impact on neurocognition and facial emotion processing. An attempt was made by some authors to control for the severity of these disorders by statistically covarying data on neurocognitive measures and/or facial emotion labelling with scores of severity of psychopathology (eg ADHD).

A better approach, however, would be to assess OBP who had no recognised neurodevelopmental and mental health disorders at the time of assessment. However, this has the down side of potentially making the the sample unrepresentative of OBP group. Further by only including OBP with no psychopathology in the final dataset, it might only include OBP who are at low risk for BD. Deveci and colleagues recruited OBP with no psychopathology (but

do not explain how they screened offspring to do so) (Deveci et al. 2013). Therefore for this project an 'a priori' decision was made to exclude OBP with identified psychopathology from the final dataset. This procedure provided a more rigorous approach towards the identification of a potential endophenotype for BDI.

6.4.3 Model mixing

Previous studies assessing OBP have reported relatively small sample sizes (data presented in Chapter 3). To increase rates of recruitment, more than one offspring of a bipolar proband had been recruited into studies. These offspring are therefore nested within the same family. Data collected in this way will share the common feature of correlation of observations within the sibs nested in a sibling group. Use of analyses that assume independence of observations (i.e. ANOVA, MANOVA, ANCOVA) is not appropriate in this situation (Faraway 2006). A mixed effects model is a statistical method that contains both fixed effects and random effects. A fixed effect is an unknown constant that is estimated from the data. In contrast, for random effects an estimate is made of the parameters that describe the distribution of these random effects (Faraway 2006). Multilevel mixed effects models are particularly appropriate for research designs in which participants data is organized at more than one level (i.e., nested data) such as in this project where offspring in both OBP and OHC groups are nested within families (McArdle and Prescott 2005). These models are useful in a wide variety of disciplines in the physical, biological and social sciences. They are particularly useful in settings where repeated measurements are made on the same statistical units, or where measurements are made on clusters of related statistical units. The statistical packages used to run mixed models analyses include Stata, S-PLUS, 'R', SPSS, and SAS, as well as stand-alone software such as MLwiN and HLM (Rabe-Hesketh et al. 2008).

In this project, 'R' was used to produce the linear mixed models using the lme4 package produced by Bates (Bates 2005). The lme function was employed to fit the linear mixed models described by Pinheiro and Bates for use in S and S-

PLUS (Pinheiro and Bates 2000). The lme4 and its lmer function were used for this study as it provided more flexible fitting of linear mixed models; and was more reliable and faster than the original lme function (Bates 2005). Using R, the individuals models all generate 't-values' and not p values (Bates 2006). To generate p values parametric bootstrapping using the pbkrtest function in 'R' was utilised. This function takes into account the multiple tests done on the same data sample thereby reducing the need to conduct any post hoc analyses (Halekoh and Hojsgaard 2012).

6.4.4 Covariates

Covariates are defined as the variables that would explain some of the variance in the samples under study. Given the discussion regarding IQ as a composite measure of neurocognitive function (discussed in Chapter 3.4.2), an 'a priori' decision was made to use the following covariates for the mixed model analysis of tasks assessing neurocognitive functions: presence or absence of BD in parent (BPD), age and gender of offspring and SES of family. IQ was not included in this mixed effects analysis as a covariate (reasons discussed in chapter 3.4.2). There is data suggesting that IQ does not contribute to the variance of scores on DANVA 2 (Baum et al. 1996). However, as DANVA 2 had not been employed in studies of OBP, a decision was made to use FSIQ scores as a covariate in the statistical analysis in the facial emotion labeling scores. For the analysis of facial emotion labelling deficits the following factors were used as covariates in the mixed models analysis: bipolar status of parent (BPD), age, gender, SES, IQ, intensity (high vs low) of stimuli, child vs adult faces as stimuli.

6.4.5 Model building

Mixed models analyses using lme4 and lmer were built with data nested within families. Further, multiple models were developed with data nested within families and SES. For example, in the analysis of FSIQ the 2 models developed were as follows:

mod1A: FIQ ~ BPD + SES + age + gender + (1 | family)
mod1B: FIQ ~ BPD + SES + age + gender + (SES | family)

Model 1 A had the subjects nested within families only whereas model 1 B had the same data nested within families as well as socioeconomic classes. The method of choosing the 'best' model from these was to select the model for which Bayesian information criterion (BIC) (Schwarz 1978) was lowest (Jones 2011).

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	7	474.23	488.65	-230.12			
Mod 1B	9	473.05	491.59	-227.52	5.18	2	0.08

Therefore the model that best fit the random and fixed effects was model 1 B in this case. BIC penalizes -2 log likelihood by adding the number of estimated parameters multiplied by the log of the sample size. It is most useful in identifying the true model (Acquah 2010). Another approach could have been to compare the Akaike's information criterion (AIC) (Akaike 1973) for the model and use the model with the lower AIC. The BIC is more robust to distributional misspecification than AIC, and outperforms AIC when comparing more complex models (Markon and Krueger 2004). This strategy of model building (selecting the model with lower BIC) was used for each neurocognitive test (see Chapter 10) and facial emotion labelling task (see Chapter 11) (described in the relevant appendix where the multiple models developed and AIC, BIC scores have been presented).

Chapter 7: Aims and hypotheses

7.1 Aims

1. Recruit a sample of 28 OBP and 28 OHC (matched for age, gender and SES) from North East England

2. Investigate neurocognitive function and facial emotion labelling in OBP and OHC groups and assess the statistical difference between the groups.

7.2 Hypotheses

1. OBP will show impairment in the neurocognitive domains of memory, learning and executive function

2. OBP will demonstrate more errors on facial emotion labelling task particularly on low intensity stimuli and on stimuli with child faces.

3. The deficits in facial emotion labelling will not be related to impairments demonstrated in the domains of memory, learning and executive function.

Chapter 8: COMPIC - project protocol

8.1 Introduction

This chapter will describe the project protocol as well as the pathway of assessment for the study participants.

8.2 Explanation of project in study documents

As part of protocol development the candidate presented the protocol to the Newcastle chapter of the Manic Depressive Fellowship (Bipolar Organisation). Members of the Manic Depressive Fellowship (Bipolar Organisation) Newcastle chapter represented stakeholders as part of Public and Patient Involvement (PPI). Based on their input, it was felt that in order to maintain ethical practice and confidentiality the project be called ‘COMPIC: Neuropsychological function and Facial Affect Recognition in Children and Young People’. The project title and the information sheet for the OBP group did not mention BD. This was to ensure that participation in the research did not inadvertently cause concern for any/all of the children who may or may not have been aware of their parents’ psychiatric diagnosis in the OBP group.

8.3 Ethical opinion

A favourable ethical opinion was obtained from NHS Northumberland Research Ethics Committee (ref 08/40902/12).

8.4 Role of author

Dr. Sharma conducted the literature reviews both at the start of the project to inform the development of the and choice of experimental measures and plan of analysis and throughout the course of this project. The author has been supported by a joint supervisory team (Prof Ann Le Couteur, Prof Ian Nicol Ferrier and Dr Thomas Kelly). Additional support was provided by 2 Newcastle

University internal assessors (Prof Helen McConachie and Dr Peter Brian Moore) at annual assessments over the course of the study.

Further, the author collaborated with stakeholders (presented in section 8.2), completed documentation for an ethical opinion, applied for funding from the North East Branch of the Mental Health Foundation and R&D Department of Northumberland, Tyne and Wear NHS Foundation Trust. He advertised the project to consultants in adult psychiatry in North East England for recruitment of adult subjects with BDI and selected primary and secondary schools in the same geographical areas to recruit the matched OHC. Dr. Sharma sought consent and assent as appropriate, conducted the assessments with parents (SCID, WASH-U-KSADS), supervised the research assistants with reference to neurocognitive assessment and the DANVA 2. The mixed model analyses were conducted under supervision from the School of Biology (Prof S Rushton and Dr. Andrew Close Research Associate).

Data from DANVA 2 was presented by Dr. Sharma at the Faculty of Child and Adolescent Psychiatry (RCPsych) Annual Conference at Oxford in 2010 for which he was awarded the Margaret Davenport Award for best research presentation. Data from the neurocognitive battery was presented at the Faculty of Child and Adolescent Psychiatry (RCPsych) Annual Conference at Cambridge in 2011. Data from on the neurocognitive deficits was also presented by the author at the Ninth International Conference on Bipolar Disorders in Pittsburgh USA leading to the award of the Young Investigator Award (Sharma et al. 2011).

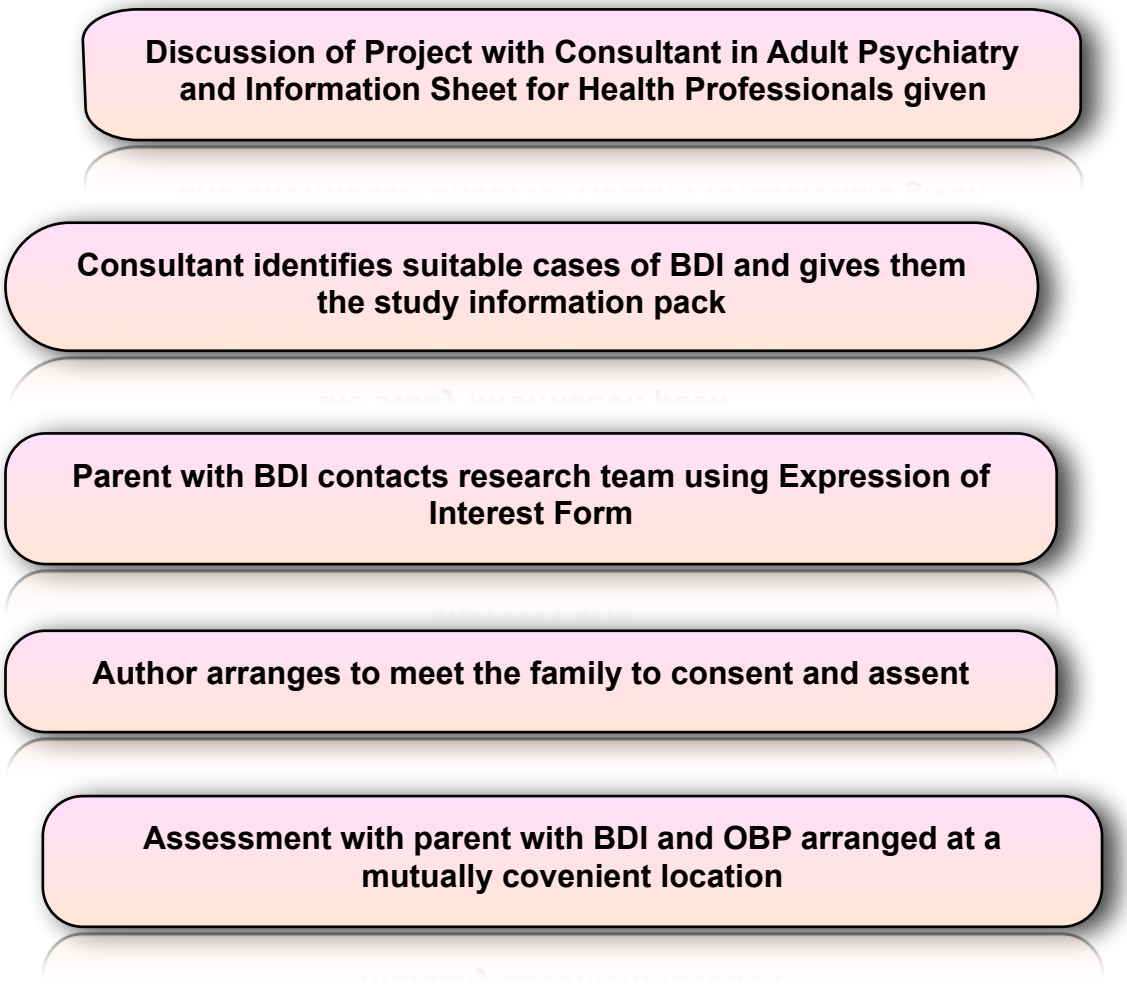
8.5 Location

The project was conducted and coordinated in the North East of England by the author under the supervision of Prof AS Le Couteur, Prof IN Ferrier and Dr Thomas Kelly. It received R&D sponsorship from the Northumberland, Tyne and Wear NHS Foundation Trust.

8.6 Recruitment strategy

8.6.1 Offspring of bipolar parent

Figure 8.1 Pathway for OBP Recruitment



Once the project had received a favourable opinion from the ethics committee, consultant psychiatrists working within Community Mental Health Teams (CMHT) in North East England were approached by the author and provided with the Information Sheet for Health Professionals (Appendix i). Consultant Psychiatrists were asked to identify from their current clinical caseloads, adults with BDI who had biological offspring (age 6-14 years; either gender) living with them. Consultant psychiatrists informed eligible patients (parents with BDI) about the project at their next scheduled appointment. An information pack consisting of 2 written information sheets (adult version for parent with bipolar disorder (Appendix ii) and child version for their offspring (Appendix iii) and an expression of interest form (Appendix iv) were given to these patients. Families

then contacted the research team using contact details provided on the Expression of Interest (EOI) form if they were interested in taking part in the research.

8.6.2 Offspring of healthy controls

Following receipt of the favourable ethical opinion, OHC were recruited using the following strategy: Data on the school and year group attended by subjects in the OBP group was collected during OBP recruitment. Parents with BDI and OBP were aware that the author would be approaching other students in the same year group to recruit OHC. With the permission of the head teacher of each of these schools, the author discussed the project during school time to all the children and young people in the same year group attended by subjects in the OBP group. The author explained that the purpose of the study was to better understand how typically developing children and young people think and feel. There was no mention by the author of the participation by subjects in OBP group with other children and young people in their year group at school to ensure confidentiality and privacy. All the students were informed by the author that their parents would need to consent to allow the students' participation in the project. All the children and young people who stated that they would like more information to discuss the study with their parents were provided with appropriate versions of the written information sheets (adult version (Appendix v) and child version (Appendix vi)) and expression of interest form (Appendix iv). The author met all the families who contacted the research team using contact details (telephone, email, post) provided on the EOI Form at a venue and time that was mutually convenient. This strategy was employed with the aim of obtaining a sample of OHC matched with the sample of OBP on age, gender and socio economic status.

8.7 Inclusion criteria

8.7.1 Adults with bipolar I disorder

Clinical diagnosis of BDI, currently euthymic at the time of recruitment, which was confirmed using the Structured Clinical Interview for DSM IV disorders (SCID) (First et al. 2002).

8.7.2 Offspring of bipolar parents

1. Age range: 6 to 14 years of age at the time of testing
2. At least low average intellectual ability to undertake the neurocognitive assessment battery and facial emotion labelling task.
3. Sufficiently familiar with the use of the English language to be able to complete the neurocognitive assessment battery and facial emotion labelling task.

8.7.3 Healthy control parents

Both parents to have had no personal or family history of psychiatric disorder as confirmed by Structured Clinical Interview for DSM IV disorders (SCID) (First et al. 2002)

8.7.4 Offspring of healthy controls

1. Age range 6-14 years at the time of testing
2. At least low average intellectual ability to undertake the neuropsychological assessment battery and facial emotion labelling task
3. Sufficiently familiar with the use of the English language to be able to complete the neuropsychological assessment battery and facial emotion labelling task

8.8 Exclusion criteria

8.8.1 Offspring of bipolar parents

1. Presence of currently recognised medical condition that would impact on neurocognitive functioning and facial emotion labelling task.
2. Substance abuse/dependence

8.8.2 Offspring of healthy controls

1. Presence of currently recognised medical condition that would have impact on neuropsychological functioning.
2. Substance abuse/dependence
3. A personal/family history of psychiatric disorder

8.9 Post expression of interest phase

Once a parent from either OBP or OHC group contacted the research team to express an interest to participate in the project, a mutually convenient time and venue was agreed upon to meet with the parent and young person. At this appointment written informed consent (Appendices vii, viii) from the parent and assent (Appendices ix) from any child 10 years or older participating in the project was obtained. Following this an appointment was made to start the assessment schedule. The families in both groups were offered to have the assessments at Newcastle University, their home or another mutually convenient venue. All families apart from one in the test (OBP) group had the assessments at their home. This one family opted to have the assessment at the Assessment Suite within Child Health at Newcastle University.

8.10 Assessment schedule

8.10.1 Assessments with parents

All parents participating in the research underwent the following assessments in the same order:

The Structured Clinical Interviews for DSM Disorders (SCID) (First et al. 1996) is a semi structured interview. This is a well validated research interview that is frequently used in psychiatric research with adult patients to confirm clinical diagnoses. The interview is largely based on diagnostic criteria laid out in the Diagnostic and Statistical Manual IVth version (DSM-IV) (American

Psychiatric Association 1994). The interview takes about 90-120 minutes to administer.

Washington University version of the Kiddies Schedule for Affective Disorders and Schizophrenia (WASH U KSADS): Psychopathology in the OBP and OHC groups was assessed using the WASH-U-KSADS (Geller et al. 1996). The Washington University version of the Kiddies Schedule for Affective Disorders and Schizophrenia is a semi-structured interview with excellent reliability for mania symptoms, mood diagnoses, rapid cycling patterns and time frames. It is the most widely used instrument in NIMH funded studies of childhood mania (Geller et al. 2002). The interview provides a framework to assess onset, offset, frequency, duration, intensity and specific examples of behaviours. This interview takes between 180-240 minutes to administer.

Hollingshead and Redlich Scale: Parental SES was ascertained from all participants, by using the Hollingshead and Redlich Scale (Hollingshead and Redlich 2007). This is a widely used system that derives a score for SES based upon parental occupation and educational levels (years of education and educational degree earned). Lower parental SES scores indicate higher socioeconomic position. SES was rated for each parent or guardian living in the home. As is standard practice, if there were two parents or guardians in the home, the lowest score (highest socioeconomic position) was used for the analyses (Shashi et al. 2010). The assessment took about 10-15 minutes to complete.

Demographic data was collected on parental gender, severity of parental BDI (presence/absence of psychotic episodes, need for hospitalisation), parental marital status, parental educational qualifications (presented in table 9.1 in chapter 9.2.1).

8.10.2 Assessment with offspring

The subjects in both OBP and OHC group completed the assessment battery (consisting of neurocognitive tests and a facial emotion labelling task) in the same order (see Fig 8.2 for details). The assessment battery has been

described in chapter 6.3.3 and 6.3.4. All assessments were conducted after school hours (3.30 pm-6.30 pm). The assessment took between 90-120 minutes. All children were allowed between 1-2 breaks at designated times. The procedure to maintain the same order of presentation of tasks, at about the same time of day with no more than 1-2 breaks was done to ensure comparability of administration across all subjects in both groups.The assessments with the subjects in both OBP and OHC groups were conducted by research assistants. The research assistants were not blind to group allocation. The details of administration of each task is outlined in chapters 10 and 11.

Figure 8.2 Assessment Schedule with offspring

Assessment Schedule

- **WASI 4**
- **California Verbal Learning Task-Children's Version (Trials 1-5)**
- **Motor Screening Test (MOT) (CANTAB)**
- **Choice Reaction Time (CRT) (CANTAB)**
- **Spatial Working Memory (SWM) (CANTAB)**
- **California Verbal Learning Task-Children's version (Delayed Recall)**
- **Forward Digit Span**
- **Reverse Digit Span**
- **Paired Associates Learning (PAL) (CANTAB)**
- **Stockings of Cambridge (SOC) (CANTAB)**
- **Category Naming Test**
- **DANVA 2**
- **TeaCh Score! Sustained Attention**

8.11 Data analysis

Double data entry was completed and database established. Data for FSIQ, VIQ and PIQ were all converted to standardised scores. However, for all other tests the raw scores were used for data analyses. Mixed-effects models were used to assess differences in the neurocognitive domains and facial emotion labelling of OBP and OHC. Families were grouped according to the bipolar status of their parents. Bipolar status of the parent was designated as random effect. Socio-demographic variables were included as fixed-effects; namely age and gender of the offspring as well as socio-economic status of the family. All analyses were undertaken in the 'R' package for Statistical computing, release R 2.11.1 (R Development Core Team 2010).

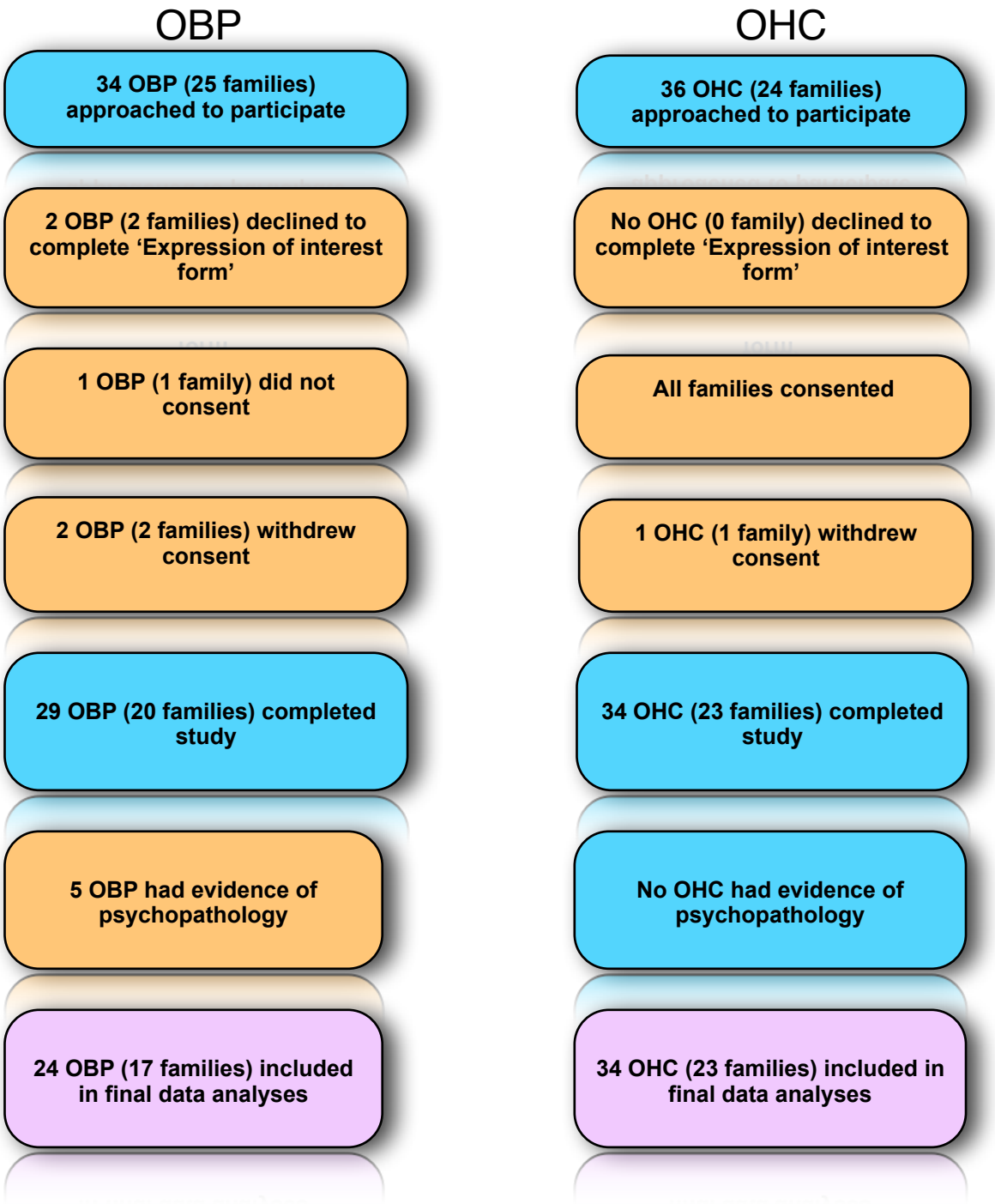
Chapter 9: COMPIC - participants

9.1 Introduction

This chapter will present results and a brief discussion on the recruitment, participants' characteristics (parents and offspring) in the OBP and OHC group.

9.2 Sample characteristics

Fig 9.1 Rates of recruitment of OBP & OHC in the study



9.2.1 Group characteristics

Table 9.1 COMPIC Group characteristics

	OBP (n=17)	OHC (n=23)
Parents		
	(n=17)	(n=23)
M:F ratio	1:16	-
Illness Characteristics		
Psychotic Episodes in	7/17	-
Need for hospitalisation	10/17	-
Marital Status of Parents		
Never married	1(5.87%)	0 (0)
Married/cohabitating	10 (58.87%)	20 (87%)
Divorced/separated	6 (35.26%)	3 (13%)
Educational Status of Parents		
GCSE	3 (17.65%)	1 (4.3%)
A level/Foundation degree	9 (52.94%)	9 (49.1%)
Undergraduate degree	3 (17.65%)	6 (26.1%)
Graduate degree	2 (11.76%)	7 (30.5%)
Socioeconomic status (Hollingshead and Redlich Scale)		
1	1 (5.88%)	1 (4.34%)
2	5 (29.41%)	8 (34.78%)
3	9 (52.94%)	11 (47.83%)
4	2 (11.77%)	3 (13.05%)
Offspring Characteristics		
	(n=24)	(n=34)
M:F	14:10	21:13
Age Range (months)	76-178	76-179
Mean age±SD (months)	141.13±31.89	124.18±28.92

Using the structure of the SCID it was confirmed in 16 families in OBP group that the parent with BD was the mother. The diagnosis of BD was made after the birth of the child or children (under study). This meant that the OBP were not exposed to any psychotropic medication during pregnancy.

9.3 Psychopathology in offspring

9.3.1 Offspring of bipolar parents

5 (17%) OBP had current psychopathology as assessed using the structure of the WASH-U-KSADS. This is described further below:

OBP 1: PDD (Clinical diagnosis) + PBD+ ADHD

Current Treatment: Methylphenidate XL 54 mg mane and Quetiapine 300 mg daily

OBP 2: PDD

OBP 3: Post Traumatic Stress Disorder

OBP 4: ADHD

Current Treatment: Methylphenidate XL 36 mg mane

OBP 5: ADHD and ASD

Current Treatment: Atomoxetine 30 mg mane

9.3.2 Offspring of healthy controls

None of the OHC had any psychopathology on screening using the WASH-U-KSADS.

9.4 Discussion

The target to recruit at least 28 OBP and 28 OHC was achieved. The groups were matched on age, gender and SES demonstrating the strength of the recruitment strategy. There was an unequal number of participants in OBP (n=24) and OHC (n=34) groups included in the final analysis. The ratio of participants to family was, however, comparable in both groups (BD:HC:: 1.41:1.47).

This project recruited OBP from families in which the bipolar proband had a diagnosis of BDI. This strict inclusion criteria has meant that the OBP sample is more likely to be homogenous in relation to the underlying genetic risk for BD. The clinical differences in presentation as well as possible differences in neurocognitive function between BDI and BDII have been previously discussed in chapter 2.4. Further in the sample of OBP assessed in this project only 17% (n=5) OBP had any Axis I/II DSM-IV disorders. Surprisingly none of the OHC recruited and assessed displayed any psychopathology. This is a lower rate than what has been reported previously in data from the USA (Duffy et al. 2007; Birmaher et al. 2009) and Europe (Garcia-Amador et al. 2012; Vandeleur et al. 2012) (previously discussed in chapter 2.15).

One possible explanation is that most previous studies assessing psychopathology in OBP have recruited parents with difficult to treat BD from tertiary specialist clinics. The sample in this project was recruited from community based seconday care adult mental health services. It is likely that the parent probands in this project may have a less severe form (with lower psychosocial morbidity) of BD. This less severe form might contribute better psychosocial suport for the offspring within the family unit which in turn would reduce the risk of additional psychopathology. In the study by Garcia-Amador and colleagues a higher Global Assessment of Functioning score (indicating better psychosocial functioning) in the parent with BD was associated with a significantly lower frequency of axis I disorders in OBP (Garcia-Amador et al. 2012). Another explanation might be that higher rates of psychopathology in OBP are associated with increasing age (Singh et al. 2007). The children in this project were quite young and perhaps, as a result, not displaying symtoms to meet the diagnostic threshold for a recognised disorder.

Given the nature of the neurodevelopmental and mental health diagnoses recorded (PDD, ADHD, PBD, PTSD) in OBP, these disorders may have directly (and indirectly via pharmacological treatment) impacted on neurocognitive function and facial affect labelling. For this reason, an ‘a priori’ decision was made prior to data collection to exclude OBP with psychopathology from the

final analyses (discussed in chapter 6.4.2). This is a particular strength of this project. The 24 OBP included in the final analyses had no evidence of any current/lifetime psychopathology. Previous OBP studies have included OBP with psychopathology (to varying degrees) in their final analyses. Although researchers have attempted to control for the effects of medication and psychopathology by 'within group' analyses, this is likely to have reduced the power of the analysis to detect statistically significant deficits in neurocognitive function and facial emotion labelling. However, although OBP with established psychopathology were excluded from the final statistical analysis, the presence of subsyndromal psychopathology (below the threshold detected on the WASH-U-KSADS) cannot be ruled out as the project did not have rating scales assessing anxiety and mood symptoms. Any such subsyndromal psychopathology may have affected the neurocognitive profile and facial emotion labelling eg sub-syndromal mood symptoms produced small cognitive effects, predominantly on verbal memory (Goswami et al. 2006).

Chapter 10: COMPIC - neurocognitive function

10.1 Introduction

This chapter will focus on the neurocognitive assessment battery: administration of the tests, the mixed models that were used to analyse the data, the results and a discussion of the key findings. The chapter is set out to present the administration of each neurocognitive test, the mixed model that was 'best fit' for the analysis of each aspect studied for a particular test and the results of these aspects for the tests. A power calculation for those tests on which OBP differed statistically from OHC is presented. The overall discussion of the key findings is presented at the end of this chapter.

10.2 WASI 4 (Wechsler Abbreviated Scale for Intelligence)

10.2.1 Administration

WASI 4 consists of 4 subtests: Vocabulary, Block Design, Similarities and Matrix Reasoning (Wechsler 1999). The four subtests comprise the full scale and yield the Full Scale IQ (FSIQ). The Vocabulary and Similarities subtests are combined to form the verbal scale and yield a Verbal IQ (VIQ) score, and the Block Design and Matrix Reasoning subtests form the Performance Scale and yield a Performance IQ (PIQ) Score. The WASI 4 can be administered in about 30 minutes. It takes about 10 minutes to score.

10.2.2 Mixed models

Model building techniques were utilised and the models that best fit for analysis of data were as folows:

- FSIQ~BPD+SES+age+gender+(SES|family) (Appendix x)
- VIQ~BPD+SES+age+gender+(1|family) (Appendix xi)
- PIQ~BPD+SES+age+gender+(SES|family). (Appendix xii)

10.2.3 Result

The results are presented in table 10.1. FSIQ in the OBP had a mean value of 92.75 (SD 11.97; range 74-114) which was significantly lower (p=0.0001) than the FSIQ in the OHC group where the value was 106.94 (SD 16.43; range 77-146). The trend was the same when data was analysed for VIQ; the OBP group had a mean value of 88.25 (SD 12.46; range 74-112) which was significantly lower (p=0.0001) than VIQ in the OHC group (mean=106.35; SD18.27; range 75-142). PIQ in OBP had a mean value of 97.33 (SD 12.87; range 80-126). In the OHC group PIQ had a mean value of 106.12 (SD 14.59; range 79-147). PIQ in OBP was lower than that seen in OHC (p=0.028).

The higher the SES of the children under study the higher the FSIQ scores (p=0.0004). This has been reported previously (Duncan et al. 1994). VIQ too demonstrated a similar relationship with SES (p=0.0001). Similarly, SES was a significant covariate in explaining the variance in the PIQ scores; however the value (p=0.022) was lower than that for FSIQ and PIQ. Age and gender did not statistically contribute to any of the variance in the FSIQ, VIQ and PIQ scores. The former is not surprising given that IQ scores had been coverted into standardised scores (which takes age into account).

Using Mixed Models analysis, no statistical difference (p=0.134) was found in VIQ-PIQ split in both groups. Clinically significant differences between the VIQ-PIQ scores as defined according to the WASI Manual (Wechsler 1999) is a variation of 20 points or more. This was seen in 6 OBP (25%) compared with 5 OHC (14.7%).

Table 10.1 Statistical contribution of covariates to IQ

IQ (WASI 4)				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
FSIQ				
Intercept	129.37	11.43	11.32	0.0000
Parental BD	-15.12	3.83	-3.95	0.0001
SES	-11.07	3.10	-3.57	0.0004
Age	0.06	0.06	1.06	0.29
Male gender	1.23	3.42	0.36	0.72
VIQ				
Intercept	128.96	11.32	11.39	0.0000
Parental BD	-16.83	4.27	-3.94	0.0001
SES	-12.36	3.25	-3.80	0.0001
Age	0.079	0.06	1.27	0.20
Male Gender	-0.12	3.85	-0.03	0.98
PIQ				
Intercept	124.62	10.41	11.97	0.0000
Parental BD	-8.79	3.99	-2.20	0.028
SES	-6.92	3.02	-2.29	0.022
Age	-0.003	0.06	-0.006	0.96
Male gender	0.09	3.46	0.26	0.79

Data was further analysed to calculate effect sizes to estimate the magnitude of difference between OBP and OHC on FSIQ, VIQ and PIQ. This is represented in Table 10.2

Table 10.2 Effect Sizes for FSIQ, VIQ and PIQ

IQ	Cohen's d
FSIQ	-0.62
VIQ	-0.77
PIQ	-0.38

Key finding: subjects in the OBP group had significantly lower FSIQ, VIQ and PIQ compared to OHC. This would imply lower global intellectual function in this sample of OBP studied.

10.3 Motor Screening Test (MOT) (CANTAB)

10.3.1 Administration

Figure 10.1 MOT stimulus

MOT is common to all of the CANTAB test batteries and is administered at the beginning of the CANTAB tests (see chapter 6.3.4 for details of underlying purpose of task). A series of crosses were shown in different locations on the screen. After a demonstration of the correct way to point using the forefinger of the dominant hand, the subject was asked to point to the crosses in turn.

10.3.2 Mixed model

The 'best fit' model used to analyse the data was:

~MOT~BPD+SES+age+gender=(1|family) (Appendix xiii)

10.3.3 Results

Mean latency (mean time taken to touch cross after it appears on the screen) in OBP group had a mean value of 748 milliseconds (SD 9.16; range 581-1600 milliseconds) which was a non-significant finding (p=0.1) in comparison to the OHC group who had a mean value of 711 milliseconds (SD 20.54; range 496-1200 milliseconds). The results from the mixed-models analysis are presented below in table 10.3.

Table 10.3 Statistical contribution of covariates to MOT

MOT (Mean Latency)				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	734	124	5.92	0.0000
Parental BD	70.9	43	1.65	0.1
SES	102	34.20	2.99	**0.003**
Age	-2.80	0.72	-3.88	**0.0001**
Male gender	84.7	45.5	1.86	0.06

A parental history of bipolar disorder did not contribute to any differences in scores between OBP and OHC groups (p=0.099). The SES status of the families in both groups contributed significantly to the scores (p=0.003). The t value of 2.99 indicated that the higher the SES of the family the less time taken by the child to complete the task. Furthermore, the age of the child also contributed significantly to the model (p=0.0001) and a t value of -3.88 indicating that the lower the age of the child the longer they took to complete the task.

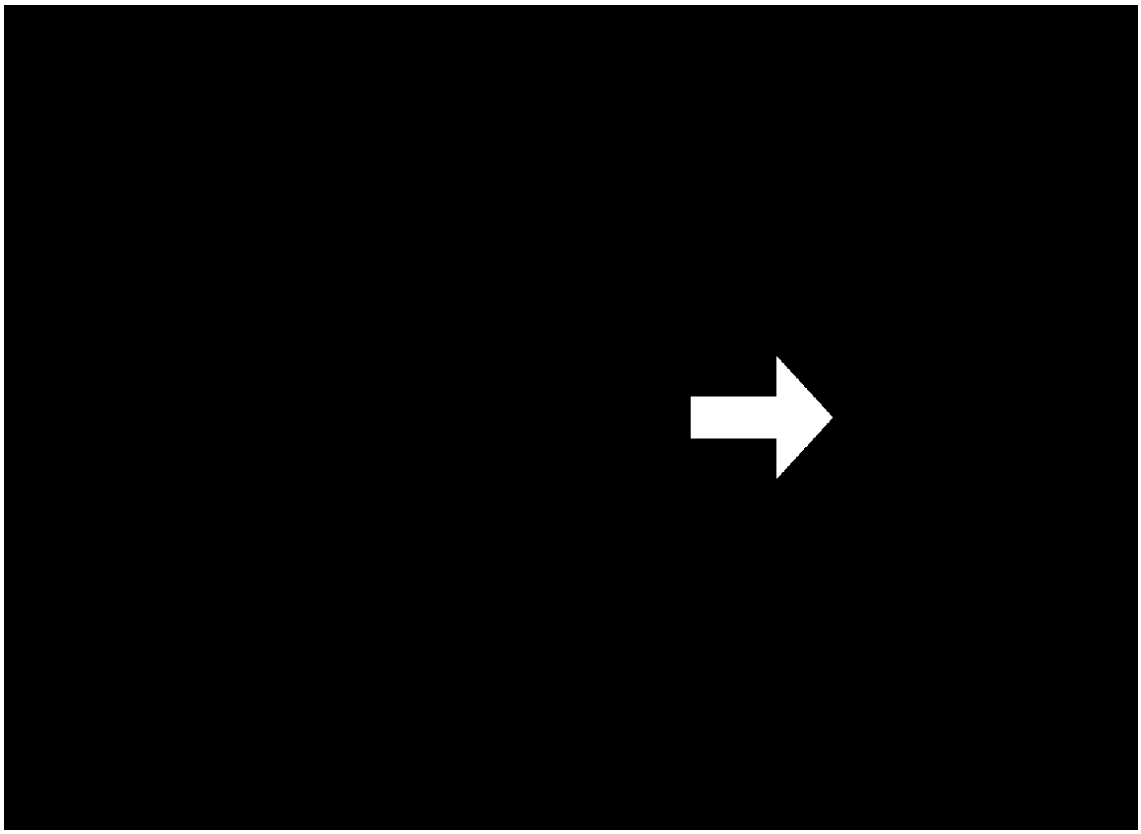
The key finding was that the children in the OBP and OHC group did not differ on their performance on the MOT implying no differences with speed as well as with the use of the CANTAB. The latter finding was

relevant as it confirmed that the subjects under study had satisfactorily 'trained' to use the CANTAB thereby increasing the validity of findings from the other CANTAB tests.

10.4 Choice Reaction Time (CRT) CANTAB

10.4.1 Administration

Figure 10.2 CRT Stimulus



This 2-choice reaction time test has a visual stimulus and response uncertainty, with 2 possible stimuli (left and right) and 2 possible outcomes (left and right press pad buttons). The subject is asked to press the left hand side of the screen or the right hand button on the press pad depending on which side of the screen the stimulus has been displayed (see chapter 6.3.4 for details of underlying purpose of task).

10.4.2 Measures studied

1. Mean Latency (mean latency of response from stimulus apperance to button press)

2. Total Correct Trials (Number of trials for which outcome was correct)

3. Total Commission Errors (Number of trials for which outcome was an error by pressing button too soon ie pressing the button on press pad prior to stimulus presentation)

4. Total Omission errors (number of trials in which outcome was an error by pressing button too lateie pressing the button on press pad after the stimulus presentation)

10.4.3 Mixed models

Mean Latency~BPD+SES+age+gender+(1Ifamily) (Appendix xiv)
Total correct trials~BPD+SES+age+gender+(1Ifamily) (Appendix xv)
Total commission errors~BPD+SES+age+gender+(1Ifamily) (Appendix xvi)
Total ommission errors~BPD+SES+age+genger+(1Ifamily) (Appendix xvii)

10.4.4 Results

The results are presented in table 10.4. The mean latency score in OBP group had an average value of 749 milliseconds (SD 124.69; range 581-1600 milliseconds) which was statistically not significant (p=0.1) in comparison with OHC group who had an average value of 712 milliseconds (SD 123.59; range 496-1200 milliseconds). The number of total correct trials in the OBP group had a mean value of 427 (SD 84.5; range 282-801) which again was not statistically significant (p=0.2) in comparison with the OHC group which had a mean value of 437 (SD 86.71; range 282-825). The number of total commission errors in OBP (mean: 95.3; SD; 21.65; range 25-100) was comparable to that in OHC group (mean: 98.1; SD 22.8; range 91-100) and did not reach the level of statistical significance (p=0.82). The number of total ommission errors in OBP (mean: 0.21; SD 0.09; range: 0-3) was comparable to that seen in OHC (mean: 0.29; SD0.08; range: 0-3) and was not significant statistically (p=0.22).

Table 10.4 Statistical contribution of covariates to Choice Reaction Time

Choice Reaction Time (CANTAB)				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Mean Latency				
Intercept	795.78	67.07	11.87	0.0000
Parental BD	38.48	23.65	1.63	0.1
SES	6.36	18.62	0.34	0.73
Age	-3.06	0.39	-7.9	**<0.0001**
Male gender	11.61	24.33	0.48	0.63
Total Correct Trials				
Intercept	95.38	7.68	12.41	0.0000
Parental BD	-4.70	3.65	-1.29	0.2
SES	-1.07	2.62	-0.41	0.68
Age	0.05	0.018	2.95	**0.003**
Male gender	-1.61	1.02	-1.58	0.11
Total Commission Errors				
Intercept	0.74	0.56	1.32	0.19
Parental BD	-0.04	0.19	-0.23	0.82
SES	-0.2	0.15	-1.28	0.2
Age	-0.0001	0.003	-0.15	0.88
Male gender	0.25	0.21	1.19	0.23
Total Omission Errors				
Intercept	-0.32	2.45	-0.13	0.9
Parental BD	1.46	1.2	1.22	0.22
SES	0.23	0.85	0.27	0.79
Age	-0.003	0.002	-1.62	0.11
Male gender	0.03	0.09	0.35	0.73

Parental BD did not contribute to any differences in the scores of OBP group versus the OHC group (p=0.1) on measures of mean latency. Similarly, parental BD did not contribute significantly to the differences in the scores of OBP versus OHC group (p=0.2) on the number of total correct trials. SES (p=0.73) and male gender (p=0.63) too did not contribute significantly to the model assessing variance on measures of mean latency. Age did provide a statistically significant contribution to the model assessing mean latency as a covariate (p<0.0001). The t value of -7.9 indicated that the younger the child the longer the time duration between stimulus appearing on the screen and the child pressing the button. SES and male gender did not contribute significantly to the model of toal correct trials as covariates. Age did have a statistically significant contribution (p=0.003). The t value of 2.95 indicated that the lower the age of the child the more likely they were to have a higher number of correct trials. None of the covariates under study contributed significantly to the models trying to explain the variance in total commission errors and total omission errors.

The key finding was that the children in the OBP and OHC group did not differ on their performance on the CRT (CANTAB) implying no difficulties in the domain of visual attention. This finding of a lack of difference on attentional tasks between OBP and OHC will be discussed further in the next section 10.5 which focusses on sustained attention.

10.5 TeaCh Score! Sustained attention

10.5.1 Administration

This was a children's version of a well validated measure of sustained attention (see chapter 6.3.2 for details of underlying purpose of task) (Manly et al. 1999). Children had to keep a count of the number of 'scoring' sounds they heard on a tape, as if they were keeping the score on a computer game. Because this seemed so simple and due to the long gaps between the sounds, the task did very little to 'grab' the child's attention. It was, therefore, a good test of the child's ability to *self*-sustain his or her own attention.

10.5.2 Mixed model

The model that best fit was:

~TeaCh~BPD+SES+age+gender+(1|family) (Appendix xviii)

10.5.3 Result

The scores in OBP (mean: 7.6; SD 2.73; range: 1-10) appeared comparable to those seen in OHC (mean: 7.79; SD 2.36; range: 2-10). The results of the mixed models analysis are presented in table 10.5.

Table 10.5 Statistical contribution of covariates to TeaCh

TeaCh Score! Sustained Attention				
Covariates	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	2.08	1.67	1.25	0.21
Parental BD	-0.87	0.58	-1.52	0.13
SES	0.44	0.46	1.0	0.33
Age	0.04	0.01	4.03	**0.0001**
Male gender	-0.62	0.61	-1.02	0.31

Parental BD did not contribute significantly to the model. The OBP and OHC did not differ on their sustained attention scores on the TeaCh (p=0.13). SES and male gender too did not contribute to the model. Interestingly, age (p=0.0001) did contribute significantly. The t value of 4.03 indicates that the higher the age the higher the scores implying that the older children had better sustained attention; a finding seen extensively in both research and clinical settings.

The key finding was that the children in the OBP and OHC group did not differ on their performance on the TeaCh Score! Sustained attention implying no difficulties in the domain of concentration. The OBP and OHC groups did not differ on tasks assessing attention and concentration. This is not keeping with literature emerging from studies assessing attention in euthymic adults with BD where this deficit appears to be a key finding. This will be discussed in section 10.12.3. These findings did mean that the scores on tasks assessing attention and concentration did not need to be included as covariates in further mixed models analyses.

10.6 Digit span: forward, reverse and forward-reverse

10.6.1 Administration: forward digit span

A series of digits were presented to the individual at a rate of 1 digit/ second. The individual had been instructed that the aim of the test was for the individual to remember the order in which the digits had been presented to them. The number of digits requiring remembering increased after every 2 presentations. The score was the maximum number of digits recalled before 2 successive errors had been made (see chapter 6.3.4 for details of underlying purpose of task).

10.6.2 Administration: reverse digit span

A series of digits were presented to the individual at a rate of 1 digit/second. The individual was instructed that the aim of the test was for the them to reverse the order in which they have been presented to them. The number of digits requiring 'reversal' increased after every 2 presentations. The score was the maximum number of digits recalled before 2 successive errors had been made (see chapter 6.3.4 for details of underlying purpose of task).

10.6.3 Mixed models

Analyses were conducted by model building and the 'best fit' models were:
Forward digit span~BPD+SES+age+gender+(1Ifamily). (Appendix xix)
Reverse digit span~BPD+SES+age+gender+(1Ifamily) (Appendix xx)
FR score~BPD+SES+age+gender+(1Ifamily) (Appendix xxi)

10.6.4 Results

The forward digit span in OBP (mean:7.79; SD 2.3; range: 4-13) was comparable to that in OHC (mean: 8.23; SD 2.54; range: 4-14). The reverse digit span in OBP (mean: 5; SD 2.18; range 2-11) was also comparable to that seen in OHC (mean: 5.59; SD 2.26; range 2-12). To get a better estimate of the

ability to manipulate information the difference between the scores on the Forward Digit Span and Reverse Digit Span was calculated. The values for this in OBP group (mean 2.79 digits; SD 2.13; range: -1 to 7 digits) was similar to that in OHC (mean: 2.64 digits; SD 2.33; range: -2 to 7 digits).

Table 10.6 Statistical contribution of covariates to Digit Span

Digit Span				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Forward Digit Span				
Intercept	3.93	1.78	2.2	0.0000
Parental BD	-1.02	0.62	-1.65	0.16
SES	-0.22	0.49	-0.44	0.76
Age	0.04	0.01	3.68	**0.01**
Male gender	0.2	0.65	0.30	0.81
Reverse Digit Span				
Intercept	5.07	1.7	2.98	0.003
Parental BD	-0.87	0.6	-1.46	0.15
SES	-0.74	0.47	-1.57	0.12
Age	0.02	0.01	2.47	**0.01**
Male gender	-0.87	0.62	-1.40	0.16
Forward-Reverse Digit Span				
Intercept	-1.11	1.8	-0.62	0.54
Parental BD	-0.17	0.63	-0.26	0.79
SES	0.53	0.5	1.06	0.29
Age	0.01	0.01	1.29	0.2
Male gender	1.06	0.65	1.63	0.10

Parental BD, SES and male gender did not contribute significantly to any of the models. Age did contribute significantly to the model assessing Forward Digit

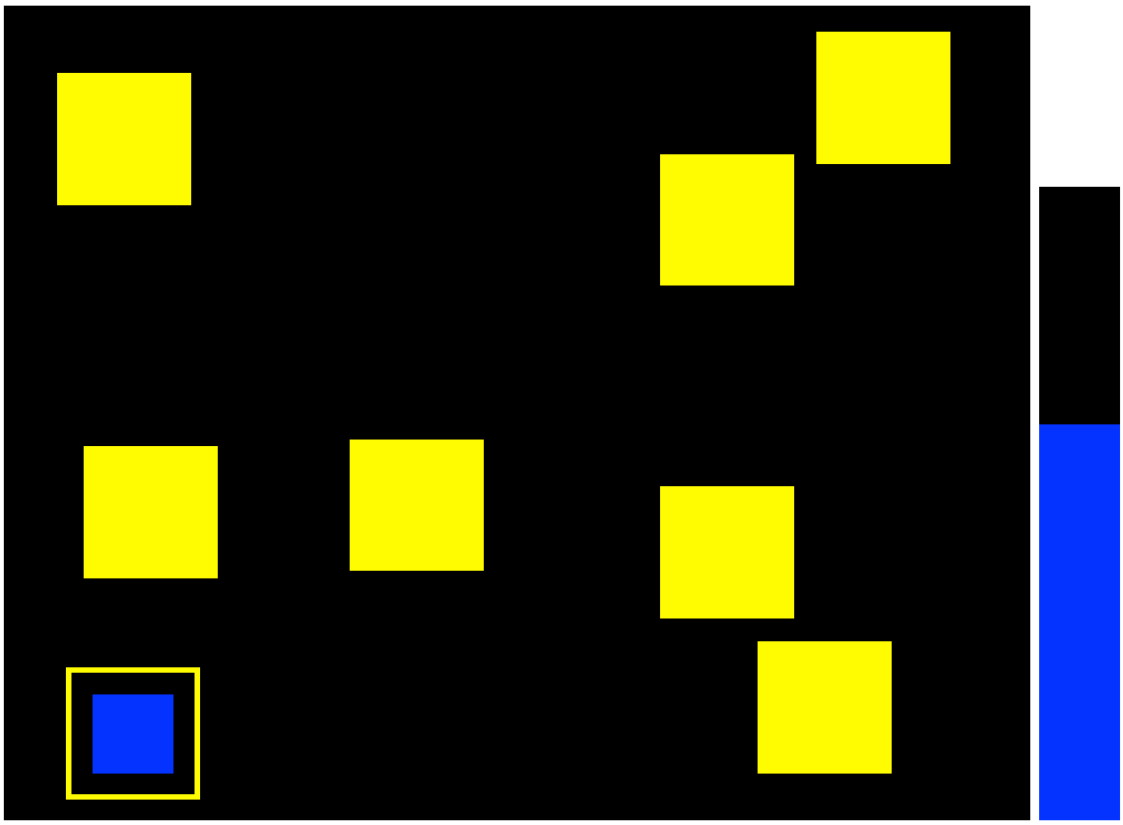
Span (p=0.01) as well as Reverse Digit Span (p=0.01). The latter finding implied that with higher developmental age the better was the ability of the child to manipulate information that had been verbally presented.

The key finding was that children from the OBP group and OHC group did not differ on forward and reverse digit span implying that there were no differences in attention span and verbal working memory.

10.7 Spatial Working Memory (SWM) (CANTAB)

10.7.1 Administration

Figure 10.3 SWM stimulus



A trial began with a number of coloured squares (boxes) being shown on the screen. The overall aim was that the subject had to find a blue 'counter' in each of the boxes and use them to fill up an empty column on the right hand side of the screen. The subject had to touch each box in turn until one opened with a blue 'counter' inside (a search). Returning to an empty box already sampled on this search was an error (see chapter 6.3.4 for details of underlying purpose of task).

10.7.2 Measures studied

1. Between errors total (number of times a box is revisited where a token has already been found)
2. Within errors total (number of times a box is revisited which has already been found to be empty during the same search)

10.7.3 Mixed models

The best fit mixed models used in the analyses were:
SWM BE~ BPD + SES + age + gender + (1 | family) (Appendix xxii)
SWM WE~ BPD + SES + age + gender + (1 | family) (Appendix xxiii)

10.7.4 Results

The score in the OBP group (mean: 39.5; SD 12.64; range: 14-55) was higher for the between errors score than in the OHC group (mean: 32.26; SD 18.22; range: 3-75). The score in OBP group (mean: 1.83; SD 0.54; range: 0-10) for within errors score was higher than in the OHC group (mean:0.94; SD 0.23; range: 0-6).

Table 10.7 Statistical contribution of covariates to SWM

Spatial Working Memory (CANTAB)				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Spatial Working Memory (CANTAB) Between Errors Score				
Intercept	80.34	10.46	7.68	0.0000
Parental BD	12.34	3.62	3.41	**0.0007**
SES	-2.74	2.88	-0.95	0.34
Age	-0.31	0.06	-5.01	**<0.00001**
Male gender	-4.01	3.84	-1.04	0.3
Spatial Working Memory (CANTAB) Within Errors Score				
Intercept	2.44	1.5	1.63	**0.10**
Parental BD	1.12	0.52	2.16	**0.03**
SES	0.26	0.41	0.62	0.54
Age	-0.02	0.01	-1.92	0.05
Male gender	-0.15	0.55	-0.28	0.78

The model indicates that parental BD provided a statistically significant contribution. The OBP group had a statistically higher score on 'between errors total' (p=0.0007) and 'within errors total' (p=0.03) than the OHC group, implying a poor visual working memory. SES and male gender did not contribute any statistical significance in the sample. Age did provide a highly significant statistical contribution to the 'between errors total' score implying that the lower the age, the less developed the visual working memory. Data was further analysed to calculate effect sizes to estimate the magnitude of difference between OBP and OHC on SWM between errors total and within errors total. This is represented in table 10.8

Table 10.8 Effect sizes for SWM

	Cohen's d
SWM between errors total	0.46
SWM within errors total	0.41

The key finding was that the OBP group performed significantly worse than the OHC group on Spatial Working Memory (CANTAB). This demonstrated visual working memory deficits in the OBP group.

10.8 California Verbal Learning Test-Children's Version (CVLT-C)

10.8.1 Administration

This list learning task (Delis et al. 1987) assessed the ability of the participants to learn a list of items to be purchased (i.e. grocery list) over 5 successive learning trials, and then following a single attempt to learn a novel list of items to be purchased, the ability to immediately recall the previously learned words (with and without being cued). After 20 minutes during which unrelated non-verbal tasks are performed, ability to recall (with and without being cued) and recognise the words was again tested (chapter 6.3.4 for details of underlying purpose of task).

10.8.2 Measures studied

1. Level of learning (sum of trials 3-5)
2. Perseverations
3. Intrusions
4. Intrusion perseverations

10.8.3 Mixed models:

Level of learning score~BPD + SES + age + (1 | family) (Appendix xxiv)
Perseverations~BPD + SES + age + (1 | family). (Appendix xxv).
Intrusions~BPD + SES + age + (1 | family) (Appendix xxvi)
Intrusion Perseverations~BPD + SES + age + (1 | family) (Appendix xxvii)

10.8.4 Results

Scores for level of learning in OBP group (mean: 26.21; SD 9.49; range: 6-40) were lower than those in the OHC group (mean:29.71; SD 10.26; range: 4-43). The number of perseverations in OBP group (mean: 4.17; SD 1.45; range: 0-11) was higher than the number in the OHC group (mean: 3.59; SD 0.97; range: 0-13). The number of intrusions in OBP group (mean: 4.29; SD 1.51; range: 0-15) was lower than the number of intrusions in the OHC group (mean: 7.32;

SD 1.93; range: 0-32). The number of intrusion perseverations in OBP group (mean: 0.25; SD 0.07; range: 0-3) was higher than that in the OHC group (mean: 0.18; SD 0.06; range: 0-2).

Table 10.9 Statistical contribution of covariates to CVLT-C

California Verbal Learning Test-Children's Version				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Level of Learning				
Intercept	16.98	6.47	2.62	**0.0087**
Parental BD	-6.48	2.64	-2.45	**0.01**
SES	-2.38	1.86	-1.28	0.2
Age	0.15	0.04	3.64	**0.0003**
Male Gender	2.1	1.67	1.3	0.3
Perseverations				
Intercept	8.55	2.61	3.28	0.001
Parental BD	-3.08	1.76	-1.75	0.08
SES	-1.73	1.29	-1.35	0.18
Age	0.02	0.03	0.56	0.58
Male Gender	1.51	1.21	1.2	0.21
Intrusions				
Intercept	9.94	4.47	2.22	0.026
Parental BD	1.07	1.02	1.04	0.3
SES	-0.67	0.75	-0.9	0.37
Age	-0.03	0.02	-1.46	0.14
Male Gender	0.05	0.01	0.12	0.23
Intrusion Perseverations				
Intercept	0.39	0.38	1.01	0.31
Parental BD	0.16	0.15	1.10	0.27
SES	-0.008	0.11	-0.08	0.94
Age	-0.002	0.002	-0.78	0.43
Male Gender	0.07	0.12	0.08	0.92

The models indicated that parental BD provided a statistically significant contribution to the model (p=0.01). OBP scores on level of learning were lower (t value: -2.45) than those in OHC group providing evidence of deficits in verbal learning. Furthermore age (p=0.0003) also contributed significantly to the model assessing level of learning. This implied that level of learning was higher in the older children (t value: 3.64). SES did not contribute significance to the model. The covariates under study did not contribute statistically to help explain the variance in the scores on models assessing perseverations, intrusions and intrusion perseverations. Although as previously mentioned, OBP had more perseverations and intrusion perseverations than the OHC group this did not reach the level of statistical significance. Further analysis was conducted to assess the effect size of the contribution made by parental BD to the Level of Learning. This is represented in table 10.10.

Table 10.10 Effect Size for Level of Learning CVLT-C

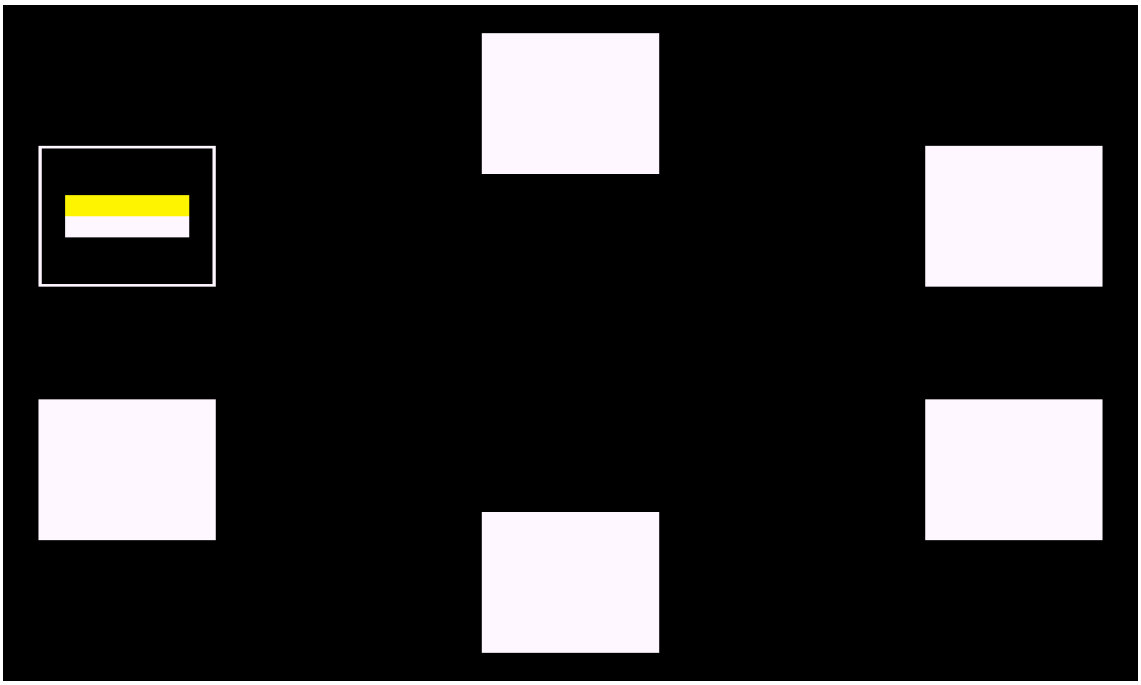
	Cohen's d
Level of Learning	-0.32

The key finding was that the children in the OBP demonstrated statistically significant deficits on CVLT-C in comparison with OHC. This implies neurocognitive deficits in verbal learning.

10.9 Paired Associates Learning (PAL) CANTAB

10.9.1 Administration

Figure 10.4 PAL Stimulus



Six boxes were displayed on the screen. All were opened in a randomised order. One or more of them contained a pattern. The subject was required to remember patterns associated with different locations on the screen, and during the test phase, as each pattern was presented, point to the appropriate location. The test started at a very simple level with only 1 pattern in a box and gradually increased in difficulty to have 6 different patterns in each of the boxes (see chapter 6.3.4 for details of underlying purpose of task).

10.9.2 Measure studied

Mean Trials to Success: Total number of trials required to locate all the patterns correctly in all stages attempted and dividing result by number of successfully completed stages. This particular parameter was selected to provide an overall average of visual learning ability as it included the number of successfully completed stages.

10.9.3 Mixed model

The model that best fit was:
Mean Trials to Success~ BPD + SES + age + gender + (1 | family) (Appendix xxviii)

10.9.4 Results

The score in OBP group (mean: 1.47; SD 0.81; range: 1-3) was higher than that in OHC group (mean: 1.28; SD 0.76; range: 1-2.25).

Table 10.11 Statistical contribution of covariates to PAL

Paired Associates Learning Mean Trials to Success				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	1.91	0.27	7.06	**0.000**
Parental BD	0.29	0.11	2.75	**0.006**
SES	-0.04	0.08	-0.56	0.58
Age	-0.005	0.001	-3.17	**0.002**
Male gender	0.09	0.09	0.99	0.32

The model indicated that Parental BD provided a statistically significant contribution to the model. The OBP group score was higher than that seen in OHC group (p=0.006) indicating that they required more trials to locate the patterns. This implies that deficits in the visual learning tasks (similar to auditory learning (CVLT-C: level of learning)) was statistically lower in OBP group than in OHC group. Age, too provided a statistically significant contribution to the model (p=0.0015). The t value (-3.1690157) indicated that the older children required fewer trials to locate all the patterns and vice versa. SES and male gender did not contribute any statistical significance to the model. Further analysis was conducted to assess the effect size of the contribution made by parental BD to PAL Mean Trials to Success. This is represented in table 10.12.

Table 10.12 Effect size PAL Mean Trials to Success

	Cohen's d
PAL Mean Trials to Success	0.41

The key finding was that the OBP group performed significantly worse than the OHC group on Paired Associates Learning (CANTAB). This implies statistically significant impairment in visual learning in the OBP group.

10.10 Category Naming Test (CNT)

10.10.1 Administration

The subject was asked to generate a list of words belonging to a certain category that had been verbally presented to them. For the 1st attempt the subjects were given the category: Animals and for the 2nd attempt; the category: Boys' names. The individual needed to generate as many items from each category in 60 seconds as they could. For the 3rd attempt, the subjects were asked to generate as many words in 60 seconds as possible but they had to switch between the categories of fruit and furniture and generate words belonging to each of these alternately (requiring them to shift set) (see chapter 6.3.4 for details of underlying purpose of task).

10.10.2 Measures studied

1. Number of correct responses
2. Perseverations

10.10.3 Mixed models

⋆CNTCorrectResponses~BPD+SES+age+gender+(1|family)(Appendix xxix)
⋆CNT Perseverations~BPD+SES+age+gender+(1 | family) (Appendix xxx)

10.10.4 Results

The number of correct responses in OBP group (mean: 41.54; SD 8.72; range: 21-61) was similar to OHC group (mean: 41.5; SD 10.92; range: 11-64). The number of perseverations in the OBP group (mean: 1.5; SD 2.01; range: 0-7) was higher than OHC group (mean: 1; SD 1.37; range:0-5).

Table 10.13 Statistical contribution of covariates to Category Naming Task

Category Naming Task				
Covariates	**Estimate**	**Std. Error**	**t value**	**p value**
Correct Responses				
Intercept	22.57	7.11	3.18	0.002
Parental BD	-2.85	2.84	-1.00	0.32
SES	-1.28	2.12	-0.60	0.55
Age	0.19	0.04	5.15	**<0.00001**
Male gender	-2.05	2.19	-0.94	0.35
Perseverations				
Intercept	1.36	1.33	1.02	0.31
Parental BD	0.57	0.48	1.20	0.23
SES	-0.30	0.37	-0.81	0.42
Age	0.003	0.01	0.34	0.73
Male gender	0.14	0.48	0.29	0.77

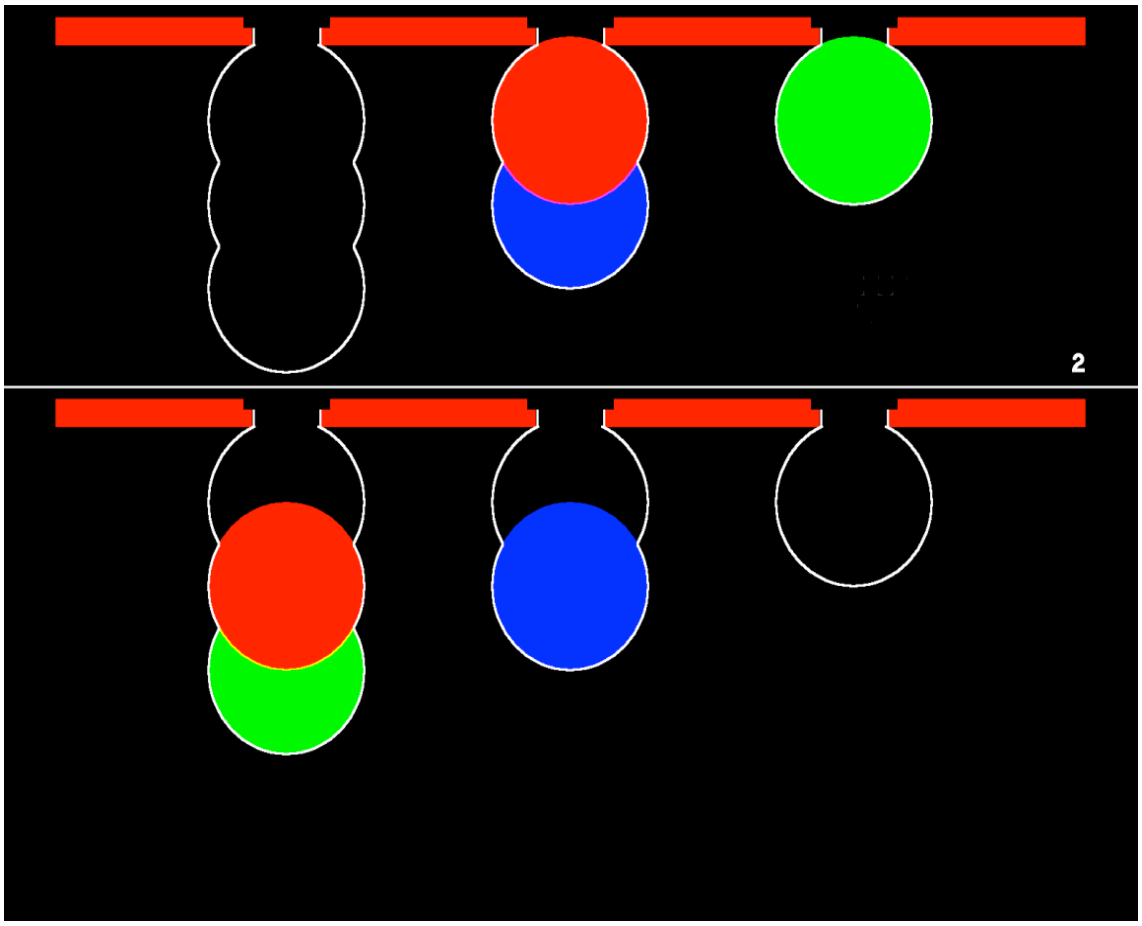
Parental BD, SES and male gender did not provide statistically significant contributions to the aforementioned models. Age, did provide a highly significant contribution ($p<0.0001$) to the number of correct responses. In this sample the older the child; the higher the number of correct responses which from a developmental perspective is what would be expected from such a developmentally varied sample (age range 6-14 years). Although the number of perseverations was higher in the OBP, in the model for perseverations this did not reach the level of statistical significance.

The key findings was that bipolar status of parent did not influence the scores of the offspring on the Category Naming Task, a measure of verbal fluency (an aspect of executive Function).

10.11 Stockings of Cambridge (SOC) (CANTAB)

10.11.1 Administration

Figure 10.5 SOC Stimulus



This was a test of spatial planning based upon the 'Tower of London' test. The subjects were shown 2 displays containing 3 coloured balls. The displays could easily be perceived as stacks of coloured balls held in stockings or socks suspended from a beam. This arrangement was meant to assist subjects to come to grips with some of the rules of the problems which involve 3-D concepts, and to fit in with the verbal instructions. The subject had to use the balls in the lower display in increasing number of stipulated moves to copy the pattern shown in the upper one (see chapter 6.3.4 for details of underlying purpose of task).

10.11.2 Measures studied

1. Minimum Moves (SOC MM) (number of occasions when subjects completed a problem in minimum number of possible moves)
2. Total mean initial thinking time (SOC TMITT) (indicative of time taken to plan solution to the problem)

10.11.3 Mixed models

The models that best fit were:
SOC MM~ BPD + SES + age + gender + (1 | family) (Appendix xxxi)
SOC TMITT~ BPD + SES + age + gender + (1 | family) (Appendix xxxii)

10.11.4 Results

The score for the minimum moves in the OBP group (mean: 7.38; SD 1.66; range: 5-10) was slightly higher than in the OHC group (mean: 7.26; SD 2; range: 3-11) but did not reach the level of statistical significance (p=0.4). The scores for the total mean initial thinking time in the OBP group (mean: 4225; SD 3832.35; range: 596-16,537) was lower in comparison to OHC group (mean: 4507; SD 3939.18; range: 354-19332) but this too was not statistically significant (p=0.16). These are represented in table 10.14.

The model findings were that parental BD, SES and gender did not provide any statistical significance (p=0.4033) to either model. Age did provide a statistically significant contribution to both the minimum moves model (p=0.002) as well as the Total Mean Initial Thinking Time (p=0.0001). This meant that the older the subject the more the likelihood that they would be able to complete the task in the minimum number of moves assigned. Furthermore the older children took longer to start the task after presentation of stimulus on screen which was a measure of the planning time.

Table 10.14 Statistical Contribution of covariates to SOC

Stockings of Cambridge				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Minimum Moves				
Intercept	3.77	1.42	2.65	0.008
Parental BD	-0.46	0.55	-0.84	0.40
SES	0.35	0.42	0.83	0.41
Age	0.02	0.01	3.07	**0.002**
Male gender	-0.73	0.47	-1.58	0.11
Total Mean Initial Thinking Time				
Intercept	-5521.36	2703.83	-2.04	0.041
Parental BD	-1359.16	957.92	-1.42	0.16
SES	595.64	752.33	0.79	0.43
Age	62.87	15.60	4.03	**0.0001**
Male gender	789.74	977.58	0.81	0.42

The key finding was that the bipolar status of the parent did not statistically contribute to the models used to assess executive function deficits.

10.12 Discussion

10.12.1 Principal findings

The principal findings from this study were that OBP differed from OHC in having consistently lower IQ (FSIQ, VIQ and PIQ) on WASI 4 (section 10.2), deficits in visual working memory (as assessed by CANTAB Spatial Working Memory: section 10.7), verbal learning (as assessed by CVLT-C: section 10.8) and visual learning (as assessed by PAL: section 10.9). The groups did not differ on the other neurocognitive assessments. These findings can be summarised as OBP demonstrated deficits primarily in IQ, working memory and learning. The tasks (CVLT-C, PAL, SWM) employed some degrees of strategy formation which might be indicative of some degree of executive function impairment. Interestingly though this was not seen on the SOC which is a more selective measure of the ability to form a strategy. Its unclear why this might be. These key findings using the tests in this project could be potential endophenotypes for BDI.

10.12.2 Full scale, verbal and performance IQ

The study reported significantly lower FSIQ in OBP vs OHC (p=0.0001). These findings provide a UK replication of the results from previous studies that have compared FSIQ between OBP and OHC (Klimes-Dougan et al. 2006; Maziade et al. 2009; Diwadkar et al. 2011). The latter two studies were comparing OSP, OBP and OHC. The most recent study from Turkey matched OBP and OHC on IQ so comparisons are not possible (Deveci et al. 2013). In contrast other studies have reported no difference on FSIQ between OBP and OHC (Waters et al. 1981; Decina et al. 1983; McDonough-Ryan et al. 2002). The study by Waters and colleagues, however, relied on retrospective collection of FSIQ scores conducted by school boards using various IQ assessment techniques (Waters et al. 1981). In the studies conducted by Decina and colleagues and McDonough-Ryan and colleagues it is likely that the sample of OBP recruited was from multiplex families and therefore nested within families violating the assumptions of ANOVA (chapters 6.3.7 and 6.4.3) used for data analysis

(Decina et al. 1983; McDonough-Ryan et al. 2002). Whether the use of an inappropriate statistical technique could explain the findings that differ from those in this project is not certain. This project also reported lower VIQ and PIQ in OBP than OHC. The more recent studies have not reported VIQ and PIQ data so comparisons are not possible (Klimes-Dougan et al. 2006; Maziade et al. 2009; Diwadkar et al. 2011).

The PIQ-VIQ split in OBP vs OHC was also compared as part of a pre-specified plan of analysis informed by the literature. Using mixed models analysis, this difference did not reach statistical significance. This lack of difference replicates the findings reported by previous studies (Waters et al. 1981; Winters et al. 1981; Decina et al. 1983). Further, the PIQ-VIQ split was examined using the technique employed by Kaufman (Kaufman 1979). The WASI manual states that a PIQ-VIQ discrepancy of more than 20 points is clinically significant . In this project, this was found in 25% OBP in comparison with 14.7% OHC. Previous studies using the Kaufman method (Kaufman 1979) reported a higher VIQ when compared to PIQ in a significant proportion of the OBP group compared to OHC group (Kestenbaum 1979; Kron et al. 1982; Decina et al. 1983; McDonough-Ryan et al. 2002). The finding in this study could be explained by the fact that PIQ is more a test of innate ability, whilst VIQ is more likely to be influenced by education and SES, and is also culturally biased (Shuttleworth-Edwards et al. 2004). Although there are studies that question this view and suggest that PIQ too is influenced by levels of education (Rosselli and Ardila 2003). This debate about determinants of PIQ and VIQ could mean the clinically significantly higher PIQ than VIQ in OBP in this project could be the result of other factors not investigated in this project. Further, the scores of FSIQ, PIQ and VIQ were derived from WASI which included 4 subtests. A more comprehensive measure of IQ such as WISC-IV (Wechsler 2004), might have been a more appropriate instrument. The decision to investigate IQ using WASI 4 was based on having a measure of IQ to use as a covariate in the facial emotion labelling task analysis.

As IQ is a summative global measure of discrete neurocognitive function which rely on brain integrity it might be that these deficits on FSIQ, VIQ and PIQ might be a result of the neural connectivity deficits described in BD (Vederine et al. 2011). The clinical implications of these deficits are discussed further in chapter 12.6.2.

10.12.3 Attention and concentration

In this project no difference on tasks assessing attention (CRT) and sustained attention (TeaCh, Digit Span Forward) was observed in OBP in comparison with OHC. The assessment of domains of attention and sustained attention included both verbal (Digit Span Forward, TeaCh) and visual (CRT) tasks. For the Digit Span Forward task, OBP had a mean value of 7.79 digits which was lower than that in OHC (mean 8.23 digits) but this was not statistically significant. On the CRT, robust and detailed analyses using various attentional domains were constructed including mean latency, total correct trials, total commission errors and total omission errors. The mean latency scores on the CRT (i.e. the mean latency of response by subject from stimulus appearance to button press) were higher for OBP group (749 milliseconds) than for OHC group (mean 712 milliseconds) which was not a statistically significant difference (p=0.1).

In this project the OBP and OHC that were included in the mixed models analyses were without any recognised psychopathology and not receiving any psychotropic medication. Neurodevelopmental disorders and mental health disorders as well as psychotropic medication are known to contribute to attentional problems (Ellison et al. 2007). If attentional deficits had been present these would have been required to be controlled for as they might have interfered with performance on neurocognitive tasks such as memory, learning and executive function) and emotion labelling tasks.

Previous studies (section 3.9) assessing neurocognitive function have reported impairment in attention in OBP groups in comparison with OHC (Klimes-Dougan et al. 2006; Maziade et al. 2009; Diwadkar et al. 2011; Deveci et al. 2013). The studies by Klimes-Dougan and colleagues, Maziade and colleagues as well as

Diwadkar and colleagues included OBP with high rates of co-occurring psychopathology including ADHD. Perhaps the presence of co-occurring ADHD was a factor for these reported impairment in attention reported (Balint et al. 2009). In the most recent study by Devici and colleagues, attentional deficits were reported on TMT-A but surprisingly not on TOVA. Both of these assessments measure sustained attention and the inconsistent findings are not discussed by the authors. Rucklidge conducted a study of subjects (aged 14-17 years) with ADHD, ADHD and BD, BD alone and healthy controls using tests of processing speed, memory, executive functioning, set shifting, and inhibition (Rucklidge 2006). The ADHD-only and combined ADHD and BD groups displayed deficits on tasks assessing processing and naming speed, working memory, and response inhibition. These findings add additional support for not including OBP with psychopathology in studies aiming to identify a potential endophenotype in this case for BD. Other studies have assessed adult individuals including those 'at risk' for BD (such as subjects who are a first degree relative of a bipolar proband). These studies did not report attentional deficits in the 'at risk' individuals (Ferrier et al. 2004; Clark et al. 2005; Frantom et al. 2008). A second problem with trying to compare the findings of various studies regarding neurocognitive function is the diverse tests used to assess neurocognitive function by these studies. Although this project attempted to build on the evidence base to allow for comparison of findings between the studies this has been further complicated by the disparate nature of tasks that have been used by studies.

Attentional difficulties are well documented in meta analyses and reviews of neurocognitive function in adults with BD (Torres et al. 2007; Bora et al. 2009; Stefanopoulou et al. 2009; Mann-Wrobel et al. 2011) and PBD (Joseph et al. 2008). This project did not report attentional impairment. Could it be that the attentional difficulties in studies with subjects who have already developed BD are perhaps a consequence of BD or the psychotropic medication. Further research is needed to investigate the development and evolution of these deficits and this is is discussed further in chapter 12.7.

10.12.4 Memory and learning

In this study, OBP displayed statistically significant deficits in visual working memory (SWM), verbal learning (CVLT-C) and visual learning (PAL) in comparison with OHC. In contrast, although the scores for the task assessing verbal working memory (Reverse Digit Span) were lower in OBP (mean 5) in comparison with OHC (mean 5.59) these were not statistically significant ($p=0.15$). On the SWM task comparisons of the performance of OBP and OHC were made on Between Errors Total (SWM: BET) (the number of times a box was revisited where a token had already been found) and Within Errors Total (SWM: WET) (the number of times a box was revisited which had already been found empty during the same search). On both measures the bipolar status of the parents contributed statistical significance (SWM: BET $p=0.0007$; SWM: WET $p=0.03$). Apart from measuring visual memory, this task also relies on the ability of subjects to form a strategy to search for the 'blue tokens' (Curtis et al. 2002). Thus this could also be considered as a measure of an aspect of executive function. Such deficits have also been reported in subjects with damage to the dorsal and ventral prefrontal areas (Owen et al. 1995). This finding of visual memory deficits has been previously reported in some recent studies for adult subjects at risk for BD (Maziade et al. 2009; Diwadkar et al. 2011; Maziade et al. 2011). However other studies have not reported visual memory deficits in OBP (Klimes-Dougan et al. 2006).

On the verbal learning task (CVLT-C) the measures studied were Level of Learning (sum of Trials 3-5), perseverations, Intrusions and Intrusion Perseverations. On the Level of Learning, OBP (mean 26.21) had statistically significantly ($p=0.01$) lower scores than OHC (mean 29.71). This deficit in the ability of OBP to recall verbally presented information might be indicative of fronto-temporal involvement (Salorio et al. 2005). The number of perseverations made by OBP (mean 4.17) were compared with OHC (mean 3.59) but these were found not to reach the level of statistical significance ($p=0.08$). These findings are similar to those reported by Klimes-Dougan and colleagues who reported that OBP had a statistically significant 'short free recall scores' ($p<0.007$) as well as perseverations ($p<0.03$) on the CVLT in

comparison with OHC (Klimes-Dougan et al. 2006). Maziade and colleagues also reported similar deficits on CVLT (p=0.0005) (Maziade et al. 2009). This finding is a replication of the findings reported from the most recent study by Deveci and colleagues that used the RAVLT (p=0.009) (Deveci et al. 2013). The study conducted by Diwadkar and colleagues did not include an assessment of verbal learning so a comparison was not possible (Diwadkar et al. 2011).

Visual learning in this project was assessed using PAL. The specific measure assessed was mean trials to success which was defined as the total number of trials required to locate all the patterns correctly in all stages attempted. Dividing the result by the number of successfully completed stages provided an overall measure of competence in the visual learning domain. The scores in OBP (mean 1.47) was statistically significantly higher (p=0.006) than in the OHC group (mean 1.28) implying that OBP required more trials than OHC to complete the task. This would indicate visual learning deficits in OBP which is a replication of findings from other OBP studies (Klimes-Dougan et al. 2006).

These findings may assist in gaining a better understanding of the possible neural location and neural connectivity changes that might account for the deficits and therefore perhaps provide a better understanding of BD. Studies have indicated that the temporal lobe and amygdala-hippocampus have a role in visuo-spatial learning tasks such as PAL with contribution from the frontal lobe (Owen et al. 1995). Deficits in verbal learning may be associated with abnormalities in the functional connectivity between frontal and mesial temporal systems in patients with PBD (Botteron et al. 1995; Gogtay et al. 2007). Furthermore, structural imaging studies in PBD indicate reduced volumes in medial temporal lobe structures (Blumberg et al. 2003), and recent data from the Chicago group who have used DTI indicate abnormalities in frontotempo-occipital and prefrontal-bulbar tracts among PBD patients that would explain these deficits (Pavuluri et al. 2009).

These learning and memory deficits also implicate dorsal and ventral prefrontal cortex along with the temporo-hippocampal-amygdala region as the neural

connections for these deficits. These finding would be in keeping with the suggestion that an 'Anterior Limbic Network' (ALN) [which includes the prefrontal, subcortical (amygdala and hippocampus) as well as temporal regions of the brain] are key in the pathogenesis of BD (Strakowski et al. 2005). Further the dysfunction demonstrated in the SLF on DTI would also help explain these deficits as its disruption could explain the fronto-temporal disconnect (Vederine et al. 2011).

In a recent study, Drysdale and colleagues studied neurocognitive function in *high-risk* relatives belonging to a single extended family showing linkage of BD to a locus on chromosome 4 (Drysdale et al. 2013). *High-risk* relatives were defined as those that carried the risk haplotype of polymorphic markers, identified in a previous linkage study (Blackwood et al. 1996). This family provides a rare opportunity to investigate aspects of neurocognitive function in a homogeneous sample of relatives with an apparently shared genetic risk factor. Pronounced deficits in the encoding stage of verbal memory (on CVLT) and category verbal fluency were evident in individuals with the risk haplotype. In particular, high-risk related individuals were significantly impaired in the first trial of the word list. The authors suggest that this may be due to a deficit in the encoding of verbal memory. In this project, however, this analysis was not carried out but instead list learning (summation of trials 1-5) was analysed. Future research studies could target dissecting this further by investigating genetic loci and putatively associated neurocognitive tasks.

10.2.5 Executive function

In this project, OBP group did not differ from OHC group in their performance on SOC and CNT. Other studies that have assessed executive function in OBP have not used the same tests as in this study (Klimes-Dougan et al. 2006; Maziade et al. 2009; Diwadkar et al. 2011; Deveci et al. 2013). In the study by Klimes-Dougan and colleagues, deficits on WCST were demonstrated on the number of nonperseverative errors (Klimes-Dougan et al. 2006). One factor that might account for this could be the inclusion of OBP with ADHD. Although the

authors stated that they controlled for the ADHD scores (from DICA) statistically, it is known that children and young people with ADHD demonstrate deficits on the WCST (Romine et al. 2004). Deveci and colleagues also used the WCST but did not find the performance of the OBP any worse than that of OHC (Deveci et al. 2013). Maziade and colleagues also reported executive function deficits in OBP on WCST, letter fluency test and Tower of London task; however 60.9% of the OBP sample in their study had additional psychopathology (previously described in Chapter 3.9) (Maziade et al. 2009). The authors attempted to control for the presence of comorbid psychopathology in a sample size comparable to this study (n=23).

Although the project did not demonstrate any deficits on the tasks assessing verbal fluency (Category Naming Task) and strategy formation (Stockings of Cambridge); it did demonstrate deficits on tasks assessing visual working memory (SWM), verbal learning (CVLT-C) and visual learning (PAL). The latter group of tasks are not specifically assessing executive function. However, there is considerable overlap in their construct as they all have elements which require strategy formation; an aspect of executive function.

10.12.4 IQ as a covariate for neurocognitive function

In this study, an 'a priori' decision had been made not to use IQ as a covariate in the mixed models analysis for neurocognitive function. The reasons for which have been previously discussed in Chapters 3.4.2 and 6.4.4. After the start of this PhD project, 4 related studies have been published. Three of these studies (Klimes-Dougan et al. 2006; Maziade et al. 2009; Diwadkar et al. 2011) have covaried neurocognitive function scores with IQ. The reasons cited by all 3 studies was that in their samples IQ scores were statistically associated with the scores on neurocognitive performance. In the most recent study, the authors matched OBP and OHC on IQ (Deveci et al. 2013). By doing so the authors admit they might have minimised the subtle group differences.

Using the data from this project a regression analysis was carried out to assess the statistical association of IQ with scores for the OBP group (on those tests on which the OBP group differed from OHC group) and this is presented in table 10.15:

Table 10.15 Regression analysis of IQ scores with neurocognitive tests

Correlation of IQ vs	R value
CAVLT Level of Learning	0.26
SWM between errors total	0.04
SWM within errors total	-0.13
PAL mean trials to success	0.17

The lack of significant correlations further strengthen the 'a priori' decision to not use IQ as a covariate in the mixed models analysis of neurocognitive tests.

10.13 Summary

In the OBP sample in this project, deficits in the domains of verbal working memory, visual memory and visual learning have been found with medium effect sizes (Cohen's d ranging from 0.32 to 0.47). No deficits were found in this sample on tasks specifically assessing: attention, concentration and aspects of executive function. However deficits were seen in OBP compared with OHC on CVLT-C, SWM and PAL which although not specifically designed to assess executive function, incorporate aspects of strategy formation. Previous studies have reported attentional difficulties and executive function deficits consistently in adults with BD (Torres et al. 2007; Joseph et al. 2008; Bora et al. 2009; Stefanopoulou et al. 2009; Mann-Wrobel et al. 2011). In the studies that report attentional difficulties and executive dysfunction, this appears to be a result of disruption to the WM neural connectivity. WM changes in corpus callosum and temporal lobe have been reported in OBP in comparison with OHC (Versace et al. 2010; Sprooten et al. 2011). Decreased FA in the SLF was reported by

Frazier and colleagues prior to the onset of BD in OBP (Frazier et al. 2007). These findings suggest that the WM changes evident on DTI antedate the onset of the broader neurocognitive impairment seen after the onset of BD. This suggests that OBP may already have some of the WM changes and the FA reported, without the neurocognitive impairment. This could have clinical implications for early intervention in OBP and needs to be the focus of future research that combines neurocognitive assessment with neuro-imaging (fMRI and DTI).

An attempt was made in the project design to include tests that would be sensitive to assess neurocognitive impairment in specific domains. It should be highlighted, however, that the extent of overlap between the cognitive functions assessed by each test makes any interpretation of the pattern of results speculative (Ferrier and Thompson 2002). For example, the CVLT-C incorporates a strategic (executive) component in that subjects can use semantic organisation of the list to aid performance (Robinson and Ferrier 2005). Significant overlap between verbal learning and executive function has been documented in clinical groups. Duff and colleagues found that these two cognitive domains shared 50–60% of variance (Duff et al. 2005). In particular, this overlap was especially marked for the CVLT (Tremont et al. 2000). The diverse developmental age range (6-14 years) too would have undoubtedly had an impact on these findings. Notwithstanding these potential limitations, the project has furthered the field in the identification of putative endophenotypes for BD which could include tests assessing verbal and visual learning and visual memory.

Chapter 11: COMPIC - facial emotion labelling

11.1 Introduction

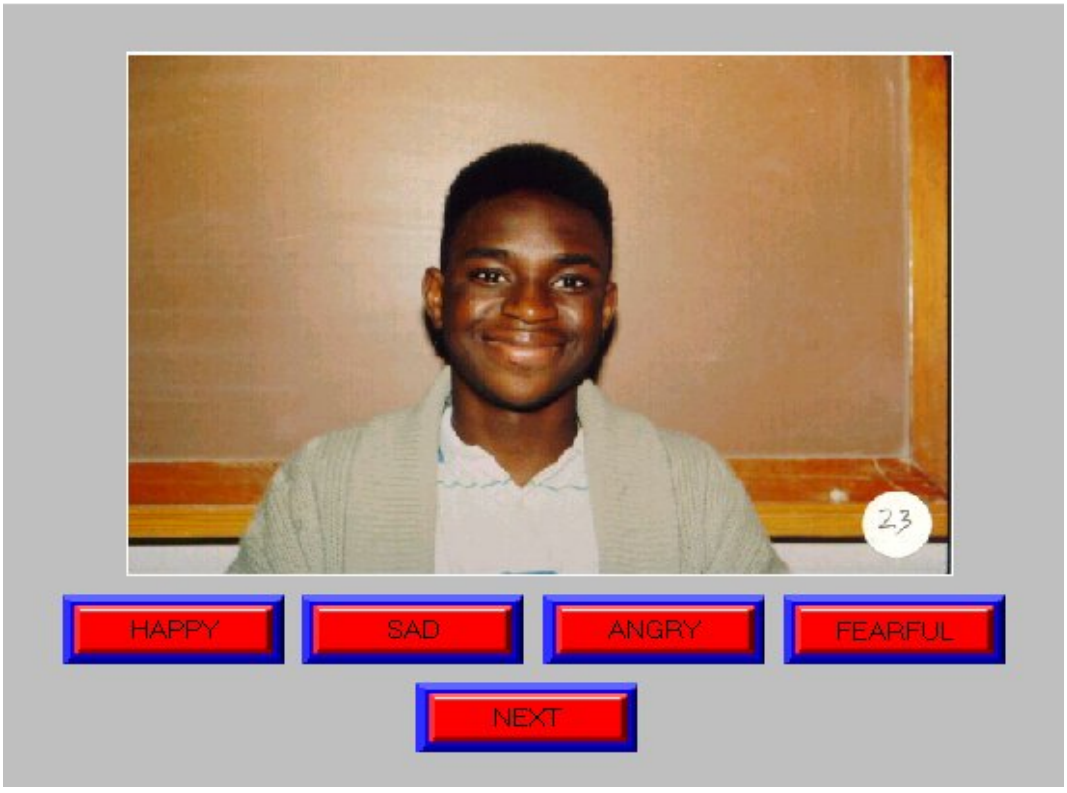
This chapter will present the details of the administration of the DANVA 2 (Nowicki and Duke 1994) used to assess facial emotion labelling. The results from these tests will be presented. The chapter will close with a discussion of the findings.

11.2 DANVA 2

11.2.1 Description and administration

The Diagnostic Analysis of Nonverbal Accuracy DANVA 2 was administered to assess the subjects' ability to recognise four facial emotions: happiness, sadness, anger, and fear. An example of the stimulus is shown in figure 11.1.

Figure 11.1 DANVA 2 Stimulus



The two subtests in the DANVA2 were: Adult Facial Expressions Test (DANVA2-AF) and the DANVA2--Child Facial Expression Test (DANVA2-CF). The DANVA2-AF includes 24 photographs of adult facial expressions of emotions. The DANVA2-CF consists of 24 photographs of child facial expressions of emotions. Facial expressions include an equal number of male and female faces and high- and low-intensity faces. For the present study, the photos were presented to participants on a laptop computer. Each participants was shown an image on the screen and after 2 seconds the 4 possible emotions came on the same screen as options. The participants had to decide whether they thought the expression was happy, sad, angry or fearful and click on the response they thought was the correct one. All participants had the images presented to them in the same order. Responses were recorded on the laptop computer. The possible range for scores on accuracy for the DANVA2-AF is 0 to 24 and for the DANVA2-CF is 0 to 24.

11.2.2 Measures studied

⋆Total number of errors on DANVA (all 4 emotions combined)
⋆Total number of errors Angry faces (DANVA)
⋆Total number of errors Sad faces (DANVA)
⋆Total number of errors Fearful faces (DANVA)
⋆Total number of errors Happy faces (DANVA)

11.2.3 Mixed models

The models of best fit were:
DANVA Errors all emotions~ BPD + SES + IQ + age + male gender + child faces + low intensity + (1I family) (Appendix xxxiii)

DANVA errors Angry faces ~ BPD + SES + IQ + age + gender + child faces + low intensity + (1 | family) (Appendix xxxiv)

DANVA errors Sad faces ~ BPD + SES + IQ + age + gender + child faces + low intensity + (1 | family) (Appendix xxxv)

DANVA errors Fearful faces ~ BPD + SES + IQ + age + gender + child faces + low intensity + (1 | family) (Appendix xxxvi)

DANVA errors Happy faces ~ BPD + SES + IQ + age + gender + child faces + low intensity + (1 | family) (Appendix xxxvii)

11.2.4 Total errors

The number of total errors in the OBP group (mean: 12.13; SD 7.59; range: 3-33) was significantly higher (p=0.03) than in the OHC group (mean: 10.03; SD 4.82; range: 4-26). This is shown below in table 11.1.

Table 11.1 Statistical contribution of covariates to DANVA 2 (total errors)

DANVA 2 Total Errors: 4 emotions combined				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	1.41	0.37	3.86	**0.0001**
Parental BD	0.21	0.10	2.09	**0.03**
SES	0.05	0.07	0.75	0.45
IQ	0.0005	0.002	-0.21	0.83
Age	-0.006	0.001	-4.77	**<0.00001**
Male gender	0.16	0.07	2.17	**0.03**
Child faces	-0.17	0.05	-3.50	**0.0005**
Low Intensity	0.41	0.05	8.42	**<0.00001**

SES and IQ did not contribute to the model even though OBP and OHC groups differed statistically on FSIQ, PIQ and VIQ scores. Other studies using the DANVA in 'at risk; subjects have used IQ as a covariate in analyses (Brotman et al. 2008). The study by Baum and colleagues however did not report any

contribution made by IQ scores to the ability of individual to label facial emotion (Baum et al. 1996). Age of the subject contributed to the model ($p<0.00001$; t value: -4.7680) implying that the older the child the lower the number of errors made in recognising facial emotions. This is in keeping with the theory of development of ability to label facial affect with age. The groups were also not as good at labelling facial emotions when shown child faces as compared to when shown adult faces ($p<0.0005$). The intensity of stimulus also contributed statistically to the model ($p<<0.0001$) implying that children made a higher number of errors when shown stimuli of low intensity as when compared to stimuli of high intensity.

11.2.5 Errors by emotion

The number of errors whilst labelling angry faces in OBP group (mean: 4.41; SD 2.11; range: 1-9) was higher than in OHC group (mean: 3.91; SD 1.93; range: 0-9); however this was not significant ($p=0.21$). The number of errors whilst labelling sad faces in OBP group (mean: 2.04; SD 3.2; range: 0-10) was not statistically different ($p=0.64$) from OHC group (mean: 2.12; SD 2.8; range: 0-8). The number of errors whilst labelling fearful faces in OBP group (mean: 4; SD 3.2; range: 1-12) was significantly higher ($p=0.04$) than in OHC group (mean: 3.09; SD 2.4; range: 0-11). The number of errors whilst labelling happy faces in OBP group (mean: 1.21; SD 1.97; range: 0-8) was higher than in OHC group (mean: 0.79; SD 1.31; range: 0-4) but this did not attain statistical significance ($p=0.15$).

SES and IQ did not provide statistical significance as covariates to help explain the variance in errors for any of the 4 emotions. Age provided statistically significant contribution as a covariate for sad, fearful and happy faces but not angry faces. This means that the lower the age of the subject the more errors they made on recognising the emotion correctly when presented with happy, sad and fearful faces. Male gender of the subjects being assessed and child faces as stimuli were statistically significant covariates for sad and fearful faces but not happy or angry faces. Male subjects made more errors labelling emotion when presented with sad and fearful faces. This is displayed in table 11.2.

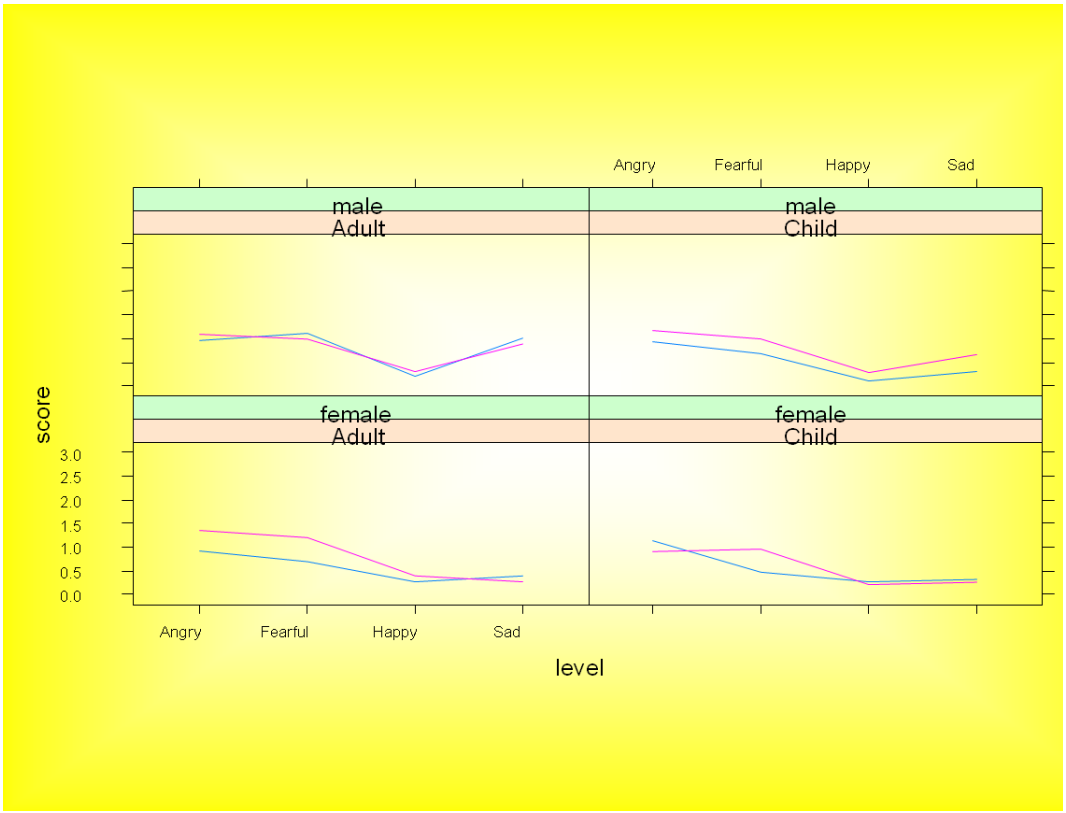
Table 11.2 Statistical contribution of covariates to specific emotions

DANVA 2 Errors by Emotion				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Angry				
Intercept	0.54	0.65	0.82	0.41
Parental BD	0.22	0.17	1.26	0.21
SES	0.06	0.12	0.50	0.62
IQ	0.002	0.004	0.39	0.70
Age	-0.003	0.002	-1.33	0.19
Male gender	-0.0009	0.14	-0.007	1.0
Child faces	-0.03	0.10	-0.26	0.80
Low intensity	1.0	0.10	9.86	**<0.00001**
Sad				
Intercept	1.74	0.62	2.79	0.005
Parental BD	0.08	0.17	0.47	0.64
SES	-0.03	0.12	-0.22	0.83
IQ	-0.003	0.004	-0.86	0.39
Age	-0.007	0.002	-3.15	**0.002**
Male gender	0.46	0.13	3.47	**0.0005**
Child faces	-0.33	0.10	-3.54	**0.0004**
Low intensity	-0.09	0.09	-0.93	0.35
Fearful				
Intercept	1.1	0.72	1.53	**0.13**
Parental BD	0.40	0.20	2.00	**0.04**
SES	0.15	0.14	1.07	0.29
IQ	0.0009	0.005	0.20	0.84
Age	-0.009	0.003	-3.60	**0.0003**
Male gender	0.30	0.15	1.99	**0.047**
Child faces	-0.25	0.10	-2.50	**0.013**
Low intensity	0.46	0.10	4.56	**<0.00001**
Happy				
Intercept	0.93	0.37	2.5	0.01
Parental BD	0.14	0.10	1.44	0.15
SES	0.02	0.07	0.34	0.73
IQ	-0.002	0.002	-0.71	0.48
Age	-0.005	0.001	-4.00	**0.0001**
Male gender	-0.11	0.08	-1.33	0.18
Child faces	-0.09	0.06	-1.50	0.13
Low intensity	0.29	0.06	5.10	**<0.00001**

Furthermore, subjects made more errors when presented with child faces as stimuli when the emotion to be recognised was sad and fearful. Subjects of a male gender making more errors labelling affect has been previously described

in young adults as well as adolescents (Mufson and Nowicki 1991; McClure 2000). Low intensity stimuli covariate contributed significantly to the models for angry, fearful and happy emotions. This implied that the subjects made more errors when presented with low intensity stimuli for these emotions than when presented with high intensity stimuli.

Figure 11.2 DANVA 2 results by emotions



Further analyses were conducted to assess the effect size of the contribution made by parental BD to DANVA: errors on all emotions combined and DANVA: errors on fearful faces. This is represented in Table 11.3.

Table 11.3 Effect sizes for DANVA 2

	Cohen's d
DANVA: errors on all emotions combined	0.34
DANVA: errors on fearful faces	0.34

The key finding was that OBP made more errors than OHC in labelling facial emotion not only on all 4 emotions combined but also specifically when presented with fearful faces.

11.3 Discussion

11.3.1 Total errors

This project reported that bipolar status of parent had a statistically significant contribution to the number of errors made by the offspring in this study i.e. OBP made more errors in labelling and identifying facial emotion (across all 4 emotions *viz.* happy, sad, fearful and angry) with a medium effect size (Cohen's d=0.34). This finding that subjects in the OBP group made more errors in facial emotion labelling compared to subjects in the OHC group is a replication of the finding previously reported by the NIH group (Brotman et al. 2008). The recent study by the Stanford group did not report this finding (Whitney et al. 2013). However in this study all the OBP had psychopathology (as per inclusion criteria).

In the NIH study, 3 groups were studied: subjects with PBD, subjects 'at risk' for BD and HC. The subjects with PBD and those 'at risk' for BD did not differ from each other in the ability to label facial emotion using the DANVA. This study did not (by design) include a group of adolescents with BDI. This project adds to the evidence base by increasing the robustness of the findings as the 'at risk' group included OBP whereas in the NIH group the group consisted of both OBP (n=10) and siblings of adolescents with BDI (n=14). The degree of genetic loading and vulnerability in siblings of adolescents with BDI and OBP could be different and therefore might have influenced the results, however, this has not been examined yet. Furthermore, in this project all 23 OBP, included in the analysis did not have recognised psychopathology. Another mental health/ neurodevelopmental disorder such as anxiety, ADHD, ASD could have contributed to errors seen in 'at risk' samples as in previous studies (Brotman et al. 2008; Whitney et al. 2013).

11.3.2 Errors by emotion

Further analyses identified that OBP made most errors labelling fearful facial emotions compared with OHC (p=0.04; Cohen's d=0.34). This finding has been reported in studies of adults with BD (Lembke and Ketter 2002; Venn et al. 2004) and in adolescents with BD (Rich et al. 2006; Dickstein et al. 2007). In a recent study by the NIH group subjects with PBD, subjects 'at risk' for BD (siblings of subjects with PBD and OBP) and HC were asked to rate their fear of fearful faces (Olsavsky et al. 2012). Both PBD and unaffected at-risk subjects exhibited amygdala hyperactivity vs. HC on fMRI. The authors hypothesise that amygdala activation specifically to fearful faces may be an endophenotype for BD. However, in two other NIH studies of youth 'at risk' for BD, errors when labelling specific facial emotions was not studied (Brotman et al. 2008; Brotman et al. 2008).

Roberts and colleagues studying youth (18- to 30-year-olds) at risk for BD demonstrated reduced brain signal of the left IFG when inhibiting responses to fearful face stimuli, compared with subjects from control families (Roberts et al. 2012). The differential IFG response was not related to behavioral performance, current mood state, or use of psychotropic medications. This is an interesting finding when combined with data from this project. One interpretation might be that the failure to inhibit responses to fearful faces in the study by Roberts and colleagues was due to an inability to recognise fear (Roberts et al. 2012). This lends further credence to the hypothesis that the aetiology for the development of BD may lie in the neural (dys)connectivity between prefrontal and subcortical limbic structures. The deficit in the neural disconnect might be the lack of inhibition to the limbic structures (in particular the amygdala largely implicated in recognition of fear) by the frontal areas in BD. However, a recent fMRI study has demonstrated that the largest BOLD signal might be in the medial prefrontal area as well as the putamen (Surguladze et al. 2010). Indeed the role of the amygdala in processing fear threats may not be as prominent as previously thought as recent evidence suggests that it may respond to a wide range of emotional facial expression (Fitzgerald et al. 2006).

11.3.3 Errors by intensity of stimulus

This project reported more facial emotion labelling deficits when subjects were presented with low intensity stimuli ($p<0.00001$). Further analyses demonstrated that low intensity stimuli contributed significantly to the models when analysing data for specific emotions viz. happy, fear and angry but not sad faces. These findings replicate findings reported by the NIH group (Brotman et al. 2008; Brotman et al. 2008). In the first study by Brotman and colleagues which also used the DANVA with subjects 'at risk' for BD, the 'at risk' participants made more errors on labelling facial emotions when shown low intensity stimuli (Brotman et al. 2008). In the second study the NPBD and adolescents 'at risk' for BD required a higher intensity of stimuli before being able to identify facial emotion correctly on the emotional expression multimorph task (Brotman et al. 2008). This finding has also been reported in adolescents with BD (McClure et al. 2003).

This is an important finding as in real life situations faces show subtle variations in expression; people rarely display extremes of emotion (Schepman et al. 2012). The higher rates of errors on 'low intensity' stimuli in the OBP sample under study in this project may translate to an inability to identify the subtlety in emotional variations of real life. This, in turn, could impact on psychosocial function which could contribute to the vulnerabilities (memory and learning deficits) in such a sample.

11.3.4 Errors: child vs adult stimuli

Turning to the analysis of child faces as stimuli. More errors were made by OBP than OHC when subjects were presented with 'child faces' ($p=0.0005$). This has been previously reported in studies assessing adolescents 'at risk' for BD (Brotman et al. 2008) as well as adolescents with BD (McClure et al. 2003). This is an important finding that should influence choice of test stimuli in further research studying facial emotion labelling in adolescents at risk for BD. The NIH group have been developing the the NIMH Child Emotional Faces Picture Set

(NIMH-ChEFS) which may be helpful as a social cognitive remediation strategy and will be discussed further in chapter 12.6.3 (Egger et al. 2011). Also clinically, young OBP (as in this project) spend a considerable amount of time interacting with peers. A deficit in face emotion labelling on 'child faces' could also add to the vulnerabilities in these youth. How this might impact on the trajectory of emotional processing in OBP needs careful evaluation.

11.3.5 Other factors

Age and gender (male) of the subjects (in both OBP and OHC) made a statistically significant contribution to the number of errors made in the facial emotion labelling task. Studies have identified that with increasing age the ability to recognise and label facial emotions continually improves (Boyatzis et al. 1993). Further, data from typically developing subjects indicates that the ability to recognise *different facial emotions* develops at different stages in the lifespan (De Sonneville et al. 2002). However, other authors have reported that face emotion labelling deficits are not related to the age of onset in adults with BD (Bozikas et al. 2006) or with current age at time of assessment in NPBD (Rich et al. 2008). Some authors have stated that age (particularly older than 6 years) does not improve face emotion labelling (for the 6 basic emotions) (Markham and Adams 1992; McClure 2000). There is therefore, uncertainty about the impact of age on face emotion labelling.

Turning to gender and its association with face emotion labelling, a meta-analytic review by McClure focussing on facial emotion processing in infants, children and adolescents reported that males make more errors in labelling face emotion (McClure 2000). In an NIH study, using the emotional expression multimorph task males with NPBD too labelled face emotions at a higher intensity than female subjects (Rich et al. 2008). Further studies investigating facial emotion labelling should bear these factors (age and gender of subjects) in mind, when choosing face emotion labelling tasks and designing study protocols.

11.4 Summary

The project has demonstrated that the OBP made more errors (across all 4 emotions) in comparison with OHC. In particular OBP made more errors in recognising fearful faces. DTI studies have identified ILF and IFOF as areas demonstrating AF in BD (Vederine et al. 2011). These areas have been implicated in the ability to label facial emotion (Philippi et al. 2009). It could be that the deficits identified in this project are endophenotypes for BD or perhaps are behavioural products of brain changes (eg WM changes) which could be the putative endophenotype for BD.

Chapter 12: Discussion

This concluding chapter will consider the principal findings from the project, and present the results from secondary analyses on the relationship between neurocognitive function and facial emotion labelling tasks. This is followed by a general discussion about whether the project was able to meet the original aims and hypotheses. The strengths and limitations of this project are reviewed and consideration is given to how research in this field could be taken forward.

12.1 Principal findings

The key findings from this project were that the OBP group had lower scores than the the OHC group on FSIQ, VIQ and PIQ (as measured by WASI 4). In addition the OBP group demonstrated deficits on tasks assessing Visual Working Memory (as measured by the Spatial Working Memory task of CANTAB), Verbal Learning (as measured by California Verbal Learning Test-Children's version: Level of Learning), Visual Learning (as measured by the Paired Associates Learning) in comparison with OHC. Further, the OBP group made more errors labelling facial emotions using the DANVA; in particular in labelling fearful emotions when this was compared to subjects in the OHC group. Mixed models analysis using R software was utilised in analysis and this allowed the project to report statistical significance with low to medium effect sizes. The OBP and OHC groups did not differ on assessments of attention, sustained attention, verbal working memory (as measured by Reversed Digit Span) and some aspects of executive function (verbal fluency assessed by Category Naming Test and visual planning assessed by Stockings of Cambridge).

This is the first UK project which has assessed these aspects of neurocognition and emotional processing in OBP. In addition, to the best of the author's knowledge, no other published research has reported results of a neurocognitive assessment battery and facial emotion labelling tasks in the same group of offspring of adults with bipolar I disorder (free from

psychopathology and not on any psychotropic medication) in comparison with offspring of healthy controls. These findings are novel and potentially make an important contribution to the scientific literature.

12.2 Neurocognitive deficits and facial emotion labelling deficits

This section discusses the relationship between neurocognitive deficits and face emotion labelling deficits identified and discussed in chapters 10 and 11. Few studies have assessed this. In Chapter 5.2, two studies were considered that have assessed neurocognitive function and facial emotion labelling tasks (and their association) in the same groups of subjects with BD (Addington and Addington 1998; Summers et al. 2006).

12.2.1 Impact on each other

Regression analyses were used to study the association between neurocognitive tasks and the facial emotion labelling tasks in OBP and OHC. This analysis was restricted to those domains of neurocognition on which OBP statistically differed from OHC. This is presented in table 12.1.

Table 12.1 Correlational analysis of Facial Emotion Labelling & Neurocognitive Measures

	DANVA Total Errors (Pearson's r; p value)	DANVA Fearful (Pearson's r; p value)
CVLT-C	**-0.37; 0.08**	**-0.25; 0.25**
SWM Between Errors	**-0.002; 0.99**	**0.02; 0.93**
SWM Within Errors	**-0.26; 0.23**	**-0.25; 0.25**
PAL	**0.26; 0.23**	**0.16; 0.47**

There was a low negative correlation with a trend towards statistical significance using 2 tailed analysis (r=-0.37; p=0.08) between CVLT-C Level of Learning and DANVA total errors. This suggests that in this project verbal learning deficits had a weak correlation with the ability to identify facial emotions correctly. None of

the other correlational analyses were at a significant level as shown in the table 12.1. These findings are not in keeping with the 2 other studies that have investigated the strength of statistical association between aspects of neurocognitive deficits and facial emotion processing (Addington and Addington 1998; Summers et al. 2006). Both these studies were conducted after the onset of BD in the adult participants. The confounding variables include the WM changes seen with progression in BD as well as psychopharmacology to manage BD.

The weak statistical association reported in this project (see table 12.1) suggests that the neurocognitive deficits and facial emotion labelling deficits seen in OBP in comparison with OHC might be unrelated. This would appear to support the third null hypothesis as listed in chapter 7.2. However, there are important factors that need to be considered when attempting to interpret this apparent independence. Firstly, the reduced recruitment to the OBP group led to a possible lack of power. This potential reduction in statistical power would influence the ability to test the null hypothesis thereby reducing the level of confidence in stating true independence. Secondly, the assessment battery was administered in a fixed order to the participants in both groups. It was not possible to ascertain whether this fixed order affected (improved or hindered) the performance of the subjects. Furthermore, there is a lack of information about the test reliability data for several of the CANTAB tests especially for the younger participants. These factors need to be considered whilst interpreting the results of the regression analyses that suggest independence of these domains.

12.2.2 Neural basis

The key findings from neuroimaging studies in BD were previously presented in chapter 5.4.2. It was suggested that multiple brain areas including the temporal lobe, dorsolateral and ventrolateral prefrontal cortex abnormalities along with their connections to the subcortical structures (amygdala, hippocampus and thalamus) may be critical in the development of BD. More recently, there has

been increasing interest in neural connectivity. Vederine and colleagues reported WM changes and FA using DTI implicating the ILF, IFOF and SLF as important tracts that may be involved in the development of BD (Vederine et al. 2011). These initial findings may, however, be insufficient to establish a specific neural basis for BD (Kuiper et al. 2013). This could be due to the variability in reported findings between studies and the fact that to date studies have only been conducted in adults with BD, young people with BD and the few that have assessed children and young people at risk for BD. This means that it is not possible yet to identify a specific neural location for BD although there is considerable interest in several candidate areas and their connections. In this project, the neurocognitive deficits in learning and memory were not statistically associated with the facial emotion labelling deficit seen in the subjects in the OBP group albeit with the limitations outlined in section 12.2.1. The lack of a significant finding on the regression analysis cannot exclude a possible commonality of neural basis with regards to multiple related brain areas and their connections. However, this project did not include an imaging component. Further, no study has reported this proposed mechanism of a common neural basis for neurocognitive deficits and facial emotion labelling deficits in OBP. Future studies that assess neurocognitive function and facial emotion labelling in combination with neuroimaging in OBP will expand the understanding of the neural basis of BD (section 12.7.3).

12.2.3 Inference from findings

Intact neurocognitive function and social cognitive function are critical to cognitive and behavioral self-control (Doyle et al. 2009). In subjects (both adults and youth) with BD compromised performance on these domains could represent sequelae of residual mood (sub-syndromal) symptoms, a degenerative process related to the illness or a consequence of treatment (Doyle et al. 2009). The deficits seen in this project on aspects of neurocognition and face emotion labelling task make the author ask the question whether this impaired performance reflects the underlying risk for BD?

Underlying deficits such as those identified in the project could lead to difficulties with goal attainment and be perceived as goal thwarting leading to a feeling of being frustrated. There is some evidence that subjects diagnosed with BD stay engaged in efforts as goals become more difficult (Harmon-Jones et al. 2008). The NIH group have studied frustration inducing tasks in PBD in comparison with HC and reported a more adverse affective response to negative feedback in the frustrating context than controls (Rich et al. 2005; Rich et al. 2007; Rich et al. 2010). While not a measure specifically of irritability, this result suggests that subjects with PBD were more upset by the frustration-inducing condition than were HC. In another study, Harmon-Jones and colleagues studied goal frustration among students at risk for mania (Harmon-Jones et al. 2002). They asked students to listen to pilot radio broadcasts in which the broadcaster described upcoming serious tuition increases at their school. In this study, proneness to mania was associated with greater anger. Deficits in neurocognition and emotional processing might therefore contribute to the development of BD in OBP.

Deficits in memory, learning and face emotion labelling may interfere with the ability to process information from the environment. The fact that these are present at a developmentally crucial phase suggests a neurodevelopmental model for the development of BD. Intact neurocognition and face emotion processing are some of the aspects which in conjunction with known rules and expectations, identify pro-social options for behavior and disregard provocative or distracting stimuli. Whether this disruption contributes to the development of BD requires careful evaluation in longitudinal studies.

Learning and memory difficulties are thought to underlie socio-emotional disturbances because the ability to store information and recall information without bias subserves the ability to remember an emotion or integrate past positive and negative emotional experiences (Showers and Zeigler-Hill 2007). Memory capacity may play an important contributing role in emotion abnormalities because smaller memory span could reduce the aptitude to learn, to analyse different perspectives concurrently, or to carry out tasks or make immediate decisions (Van Rheenen and Rossell 2013). This mechanism of

interaction between aspects of learning, memory and emotion processing may be a possible pathway in the development of BD. Further evidence for this is suggested by the fact that memory, learning and emotion processing are pathophysiologically influenced by the dopamine and serotonin neurotransmitter circuits (Canli and Lesch 2007) and these circuit have also been posited to be involved in the pathogenesis of BD (Cousins et al. 2009).

There is considerable evidence to suggest the role of dopamine (Cousins et al. 2009) and serotonin (Mahmood and Silverstone 2001) in the development of BD . The COMT gene codes for a protein that catabolises a range of catechol chemicals including dopamine, and is implicated in its synaptic degradation (Van Rheenen and Rossell 2013). It is located in a bipolar candidate region on chromosome 22 and is well recognised as a candidate gene in the pathogenesis of BD (Jones and Craddock 2001; Shifman et al. 2004; Burdick et al. 2007). Similarly, BD has been associated with abnormal levels of 5HT and given that TPH2 is the first and rate limiting enzyme in the biosynthesis of 5HT, it has been considered to be a viable candidate gene in the disorder (Wiste et al. 2008). There has been some studies providing evidence to link the gene for TPH2 to BD (Cichon et al. 2008; Roche and McKeon 2009). Other studies have refuted this (Campos et al. 2010; Serretti et al. 2011).

There is growing evidence to suggest that COMT is associated with neurocognition (Farrell et al. 2012) and emotional functions including emotion processing and emotion regulation (Bevilacqua and Goldman 2011). TPH2 polymorphisms G844T and G703T have been linked to the amygdala, a neural structure implicated in the processing of emotion (Adolphs et al. 2002; Phillips et al. 2003). In another study, carriers of the T allele of TPH2 demonstrated more activation of the putamen in response to fearful faces than in non carriers (Canli et al. 2008).

The behavioural expressions of COMT and TPH2 have been frequently associated with the BD phenotype (Van Den Bogaert et al. 2006). A possible pathway for the development of BD pathology in which genetic variants of the serotonin and dopamine systems contribute susceptibility to abnormal prefrontal

neurocognitive function which oversees the processing and regulation of emotion (Van Rheenen and Rossell 2013). This hypothesis would explain at least some of the overlap of symptoms amongst several disorders. For example, disruption in the circadian rhythm is a potential endophenotype for BD (Lenox et al. 2002). GSK3-B is involved in the regulation of circadian rhythm and also implicated in lithium action (Kaladchibachi et al. 2007). It has been tied to BD but not with disorders such as ASD which are also exemplified by neurocognitive and emotional processing deficits (Le-Niculescu et al. 2009).

These findings of neurocognitive dysfunction as well as face emotion labelling might be due to the model suggested by Rheenen and Rossell in which the interaction amongst COMT, TPH2 and GSK3-B might contribute to the phenotypic expression of BD, whereas ASD might arise from the interaction between COMT, TPH2 and another (yet to be hypothesised) gene (Van Rheenen and Rossell 2013). This model requires careful evaluation.

12.3 Candidate endophenotype

The criteria for a variable to be considered as an endophenotype have been previously discussed in chapter 2.12 and include:

Criterion 1: The endophenotype is associated with illness in the population.
Criterion 2: The endophenotype is heritable.
Criterion 3: The endophenotype is primarily state-independent (manifests in an individual whether or not illness is active).
Criterion 4: Within families, endophenotype and illness co-segregate.
Criterion 5: The endophenotype found in affected family members is found in non-affected family members at a higher rate than in the general population.

Current evidence base and the neurocognitive deficits and facial emotion labeling deficits identified in this project fulfilled the following criteria: association with illness, being heritable, being state-independent and co-segregating within families with illness. However, as the data is from unaffected OBP who have yet

to develop the disorder and not the affected BD proband this project could not confirm the last criterion. An important consideration in considering the deficits identified in this project as endophenotypes is ascertaining the specificity of these deficits for BD as a lot of these deficits are reported in other mental health and neurodevelopmental disorders thereby not being unique to BD. This will be discussed further in section 12.5.5.

12.4 Strengths of study

12.4.1 Recruitment

Twenty five adult patients with BDI with children in age range 6-14 years were approached to participate in this project by their treating Consultants in Adult Psychiatry of which 20 patients finally participated in study. This represents 80% success using this recruitment strategy. Three patients either did not consent (n=1) or withdrew consent (n=2). The reasons that the subjects did not consent or withdrew consent are not known. The families that did participate in the project provided positive verbal feedback to the author during the course of the project about how important they felt this research was. The patients with BDI and their partners also expressed a desire to participate in similar studies. They hoped that research in the field could lead to the identification of tests that might help identify BD early especially for those individuals who have family history of BD.

Most other studies to date assessing neurocognitive function and facial emotion labelling in OBP have taken place in USA. Recruitment into these studies relies upon advertisements and free healthcare provision for the study duration. Samples recruited in this way may not be representative of the wider community. Such strategies are likely to introduce a recruitment bias. For example, families who otherwise may be unable to afford healthcare insurance and/or have a more severe form of mental health disorder may be more likely to volunteer for the study. This would impact on the generalisability of the results. Further a lot of the studies to date that have recruited young subjects ‘at risk’ for BD have included both siblings of adolescents with BD as well as offspring of

bipolar parents (BDI and BDII). As discussed in chapter 2.4, BDI and BDII are clinically distinct disorders. Research also suggests that these 2 types of BD may differ in the severity of neurocognitive deficits, social cognitive deficits and psychosocial impairment although which type has more deficits is still not established (Judd et al. 2005; Torrent et al. 2006; Simonsen et al. 2008; Wingo et al. 2010). Merging subjects who are 'at risk' for BD by being biologically related to a proband with either type of BD might not be the most suitable strategy as the genetic contribution towards the deficits may vary.

The 'at risk' studies have often included individuals with established mental health/neurodevelopmental disorders eg ADHD and BD into the final analysis. Some of these studies have attempted to control for the high rates of psychopathology (ADHD, anxiety, depression) by covarying the scores on neurocognitive tests and facial emotion labelling tasks with scores of symptom severity. This statistical attempt to control for the high rates of psychopathology makes it hard to infer how much of the neurocognitive and facial emotion labelling deficits are an endophenotype or directly related to the psychopathology.

12.4.2 Assessment schedule and battery

All the parents in both groups completed the SCID as well as the WASH U K SADS. Further, all the offspring in both groups completed all the tasks in the assessment battery assessing neurocognitive function and facial emotion labelling. The assessment schedule as well as battery was suitable for the participants. The high rates of completion from participants would suggest that parents and offspring found the detailed assessment schedule acceptable.

12.4.3 Aims and hypotheses

The aims of these study have been described in chapter 7.1 and included recruiting a sample of 28 OBP and 28 OHC (matched for age, gender and SES) from North East England, investigating neurocognitive function and facial emotion labelling in OBP and OHC groups and assessing the statistical difference between the groups. The study was successful in recruiting 29 OBP and 34 OHC matched for age, gender and SES. However, as 5 OBP had psychopathology, data from these subjects were not included in the final statistical analysis.

The hypotheses for this project have been described in chapter 7.2 and included: OBP will show impairment on the domain of memory, learning and executive function, OBP will demonstrate more errors on facial emotion labelling task particularly those with low intensity stimuli and on stimuli with child faces and the deficits in facial emotion labelling will not be related to impairments demonstrated on the domains of memory, learning and executive function. The study was able to confirm the first hypothesis. OBP had statistically significant neurocognitive dysfunction as compared to OHC on CVLT-C Level of Learning, PALS, SWM implying visual working memory impairment, visual and verbal learning impairment and a degree of impairment in executive function (as the tests employ degrees of strategy formation). On the second hypothesis, OBP made more errors compared to OHC on DANVA 2 when asked to

1. Label facial emotion across all emotions and specifically fear
2. Label facial emotion with low intensity stimuli and when the stimuli were child faces.

The weak statistical association on regression analysis and the lack of statistical significance for these associations confirmed the third hypothesis that the neurocognitive deficits and facial emotion labelling deficits in this study appear to be unrelated and perhaps independent putative endophenotypes for BD. These deficits considered together only serve to increase the vulnerability of OBP when compared with OHC.

Previous studies that have attempted to investigate whether deficits in neurocognitive function and face emotion labelling might be putative endophenotypes have done so by assessing these functions independently. As discussed in chapter 5, face emotion labelling deficits can be influenced by neurocognitive deficits. This project presents data to suggest that these deficits appear to occur independent of each other albeit a result of shared neural basis. It may be that the neural connectivity issues manifests itself in the form of neurocognitive and facial emotion labelling deficits. This would add strength to the proposal that these deficits be considered as a putative endophenotype.

Overall this project was able to successfully recruit a sample of adults with BDI from the community with children in the age range of 6-14 years free of psychopathology and not on any psychotropic medication. An OHC group matched on age, gender and SES to the OBP was also successfully recruited. The participants completed the assessment battery and the data collected was analysed using appropriate statistical technique of mixed effects modelling. Adequate matching of the sample, the comprehensive assessment battery and the use of appropriate statistical techniques serves to increase the validity of the findings.

12.4 Limitations of study

12.5.1 Sample size

Although the study was successful in recruiting 29 OBP and 34 OHC, the sample for the main analysis was 23 OBP and was thus underpowered according to the initial power calculation. Attempts were made by the study team to recruit more OBP by keeping recruitment open for 20 months. Despite extending the recruitment it was not possible during the study period to increase the OBP sample further. Further these findings differentiate OBP and OHC as groups. They do not inform us of the performance of the individuals on the assessment battery.

12.5.2 Recruitment of OHC group

The recruitment strategy used to employ participants in the OHC group has been outlined in chapter 8.6.2. It was designed with the aim of recruiting a sample of participants in the OBP and OHC groups matched on age, gender and socioeconomic status. Another limitation could have been that the parents who consented for their children to participate in the OHC group may have had specific characteristics such as an unrepresentatively higher IQ. This potential recruitment bias could have contributed to the the statistically significant difference between participants in the OBP and OHC groups and thus the findings of higher FSIQ, PIQ and VIQ need to be interpreted with caution.

12.5.3 Lack of blinding

The project team (author and research assistant) were not blind to the group that the subjects belonged to. They knew whether the individual being assessed was from the OBP or OHC group. This lack of blinding could have introduced a bias and as a result influenced the findings. However, the use of objective measures in the assessment battery make this unlikely.

12.5.4 Subsyndromal psychopathology

Although OBP with recognised current/lifetime psychopathology were excluded from the analyses, the project did not have rating scales that assessed for subsyndromal attentional difficulties (ADHD), mood and anxiety symptoms. Further, WASH-U-KSADS does not screen for ASD and there were no screening measures for ASD incorporated into project protocol. The project team did exclude 3 cases with ASD and PDD but these were based on clinical diagnoses made by the children's treating team.

12.5.5 Neurocognitive assessment

The study employed a comprehensive neurocognitive assessment battery assessing attention, sustained attention, working memory, learning and executive function in both verbal and visual domains. The WASI 4 is a brief assessment of IQ and therefore does not provide the same detail as with the use of WISC-IV. The CANTAB is a neurocognitive assessment battery which is computer based using a touch screen. This did engage the subjects (age 6-14 years in this project) in the assessment. However, the CANTAB has limited normative data for subjects in this age range. The project attempted to minimise this limitation by not using the normative data but using instead the data from the matched OHC group. Further, the project set out to assess specific neurocognitive domains. This was to be done using the tests selected. However, neurocognitive tests very rarely test just one specific neurocognitive domain. The tasks used in the study assess multiple neurocognitive domains (eg digit span assess both attention and working memory). Therefore a deficit as identified by a task may have been a result of this overlap not necessarily due to a deficit in that particular neurocognitive domain. Further, neurocognitive (dys)function in one domain could impact on other domains eg limited attention span contributing to learning and memory difficulties which would undoubtedly have an impact on strategy formation as an aspect of executive function.

12.5.6 Facial emotion labelling assessment

Although the DANVA 2 is a standardised emotion labelling paradigm, the number of items is small (24 child and 24 adult faces), particularly when broken down by emotion (6 stimuli per emotion per face-age) with no neutral faces. Therefore the power to detect emotion specific differences may be limited (Guyer et al. 2007). Another potential limitation is that photographs of posed facial expressions may not be as ecologically valid as other types of stimuli (Guyer et al. 2007). Posed photographs do not fully capture the intricacies of spontaneous non-verbal communication that occur in real life social interactions. Further, in real life situations faces show subtle variations in expression with people rarely display extremes of emotion (Schepman et al.

2012). However, because non-verbal cues generally are displayed briefly and dynamically, the 2-second presentation of DANVA items approximates the short time frame in which individuals must classify facial expressions encountered in daily social interactions. Furthermore, research demonstrates the utility of photographed facial expressions for engaging neural regions (Haxby et al. 2000; Adolphs 2002). These limitations highlight the need to develop face emotion labelling tasks that address these issues.

It is also important when studying facial emotion labelling that a distinction is made between accuracy and bias (Schepman et al. 2012). According to signal detection theory, accuracy of identification of specific facial expression requires taking account of both correct identifications and of misidentifications. By design, this was an exploratory project. The DANVA 2 analysis focussed on number of correct identifications. Data from misidentifications was not analysed. This is a limitation of the project as previous studies have identified deficits in emotional processing which consist of misidentification of facial emotions (Yurgelun-Todd et al. 2000; Hoertnagl et al. 2011). The study by Hoertnagl and colleagues also reported a statistical association between the face emotion misrecognition errors and psychosocial function (Hoertnagl et al. 2011). This would suggest a possible contribution made by the emotional processing deficits to the functional impairment seen in BD.

12.5.7 Specificity of deficits

Neurocognitive dysfunction and face emotion labelling deficits were identified in this study. These deficits fulfil criteria 1-4 for a potential candidate endophenotype as presented in section 12.3. However, an important factor to consider in this process is that these deficits are not unique to BD even though they were identified in offspring with no current/lifetime mental health/ neurodevelopmental disorder. The deficits have been seen in other mental health disorders and neurodevelopmental disorders. Neurocognitive deficits, in particular, were initially studied in schizophrenia. The differentiating factor between the deficits seen in schizophrenia and BD includes the increased

severity, more global nature of deficits and larger effect sizes in schizophrenia (Bora et al. 2010). Other disorders in which similar neurocognitive deficits have been reported include neurodevelopmental disorders such as ASD (Andersen et al. 2013; Kaufmann et al. 2013) and ADHD (Nikolas and Nigg 2013). Face emotion labelling tasks have been studied in autism (Harms et al. 2010), depression (Bourke et al. 2010), ADHD (Yuill and Lyon 2007), schizophrenia (Laroi et al. 2010) and psychopathy (Dolan and Fullam 2006). Given that these deficits have been reported in a very diverse range of disorders it does raise the question whether the deficits have the specificity to be considered a potential candidate endophenotype for BD. The data does emphasise that even in these 'apparently well' offspring there is increased vulnerability that warrant further investigation which will be discussed in section 12.7.

12.6 Implications

12.6.1 Service provision

The data from this project and related studies demonstrate that OBP are at an increased risk for development of psychopathology, demonstrate neurocognitive deficits and facial emotion labelling deficits in comparison with OHC. This increases the vulnerability for OBP. Families in which a parent has BD face many pressures. BD itself is an unpredictable mainly episodic disorder with significant impact on the individual affected and their family. The feedback from adult bipolar probands who participated in this project as well as members of the Bipolar Organisation North East England chapter who contributed to protocol development was that service users would prefer a dedicated service where adults with BD as well as their offspring are seen as a family unit. Very few units in the NHS are able to provide family based mental health provision.

12.6.2 Clinical and educational setting

The neurocognitive deficits of lower FSIQ, memory and learning as well as the facial emotion learning deficits reported in this study have implications for OBP

in the educational setting. Intact verbal learning and memory is a key factor in successful academic and psychosocial functioning (Schenkel et al. 2012). The ability to attend to and remember information is essential for more complex cognitive functions such as vocal and subvocal rehearsal of new information, critical thinking, and problem solving. Deficits in these areas could cause significant functional impairment. This functional impairment could lead to increased distress and even greater difficulties in the ability to successfully interact with others, as well as study and learn new information (Martinez-Aran et al. 2004). Consistent with this, a recent longitudinal investigation of subjects with PBD found that PBD showed significant delay in the development of executive functions and verbal memory ability over time compared to their same age peers, and that these deficits were associated with greater academic impairment (Pavuluri et al. 2009). Cognitive deficits would also likely interfere with the ability to benefit from psychotherapy techniques, psychoeducation, and social skills training (Simonsen et al. 2008).

Many of the functional impairments reported among PBD subjects such as difficulty listening to and following directions, remembering verbal instructions given by parents and teachers, and processing and remembering details while engaged in conversations and interactions with others can be explained by deficits in the ability to process verbally and visually mediated information (Schenkel et al. 2012). Interventions in subjects who are ‘at risk’ for or may already have PBD should take into account neurocognitive impairments in memory and learning, and their relationship to real-world functional outcomes (discussed in section 12.6.3). It is also worth bearing in mind that the deficits in learning and memory would impact on any interventions attempted to address social cognition (face emotion labelling). Most mainstream schools employ social and emotional literacy programmes to target these domains in youth with ASD. It would be worth trialling and assessing the efficacy of using these to address the facial emotional processing difficulties (social cognition) in future research.

12.6.3 Functional remediation

Functional (neurocognitive) remediation to help address neurocognitive deficits in BD (Martinez-Aran et al. 2011; Fuentes-Dura et al. 2012) as well as OBP (Pavuluri et al. 2009) have attracted considerable attention. The term “functional remediation” refers to interventions aimed at restoring psychosocial functioning in patients with brain disorders, including, those with mental disorders, by means of ecological neurocognitive techniques (Martinez-Aran et al. 2011). The term “ecological” refers to focussing on the practical impact of the neurocognitive techniques on interventions on daily life, as opposed to “brain training”. Functional remediation involves psychoeducation about cognitive dysfunctions and their impact on the general functioning of an individual. Similarly there has been interest in facial emotion learning paradigms by the NIH group led by Leibenluft and colleagues (Egger et al. 2011). Other strategies being evaluated include the Social cognition and Interaction Training (SCIT) developed in Madrid to assist adult outpatients with BD (Lahera et al. 2013).

Findings from this project also highlight the need to investigate the potential benefits of cognitive rehabilitation for OBP who already displaying deficits in social cognition and memory and learning (the implications of which have been discussed in section 12.6.2). The neurocognitive deficits (reported in this project) would make it harder for the OBP to achieve the same educational targets as other typically developing peers in the same time. More time to learn and repeated presentations may benefit OBP but this requires careful evaluation. It also remains to be seen whether laboratory based learning and remediation can transfer to real life scenarios or indeed improve psychosocial function over the long term in those patients who have BD and those ‘at risk’ for developing BD.

12.7 Future research

12.7.1 Design

Identifying and confirming an endophenotype for BD would aid in early recognition, diagnosis and institution of appropriate management in those 'at risk' for BD. The next step should be to develop studies that could investigate/ replicate these findings and evaluate whether the pattern of neurocognitive and facial emotion labelling deficits reported in this project confirms all the 5 criteria presented (chapters 2.12 and section 12.6). This could be accomplished by identification of a large cohort (multi-centre) of adult BDI parents (to ensure homogeneity of diagnosis: chapter 6.3.2) and their young offspring (with no current/lifetime psychopathology: chapters 6.3.1 and 6.3.3). The large sample size will increase power and the effect size of the findings.

The study should aim to prospectively compare and follow-up neurocognition and emotional processing in the BDI bipolar parent proband, their OBP and HC parents and OHC. The longitudinal design would allow the study of neurocognitive and facial emotion labelling deficits and inform what the pattern of progression of these deficits is. Further, longitudinal studies will permit characterisation of risk and resilience factors in those OBP who do eventually develop BD in comparison with those OBP who do not develop BD. These could include neurocognitive deficits and facial emotion labelling deficits. In particular, these studies should also use robust statistical analyses (mixed-effects models and structured equational modelling). These analyses will allow the researchers to assess the contribution made to the variance on the scores of neurocognitive function and emotional processing by factors such as severity of parental disorder, family environment, brain findings (assessed by MEG, fMRI and DTI) as well as the genetic markers (eg COMT, TPH2 and/or GSK3-B).

12.7.2 Nature vs nurture

Another unanswered question that remains regarding the neurocognitive deficits and facial emotion labelling deficits identified is to what extent are these genetic and to what extent does family environment and parental upbringing contribute to these deficits. Studies assessing neurocognitive function in BD have reported that in subjects with psychotic episodes the neurocognitive impairment includes verbal memory impairment along with response inhibition deficits whilst subjects with non-psychotic episodes only display the response inhibition deficits (Bora et al. 2010). This implies a differential pattern of neurocognitive impairment in subjects with a psychotic (perhaps more severe) variant of BD. In addition, the relationship between impaired face processing and family dysfunction may be bidirectional (Rich et al. 2008). Studies focussing on assessing the contribution made by the severity of parental BD vs family environment on the neurocognitive function as well as ability to label facial emotion would be the next step. Severity of parental BD could be assessed by proxy indicators such as presence of psychotic episodes and need for hospitalisation.

Family environment has been shown to play a role in the development of many disorders in at risk children. For example, high levels of family conflict are associated with more symptoms of depression in adolescents (Sheeber et al. 1997) and increased risk of substance use disorder (Skeer et al. 2009). High levels of expressed emotion have been linked with longer depressive episodes, greater manic and depressive symptomatology at follow up and greater risk of relapse (Belardinelli et al. 2008). For OBP, the effects of FE have been shown to include increased risk of BD with features such as family support, organisational structure and levels of conflict thought to have a significant contribution (Ostiguy et al. 2009). Family environment studies could use assessments tools such as Family Environment Scale (Moos and Moos 1994; 96), MacMaster's Family Assessment Device (Epstein et al. 1983) to investigate various aspects of family environment such as conflict, cohesion and organisation. Studies assessing family environment in families with BD have reported less organisation, decreased levels of cohesion and higher levels of

conflict in BD families (Chang et al. 2001), and findings of lower levels of expressiveness and decreased levels of cohesion in BD families (Romero et al. 2005). Another way to assess the GXE interaction contributing to neurocognitive and face emotion labelling in BD would be to study the same in adoption and cross fostering studies.

12.7.3 Combination with neuro-imaging

Although this project did not find any statistically significant association between neurocognitive dysfunction and facial emotion labelling, the deficits identified in this project may have common neural underpinnings. Another way to improve future studies would be to incorporate imaging (fMRI and DTI) to better understand whether the neural basis of these deficits do in fact have a common basis.

12.7.4 Combination with genetic markers

Studies should also attempt to investigate potential endophenotypes to gain a better understanding of the polygenic inheritance seen in BD. Genetic markers such as COMT, TPH2 and GSK3-B could be the focus of future studies. The association of a genetic marker with neurocognitive and facial emotion labelling deficits could lead to increased specificity for these deficits to be considered as candidate endophenotypes for BD.

12.8 Conclusion

In conclusion, this project has demonstrated that OBP in comparison with a matched sample of OHC displayed deficits in visual working memory, verbal learning, visual learning and made more errors labelling facial emotion (in particular fear). Regression analyses demonstrated that the neurocognitive and facial emotion labelling deficits were unrelated which was the novel finding from this project. These deficits could be considered potential candidate endophenotypes for BD.

The strengths of this project included the recruitment of offspring of parents with BDI (a homogenous sample), none of whom (included in final analysis) displayed any psychopathology or pharmacological treatment (confounding variables) and a robust statistical plan of analysis using mixed models. The limitations included a small sample size, lack of blinding and a lack of specificity of the deficits identified for BD. Further prospective work is needed to replicate these findings with longitudinal studies assessing a larger cohort incorporating neuro-imaging techniques and genetic markers. The studies should also attempt to investigate the contribution made to any deficits identified by severity of parental disorder versus family environment to gain a better understanding of the GXE interaction in the development and progression of BD.

Appendices

Appendix i: Information sheet for health professionals

COMPIC: The study of Neuropsychological function and Facial Affect Recognition in Children and Young People using Computer puzzles and Pictures

INFORMATION SHEET FOR HEALTH PROFESSIONALS

Why is this study being done?

There is a substantial body of evidence to suggest that patients with Bipolar Disorder have neuropsychological difficulties even in the symptomatically improved stage of bipolar disorder. In addition, they appear to make errors in recognition of facial affect. These studies, however, have all been carried out after the onset of the disorder making interpretation of these findings difficult *i.e.* are these deficits a part of, a cause of or a result of the disorder. To better answer this question, the research team at Newcastle University are planning a study of assessing neuropsychological function and facial affect recognition in children of adults with bipolar disorder and comparing that with functioning in children of healthy controls with no family history of psychiatric illness. We also plan to study if there is any relationship between severity of parental bipolar disorder and the neuropsychological function and facial affect recognition.

Who is being invited to participate?

Children of adults with Bipolar I disorder in the age range of 6-14 years will be invited to participate in the study.

What does the study involve?

The Consultant Psychiatrist will approach the parent with bipolar disorder who has children in the age range of 6-14 and provide them with a Study Information

Pack-Test, which consists of Parent Information Sheet (Test Version), the Child Information Sheet (Test Version) and the Expression of Interest Form along with an addressed stamped envelope. The patient can then send the Expression of Interest form to the Research Team or call the Research Team to express interest in the study using the contact details provided.

Families who agree to be contacted by the research team will initially be contacted by telephone. A mutually convenient time will be arranged for a member of the research team to meet with the family to discuss the study and answer any questions. After this written informed consent to participate in the study will be sought from the parent and assent sought from children aged 10 and over. If the parents decline to give consent and/or the young person does not assent then no further appointments will be arranged. Parents will also be asked to provide the name of their child's school and the name of the child's class teacher.

The following assessments shall be carried out with the family:

With parents:

The parents shall attend the Newcastle University Department of Psychiatry. They will be met by a member of the research team. A brief psychiatric interview to confirm their bipolar diagnosis and current symptom control will be carried out using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). Subsequently an interview focussing on the child's presentation will be conducted using the structure of the Washington University version of the Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS). In addition, a member of the research team will explore the family environment in the family using an interview called the Family Environment Scale (FES). These assessments will take up to a maximum of 5 hours to complete. Breaks will be provided when requested during the course of the assessments.

A brief verbal feedback after completion of these interviews will be provided to the families.

A member of the research team will arrange to review the adult bipolar parent's clinical notes to gather information about:

1. number of hospital admissions for treatment of bipolar disorder
2. presence/absence of psychotic features during episodes.

Details of school attended by their child including class and name of teacher will be collected.

With children:

Parents and children will be offered the option of having the assessments with the children in the test and control group at their school or at Newcastle University. If they choose to have the assessments completed at school, permission will be sought from the Head Teacher for this and arrangements made for a suitable room to conduct the assessment in. At Newcastle University provision will be made to assess the children in a quiet office in Department of Child Health, Royal Victoria Infirmary, Newcastle upon Tyne.

The assessments will require 90 minutes. These assessments will be conducted in 45 minute blocks with a 15 minute break in between. The assessments will be mostly on a lap top computer but some assessments will be pen and paper exercises.

After completion of the tasks the child will be thanked by a member of the research team.

A £10 book voucher will be sent to the child's home address after completion of assessments.

How can you help us as health professionals?

Please refer any adults who have Bipolar I Disorder and have children of either sex in the age range of 6-14 years of age to the research team by faxing the enclosed participant referral form. If you have any queries/questions on the study please contact me using the details provided.

Contact Details

Dr Aditya Sharma
Department of Child Health
Sir James Spence Institute
Newcastle University
Royal Victoria Infirmary
Newcastle upon Tyne
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Tel: 0191 2821371/ 0191 2821400/ 0191 2821384
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Appendix ii: information for parents with bipolar I disorder

COMPIC: The study of Neuropsychological function and Facial Affect Recognition in Children and Young People using Computer puzzles and Pictures

INFORMATION SHEET FOR PARENTS

Information sheet about the research (please keep this copy)

Before you decide whether to take part in this research, it is important that you understand why the research is being done and what it will involve. Please take your time to read the following information carefully. Please feel free to contact us if there is anything that is not clear or if you would like more information.

What is Neuropsychological function and facial affect recognition?

Neuropsychological function refers to the ability of an individual to pay attention to a task, think about it, remember some details and then come up with a plan to solve the task. It can be assessed in various ways but in this study we are going to use some games on the laptop and some paper and pencil activities to study how children and young people perform.

Facial affect recognition refers to the ability to correctly identify a facial expression. So in this study the children and young people will be shown some photographs on the computer with people having different expressions on their face such as happy or sad. They will then be asked to tell us which expression it is.

- **What is the purpose of this study?**

The purpose of the study is to learn more about how children are able to perform on these tasks in comparison with children and young people without any family history of psychiatric difficulties.

- **Why have I been chosen?**

Families with children aged between 6 and 14 years who have a biological parent with a history of bipolar disorder are being invited to participate in this study.

- **Do I have to take part?**

It is entirely up to you whether you would like to take part. If you decide to take part you are still free to withdraw at any time, without giving a reason. A decision not to take part or to withdraw will not affect either the standard of care, or the services you and your family receive now or in the future.

- **What does the study involve?**

1. Your consultant psychiatrist will have told you about this research study and given you an Information Pack, which consists of this information sheet, an information sheet for your child and an expression of interest form along with an addressed stamped envelope.
2. We hope that you will express an interest to opt into the study either by sending the expression of interest form to the research team via the post or by contacting us on the telephone numbers provided on this sheet and the expression of interest form.
3. Once you express interest in our study the research team will contact you to make an appointment to meet with your family including your child at a mutually convenient time and place (e.g. at your home). This is so that we can discuss the study further with you and answer any queries that you may have.
4. Written, informed consent will be taken from you after at least 48 hours from the time when you initially expressed interest in the study. Written assent will be taken from your child if he (she) is older than 10 years of age. We will only proceed if we have consent and assent (where appropriate). You will be asked to provide the

name of the school attended by your child and the name of his teacher. This is so that we can arrange to contact your child's teacher to request them to complete a brief questionnaire.

5. We will also ask your permission to inform your GP of your family's participation in this study.
6. The research team will then arrange a mutually convenient time for you to attend an appointment at Newcastle University. The appointment will last up to a maximum of 5 hours with breaks part way through.
7. At this appointment you will meet a member of the research team who will first conduct a brief psychiatric interview called the Structured Clinical Interview for DSM Disorders (SCID) with you to confirm your diagnosis of bipolar disorder. There will be a break for lunch.
8. In the afternoon session, you will be interviewed about your child's health and development using the structure of the Washington University Version of the Kiddie Schedule for Affective Disorders and Schizophrenia (WASH U KSADS). After this you will be asked about family life at home using the Family Environment Scale (FES). At the end of the session you will be provided with verbal feedback about the assessments carried out during the day.
9. We will also ask your permission to review your psychiatric case notes. This is so that a member of the research team can gather information about:

a) number of hospital admissions that you have had for the treatment of your bipolar disorder and
b) whether you have had any psychotic features during episodes. This information will help us better interpret your child's assessment.

10. We will be flexible regarding the time and format of the visits – if you want we can split the interviews over two separate days or take more breaks if needed.
11. The research team can arrange to complete the assessments with your child at their school or at Newcastle University. It is entirely up

to your child and you to decide where you would like these assessments to be completed._Your child will have to complete some games and puzzles on the computer. All the games will be explained to your child by a member of the research team who will be present throughout the assessment. The assessment will take about 1.5 hours and will take place in 2 sessions with a break part way through.

Your child will not be the only child taking part in this study. We will also be asking at least one other child in your child's class to take part in the study with their parents' permission.

- **What will this information be used for?**

All information that we receive from you will be treated as strictly confidential. We are hoping that the findings from this study will help us better understand the process of bipolar disorder and so we can better manage this condition.

- **What are the possible benefits of taking part?**

Advantages of taking part in the research include the chance to help increase knowledge and understanding about Bipolar Disorder and to eventually better help families with one or more members who have suffered from this condition.

- **What are the possible disadvantages of taking part?**

There are some people who may find it difficult or distressing to be contacted or to provide some of the information we ask. If while or after participating in this study you feel the need for support, you can contact us or the Patient Advice and Liaison Service (PALS) on the telephone numbers on this leaflet.

- **How will our time be re-imbursed?**

Each child that takes part will receive a £10 book voucher as a token of our appreciation when all parts of your involvement have been completed.

- **Will our taking part in this study be kept confidential?**

.

All data, collected during the course of the research will be kept locked up, anonymised (names and addresses removed) and will be treated as strictly confidential.

Only members of the research team and representatives from the Research Department of the NHS Trusts involved in this study (these are individuals who have responsibility for ensuring the quality of the research) will be allowed to know who is taking part in the study and to see the information you have given us.

The only exception would be if any information came to light that might affect the safety of a child such as a child protection concern. Under those circumstances the research team would have an obligation to discuss their concerns with Professor AS Le Couteur and to follow the child protection procedures in accordance with guidelines laid down by Northumberland Tyne and Wear NHS Trust on 'Safeguarding Children' version 1.1.

No participants within the study will be identified in any research report or publication. Your name and contact details will not be passed on to anyone not involved with the study.

- **What will happen to the study results?**

.

At the end of the study, the results will be summarised in an information sheet, which will be sent to all the families who have participated. The results will also be written up to help doctors, nurses, self-help groups and other professionals involved in the care of families with Bipolar Disorder.

- **Who has reviewed and approved the study?**

This study was given a favourable ethical opinion by Northumberland Research Ethics Committee.

For further information and queries please contact:

Dr Aditya Sharma
Department of Child Health
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Or
Patient Advice and Liaison Service (PALS) on 08000 320 202

Appendix iii: Information sheet for OBP

COMPIC: The study of Neuropsychological function and Facial Affect Recognition in Children and Young People using Computer puzzles and Pictures

INFORMATION SHEET FOR CHILDREN

AGED 6-14 YEARS

This is an information sheet for you. Please read it and keep it

Hello! We are a research team who would like to learn more about how children and young people think and feel. This is why we are asking you to try our computer based games and to do a few pencil and paper games.

What is research?

When people don't understand something, or want to know more about it, they have to ask questions and sometimes find out answers. We call this research. This is just like when you ask your teachers or parents about something you want to find out.

Why have I been asked?

We are asking some children and young people from the North East of England from various schools to participate in this study. Some children in your class have been chosen to participate. This is why we are asking you to help us with our research.

What is Neuropsychological function and facial affect recognition?

Neuropsychological function refers to the ability of an individual to pay attention to a game, think about it, remember some details and then come up with a plan to solve the game. It can be assessed in various ways but in this study we are going to use some games on the laptop and some other using paper and pencil to do so.

Facial affect recognition means being able to identify the emotion behind a facial expression. So in this study you will be shown some photographs with people having different expressions on their face such as happy or sad. You will then be asked to say which expression it is.

What does this study involve?

1) First, we arrange to meet you and your family at a time and place, which is best for you (for example at your house) so that we can tell you about the study and answer any questions that you or your parents might have.
2) If you and your parents are willing to participate in our COMPIC study we will then arrange to meet with your parents to ask some details about how they and you are doing in everyday life.
3) You can participate in the study at school or at Newcastle University.
4) A member of the research team will tell you about the games and activities before you start to do them.
5) You will be able to have a break part way through the assessment.
6) After you finish you will be escorted back to your class/parents by a member of the research team.
7) We will send a book token to your home address for helping us.
8) Other children in your class will also be asked to participate in the study.
9) You should not tell them anything about the study because it is TOP SECRET.

Do I have to take part?

We would like you to help us with our research, but you do not have to if you do not want to. If you want to stop, or there are any questions that you don't want to answer that is fine. You don't have to give us a reason for this.

Will joining in help me?

We cannot promise that the study will help you, but it might help us learn how children and adolescents think. We hope you will enjoy the computer games and activities.

What will this information be used for?

The research will help us understand more about how children of your age think.

Has anyone checked that this study is OK to do?

We have told your parents all about the study and they can decide if they think it is a good idea for you and your family to take part. Before any research is allowed to happen, it has to be checked by a group of people called an Ethics Committee. They make sure that the research is OK to do. Your project has been checked by the Northumberland Research Ethics Committee

Do you want to know anything else?

If you have any questions about the study please ask us either when you meet us or by contacting:

Dr Aditya Sharma
Department of Child Health
Sir James Spence Institute
Newcastle University
Royal Victoria Infirmary
Newcastle upon Tyne
NE1 4LP

Tel: 0191 2821371/ 0191 2821400/ 0191 2821384
Mob: 07500544723
Email: COMPIC@ncl.ac.uk

Appendix iv: Expression of interest form

COMPIC: The study of Neuropsychological function and Facial Affect Recognition in Children and Young People using Computer puzzles and Pictures

Expression of Interest Form

Date of expression of interest *(dd/mm/yy)*: ……

Parent's name:……

Child's name:……

Gender *(please strike out as appropriate):* Male / Female

Date of birth *(dd/mm/yy)*: ……

Home address, including postcode: ……

……

Home telephone *(including dialling code)*: ……

……

Mobile *(including dialling code)*: ……

Could you confirm that you are agreeable to be contacted by the research team *(please strike out as appropriate)*: Yes / No

Please post this form together with any further information which you think may be relevant to or call on the telephone numbers provided:

For the attention of Dr Aditya Sharma, Sir James Spence Institute, Newcastle University, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP.

Tel: 0191 2821371/ 0191 2821400/ 0191 2821384

Mob: 07500544723

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Email: COMPIC@ncl.ac.uk

Appendix v: Information sheet for healthy control parents

COMPIC: The study of Neuropsychological function and Facial Affect Recognition in Children and Young People using Computer puzzles and Pictures

INFORMATION SHEET FOR PARENTS

Information sheet about the research (please keep this copy)

Before you decide whether to take part in this research, it is important that you understand why the research is being done and what it will involve. Please take your time to read the following information carefully. Please feel free to contact us if there is anything that is not clear or if you would like more information.

What is Neuropsychological function and facial affect recognition?

Neuropsychological function refers to the ability of an individual to pay attention to a task, think about it, remember some details and then come up with a plan to solve the task. It can be assessed in various ways but in this study we are going to use some games on the laptop and some paper and pencil activities to study how children and young people perform.

Facial affect recognition refers to the ability to correctly identify a facial expression. So in this study the children and young people will be shown some photographs on the computer with people having different expressions on their face such as happy or sad. They will then be asked to tell us which expression it is.

- **What is the purpose of this study?**

The purpose of the study is to learn more about how children are able to perform on these tasks.

- **Why have I been chosen?**

Families with children aged between 6 and 14 years are being invited to participate in this study.

- **Do I have to take part?**

It is entirely up to you whether you would like to take part. If you decide to take part you are still free to withdraw at any time, without giving a reason.

- **What does the study involve?**

1. Your child's teacher has sent you this Study Information Pack, which consists of this information sheet, an information sheet for your child and an expression of interest form along with an addressed stamped envelope.
2. We hope that you will express an interest to opt into the study either by sending the expression of interest form to the research team via the post or by contacting us on the telephone numbers provided on this sheet and the expression of interest form.
3. Once you express interest in our study the research team will contact you to make an appointment to meet with your family including your child at a mutually convenient time and place (e.g. at your home). This is so that we can discuss the study further with you and answer any queries that you may have.
4. Written, informed consent will be taken from you after at least 48 hours from the time when you initially expressed interest in the study. Written assent too will be taken from young people older than 10 years of age. We will also interview you to confirm the absence of any family history of mental health difficulties. We will only proceed if we have received consent and assent (where appropriate).
5. The research team can arrange to complete the assessments with your child at their school or at Newcastle University. It is entirely up to your child

and you to decide where you would like these assessments to be completed. Your child will have to complete some games and puzzles on the computer. All the games will be explained to your child by a member of the research team who will be present throughout the assessment. The assessment will take about 1.5 hours and will take place in 2 sessions with a break part way through.

6. Your child's teacher will also be asked to complete a brief questionnaire.

· **What will this information be used for?**

All information that we receive from you will be treated as strictly confidential. We are hoping that some of the information provided by the study can help us better understand the process of neuropsychological function and facial affect recognition in children and young people.

· **What are the possible benefits of taking part?**

Advantages of taking part in the research include the chance to help increase knowledge and understanding about neuropsychological function and facial affect recognition in children and young people.

· **What are the possible disadvantages of taking part?**

There are some people who may find it difficult or distressing to be contacted or to provide some of the information we ask. If while or after participating in this study you feel the need for support, you can contact us or the Patient Advice and Liaison Service (PALS) on the telephone numbers on this leaflet.

· **How will our time be re-imbursed?**

Each child that takes part will receive a £10 book voucher as a token of our appreciation when all parts of your involvement have been completed.

· **Will our taking part in this study be kept confidential?**

All data, collected during the course of the research will be kept locked up, anonymised (names and addresses removed) and will be treated as strictly

confidential.

Only members of the research team and representatives from the Research Department of the NHS Trusts involved in this study (these are individuals who have responsibility for ensuring the quality of the research) will be allowed to know who is taking part in the study and to see the information you have given us.

The only exception would be if any information came to light that might affect the safety of a child such as a child protection concern. Under those circumstances the research team would have an obligation to discuss their concerns with Professor AS Le Couteur and to follow the child protection procedures in accordance with guidelines laid down by Northumberland Tyne and Wear NHS Trust on 'Safeguarding Children' version 1.1.

No participants within the study will be identified in any research report or publication. Your name and contact details will not be passed on to anyone not involved with the study.

.

- **Who has reviewed and approved the study?**

This study was given a favourable ethical opinion by Northumberland Research Ethics Committee.

- **For further information and queries please contact:**

Dr Aditya Sharma
Department of Child Health
Sir James Spence Institute
Newcastle University
Royal Victoria Infirmary
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Or
Patient Advice and Liaison Service (PALS) on 08000 320 202

Appendix vi: Information sheet for OHC

COMPIC: The study of Neuropsychological function and Facial Affect Recognition in Children and Young People using Computer puzzles and Pictures

INFORMATION SHEET FOR CHILDREN

AGED 6-14 YEARS

This is an information sheet for you. Please read it and keep it

Hello! We are a research team who would like to learn more about how children and young people think and feel. This is why we are asking you to try our computer based games and to do a few pencil and paper games.

What is research?

When people don't understand something, or want to know more about it, they have to ask questions and sometimes find out answers. We call this research. This is just like when you ask your teachers or parents about something you want to find out.

Why have I been asked?

We are asking some children and young people from the North East of England from various schools to participate in this study. Some children in your class have been chosen to participate. This is why we are asking you to help us with our research.

What is Neuropsychological function and facial affect recognition?

Neuropsychological function refers to the ability of an individual to pay attention to a game, think about it, remember some details and then come up with a plan to solve the game. It can be assessed in various ways but in this study we are going to use some games on the laptop and some other using paper and pencil to do so.

Facial affect recognition means being able to identify the emotion behind a facial expression. So in this study you will be shown some photographs with people having different expressions on their face such as happy or sad. You will then be asked to say which expression it is.

What does this study involve?

1) First, we arrange to meet you and your family at a time and place, which is best for you (for example at your house) so that we can tell you about the study and answer any questions that you or your parents might have.
2) If your parents and you are willing to take part in our COMPIC study we will then arrange for you to be able to do so at school or at Newcastle University.
3) A member of the research team will tell you about the games and activities before you start to do them.
4) You will be able to have a break part way through the assessment.
5) After you finish you will be escorted back to your class/parents by a member of the research team.
6) We will send a book token to your home address for helping us.
7) Other children in your class will also be asked to participate in the study.
8) You should not tell them anything about the study because it is TOP SECRET.

Do I have to take part?

We would like you to help us with our research, but you do not have to if you do not want to. If you want to stop, or there are any questions that you don't want to answer that is fine. You don't have to give us a reason for this.

Will joining in help me?

We cannot promise that the study will help you, but it might help us learn how children and adolescents think. We hope you will enjoy the computer games and activities.

What will this information be used for?

The research will help us understand more about how children of your age think.

Has anyone checked that this study is OK to do?

We have told your parents all about the study and they can decide if they think it is a good idea for you and your family to take part. Before any research is allowed to happen, it has to be checked by a group of people called an Ethics Committee. They make sure that the research is OK to do. Your project has been checked by the Northumberland Research Ethics Committee

Do you want to know anything else?

If you have any questions about the study please ask us either when you meet us or by contacting:

Dr Aditya Sharma
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Appendix vii: Consent form: OBP

Patient Identification Number *(write in)*:

CONSENT FORM

COMPIC: The study of Neuropsychological function and Facial Affect Recognition in Children and Young People using Computer puzzles and Pictures

Name of Researcher *(write in)*:

	Please tick and initial each box
1. I confirm that I have read and understand the parent information sheet version 4 dated 2nd April 2008 for the above study and have had the opportunity to ask questions about this study.	☐
2. I understand that my participation and that of my child is voluntary and that I am free to withdraw myself and my child at any time, without giving any reason, and without mine or my child's medical care or legal rights being affected.	☐
3. I understand that relevant sections of any of the data (including personal details) collected during the study may be looked at by responsible individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my and my child's data.	☐
4. I agree to the researcher accessing my clinical notes and recording aspects of my medical history and understand that this information will remain confidential.	☐
5. I agree to the researcher informing my GP regarding my family's participation in this study.	☐
6. I agree that I and my child *(enter name of child)* will take part in this study.	☐

Name of Parent	Date	Signature
Name of person taking Consent (if different from researcher)	Date	Signature
Name of Researcher	Date	Signature

When completed, 1 copy to be given to parent; 1 copy to be inserted in site file

Appendix viii: Consent form: OHC

Patient Identification Number *(write in)*:

CONSENT FORM

COMPIC: The study of Neuropsychological function and Facial Affect Recognition in Children and Young People using Computer puzzles and Pictures

Name of Researcher *(write in)*:

	Please tick and initial each box
1. I confirm that I have read and understand the parent information sheet version 4 dated 2nd April 2008 for the above study and have had the opportunity to ask questions about this study.	☐
2. I understand that my participation and that of my child is voluntary and that I am free to withdraw myself and my child at any time, without giving any reason, and without mine or my child's medical care or legal rights being affected.	☐
3. I understand that relevant sections of any of the data (including personal details) collected during the study may be looked at by responsible individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my and my child's data.	☐
4. I agree that I and my child *(enter name of child)* will take part in this study.	☐

Name of Parent	Date	Signature
Name of person taking Consent (if different from researcher)	Date	Signature
Name of Researcher	Date	Signature

When completed, 1 copy to be given to parent; 1 copy to be inserted in site file

Appendix ix: Assent Form

Child Identification Number *(write in)*:

Assent Form

COMPIC: The study of Neuropsychological function and Facial Affect Recognition in Children and Young People using Computer puzzles and Pictures

Name of Researcher *(write in)*:

	Please tick and initial each box
1. I have read and understand the Child Information Sheet version 4 dated 2nd April_2008 and have had the chance to ask questions about this.	☐
2. I understand that my involvement in the study is voluntary and I am free to withdraw from the study at any time	☐
3. I understand that some of my details (such as name, date of birth and address) collected during the study may be read by responsible adults at the University, but will not be shown to anyone else apart from people involved in the research.	☐
4. I agree to take part in a number of different tasks with the researcher.	☐
5. I would like to take part in the research study.	☐

Name of Parent	Date	Signature
Name of person taking Consent (if different from researcher)	Date	Signature
Name of Researcher	Date	Signature

When completed, 1 copy to be given to parent; 1 copy to be inserted in site file

Appendix x: FSIQ mixed model

Models:

mod1A: FIQ ~ BPD + SES + age + gender + (1 | family)
mod1B: FIQ ~ BPD + SES + age + gender + (SES | family)

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	7	474.23	488.65	-230.12			
Mod 1B	9	473.05	491.59	-227.52	5.18	2	0.08

Random effects:

Groups	Variance	Std. Dev.	Corr
Family (intercept)	796.58	28.22	
SES	46.89	6.85	-1.00
Residual	90.05	9.49	

Number of obs: 58, groups: family, 41

Fixed Effects:

FSIQ				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	129.37	11.43	11.32	0.0000
Parental BD	-15.12	3.83	-3.95	0.0001
SES	-11.07	3.10	-3.57	0.0004
Age	0.06	0.06	1.06	0.29
Male gender	1.23	3.42	0.36	0.72

Appendix xi: VIQ mixed model

Models:

mod1A: VIQ ~ BPD + SES + age + gender + (1 | family)
mod1B: VIQ ~ BPD + SES + age + gender + (SES | family)

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	7	476.24	490.66	-231.12			
Mod 1B	9	479.39	497.94	-230.7	0.84	2	0.66

Random Effects:

Groups	Variance	Std. Dev.
Family (intercept)	87.21	9.34
Residual	110.82	10.53

Number of observations: 58, groups: family: 41

Fixed Effects

VIQ				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	128.96	11.32	11.39	0.0000
Parental BD	-16.83	4.27	-3.94	0.0001
SES	-12.36	3.25	-3.80	0.0001
Age	0.079	0.06	1.27	0.20
Male Gender	-0.12	3.85	-0.03	0.98

Appendix xii: PIQ mixed model

model: PIQ ~ BPD + SES + age + gender + (SES | family)

	AIC	BIC	logLik	Deviance	REMLdev
Model	453	471.5	-217.5	445.6	435

Random Effects:

Groups	Variance	Std. Dev.	Corr
Family (intercept)	804.67	28.37	
SES	47.5	6.89	-1.00
Residual	69.21	8.32	

Number of observations: 58, groups: family: 41

Fixed Effects

PIQ				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	124.62	10.41	11.97	0.0000
Parental BD	-8.79	3.99	-2.20	0.028
SES	-6.92	3.02	-2.29	0.022
Age	-0.003	0.06	-0.006	0.96
Male gender	0.09	3.46	0.26	0.79

Appendix xiii: MOT mixed model

Models:

mod1A: score ~ BPD + SES + age + gender + (1 | family)

mod1B: score ~ BPD + SES + age + gender + (SES | family)

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	7	758.82	773.24	-372.41			
Mod 1B	9	762.88	781.43	-372.44	0	2	1

Random Effects:

Groups	Variance	Std. Dev.
Family (intercept)	1.64E-11	4.04E-06
Residual	2.42E+04	1.56E+02

Fixed effects:

MOT (Mean Latency)				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	734.82	124.04	5.92	0.0000
Parental BD	70.91	42.96	1.65	0.099
SES	102.19	34.20	2.99	**0.003**
Age	-2.80	0.72	-3.88	**0.0001**
Male gender	84.74	45.51	1.86	0.063

Appendix xiv: CRT mean latency mixed model

Models:

mod1A: score ~ BPD + SES + age + gender + (1 | family)

mod1B: score ~ BPD + SES + age + gender + (SES | family)

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	7	686.47	700.9	-336.24			
Mod 1B	9	689.05	707.6	-335.53	1.42	2	0.49

Random effects:

Groups	Variance	Std. Dev.	Corr
Family (intercept)	14579.18	120.74	
SES	983.45	31.36	-1.00
Residual	5439.21	73.75	

Number of obs: 58, groups: family, 41

Fixed effects:

Mean Latency				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	795.78	67.07	11.87	0.0000
Parental BD	38.48	23.65	1.63	0.1
SES	6.36	18.62	0.34	0.73
Age	-3.06	0.39	-7.9	**<0.0001**
Male gender	11.61	24.33	0.48	0.63

Appendix xv: CRT total correct trials mixed model

Linear mixed model fit by REML

Formula: score ~ BPD + SES + age + gender + (1 | family)

	AIC	BIC	logLik	Deviance	REMLdev
Model	399.5	413.9	-192.8	392.1	385.5

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	128.5	11.34
Residual	3.54	1.88

Number of obs: 58, groups: family, 41

Fixed effects

Total Correct Trials				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	95.38	7.68	12.41	0.0000
Parental BD	-4.70	3.65	-1.29	0.2
SES	-1.07	2.62	-0.41	0.68
Age	0.05	0.018	2.95	**0.003**
Male gender	-1.61	1.02	-1.58	0.11

Appendix xvi: CRT total commission error mixed model

Linear mixed model fit by REML

Formula: score ~ BPD + SES + age + gender + (1 | family)

	AIC	BIC	logLik	Deviance	REMLdev
Model	150.5	164.9	-68.26	118.8	136.5

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	1.15E-17	3.40E-09
Residual	4.97E-01	7.05E-01

Number of obs: 58, groups: family, 41

Fixed effects:

Total Commission Errors				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	0.74	0.56	1.32	0.19
Parental BD	-0.04	0.19	-0.23	0.82
SES	-0.2	0.15	-1.28	0.2
Age	-0.0001	0.003	-0.15	0.88
Male gender	0.25	0.21	1.19	0.23

Appendix xvii: CRT total omission error mixed model

Linear mixed model fit by REML

Formula: score ~ BPD + SES + age + gender + (1 | family)

	AIC	BIC	logLik	Deviance	REMLdev
Model	242.5	256.9	-114.2	218.8	228.5

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	14.16	3.76
Residual	0.03	0.17

Number of obs: 58, groups: family, 41

Fixed effects:

Total Omission Errors				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	-0.32	2.45	-0.13	0.9
Parental BD	1.46	1.2	1.22	0.22
SES	0.23	0.85	0.27	0.79
Age	-0.003	0.002	-1.62	0.11
Male gender	0.03	0.09	0.35	0.73

Appendix xviii: TEACh sustained attention mixed model

Models:

mod1A: score ~ BPD + SES + age + gender + (1 | family)

mod1B: score ~ BPD + SES + age + gender + (SES | family)

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	7	258.78	273.20	-122.39			
Mod 1B	9	262.5	281.05	-122.25	0.28	2	0.87

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	3.79E-14	1.94E-07
Residual	4.36E+00	2.09E+00

Number of obs: 58, groups: family, 41

Fixed effects:

TeaCh Score! Sustained Attention				
Covariates	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	2.08	1.67	1.25	0.21
Parental BD	-0.87	0.58	-1.52	0.13
SES	0.44	0.46	1.0	0.33
Age	0.04	0.01	4.03	**0.0001**
Male gender	-0.62	0.61	-1.02	0.31

Appendix xix: Digit span - forward mixed model

Models:

mod1A: Fscore ~ BPD + SES + age + gender + (1 | family)

mod1B: Fscore ~ BPD + SES + age + gender + (SES | family)

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	7	266.49	280.91	-126.24			
Mod 1B	9	270.5	289.04	-126.25	0	2	1

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.1	0.31
Residual	4.88	2.21

Number of obs: 58, groups: family, 41

Fixed effects:

Forward Digit Span				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	3.93	1.78	2.2	0.0000
Parental BD	-1.02	0.62	-1.65	0.16
SES	-0.22	0.49	-0.44	0.76
Age	0.04	0.01	3.68	**0.01**
Male gender	0.2	0.65	0.30	0.81

Appendix xx: Digit span - reverse mixed model

Models:

mod1A: Rscore ~ BPD + SES + age + gender + (1 | family)

mod1B: Rscore ~ BPD + SES + age + gender + (SES | family)

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	7	260.53	274.96	-123.27			
Mod 1B	9	264.55	283.09	-123.27	0	2	1

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.37	0.6
Residual	4.14	2.03

Number of obs: 58, groups: family, 41

Fixed effects:

Reverse Digit Span				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	5.07	1.7	2.98	0.003
Parental BD	-0.87	0.6	-1.46	0.15
SES	-0.74	0.47	-1.57	0.12
Age	0.02	0.01	2.47	**0.01**
Male gender	-0.87	0.62	-1.40	0.16

Appendix xxi: Digit span - forward-reverse mixed model

Models:

mod1A: FRscore ~ BPD + SES + age + gender + (1 | family)

mod1B: FRscore ~ BPD + SES + age + gender + (SES | family)

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	7	266.7	281.12	-126.35			
Mod 1B	9	269.99	288.53	-125.99	0.71	2	0.7

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.47	0.69
Residual	4.54	2.13

Number of obs: 58, groups: family, 41

Fixed effects:

Forward-Reverse Digit Span				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	-1.11	1.8	-0.62	0.54
Parental BD	-0.17	0.63	-0.26	0.79
SES	0.53	0.5	1.06	0.29
Age	0.01	0.01	1.29	0.2
Male gender	1.06	0.65	1.63	0.10

Appendix xxii: SWM between errors total mixed model

Linear mixed model fit by REML

Formula: score ~ BPD + SES + age + gender + (1 | family)

	AIC	BIC	logLik	Deviance	REMLdev
Model	460.5	474.9	-223.2	458	446.5

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.000	0.000
Residual	172.18	13.12

Number of obs: 58, groups: family, 41

Fixed effects:

Spatial Working Memory (CANTAB) Between Errors Score				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	80.34	10.46	7.68	0.0000
Parental BD	12.34	3.62	3.41	**0.0007**
SES	-2.74	2.88	-0.95	0.34
Age	-0.31	0.06	-5.01	**<0.00001**
Male gender	-4.01	3.84	-1.04	0.3

Appendix xxiii: SWM within errors total mixed model

Linear mixed model fit by REML

Formula: score ~ BPD + SES + age + gender + (1 | family)

	AIC	BIC	logLik	Deviance	REMLdev
Model	254.5	268.9	-120.2	232.6	240.5

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.000	0.000
Residual	3.53	1.88

Number of obs: 58, groups: family, 41

Fixed effects:

Spatial Working Memory (CANTAB) Within Errors Score				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	2.44	1.5	1.63	**0.10**
Parental BD	1.12	0.52	2.16	**0.03**
SES	0.26	0.41	0.62	0.54
Age	-0.02	0.01	-1.92	0.05
Male gender	-0.15	0.55	-0.28	0.78

Appendix xxiv: CVLT-C level of learning mixed model

Models:

mod1A: score ~ BPD + SES + age + (1 | family)

mod1B: score ~ BPD + SES + age + (SES | family)

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	6	427.4	439.76	-202.7			
Mod 1B	8	428.24	445.73	-206.62	2.15	2	0.34

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	7.84	2.8
Residual	73.5	8.57

Number of obs: 58, groups: family, 41

Fixed effects:

Level of Learning				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	16.98	6.47	2.62	**0.0087**
Parental BD	-6.48	2.64	-2.45	**0.01**
SES	-2.38	1.86	-1.28	0.2
Age	0.15	0.04	3.64	**0.0003**
Male Gender	2.1	1.67	1.3	0.3

Appendix xxv: CVLT-C perseverations mixed model

Models:

mod1A: score ~ BPD + SES + age + (1 | family)

mod1B: score ~ BPD + SES + age + (SES | family)

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	6	324.55	336.91	-156.27			
Mod 1B	8	327.47	343.95	-155.73	1.08	2	0.58

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.0000	0.0000
Residual	13.77	3.71

Number of obs: 58, groups: family, 41

Fixed effects:

Perseverations				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	8.55	2.61	3.28	0.001
Parental BD	-3.08	1.76	-1.75	0.08
SES	-1.73	1.29	-1.35	0.18
Age	0.02	0.03	0.56	0.58
Male Gender	1.51	1.21	1.2	0.21

Appendix xxvi: CVLT-C intrusions mixed model

Models:

mod1A: score ~ BPD + SES + age + (1 | family)

mod1B: score ~ BPD + SES + age + (SES | family)

mod1C: score ~ BPD + SES + age + (BPD | family)

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	6	387.08	399.44	-187.54			
Mod 1B	8	388.49	404.98	-186.25	2.59	2	0.27
Mod1C	8	389.71	406.2	-186.86	0.00	0	<2e-16

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.000	0.000
Residual	40.47	6.36

Number of obs: 58, groups: family, 41

Fixed effects:

Intrusions				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	9.94	4.47	2.22	0.026
Parental BD	1.07	1.02	1.04	0.3
SES	-0.67	0.75	-0.9	0.37
Age	-0.03	0.02	-1.46	0.14
Male Gender	0.05	0.01	0.12	0.23

Appendix xxvii: CVLT-C intrusion perseverations mixed model

Models:

mod1A: score ~ BPD + SES + age + (1 | family)

mod1B: score ~ BPD + SES + age + (SES | family)

mod1C: score ~ BPD + SES + age + (BPD | family)

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	6	101.26	113.62	-44.63			
Mod 1B	8	105.26	121.74	-44.63	9.83E-10	2	1
Mod1C	8	105.26	121.74	-44.63	1.30E-10	0	<2e-16

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.000	0.000
Residual	0.29	0.54

Number of obs: 58, groups: family, 41

Fixed effects:

Intrusion Perseverations				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	0.39	0.38	1.01	0.31
Parental BD	0.16	0.15	1.10	0.27
SES	-0.008	0.11	-0.08	0.94
Age	-0.002	0.002	-0.78	0.43
Male Gender	0.07	0.12	0.08	0.92

Appendix xxviii: PAL mean trials to success mixed model

Formula: score ~ BPD + SES + age + gender + (1 | family)

	AIC	BIC	logLik	Deviance	REMLdev
Model	66.2	80.62	-26.1	27.49	52.2

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.07	0.26
Residual	0.05	0.22

Number of obs: 58, groups: family, 41

Fixed effects:

Paired Associates Learning Mean Trials to Success				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	1.91	0.27	7.06	**0.000**
Parental BD	0.29	0.11	2.75	**0.006**
SES	-0.04	0.08	-0.56	0.58
Age	-0.005	0.001	-3.17	**0.002**
Male gender	0.09	0.09	0.99	0.32

Appendix xxix: CNT correct responses mixed model

Models:

mod1A: score ~ BPD + SES + age + gender + (1 | family)

mod1B: score ~ BPD + SES + age + gender + (SES | family)

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	7	419	433.42	-202.50			
Mod 1B	9	422.64	441.8	-202.32	0.36	2	0.83

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	56.07	7.49
Residual	26.99	5.19

Number of obs: 58, groups: family, 41

Fixed effects:

Category Naming Task				
Covariates	**Estimate**	**Std. Error**	**t value**	**p value**
Correct Responses				
Intercept	22.57	7.11	3.18	0.002
Parental BD	-2.85	2.84	-1.00	0.32
SES	-1.28	2.12	-0.60	0.55
Age	0.19	0.04	5.15	**<0.00001**
Male gender	-2.05	2.19	-0.94	0.35

Appendix xxx: CNT perseverations mixed model

Models:

mod2A: score ~ BPD + SES + age + gender + (1 | family)

mod2B: score ~ BPD + SES + age + gender + (SES | family)

	Df	AIC	BIC	logLik	Chisq	ChiDf	Pr(>Chisq)
Mod 1A	7	231.01	245.44	-108.51			
Mod 1B	9	232.95	251.49	-107.47	2.07	2	0.36

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.48	0.69
Residual	2.25	1.5

Number of obs: 58, groups: family, 41

Fixed effects:

Perseverations				
Covariates	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	1.36	1.33	1.02	0.31
Parental BD	0.57	0.48	1.20	0.23
SES	-0.30	0.37	-0.81	0.42
Age	0.003	0.01	0.34	0.73
Male gender	0.14	0.48	0.29	0.77

Appendix xxxi: SOC minimum moves mixed model

Linear mixed model fit by REML

Formula: score ~ BPD + SES + age + gender + (1 | family)

	AIC	BIC	logLik	Deviance	REMLdev
Model	242.3	256.7	-114.1	220.1	228.3

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	1.78	1.33
Residual	1.42	1.19

Number of obs: 58, groups: family, 41

Fixed effects:

Stockings of Cambridge				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Minimum Moves				
Intercept	3.77	1.42	2.65	0.008
Parental BD	-0.46	0.55	-0.84	0.40
SES	0.35	0.42	0.83	0.41
Age	0.02	0.01	3.07	**0.002**
Male gender	-0.73	0.47	-1.58	0.11

Appendix xxxii: SOC total mean initial thinking time mixed model

Linear mixed model fit by REML

Formula: score ~ BPD + SES + age + gender + (1 | family)

	AIC	BIC	logLik	Deviance	REMLdev
Model	1048	1062	-516.9	1101	1034

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	1296627	1138.7
Residual	9999273	3162.2

Number of obs: 58, groups: family, 41

Fixed effects:

Total Mean Initial Thinking Time				
Covariates	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	-5521.36	2703.83	-2.04	0.041
Parental BD	-1359.16	957.92	-1.42	0.16
SES	595.64	752.33	0.79	0.43
Age	62.87	15.60	4.03	**0.0001**
Male gender	789.74	977.58	0.81	0.42

Appendix xxxiii: DANVA 2 all emotions mixed model

Linear mixed model fit by REML

Formula: score ~ BPD + SES + IQ + age + gender + measure + intensity + (1 | family)

	AIC	BIC	logLik	Deviance	REMLdev
Model	678.7	562	-313.2	556.6	609.8

Random Effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.12	0.34
Residual	0.68	0.78

Number of obs: 928, groups: family, 41

Fixed effects:

DANVA 2 Total Errors: 4 emotions combined				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	1.41	0.37	3.86	**0.0001**
Parental BD	0.21	0.10	2.09	**0.03**
SES	0.05	0.07	0.75	0.45
IQ	0.0005	0.002	-0.21	0.83
Age	-0.006	0.001	-4.77	**<0.00001**
Male gender	0.16	0.07	2.17	**0.03**
Child faces	-0.17	0.05	-3.50	**0.0005**
Low Intensity	0.41	0.05	8.42	**<0.00001**

Appendix xxxiv: DANVA 2 angry faces mixed model

Linear mixed model fit by REML

Formula: score ~ BPD + SES + IQ + age + gender + measure + intensity + (1 | family)

	AIC	BIC	logLik	Deviance	REMLdev
Model	611.7	646.2	-295.8	556.6	591.7

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.12	0.34
Residual	0.59	0.77

Number of obs: 232, groups: family, 41

Fixed effects:

Angry				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	0.54	0.65	0.82	0.41
Parental BD	0.22	0.17	1.26	0.21
SES	0.06	0.12	0.50	0.62
IQ	0.002	0.004	0.39	0.70
Age	-0.003	0.002	-1.33	0.19
Male gender	-0.0009	0.14	-0.007	1.0
Child faces	-0.03	0.10	-0.26	0.80
Low intensity	1.0	0.10	9.86	**<0.00001**

Appendix xxxv: DANVA 2 sad faces mixed model

Linear mixed model fit by REML

Formula: score ~ BPD + SES + IQ + age + gender + measure + intensity + (1 | family)

	AIC	BIC	logLik	Deviance	REMLdev
Model	577.7	612.2	-278.9	521.8	557.7

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.12	0.34
Residual	0.5	0.7

Number of obs: 232, groups: family, 41

Fixed effects:

Sad				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	1.74	0.62	2.79	0.005
Parental BD	0.08	0.17	0.47	0.64
SES	-0.03	0.12	-0.22	0.83
IQ	-0.003	0.004	-0.86	0.39
Age	-0.007	0.002	-3.15	**0.002**
Male gender	0.46	0.13	3.47	**0.0005**
Child faces	-0.33	0.10	-3.54	**0.0004**
Low intensity	-0.09	0.09	-0.93	0.35

Appendix xxxvi: DANVA 2 fearful faces mixed model

Linear mixed model fit by REML

Formula: score ~ BPD + SES + IQ + age + gender + measure + intensity + (1 | family)

	AIC	BIC	logLik	Deviance	REMLdev
Model	619.6	654	-299.8	565.7	599.6

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.19	0.43
Residual	0.58	0.76

Number of obs: 232, groups: family, 41

Fixed effects:

Fearful				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	1.1	0.72	1.53	**0.13**
Parental BD	0.40	0.20	2.00	**0.04**
SES	0.15	0.14	1.07	0.29
IQ	0.0009	0.005	0.20	0.84
Age	-0.009	0.003	-3.60	**0.0003**
Male gender	0.30	0.15	1.99	**0.047**
Child faces	-0.25	0.10	-2.50	**0.013**
Low intensity	0.46	0.10	4.56	**<0.00001**

Appendix xxxvii: DANVA 2 happy faces mixed model

Linear mixed model fit by REML

Formula: score ~ BPD + SES + IQ + age + gender + measure + intensity + (1 | family)

	AIC	BIC	logLik	Deviance	REMLdev
Model	360.1	394.5	-170	295.9	340.1

Random effects:

Groups	Variance	Std. Dev.
Family (intercept)	0.19	0.43
Residual	0.58	0.76

Number of obs: 232, groups: family, 41

Fixed effects:

Happy				
Covariate	**Estimate**	**Std. Error**	**t value**	**p value**
Intercept	0.93	0.37	2.5	0.01
Parental BD	0.14	0.10	1.44	0.15
SES	0.02	0.07	0.34	0.73
IQ	-0.002	0.002	-0.71	0.48
Age	-0.005	0.001	-4.00	**0.0001**
Male gender	-0.11	0.08	-1.33	0.18
Child faces	-0.09	0.06	-1.50	0.13
Low intensity	0.29	0.06	5.10	**<0.00001**

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