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The neural basis of genetic vulnerability to bipolar disorder

Jessika Elizabeth Debora Sussmann

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Abstract

Abnormalities of reward processing, decision-making and emotion processing are core features of bipolar I disorder (BD). These processes are closely linked with fronto-striatal and midbrain circuitry. I sought to test whether dysfunctions of these pathways were present in BD and whether they related to genetic vulnerability to illness or resilience.

I recruited twenty-five BD I patients each with their unaffected sibling, and compared them to 24 healthy age- and gender-matched controls. In chapter 1, I provide a research background and literature review. Chapter 2 describes the neuropsychological assessments which demonstrated trait-related deficits in working memory with slower processing speed representing an endophenotype.

Chapter 3 describes the implicit/ explicit facial emotion processing task performed during event-related functional MRI (erfMRI). Pairwise comparisons demonstrated implicit processing was associated with increases in lingual gyrus and insula activations and explicit processing elicited reduced fusiform activations in patients compared with controls. Increased posterior cingulate activations and reductions in putamen and cerebellar activity were found in siblings compared to controls, and reductions in parietal activations were noted in siblings compared to their ill relatives. These findings suggest over-activations in regions involved in facial expression recognition and attentional shifting (lingual and insula respectively) and deactivations in a region important for the perception and recognition of faces (fusiform) represent correlates of disease expression. Additionally regional deactivations associated with category learning and attentional processing (parietal, putamen and cerebellar) and increased activations in a region involved in emotional salience (posterior cingulate) may represent adaptive responses associated with resilience.

Chapter 4 describes an instrumental reward-learning task performed during erfMRI. Data were analysed at whole brain level and using a priori region of interest analyses in ventral striatum/midbrain and prefrontal cortex (PFC). Results included increased ventral striatum activation in association with the difference between observed and expected rewarding outcomes (the prediction error (PE)) in patients compared to controls.

Decreased prefrontal activations were seen in the patient and sibling groups compared to controls in association with the learning of the value of the conditioned stimulus. These findings suggest that i) PE associated circuitry (striatal) overactivation, and ii) prefrontal deactivations underlie the genetic vulnerability to BD.

Lay Summary

Abnormalities of reward processing, decision-making and emotion processing are core features of bipolar I disorder (BD). These processes are closely linked with fronto-striatal and midbrain circuitry. We sought to test whether dysfunctions of these pathways were present in BD and whether they were related to genetic vulnerability to illness, or resilience. Twenty-five bipolar I patients each with their unaffected sibling, were compared to 24 healthy age- and gender-matched controls using two functional magnetic resonance imaging tasks. A reward learning task (where expectations about a financial reward were created and then altered unexpectedly) demonstrated increased activations in a reward region (the ventral striatum) in association with the difference between observed and expected rewarding outcomes (the prediction error) in patients compared to controls. Decreased prefrontal activations were seen in the patient and sibling groups compared to controls in association with the learning of the value of the stimulus. These findings suggest that greater activity in reward regions are associated with bipolar disorder itself while prefrontal deactivations underlie the genetic vulnerability to BD.

A facial emotion processing task (where emotional faces were presented and participants were asked either whether they were 'emotional or not', or 'male or female') demonstrated increased activations in regions associated with facial expression recognition and attentional shifting and reduced activation in a region important for the perception and recognition of faces in patients compared to controls. In siblings, increased activations were found in a region involved in emotional salience and reductions in regions involved in category learning and attentional processing compared to controls. These findings suggest that greater activity in regions associated with facial expression recognition and attentional shifting and reduced activity in a region important for the perception and recognition of faces relate to bipolar disorder. Additionally, altered activity in regions involved in emotional salience, category learning and attentional processing may represent adaptive responses associated with resilience.

Declaration:

This thesis has been entirely composed by me, Jess Sussmann. I designed the study and acquired funding as Primary Investigator from a Wellcome Trust Research Training Fellowship for the study. I personally recruited the participants, conducted all the clinical, psychological and personality assessments and their subsequent analyses. I supervised the adaptation of the functional magnetic resonance imaging paradigms with an expert in task design, Dr Liana Romaniuk. I conducted the initial pre-processing and quality checks of all scans. I supervised the development of the prime contrasts of interest at the individual subject level and I personally conducted the group level comparisons of these contrasts. The work has not been submitted for any other degree or professional qualification. Any included publications to which I am an author have been achieved as a member of a research group within the Department of Psychiatry at the University of Edinburgh.

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Abbreviations Table:

Abbreviation	Meaning
ACC	Anterior Cingulate Cortex
BD (BDI, BDII, BD NOS)	Bipolar disorder (Bipolar disorder I, Bipolar disorder II, Bipolar disorder not otherwise specified)
BIS	Barratt Impulsiveness Scale
BOLD	Blood oxygen level dependent
CCRTT	Cool's cued reaction time task
CR	Conditioned response
CS	Conditioned stimulus
CSF	Cerebrospinal fluid
CTR	Control participant
DA	Dopamine
DLPFC	Dorsolateral prefrontal cortex
DSM	Diagnostic statistical manual
DSST	Digit symbol substitution test
EPI	Echo planar images
ERP	Event related potential
fMRI	Functional magnetic resonance imaging
FWE	Family wise error
GABA	gamma-Aminobutyric acid
GWAS	Genome wide association study
HAM-D	Hamilton depression rating scale
HR (HR well)	High risk (High risk well)
ICD	International classification of disease
IDED	Intradimensional / extradimensional shift test
MDD	Moderate depressive disorder
MNI	Montreal neurological institute
NART	National adult reading test
NMDA	N-Methyl-D-aspartic acid
OFC	Orbital frontal cortex
PANSS	Positive and negative syndrome scale
PE	Prediction error
PET	Positron emission tomography
ROI	Region of interest
RT	Reaction time
SCID	Structured clinical interview for DSM
SD	Standard deviation
SPM	Statistical parametric mapping
SSD	Stop signal delay
SSRT	Stop signal reaction time
PCC	Posterior Cingulate Cortex
US	Unconditioned stimulus
WASI	Wechsler Abbreviated Scale of Intelligence
VLPFC	Ventrolateral prefrontal cortex
VTA	Ventral tegmental area
YMRS	Young mania rating scale

1 Chapter 1: Emotion processing in Bipolar Disorder: a review of the literature pertaining to facial emotion and reward processing.

1.1 Introduction

Bipolar Disorder (BD) is a severe and enduring mental illness and has been identified by the World Health Organisation as the 6th leading cause of disability adjusted life years in the world among people aged 15-44 years (Murray, 1997). Affecting approximately 1-3% of the population (Merikangas, 2011), the economic impact of this disease in the United Kingdom is estimated at approximately £2 billion per annum (Gupta, 2002). BD is highly heritable (Hamshere, 2011) but the underlying pathophysiology remains poorly understood.

1.1.1 Clinical syndrome

Bipolar disorder is defined by the episodic occurrence of elevated mood in both DSM 5 (American Psychiatric Association, 2013) and ICD 10 (World Health Organisation, 1992) and can be conceived as a syndrome affecting the ability to regulate mood states, inhibitory control and cognitive function. One of the difficulties with studying bipolar disorder is that there are both state (depressed, manic, euthymic) and trait aspects to the condition and therefore an individual's presentation and functioning may vary dramatically depending on the nature and severity of their current symptoms. This heterogeneity, along with the limited financial investment, may explain the lesser quantity of research in comparison to other severe, chronic mental illnesses such as schizophrenia.

1.1.2 Family Studies

BD is highly heritable (Craddock, 1999). First degree relatives have an approximate lifetime risk of developing the disorder of 5-10% and up to 75% if they have 2 affected first degree relatives compared to 0.5-1.5% in the general population (Craddock, 1999; Bechdolf, 2012; Smoller, 2003). Twin studies which included Bipolar I and Bipolar II Disorders (McGuffin, 2003; Bertelsen, 1977) have demonstrated concordance rates of 0.67 for monozygotic and approximately 0.20 for dizygotic twins. When only probands

with BD I were sampled (Kieseppa, 2004), the probandwise concordance rates decreased to 0.43 for monozygotic twins and 0.06 for dizygotic twins. Using models that incorporated genetic and specific environmental factors that explained the variance in liability, revealed a heritability estimate of 0.93 (Kieseppa, 2004).

Age of onset in Bipolar I Disorder for the majority of cases is before the age of 30 years (Bellivier, 2003) and strong correlations have been demonstrated with the age of onset between siblings and probands (Bellivier, 2003; Leboyer, 1998; Kendler, 1992) but not with gender (Leboyer, 1998). Unaffected relatives share some of the genetic material underlying the neurobiology associated with vulnerability for the disorder (Hasler, 2006). Additionally there is evidence of altered neuropsychological performance (Bora, 2009), structural (McDonald, 2005) and functional (Drapier, 2008; Surguladze, 2010) brain deficits in healthy relatives. The presence of these qualitatively similar deficits in unaffected co-twins, siblings and offspring therefore suggests that at least some of the abnormalities relate to familial (mainly genetic) risk, independent of environmental or illness effects.

Therefore, analyses of healthy siblings of bipolar probands who are passed the period of high-risk of developing the disorder due to i) being over 30 years and ii) being significantly older than the age at which their siblings developed the disorder would further our understanding of the mechanisms that underpin the pathology of Bipolar Disorder. Findings in siblings that appear intermediate between controls and patients could be hypothesized to demonstrate vulnerability markers as confounds regarding the heterogenous influence of symptoms, the pathology of disease progression and effects of medications are not present in these individuals. This research paradigm also offers an opportunity to study resilience factors.

1.1.3 Endophenotypes

There is strong evidence from genetic epidemiological research including family, twin and adoption studies, as described above, that genes affect the predisposition to BD. Genome

wide association studies (GWAS) in bipolar disorder have identified some rare and common risk variants with weak effects which account for only a small proportion of the variance in liability (Craddock, 2013). These methods of gene identification have yielded few results but confirmed the disorder involves many genes of small effect. Thus strategies that develop our knowledge of biological pathways and associate this with genetic data are likely to improve our understanding of the pathology of the disorder.

Studying an intermediate phenotype or endophenotype would enable identification of relevant neurobiological pathways that are closer to the genetic basis of the disorder and could identify cohorts with greater genetic enrichment for future analyses.

Endophenotypes are defined by Gottesman et al as “neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological in nature. Endophenotypes represent simpler clues to genetic underpinnings than the disease syndrome itself, promoting the view that psychiatric diagnoses can be decomposed or deconstructed, which can result in more straightforward and successful genetic analysis.” (Gottesman, 2003).

There are five specific criteria for endophenotypes:

- i) The endophenotype is associated with illness in the population.
- ii) The endophenotype is heritable.
- iii) The endophenotype is primarily state-independent.
- iv) Within families, endophenotype and illness co-segregate.
- v) The endophenotype found in affected family members is found in non-affected family members at a higher rate than in the general population.

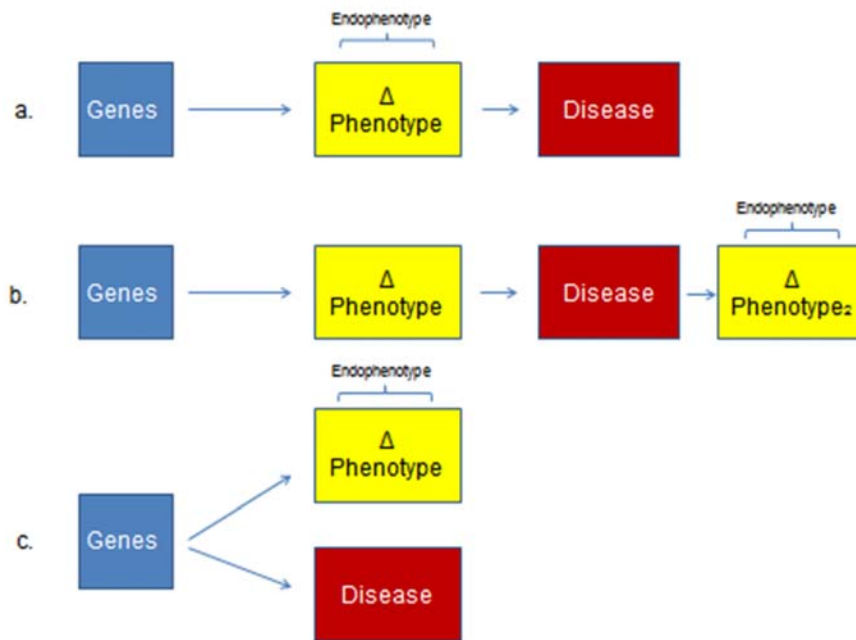


Figure 1.1: This figure demonstrates how an endophenotype may relate to the underlying genes and resultant disease. a) This is the classic assumption that an endophenotype is intermediate between genes and disease. b) An endophenotype may be the result of a disease process. c) An endophenotype may not lead to the development of the disease but still be associated with the genetic underpinning.

Studying siblings is therefore an appropriate way to detect endophenotypes but using this cohort to discover endophenotypes will not enable the distinction between an intermediate phenotype (example a.) and a phenotype that does not result in disease (example c.).

1.1.4 Resilience

Researching the neurobiology of resilience appears to be a more recent phenomenon in the literature of BD. There are a variety of ways to define resilience and these have developed from the study of ecosystems (Carpenter, 2001). In keeping with Frangou,

2012, resilience to psychiatric disorders is defined based on a lifetime absence of “adverse” clinical outcomes and refers to resilience to overt disease expression. This is the definition explored in this thesis.

As described above, there is evidence of altered cognitive performance (Arts, 2008), brain structure (McIntosh, 2004; McDonald, 2004) and function (Drapier, 2008; Thermenos, 2010; Linke, 2012) in those at genetic risk for BD. But we remain unable to specify the risk factors that are associated with an individual’s predisposition. Additionally, understanding the contribution of shared non-genetic, or environmental factors is difficult to quantify.

In this study, I have recruited a single sibling pair from each family consisting of an individual with BDI and their sibling who does not fulfil criteria for a mood disorder. This should enable us to look at resilience where effects are specific to the sibling group and therefore are not likely to relate to shared environmental factors. Resilience in this study will only be considered in relation to brain functional findings using MRI that differentiate healthy siblings from their ill relatives and controls which would suggest adaptive changes. Features that are shared by the siblings and their ill relatives in comparison to healthy controls will be conceived as evidence of shared genetic expression and potential vulnerability factors. The main caveat to this definition of resilience or adaptive functioning is that the diagnostic status of the healthy relatives could change over time. To minimize this likelihood, the cohorts have been recruited over the age of 30 years and all healthy siblings are passed the age at which their ill relative was diagnosed with BD, reducing the likelihood of them developing the disorder.

Previous findings suggestive of resilience in BD have demonstrated decreases in medial frontal cortex blood flow after induction of sadness in patients and increases in siblings (Kruger, 2006) and under-activation in superior frontal gyrus and over-activations in

lingual gyrus in well relatives elicited by negative emotional images (Sepede, 2015). Connectivity analyses during a cognitive task revealed positive coupling of ventrolateral (VLPFC) and dorsolateral prefrontal cortex (DLPFC) in healthy relatives suggesting greater functional connection while connectivity between VLPFC and insula and anterior cingulate cortex (ACC) showed dysfunction similar to that seen in the ill relatives (Pompei, 2011). These studies have, however had small sample sizes (<n=10), have not taken the approach of paired matching between the proband and unaffected relative, and/or have not specifically selected for individuals passed the typical age of onset, as in the current thesis.

1.2 Emotion Processing

Locke referred to 'emotion' in the sense of a physical stirring, agitation or perturbation in 1692 and by 1841 Emerson wrote "In poetry... the emotions of benevolence and complacency... are likened to the material effects of fire" (Stevenson, 2010). Thus the definition of 'emotion' has been and remains diverse. However, within a scientific paradigm, emotions have been associated with physiological changes that together enable an animal to avoid harm and gain advantage. Human emotion processing is considered more complex and difficult to comprehend out-with conscious interpretation, expression of 'feelings' or resultant actions. The neurobiology underpinning emotion processing can be explored in humans with experiments that, for example, assess the recognition of emotions, and others that look at decision-making based on the positive or negative consequences of those choices.

1.2.1 Emotion processing in Bipolar Disorder

Emotion processing is altered in individuals with bipolar disorder (Phillips, 2008). During a manic episode, an individual may experience elation or euphoria with intense interest in goal-directed activities. However this occurs without the monitoring and recognition of the negative consequences of their actions that would be present when they were well. Thus their decision-making may be impaired and reward-seeking behaviours amplified.

Additionally they are often optimistic and happy and focused on their own experiences such that they are less able to recognise the effects they are having on others.

When depressed, patients may lose the ability to experience pleasure and become preoccupied with feelings of worthlessness and hopelessness. They withdraw from social situations and suffer deterioration in memory, concentration and motivation. Their decision-making is impaired, rewarding activities are not considered rewarding and affected individuals report their landscape as grey and dreary, impacting on their experience of others. It is these characteristics of altered ability to recognise the emotions of others and the change in behaviours related to rewarding activities that seem particularly relevant to bipolar disorder and therefore important to study further.

Numerous behavioural and functional magnetic resonance imaging studies have been conducted over the past 20 years, contributing significant advances to our knowledge of the neural circuitry abnormalities that underpin BD. In keeping with clinical findings, these results converge to describe dysfunctions in brain circuitry that subserve emotion processing and regulation (Phillips, 2008).

1.3 Literature summary of Facial emotion processing:

1.3.1 Introduction

I intend to investigate emotion processing in patients with bipolar disorder, their first degree relatives and a group of matched healthy controls. I have chosen to first focus on facial emotion processing since there is a strong premise for deficits in this domain to be fundamental to the key features in the disorder. In this chapter I will provide a brief critical view of the current emotion processing literature. Secondly I will examine the reward processing literature in bipolar disorder, which at the time of writing is much less extensively studied than that of emotion processing. Reward processing is increasingly

viewed as central to the motivational and behavioural features of the disorder and is rapidly developing emergent field of research.

Initially, I will review both emotion processing paradigms associated with these respective domains in relation to healthy individuals and subsequently each will be discussed regarding how they relate to bipolar disorder.

Facial expressions are powerful nonverbal displays of emotion that signal information to others including valence information that is vital for complex social communication. Recognising and processing facial expression is important for human interaction as it enables us to discern another person's emotional state and provides cues as to how to respond to them.

Six different facial emotions have been identified as universal across cultures including happiness, sadness, fear, disgust, surprise and anger (Ekman, 1971). Facial emotion processing requires interpretation of the specific arrangement of facial muscles and preparation for a consequent behavioural response that takes into account additional information related to the environment and other factors. For instance, a display of sad facial expression has been linked to inhibition of aggression and elicitation of pro-social behaviour (Blair, 1999).

Of note, as in other areas of task-based functional imaging research, methodological factors such as task design, imaging parameters and analysis, as well as diversity in the participants' demographics and small sample sizes of individual studies contribute to the heterogeneity of results within the existing neuroimaging literature.

The cognitive systems being investigated in facial emotion processing begin with visual perception of the facial stimuli. Initially facial identity and subsequently facial expression have been proposed as the two main strands of visual processing and evidenced in both brain damaged patients and functional imaging studies (Adolphs, 1998; Calder, 2005; Hoffman, 2000). The neural substrates underpinning the first involve regions such as the fusiform face area (Kanwisher, 2006) which receives basic perceptual representations of faces from an occipital face-selective area (Fairhall, 2007). Those governing changeable facial information, for instance expression are considered to involve superior temporal sulcus (which responds selectively to emotional expression and eye gaze (Engell, 2007) and limbic regions (such as the amygdala), which respond selectively to fearful or unhappy facial expressions (Morris, 1996).

A recent detailed activation-likelihood estimate (ALE) meta-analysis approach of 105 facial emotion processing studies expanded on the above to indicate that processing of the emotion from facial expressions draws on a distributed network of regions with diverse psychological processes (Fusar-Poli, 2009). Here it was reported that the processing of emotional faces was associated with increased activation in a number of visual areas, along with limbic areas (amygdala and parahippocampal gyrus, posterior cingulate), temporal and temporoparietal areas, medial frontal gyrus, subcortical areas and the cerebellum. The authors suggest that early visual perceptual elements involve occipital and temporal cortices, and that subsequent processing involving the amygdala and frontal regions link these elements to the processing of emotional content.

1.3.2 Facial emotion processing in Bipolar Disorder

Facial emotion processing has been extensively studied in bipolar disorder, Indeed, altered affect recognition has been a relatively consistent finding in bipolar individuals and their relatives (Brotman, 2008; Bozikas, 2006; Getz, 2003; Lembke, 2002; Verderman, 2012). Notably, these tasks also engage the neural circuitry considered to be affected in the disorder (Savitz, 2009).

The prevailing model of bipolar disorder describes an imbalance between cortical and subcortical neural circuitry (see Figure 1.2) such that reduced dorsolateral prefrontal and orbito-frontal activation is associated with disinhibition of limbic structures such as, the amygdala and striatum (Sheline, 2003; Strakowski, 2005). Therefore, one could propose that there are impairments in higher level cognitive abilities to monitor and assess the more base or innate emotion processing of the amygdala. This results in behaviours that are unrestrained or unchecked and would be in keeping with some of the features of bipolar disorder, such as mania, disinhibition and anhedonia. The behavioural and imaging literature of facial emotion processing studies in bipolar disorder are summarised below respectively.

Proposed **reduced responsiveness** in areas of brain associated with cognitive control

DLPFC: Dorsolateral prefrontal cortex
VLPFC: Ventrolateral prefrontal cortex
DMPFC: Dorsomedial prefrontal cortex
ACG: Anterior cingulate gyrus

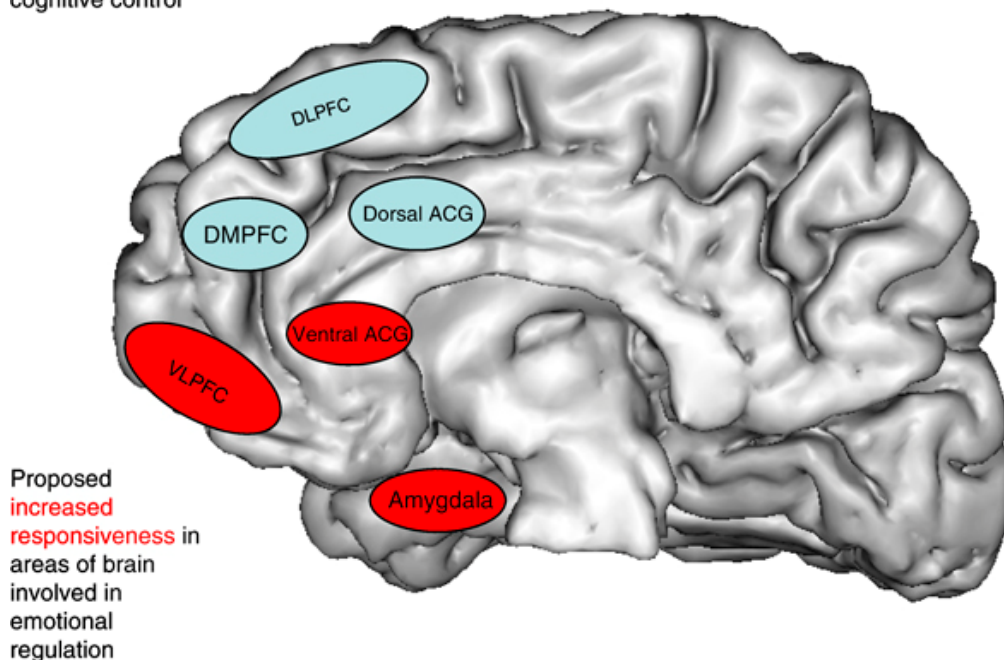


Figure 1.2: This figure represents proposed areas of under- and over-responsiveness in euthymic bipolar disorder in neural networks responsible for cognitive control and emotion regulation respectively from Langan,2009.

1.3.2.1 Behavioural Studies

Task design

Facial affect processing has been investigated using a variety of paradigms. Here I will describe some of those relevant to the current study. Most have employed the same standardised stimuli (Ekman faces) where the six universal emotions are posed by middle-aged, Caucasian faces in still black and white photographs. These can either be used as binary-based stimuli where each emotion is either present fully or absent (neutral condition), or, the intensity of emotional valence can be altered in increments of 10% from neutral (0%) to maximum (100%) or morphed for even greater ranges allowing a more nuanced understanding (Harmer, 2002) but potentially incorporating other biases, for instance reaction time and processing speed issues. Task design can also vary from i) explicit labelling of specific emotions, or (ii) implicit emotional recognition, where the decision requested is based around a non-emotional component of the stimuli (e.g. gender decision). Similar to above, stimuli can be binary or morphed according to degrees of intensity of emotion..

Facial affect studies

Due to the variability of symptomatic state in bipolar disorder, and potential impacts on behaviour, I propose to describe the findings below in relation to the state of the participants (euthymic, manic and depressed individuals separately) and subsequently discuss the results in relatives, before drawing together a summary of main findings.

Euthymia

Euthymia is derived from the Greek for “eu” meaning ‘well’ and “thymus” meaning ‘mind’. Euthymic individuals by medical definition are not experiencing marked mood symptoms, suggesting that differences observed during this mental state potentially represent trait effects. Euthymic individuals have been reported to be less accurate at matching facial affect than controls when shown two different facial stimuli with the same affect, although they showed no deficits in facial affect labelling per se (Addington, 1998). Using a task implementing morphed increments of 10% points from neutral (0%) to the 100% emotion presentation, euthymic individuals have also been shown to be less accurate at recognising the emotion of fear versus other emotions (Venn, 2004; Yurgelun-Todd, 2000), though more accurate in the recognition of disgust. The authors proposed that this difference may relate to decreased self-esteem and social functioning that persists even during euthymic phases of illness.

Mania

Higher scores on the YMRS (used in the 20 studies) to define patients as being within a manic phase of illness have demonstrated non-significant trends towards worse performance in a meta-analysis on emotion perception tasks (N = 20 studies) (Kohler, 2011). Although Kohler et al incorporated 51 studies, they combined patients with MDD and bipolar disorder for the majority of their analyses and only revealed a moderate deficit in emotion perception in these groups compared to controls (effect size = -0.49, 95%CI = -0.57 to -0.41). They subsequently assessed a variety of demographic and clinical variables as potential moderators of the results, including mania, with limited success, implicating the heterogeneity and small samples sizes of the original studies.

Individual studies have indicated that manic bipolar patients make more affect recognition errors in general versus healthy controls (Getz, 2003). There was however no euthymic bipolar group in this study, so it is unclear whether these findings reflect general deficits associated with illness, or current state effects of the patients. (Getz, 2003). In other

studies, manic bipolar patients have been reported to have deficits in recognising specifically negative affect such as sadness (Lennox, 2004), fear and disgust (Lembke, 2002). This occurred to an even greater extent than in euthymic individuals with bipolar I and II disorders (Lembke, 2002). Negative correlations between manic symptom scores, the recognition of negative emotions (Harmer, 2002), specifically sadness (Lembke, 2002) and a bias towards positive emotion recognition (Murphy, 1999) have also been demonstrated. It is important to note that due to their clinical presentation, the testing of individuals with mania is particularly challenging, especially in relation to findings below regarding the acquisition of imaging data.

Depression

Bipolar depression has been reported to affect facial emotion processing in a mood congruent manner. Negative correlations have been found between depressive symptoms and the recognition of happiness (Rubinow, 1992), while positive correlations were seen with the recognition of sad faces (Gray, 2006). Neutral faces are also increasingly identified as sad (Gur, 1992; George, 1998). Kohler's meta-analysis (Kohler 2011) of 51 studies of emotion perception in depression and BD revealed that self-rated depressive symptoms using the Beck Depression Inventory (12 studies) were a significant predictor of poor task performance ($N = 12$, mean \pm S.D. = 18.6 ± 9.4) ($Z = -4.81$, $p < 0.001$) however, the clinician-rated Hamilton Rating Scale for Depression (used in 23 studies) was not found to be a moderator of performance ($N = 23$, mean \pm S.D. = 10.6 ± 8.2) ($Z = -0.45$, $p = 0.65$).

Unaffected relatives

A study by Brotman and colleagues (2008) of behavioural facial affect processing in BD involved a paediatric sample. Researchers presented gradations of the six facial emotions to children with BD, unaffected children with a first-degree relative with BD and controls. Young unaffected first degree relatives of individuals with bipolar disorder were poorer than controls and similar to bipolar probands at labelling child and adult facial

expressions, however there were no interactions that determined a group difference based on a specific emotion (Brotman 2008). This study was, however, limited in several aspects. The Ekman faces used were not developed for a paediatric population. The slower performances of bipolar probands and first degree relatives may have been a feature of processing speed rather than difficulty with affect identification.

Our own currently unpublished data on a prospective cohort at familial high risk for BD (see Table 1.1), using the Ekman 60 task, found no differences between unaffected first-degree relatives of BD patients compared with controls on total accuracy of emotional recognition. On analysing emotions separately, unaffected first-degree relatives recognised significantly more fearful faces than controls ($p=0.03$, $U=1005.5$, $Z=-2.102$). Correct fear labelling correlated inversely with the Hamilton Rating Scale for Depression across the groups (Spearman's $\rho=-0.24$, $p=0.01$) reflecting findings in patient groups.

Table 1.1: Bipolar Family (High Risk) Study: Ekman 60 facial emotion labelling task results for adults under 30 years who were either first degree relatives of individuals with bipolar I disorder (HR) who did not have a mood disorder (HR Well) or had developed a major depressive disorder (MDD) or controls (CTR) without illness matched for age and socio-economic status.

Emotion Median (IQR)	Controls N=48	HR Well N=55	MDD N=16	ANOVA CTR vs all HR (X^2 , p)	ANOVA CTR, HR Well, MDD (X^2 , p)
Fear	7.0 (3.00)	8.0 (3.00)	4.0 (5.00)	17.43, 0.07	13.73, <0.01
Happiness	10.0 (2.00)	8.0 (2.00)	10.0 (0.00)	2.09, 0.55	1.44, 0.49
Sadness	8.0 (2.00)	8.0 (2.00)	7.0 (4.00)	9.29, 0.51	2.70, 0.26
Anger	8.0 (2.00)	8.0 (2.00)	8.0 (3.00)	5.04, 0.75	4.43, 0.11

Disgust	8.0 (3.00)	8.0 (2.00)	7.0 (3.00)	11.02, 0.27	5.67, 0.06
Surprise	9.0 (2.00)	9.0 (2.00)	9.0 (2.00)	6.31, 0.28	1.55, 0.46
Total	50.0 (6.00)	51.0 (6.00)	45.5 (9.75)	30.31, 0.11	12.72, <0.01

Demographic factors

A meta-analysis of 51 studies of emotion perception abilities (Kohler 2011) reported on the effects of demographic factors. Older participants perform better at facial emotion perception (patients ($Z = 4.61$, $p < 0.001$) and healthy controls ($Z = 4.18$, $p < 0.001$) (Kohler, 2011) implying that greater life experience and more social interaction may improve performance. Men appear to perform less well than women in healthy controls ($N = 47$ mean \pm S.D. = 50.2 ± 20.5) ($Z = -2.58$, $p = 0.01$) and there was a similar trend finding with the percentage of men in the patient groups ($N = 48$, mean \pm S.D. = 46.5 ± 21.8) ($Z = -1.85$, $p = 0.065$) (Kohler 2011). Higher educational attainment reduces impairments in patients ($N = 27$, mean \pm S.D. = 13.8 ± 1.5) ($Z = 3.42$, $p < 0.001$) but not controls ($N = 27$, mean \pm S.D. = 14.2 ± 1.2) ($Z = 1.39$, $p = 0.16$) suggesting possible cognitive reserve that may improve performance. Age of onset, duration of illness and hospitalization (a proxy for severity of illness) had no relationship to performance.

Summary

There are many behavioural studies of facial affect in bipolar disorder, however these are blighted by small numbers of participants, variations of task design, and involve differing mental states within a bipolar presentation. The above summary of the literature has therefore emphasised findings from meta analyses and focussed on categories of patients studied according to specific mood states.

Overall, a number of studies have demonstrated that in bipolar disorder facial identification remains intact while determining the emotional valence of an expression is impaired (Bozikas, 2006). These impairments are reported to occur in all phases of the illness. However, certain mental states have shown consistent deficits in the labelling of specific emotions. There are also studies that have demonstrated unimpaired emotion recognition (Harmer, 2002), highlighting the possibility that altered emotion processing may be a state-related deficit that is symptom dependent rather than a trait effect.

Taking into account the small sample sizes, variation in task design and difficulties in BD of insuring a specific state presentation, there is support for state-related altered perception of facial emotions in BD. Positive and negative biases exist during mania and depression respectively, although the relationship to symptoms seems less strong in mania. Findings are less consistent in euthymic patients, thus it is not possible to comment on trait-related features. Importantly however, these studies attempt to address facial emotion recognition, they do not investigate emotion regulation which could be considered of greater relevance to the pathology of BD.

1.3.2.2 Functional Magnetic Resonance Imaging Studies

I used functional magnetic resonance imaging (fMRI) to investigate brain activity in this study. This non-invasive technique detects changes in blood oxygenation and flow within the brain. Blood oxygenation levels vary with neural activity. When an area is more active, more oxygen is consumed by that region resulting in greater flow of oxygenated blood to that area. Importantly the magnetic properties of oxygenated and deoxygenated blood differ. FMRI uses this blood-oxygen-level dependent (BOLD) contrast change in response to neural activation to create images of the changes in blood flow, or the haemodynamic response, relating to neural activity. 'Activation maps' can then be generated using statistical software that result in images of colour coded regions representing greater or lesser activity either across the whole brain or within a specified region. These maps are then compared within and across groups to investigate differences in brain activity.

There are many considerations with this technique. Neuronal activity is not measured directly. fMRI is unable to define details such as the number of firing neurons and how they influence another region of activity. There is a lot of 'noise' from routine changes in blood flow and many criticise the statistical techniques that may result in false positives. The meaning of the changes in BOLD signal have also been questioned. The rise in blood oxygen levels may occur in preparation for as well as during neuronal activity (Sirotnin, 2009) or maybe related to factors other than neuronal activity (Maier, 2008). Yet fMRI remains the technique that best enables non-invasive research into brain activity in vivo.

In clinical studies the main contrasts are usually between patient and control groups. If a regional group difference in activity is found, the interpretation of that finding could be either: i) the cause of the illness, ii) a consequence of illness, iii) an adaptation to the illness, or (iv) due to confounding effects of medication. However, this is further complicated by performance of the task in the scanner, which is often designed to be matched between groups for ease of interpretation. It is also important to consider that regions of the brain do not act in isolation.

It is possible as a body of work develops in a field and results are replicated to conclude an association between an fMRI result and the cognitive process being performed at the time of measurement. However, it is not possible to infer that there is a difference in cognitive processing by finding a difference in BOLD signal in a region between patients and controls. Cognitive systems are highly complex and multiple. The regional change in activity may relate to other processes that are concurrent or other factors such as medication effects.

There is now a substantial literature on human face processing using functional magnetic resonance imaging. The specific neural circuitry that underpins these processes is

reported to include the ventromedial and dorsolateral prefrontal cortex, orbito-frontal cortex, the anterior cingulate cortex, fusiform gyrus, inferior temporal gyrus, occipital gyrus, amygdala, ventral striatum, hippocampus, insula and the dorsomedial nucleus of thalamus (Gur, 2002; Fusar-Poli, 2009). These findings are primarily derived from a voxel-based meta-analysis of 105 fMRI studies that yielded a sample of 1600 healthy participants. Although the authors used methods to address the effects of age, sex and magnetic intensity, they did not weight the results on the level of statistical significance reported in each study and therefore, they could not represent the relative strengths of the activation findings of each region. Amygdala activation has been most consistently associated with emotion processing especially with fear (Adolphs, 1994) but also happy and sad expressions (Fusar-Poli, 2009; Gur, 2002). Disgusted and angry faces have been primarily associated with insula activation (Harmer, 2002).

The effects of psychotropic substances on facial processing

Using healthy controls and giving single doses of mood inducing substances has improved our understanding of the neural correlates of mood states without the confounds of symptoms, course of illness and medication. In one implicit emotional processing study of acute tryptophan depletion versus a sham condition (double blinded), Fusar-Poli, 2007, reported differential effects on activation during processing of happy and sad faces according to tryptophan condition, concluding that particular regions (specifically the putamen and lateral temporal cortex) were differentially effected by serotonin modulation depending on emotional valence. Harmer's group have performed numerous studies using these techniques. A single dose of the atypical antidepressant mirtazapine, resulting in amygdala-hippocampal and frontostriatal under-activations to fearful faces and over-activations in the same regions to happy faces (Rawlings, 2011). Attenuation of amygdala activations to aversive facial expressions have also been shown with very limited exposure to citalopram, an SSRI (Harmer, 2006; Del-Ben, 2005; Murphy, 2009). One week of treatment with citalopram and reboxetine has been associated with increased amygdala responses to happy facial expressions (Murphy, 2009). The

response of the cingulate cortex to emotional faces has been shown to predict the response to serotonergic antidepressant treatment (Davidson, 2003; Fu, 2004).

1.3.2.3 Imaging the substrates facial emotions

Imaging activations have varied most noticeably with mental state although task design can also significantly impact the heterogeneity of findings as described earlier.

Euthymia

In euthymic bipolar individuals, abnormal recruitment of subcortical regions are the most common findings reported, often in the absence of significant relationships with symptoms, suggesting trait rather than state effects (Phillips, 2008; Yurgelun-Todd, 2000; Strakowski, 2004; Hassel, 2009). These are regions typically associated with emotion regulation. As these alterations in brain function were reported to occur in the absence of symptoms, there are several inferences that can be drawn: i) these are pathological features related to the underlying biology of the disorder but are in themselves not enough to cause symptoms or are not related to the symptoms being investigated, ii) symptoms are being suppressed by other mechanisms such as medications, or iii) these increases in regional activity are compensatory in order to maintain euthymia. In particular, amygdala, striatal and caudate (Delvecchio, 2012; Blumberg, 2006) over-activations to happy, sad and fearful (Yurgelun-Todd, 2000) expressions have been consistently reported. Meta-analyses concur with subcortical/limbic over-activations; left parahippocampal gyrus to happy & fearful faces, left putamen, left pulvinar thalamus in bipolar patients to fearful faces (Delvecchio, 2012), hippocampus, amygdala, superior temporal gyrus and insula (Kupferschmidt, 2011). These findings are consistent with the prevailing view that bipolar disorder is associated with increased limbic activation during emotional processing (Savitz, 2009). The parahippocampal gyri lie very close to the amygdala and are thought to activate together during emotional processing (Fusar-Poli, 2009). All these meta-analyses described detailed study characteristics, inclusion and exclusion criteria and discussed publication bias although most (Delvecchio, 2012; Kupferschmidt, 2011) did not include funnel plots or sensitivity analyses. However, several limitations need consideration regarding these findings. These meta-analyses

were based on studies with small samples sizes (n between 3-38 per group) that varied in their emotional processing paradigms, and analysis techniques at the time did not allow for a weighting related to the significance of the activation finding in each of the original studies.

Cortical activations have most consistently demonstrated reductions in euthymic patients, for instance, DLPFC (Hassel, 2009), OFC (Liu, 2012) and ventral ACC (Liu, 2012), to fear and happy faces (Delvecchio, 2012). However, over-activations in DLPFC to happy and fearful faces (Yurgelun-Todd, 2000), in ventrolateral PFC (Lawrence, 2004) and in ACC have also been noted (Brotman, 2008). Meta-analyses found bilateral inferior frontal gyrus and left anterior cingulate gyrus hypo-activations in bipolar patients to fearful faces and right anterior cingulate gyrus hypo-activations to happy faces (Lennox, 2004; Brotman, 2008). Similar caveats apply regarding the original studies that were used for these meta-analyses, however, the majority of emotional processing studies available at the time were incorporated into these meta-analyses.

Mania

Elevated mood (symptoms) have been associated with diminished responses in right PFC to both fearful and neutral stimuli (Liu, 2012). Anterior cingulate (Kupferschmidt, 2011) and amygdala activations have also been reported to be attenuated with hyper-activations found in the posterior cingulate, insula (Lennox 2004) and fusiform (Chen, 2006) during sad affect recognition in manic individuals. Meta-analytic results involving 774 BD patients and 810 controls demonstrated amygdala hyper-activations in association with increased manic symptoms.

Depression

State-related neural correlates include depressed mood associated with hypo- (Kupferschmidt, 2011) and hyper-activation of the left OFC in response to fear stimuli (Liu,

2012) and over-activation of various frontal gyri, middle temporal gyrus, cingulate, putamen and thalamus when viewing happy or fearful faces (Chen, 2006). A meta-analysis found that HAM-D scores correlated negatively with hippocampus and OFC activations (Kupferschmidt, 2011).

Unaffected relatives

The first study to address facial processing in adult relatives assessed euthymic bipolar I patients, an unrelated group of unaffected first degree relatives and controls; with 20 participants in each group. (It should be noted that several relatives may have come from just a few families, affecting the statistical methods used and possibly impacting the results). Two separate event-related paradigms were used with either fearful or happy faces shown at 0% (neutral), 50% or 100%. An implicit gender judgement was sought. Hyper-activations in the medial prefrontal cortex, putamen and amygdala in both bipolar participants and unaffected first degree relatives were found when implicitly viewing either fearful or happy faces (Surguladze, 2010).

Demographics

Functional abnormalities of the posterior cingulate cortex may become more pronounced with age (Kupferschmidt, 2011) while the anterior cingulate cortex is negatively associated illness duration (Kupferschmidt, 2011). Pharmacological treatment may dampen the degree of functional impairment in VLPFC and precentral gyrus (Kupferschmidt, 2011).

Implicit versus explicit tasks

Very few tasks have compared implicit and explicit facial emotion processing in BD (Chen, 2006; Deveney, 2014; Thomas, 2012). Most of these have been conducted in youths with BD. The neural circuitry described above is derived from implicit emotion processing where the participants are asked to make a judgment that does not reference emotion, for instance a gender or age discrimination. Explicit judgments about affect employ more

prefrontal cortical regions as these may be more complex judgments to make and face processing regions e.g. fusiform gyrus (Habel, 2007). Greater cortical processing may attenuate subcortical activations through top-down control. In controls, amygdala over-activations have been demonstrated with implicit compared to explicit processing (Critchley, 2000) although the reverse has also been seen (Chen, 2006). The latter finding seemed counterintuitive and on reviewing the manuscript, it became clear that the implicit discrimination was more difficult in the latter task (age over or under 30 years rather than a gender discrimination) which may have increased prefrontal recruitment compared to the explicit events. The authors had used specific imaging parameters to assess amygdala activity and so could not interpret prefrontal regions. Explicit processing also recruits more temporal lobe activations than implicit processing in controls (Critchley, 2000). Chen and colleagues (Chen, 2006) employed an imaging paradigm with sad, fearful and happy faces with separate small groups (n=8) of depressed bipolar patients, manic patients and controls. The discriminations were complex for both implicit (discriminate the intensity of colour; “How green?”) and explicit (discriminate the affect intensity; “How sad?”) tasks. Group by task interactions showed that manic patients recruited amygdala, hippocampus, lateral temporal cortex, ACC and medial superior frontal cortex to implicit sad faces more than depressed patients and controls. The reverse was true with explicit sad faces. Thus, a more comprehensive model of neural emotion processing circuitry may be possible by using both implicit and explicit paradigms of emotion processing.

Functional connectivity

Studies in controls have consistently found negative functional connectivity between amygdala and prefrontal regions with facial affect labelling tasks (Hariri, 2003) suggesting PFC confers inhibitory modulation of amygdala activity, enabling individuals to control and direct their responses through cognitive evaluation of their emotional experiences.

In bipolar individuals, this negative connectivity appears reduced; BOLD response in prefrontal regions is reduced while amygdala activity is increased and this may underlie features of mood instability. This has been seen between perigenual anterior cingulate and amygdala when viewing fearful and happy faces (Wang, 2009), and the orbito-medial prefrontal cortex and amygdala with happy (Almeida, 2009) and sad (Versace, 2010) faces. In manic individuals (n=9) decreased VLPFC regulation of amygdala compared to controls occurred during a negative (angry and fearful face presentations) affect labelling task (Foland, 2008).

Task design issues

Block designs are typically more powerful than event related due to increases in signal to noise from the presentation of multiple similar stimuli and resultant summing of the BOLD response, however they are notably vulnerable to habituation and task predictability and cannot be linked to individual behavioural responses (Buchel, 2000). Event-related designs are more flexible and more robust against scanner drifts and head motion but less powerful. Particularly with patient populations, task complexity is an important issue, more complex tasks may cause participants to disengage with the task and result in within-scanner behavioural differences (and increase complexity of interpretation) so simple binary discriminations may be better.

1.4 Literature Review for Reward Learning:

1.4.1 Introduction

Reward processing requires an understanding of learning models and the related complex neural mechanisms underlying them. Initially associative learning models will be described and the neurobiological underpinnings of learning will be explained. Subsequently I will use a narrative review to describe the relevant neuroimaging literature in healthy adults and then in bipolar disorder.

1.4.2 Associative learning

The ability to adapt to changing situations is essential for survival. Associative learning describes the capacity of an organism to predict future events, such as the delivery of appetitive (food) or aversive (electric shocks) stimuli, based on sensory cues. Both Pavlovian and instrumental conditioning can be used to study associative learning.

1.4.2.1 Pavlovian conditioning

Pavlovian conditioning involves a previously neutral stimulus (the conditioned stimulus (CS)), acquiring importance once paired consistently with a biologically significant reinforcer (an unconditioned stimulus (US)), which then elicits a conditioned response (CR). Learned responses might include anticipation, reward prediction as well as actions. The dorsal striatum, amygdala and cerebellum are implicated in simple CRs (Gluck, 2001; Dayan, 2002).

1.4.2.2 Instrumental conditioning

Acquiring new strategies in a changing environment is mostly studied using instrumental conditioning and it is this form of associative learning that will be used in this study. Instrumental conditioning involves the response being strengthened by a response-contingent reinforcement occurring after the response (see Figure 1.3) and in its simplest form leading to goal-directed activities. Reinforcement learning enables the development of behaviours that can maximise rewards or minimise punishments.

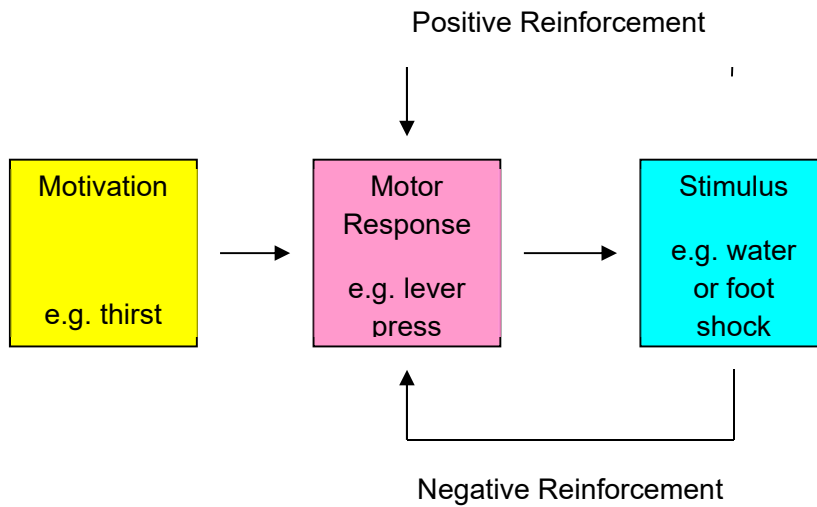


Figure 1.3: Instrumental conditioning example demonstrating that the choice of lever press (motor response) would be influenced (reinforced) through trial and error depending on whether the resultant effect (stimulus) was positive (receipt of water) or negative (foot shock)

From a neural perspective, damage to the prefrontal cortex prior to instrumental training has been shown to have an effect on conditioning while lesions after training had no effect suggesting that the prefrontal cortex is important for goal-directed learning but not the site of encoding the action-outcome association (Ostlund, 2005). The insula cortex is involved in the retrieval of the incentive value of foods (Balleine, 2000) and so learning about shifts in the rewarding nature of instrumental outcomes after accounting for motivational issues may be mediated by the insula's connections with the orbital frontal cortex and amygdala.

Motivational issues

Evaluation of the incentive value of the goal or outcome is also essential for instrumental conditioning and this is determined by the motivational and affective properties of the outcome. Incentive salience refers to the motivational, goal-directing effects elicited by dopaminergic activity such that neural representations of conditioned stimuli are converted from neutral perceptions to those that are rewarding (Berridge, 1998). Motivation encoding has been demonstrated in the nucleus accumbens, ventral pallidum, substantia nigra, ventral tegmental area, hypothalamus and lateral habenula (Berridge, 2008; Hikosaka, 2008; Matsumoto, 2009). The nucleus accumbens is vital to the generation of directed behaviour as the result of a Pavlovian CS and possibly for the motivation to choose delayed rewards rather than emotional cues and goals. (Dopaminergic effects are described in more detail below). The orbital frontal cortex has also been implicated in motivation as neuronal signals have been correlated with an animal's degree of food or water deprivation (Rolls, 2000). Thus motivation is substantially influenced by the nucleus accumbens and prefrontal cortex.

1.4.3 Dopamine and reward in healthy brain

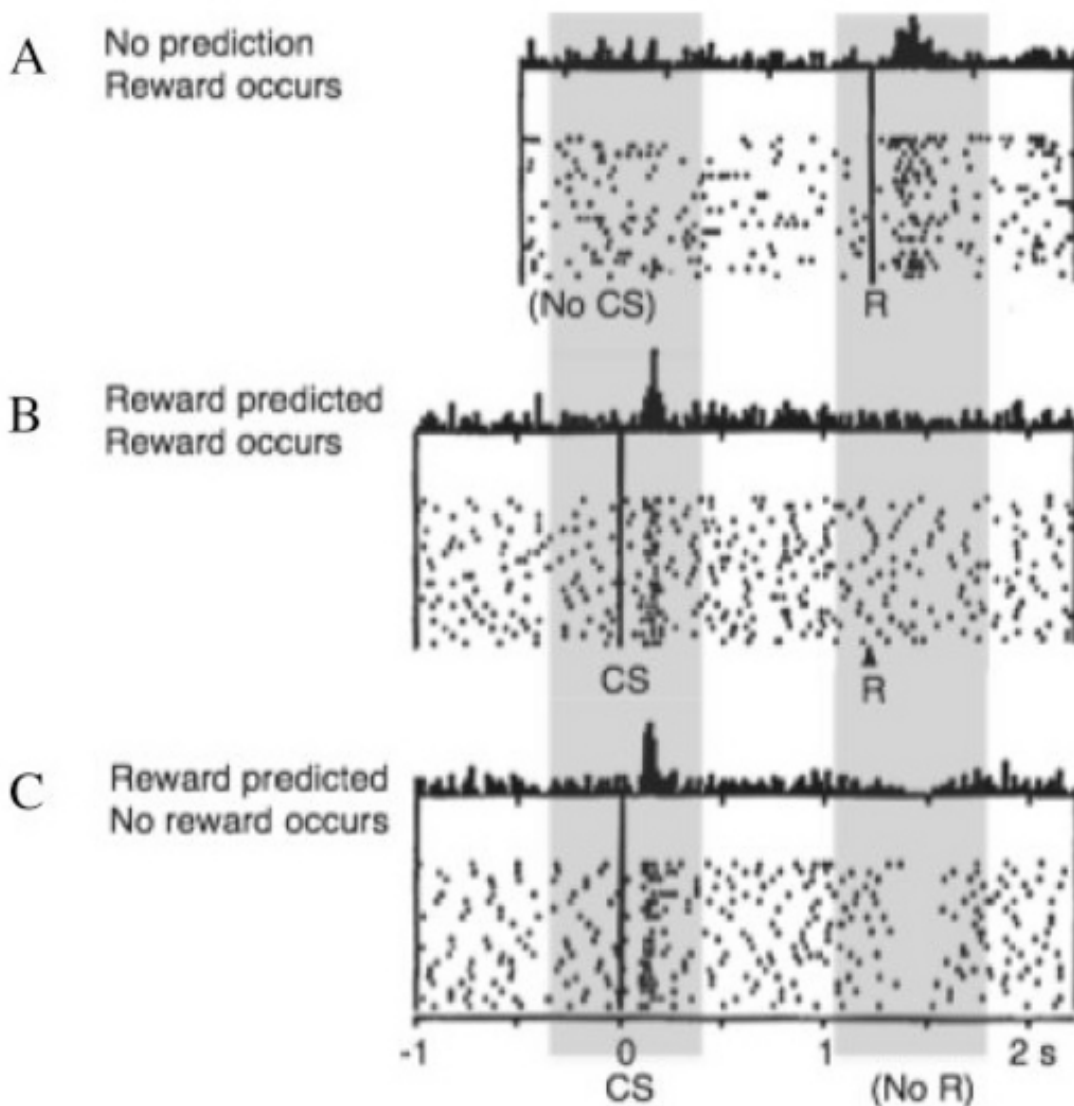
Dopamine is a neurotransmitter that fulfils a variety of functions within the brain. It is probably best known for its role in movement processing, for example, Parkinson's disease. However, dopamine is also involved in working memory (Castner, 2000), cognitive flexibility, for instance in reversal learning (Jocham, 2009), reward learning (Schultz, 1997) and for signalling the motivational importance or salience of events or objects as described above (Berridge, 1996). Different functions of dopamine are determined by a variety of mechanisms including different firing rates, receptor types, regional receptor densities and interactions with other neurotransmitters.

I intend to focus on the role of dopamine in learning about and predicting rewards and signalling prediction error, described below. Dopaminergic dorsal striatal neurons are activated during the preparation and executions of actions and by the anticipation and

receipt of rewards. The anticipatory and preparatory mechanisms of dopamine occur with activations associated with the timing of the conditioned stimulus and before the reward. In typical behavioural paradigms, the unconditioned animals activation occurs only at the delivery of food or drink (the unconditioned stimulus, Diagram A below) but moves temporally to associate with a new neutral conditioned stimulus (Diagram B below) (Schultz, 1993). It is this temporal relationship with the reward that has implicated dopamine in reward prediction. Transient phasic bursts of dopamine are also observed after expected rewards and are thought to enhance learning through dopaminergic effects on cortico-striatal plasticity. In the striata of primates D1 receptors modulate positive reinforcement and D1 blockade prevents speeding of responses to obtain large rewards. D2 receptor activity supports avoidance learning and D2 blockade slows responding to obtain small rewards (Frank, 2007). Uniquely the activity of these neurons relates to the value of specific actions resulting in a bias in the basal ganglia network to actions preferred by striatal neurons.

Schulz conducted pioneering studies showing that midbrain dopaminergic neurons encode 'reward prediction error' (Schultz, 1997). Prediction error (PE) is conceptualised as the difference between observed and expected rewarding outcomes. Reward prediction error enables rapid reversal of behaviour by stimulus reinforcement association relearning. In other words, these prediction errors enable an updating of the values associated with the available actions. Dopamine firing 'dips' below baseline when expected rewards are not received, the prediction error (PE) signal, (Diagram C below) and this transmits to the anterior cingulate cortex where the drop in dopamine levels inhibits the apical dendrites of motor neurons and generates a negative deflection of event-related potential (ERP) enabling learning to avoid unrewarding stimuli (Frank, 2007). Figure 1.4: Midbrain dopaminergic neurons encode 'reward prediction error' through a series of experiments conducted by Schultz and colleagues. (A) Before learning, a drop of appetitive fruit juice occurs in the absence of prediction— hence a positive error in the prediction of reward. The dopamine neuron is activated by this unpredicted occurrence of juice. (B) After learning, the conditioned stimulus predicts

reward, and the reward occurs according to the prediction— hence no error in the prediction of reward. The dopamine neuron is activated by the reward-predicting stimulus but fails to be activated by the predicted reward. (C) After learning, the conditioned stimulus predicts a reward, but the reward fails to occur because of a mistake in the behavioural response of the monkey. The activity of the dopamine neuron is depressed exactly at the time when the reward would have occurred. The depression occurs more than 1 s after the conditioned stimulus without any intervening stimuli, revealing an internal representation of the time of the predicted reward. (Schultz, 1997)



Pessiglione and colleagues found dopamine enhancing (L-dopa) and depleting drugs modulated the magnitude of reward PE in human striatum (Pessiglione, 2006). This suggests that dopamine-dependent plasticity (in terms of modulating synaptic efficacy) could underpin the way in which striatal neurons learn to represent expected rewards and optimal behaviours (Moustafa, 2008). Additionally, right lateral PFC activations reflect the occurrence of PEs (Corlett, 2004) using direct measurements. However, using temporal difference modeling (to be discussed later), nucleus accumbens activation correlates with the prediction of positive consequences in response to cues while the medial PFC computes PEs in response to outcomes (Knutson, 2007). The VLPFC tracks arousal during the anticipation of rewards (Rolls, 2008). The orbital frontal cortex is involved in relative reward discrimination involving prospective and counterfactual appraisal, reflecting regret avoidance (Rolls, 2008; Coricelli, 2005). The middle PFC is implicated in risky decisions in potentially rewarding contexts (Bebko, 2014; Xue, 2009; Lawrence, 2009). The dorsal ACC is involved in attention during decision-making (Bush, 2002).

1.4.4 Other neurotransmitters and reward learning

Clearly dopaminergic activity is not the only contributor to reward processing. Serotonin, GABA and glutamate also interact, however, there has been relatively little research to address their roles in motivation and reward. The role of each of these neurotransmitters is complex and their actions are likely to be dependent on their receptor subtype, receptor density, location and the context in which they have been studied, for instance, the type of behavioural paradigm or the type of drug used to analyse their actions.

1.4.4.1 Serotonin

Serotonin-containing neurons make extensive connections to reward-related neural systems across the brain. Serotonergic neurons project to neurons in the mesolimbic dopamine system and regulate dopamine transmission, potentially modulating a negative reward signal in opposition to dopamine (Daw, 2002). Hypothalamic reward processing involves natural rewards such as food and sex and serotonergic neurons are closely

connected to this region. Similarly, amygdala, lateral habenula, medial and orbitofrontal cortices all have well established serotonergic connections (Kranz, 2010)⁷. Nakamura and colleagues used single unit recordings in primates and found that many dorsal raphe neurons changed their activity in response to reward outcomes and reward-related cues (Nakamura, 2012). Firing increased with the magnitude of the reward. Dorsal raphe neurons also influence behaviour by adapting to the anticipated delay and the worth of future outcomes (Bromberg-Martin, 2011). Thus, while dopaminergic neurons show phasic changes in activity each time the reward value changes (signalling value changes), serotonergic neurons show tonic changes in activity after the reward value is updated (signalling the value state). This suggests that representing the network of signals would enable more accurate inferences about value. Additionally elevated serotonin levels promote persistence to wait for larger delayed rewards and depleted serotonin causes more impulsive choices of smaller rewards (Doya, 2002).

1.4.4.2 Glutamate

Glutamate-coded sensory and information processing signals activate NMDA receptors. Data suggests these interact with D1 receptors in various brain regions including striatum and PFC generally in a synergistic and often dependent manner to enable operant learning (Andrzejewski, 2013). The addiction literature describes drug-induced synaptic changes initially in VTA dopamine neurons that results in synaptic potentiation of glutamate AMPA receptors, triggering synaptic changes downstream in the mesocorticolimbic system (such as reduced extracellular glutamate in the nucleus accumbens) (Van Huijstee, 2014).

1.4.4.3 γ -aminobutyric acid (GABA)

The VTA consists of approximately 30% GABA inhibitory neurons. Interneurons provide local inhibition for dopamine neurons and projection neurons provide long range inhibition of many regions including the nucleus accumbens. Although poorly understood and difficult to disentangle from dopaminergic activity, these functions are thought to facilitate

the plasticity that enables reward learning. Optogenetic research has elucidated GABA's role in inhibiting VTA dopaminergic neurons in response to exposure to salient but aversive stimuli. Research into the long range projections to the nucleus accumbens have confirmed that GABA activity enhances associative learning but dopamine signalling is essential for coding the valence of stimuli as GABA is insufficient to disrupt reward or create aversion (Creed, 2014).

1.4.5 Neuroimaging of reward learning

Pessiglione, 2006 provided evidence of a more direct relationship between fMRI and dopamine signals in the ventral striatum. Using an instrumental learning paradigm together with drugs that enhanced or reduced dopaminergic function, they demonstrated that BOLD fMRI activation in the striatum in response to reward PE was influenced by the magnitude of that functioning (Pessiglione, 2006). A subsequent PET study on the same cohort showed a correlation between fMRI activity and reward-related dopamine release (Schott, 2008). There remain a number of caveats to linking BOLD signal to dopaminergic activity.

- i) Other neurotransmitters also confer reward-related activity in similar regions, as explained above.
- ii) Increased BOLD does not discern an increase in dopamine (usually to a reward) from an increase in GABA interneurons (usually to aversive stimuli).
- iii) Correlations have been specific to the ventral striatum. Other regions, including PFC, although receiving dopaminergic projections are less physiologically homogenous (Daniel, 2014).

1.4.5.1 Ventral striatum and beyond

fMRI studies have confirmed that midbrain activity in humans supports the reward prediction error hypothesis (Ablner, 2006; Haruno, 2006) whereby there is:

- i) An elevated response at the time of reward presentation in early learning.

- ii) Transfer of the PE response to the timing of the appearance of a reward-predicting stimulus once the CS-US association is established.
- iii) At which stage, a large positive PE should result from any unexpected reward
- iv) A large negative PE should result when an expected reward is omitted.

A meta-analysis (Garrison, 2013) of neuroimaging studies of prediction error confirmed the central role of the striatum (both dorsal and ventral) in instrumental reinforcement and especially reward learning but observed PE activity in medial prefrontal cortex and anterior cingulate cortex. Aversive PEs were found in the insula and habenula.

The magnitude of reward or the representation of value, influences decision-making in reward learning. Activity in the ventral striatum (Delgado, 2000), medial prefrontal cortex (Knutson, 2001), posterior cingulate cortex (Knutson, 2003), amygdala, insula and posterior parietal cortex have all correlated with reward magnitude (Levy, 2012). More specific task designs revealed ventromedial PFC and orbitofrontal cortex to encode subjective monetary value (Basten, 2010).

1.4.5.2 Summary

Associative learning occurs when a new response is associated with a stimulus. In order to make decisions in the face of alternative choices, their magnitudes and probabilities need to be converted into comparable value-based information. These can then be compared along with their projected values and the values associated with the un-chosen choice (e.g. the prediction error signal). Medial OFC and ventral striatum have been implicated in these value-based representations (Frank, 2006; Hare, 2008). The inferior parietal lobes is involved in the processing of numerical information. The valence of the outcomes and the resultant emotional responses also affects decision-making. Medial OFC and ventral striatum are implicated in detecting positive reward valence. The evaluation of negative emotional responses and therefore their associated negative reward valences occur in the lateral OFC, anterior insula, ACC and amygdala

(Kringelbach, 2005; Kringelbach, 2004; Fox, 2005; Raichle, 2001; Raichle, 2007). The anterior insula and ACC are also involved in the anticipation of risky decisions (Laird, 2009; Toro, 2008). Fronto-parietal regions integrate these signals to produce optimal decisions (Cox, 2010).

1.4.5.3 Conclusion

Instrumental learning of a reward processing paradigm, in which participants learned to associate a particular stimulus with a reward, would enable analysis of BOLD signalling as a proxy for dopamine firing in relation to rewarding stimuli. Additionally, once the rule had been learned, the contingency could be changed occasionally to elicit prediction error responses when the expected reward was not received. This experiment would highlight the activity of the reward processing circuitry which includes networks that have demonstrated pathology in bipolar disorder.

1.4.6 Reward learning & Bipolar Disorder

Increases in reward sensitivity have been reported in BD (Meyer, 2001; Nusslock, 2012; Urosevic, 2008). High self-reported sensitivity to reward-relevant stimuli has been associated with an increased risk of developing a bipolar spectrum disorder (Urosevic, 2008) and having a manic/hypomanic episode (Alloy, 2008).

1.4.6.1 Behavioural Studies

There have been very few tasks that directly address reward processing in bipolar disorder. However, decision-making paradigms and the reward-based decision-making Iowa gambling task (IGT) have been employed most frequently. These tasks indirectly explore reward processing but also involve several other cognitive processes.

Overall, previous studies have shown that bipolar patients exhibit increased behavioural responses to reward or anticipation of reward compared to healthy controls (Alloy, 2008; Johnson, 2013; Gruber, 2011). This suggests that they are more sensitive to rewarding experiences. Yet individuals with BD are not faster to learn stimulus-reward associations (O'Sullivan, 2011) and demonstrate deficits in probabilistic reversal learning (Dickstein, 2010). Additionally, once they have learned a stimulus-reward association, they are slower to realise changes in contingencies (Johnson, 2013) In general therefore, bipolar patients appear more sensitive to rewarding stimuli but less able to adjust when those stimuli are no longer rewarding. As above, the behavioural literature pertaining to the different bipolar states will be described in turn.

Euthymia

Using a probabilistic reward task, euthymic bipolar individuals have been shown to demonstrate reduced and delayed acquisition of response bias to more frequent rewards, and elevated miss rates for the more rewarding stimulus when immediately preceded by either a high-reward stimulus that did not get rewarded or by a rewarded low-reward

stimulus (Pizzagalli, 2008b). This suggests difficulties in adaptation to changing reward contingencies. This could be an issue of set shifting (Lawrence, 2009) or possibly a bias of response to the immediately preceding scenario rather than the overall goal of the task, suggesting that the temporal relationship to learning is particularly important for these individuals.

Mania

Lesion studies of the ventro-medial PFC or OFC result in symptoms similar to mania¹³³. While these individuals perform appropriately on many cognitive tasks, they have specific deficits on gambling tasks (Bechara, 2000). This partly explains the use of gambling tasks to assess decision-making function in bipolar individuals. However, in mania, the Iowa Gambling Task has failed to elicit such differences (Clark, 2001) and, in a separate experiment, has demonstrated 'low choice consistency' (Yechiam, 2008). Manic patients were reported to make suboptimal choices that correlated with their symptom scores on a decision-making task involving probabilities and 'betting' (Murphy, 2001). They also have greater sensitivity to increasing error rates on a two choice prediction test (Minassian, 2004) suggesting that their decision-making may be impaired when a successful outcome appears less certain. In a delayed reward task they also chose the more immediate lower value reward reflecting possible impulsivity and a difference in valuation of rewards (Strakowski, 2009).

Depression

The majority of studies examining bipolar depression, do so in the context of comparison to unipolar depression rather than euthymic bipolar individuals. However, in a depressed cohort of bipolar children, a decision-making task involving monetary gains or losses did not demonstrate differences between children with BPD and controls. However, it should be noted that the children in this study also had additional comorbidities (Ernst, 2004).

Summary

In general bipolar individuals perform less well on decision-making and gambling tasks although it remains unclear as to the specific nature of the cognitive deficit. Poorer performance most consistently related to the negative result of the most recent prior event.

1.4.6.2 Magnetic Imaging Studies

There have been few functional imaging studies of reward processing in bipolar patients. Those that have been conducted are heterogeneous in their choice of participants, task design and analyses. The functional findings addressing the activations of various structures, the study design, the nature of the mood symptoms and the analysis modelling will be discussed.

1.4.6.3 Functional imaging anatomy

PET and fMRI studies have found alterations in the functioning of various anatomical regions important for reward processing. Here the basal ganglia, amygdala and prefrontal cortex will be discussed in turn.

Basal ganglia

Neuroimaging studies of reward processing in BD converge on results of abnormally elevated ventral striatal activity especially in relation to reward anticipation (Mason, 2014; Caseras, 2013; Nusslock, 2012) (BDII). These striatal hyper-activations have been reported in subclinical hypomanic (O'Sullivan, 2011), manic (Abler, 2008) and euthymic patients (Mason, 2014) not in receipt of antipsychotic medication (Mason, 2014), although these patients may have been prescribed other psychotropic medications that could affect striatal function. Others have found ventral putamen over-activity present in BD but not siblings (Linke, 2012). These exaggerated PE signals have therefore been demonstrated across most states in BD although the only study to recruit depressed BD patients did not

find any striatal differences with PE signalling (Chase, 2013). Singh and colleagues (Singh, 2014; Singh, 2013) found no striatal differences in adolescent BDI patients. Additionally under-activity has also been reported during reward anticipation in the dorsal striatum in unmedicated BDII or BD NOS (Yip, 2015) and nucleus accumbens in manic patients (Abler, 2006; Haruno, 2006). However the latter finding reflected a comparatively high fMRI signal to the not rewarded condition rather than a decrease to the rewarded stimuli. Additionally manic patients did not show any speeding of reaction time to the more rewarding stimuli suggesting a deficit in distinguishing potentially rewarding stimuli.

Amygdala

Amygdala over-activation has been demonstrated consistently in mania (Alshuler, 2005) and depression (Savitz, 2009). A reversal learning task involving monetary rewards also elicited amygdala over-activation during wins and during rule reversal (representing PE signalling) in BD patients and unaffected relatives (Linke, 2012).

Prefrontal cortex

Likely state-related effects were noted in manic patients whose representations of expected value in the OFC were greater during gains and lower during expectations of loss than controls but became more like controls during remission (Berpohl, 2010). In contrast, Linke, 2012, using a probabilistic reversal learning task, demonstrated OFC over-activity in euthymic patients in response to reward and similar activations have been elicited in high-risk children (Singh, 2014; Singh, 2013). Neither result demonstrated a state-related effect.

Elevated ventrolateral PFC activity has been demonstrated (Nusslock, 2012; Caseras, 2013; Berpohl, 2010), specifically in anticipation of reward in depressed (Chase, 2013) and euthymic (Nusslock, 2012; Caseras, 2013; Berpohl, 2010) BDI patients.

ACC activations may be state-related as decreases were observed to reward expectancy in a combined group of depressed BDI and MDD patients (Chase, 2013). Rubinsztein and colleagues found manic individuals had greater activation in the left dorsal ACC and under-activation in the right frontal polar region in a decision-making task with PET scanning (Rubinsztein, 2001).

1.4.6.4 Study design

As can be seen above, paradigms used to study reward processing have varied considerably. Some (The monetary incentive delay task MID (Ablner, 2008; Singh, 2014; Singh, 2013; Yip, 2015; Bermpohl, 2010)) and the card guessing game (Chase, 2013) have probed neural responses to anticipation and receipt of gain and loss outcomes by using a set of cues that indicate whether participants can win or avoid losing money depending on their responses. One study used affective priming prior to MID in order to limit the impact of the diversity of mood states of their adolescent participants before assessment (Singh, 2014; Singh, 2013). Other tasks included:

- i) the Roulette task (Mason, 2014) where there are selection, anticipation and outcome phases with low and high probability conditions,
- ii) the desire-reason dilemma (Trost, 2014) in which a stimulus-response-reward contingency was conditioned prior to scanning and subsequently a forced choice task was presented in which participants had to either collect or reject rewarding stimuli in order to successfully pursue a long-term goal,
- iii) a reinforcement learning task (Pessiglione, 2006), where participants choose one of a pair of stimuli from either a neutral or rewarding (money) set and learn through trial and error which has a high probability of reward and subsequently prediction error is increased.
- iv) a probabilistic reversal learning task (Linke, 2012) in which participants chose one of two playing cards with immediate win or loss (of money) feedback. A rule reversal occurred after 5-8 consecutive choices of the winning card.

1.4.7 Task analyses

Prediction error has been addressed in many of the studies described (Abler, 2008; Singh, 2014; Singh, 2013), but there has been no specific modelling of reward learning in the analyses of data that incorporates the association of timing and motivational drive. Reward processing, timing and decision-making processes are part of a larger integrated network that underpins the function of learning about gains and losses of rewards and the stimuli that predict those outcomes. Within that network, functions include: determining the probability of reward, the value of the reward, the delay to reward, the choices for gaining rewards and encodes the cost and effort associated with responses for rewards (Galtress, 2012). The degree of motivation effects the timing of responses. Therefore modelling techniques that incorporate motivation, reward processing, value and timing will enable more accurate brain activity representations, leading to more consistent neural correlations.

There have been a limited number of studies of reward processing or decision-making in bipolar disorder but results have been varied. Heterogeneity is likely to be attributable to small sample sizes, variation in task design and the variable mood states of participants due to the polarisation (the extremes of manic and depressive symptoms) that defines the disorder. However, the most consistent findings appear to demonstrate over-activations in striatum to rewards and both over- and prefrontal under-activations that may represent state-related activity. It is important to note that manic individuals show striatal over-activation to non-rewarding stimuli reducing their measured relative activation to rewarding stimuli (Abler, 2008).

To date there have been only two published studies of reward processing in euthymic bipolar individuals that also recruited relatives. Neither study specified that the relatives

were directly related to the euthymic bipolar participants within the studies. Linke and colleagues used a probabilistic reversal learning task (Linke, 2012). The unaffected relatives were also younger and unlikely to be passed the age of greatest risk for developing BD. Additionally the task was not primarily designed to address prediction error which was interpreted as the point of rule reversal, as such there were only a small number of appropriate trials to investigate. The most recent publication (Kollmann, 2017) is by the same research group and used the Monetary incentive delay task. Again, the task focussed on reward anticipation rather than prediction error and the number of participants was small (16 BD participants).

1.4.8 Chapter Summary

In order to gain a better understanding of the behavioural and neural correlates that underlie the disorder without the confounds of symptoms and medications, euthymic individuals with BDI who each have a healthy sibling who is passed the age of greatest risk for developing the disorder will be recruited. A battery of behavioural, clinical and neuroimaging assessments will be implemented that target the areas that have been discussed in the above literature.

1.4.9 Hypotheses

Bipolar patients will demonstrate deficits in performance, worse clinical symptoms and greater deficits in cortical control / increased limbic responses to emotional faces / deficits in regions involved in reward learning compared to controls.

More detailed, study specific hypotheses will be included in each of the experimental chapters below. Further, unaffected siblings of bipolar probands will lie in between patients and controls for all performance, clinical and imaging assessments.

Additional postulates:

- a) Where siblings' brain activity and performance are shared with their BD relatives and differentiate both groups from controls this would reflect genetic predisposition to the disorder.
- b) Where siblings' brain activations and performance differentiate them from controls and/or their BD relatives, or controls' activations are intermediate between the siblings and patients, this may represent adaptive responses associated with resilience.
- c) Where patients' brain activations and performance differentiate them from controls and their siblings, these changes will be considered as correlates of disease expression.

2 Chapter 2:

Experiment 1: Clinical & neuropsychological comparisons of individuals with Bipolar Disorder and their siblings.

2.1 Abstract

Deficits in a variety of neuropsychological domains including personality and temperament have been demonstrated repeatedly in individuals with Bipolar Disorder. I sought to test whether these features represent state or trait effects, or whether they are secondary to medication or the chronicity of the illness. Twenty-five bipolar I patients each with their unaffected sibling, were compared to 27 healthy age- and gender-matched controls on measures of mood symptoms and impulsivity, temperament and personality factors, and cognitive measures including Intelligence Quotient, processing speed, set-shifting, reaction time tasks related to reward and response inhibition, and facial emotion recognition. Data were analysed using appropriate pairwise comparisons. Trait-related findings included deficits in processing speed, working memory and decreasing intelligence. Response inhibition and set-shifting did not represent candidate endophenotypes. Personality and temperament measures associated with BD (increased neuroticism and cyclothymia, and decreased extraversion) were only marked in patients and correlated with symptoms. The sibling group demonstrated less vulnerability markers than expected from the literature. This may be due to their greater resilience.

2.2 Introduction

Deficits in neuropsychological domains including processing speed (Glahn, 2010), verbal fluency (Dixon, 2004), memory and executive function (Arts, 2008) have been frequently demonstrated in individuals with Bipolar Disorder. Depressive symptoms such as psychomotor retardation, poor concentration or the diminished ability to think and manic distractibility are the result of and represent these cognitive function deficits. Personality measures such as increases in neuroticism and decreases in extraversion, and increased cyclothymic temperament have also been associated with the disorder. However it remains unclear as to whether these features represent state or trait effects, or whether they are secondary to medication or the chronicity of the illness.

Studies of unaffected relatives of individuals with bipolar disorder have demonstrated deficits in memory (Kieseppa, 2005; Gourovitch, 1999), response inhibition (Frangou, 2005) and other cognitive domains (Arts, 2008; Meyer, 2004) as well as the personality and temperament measures cited above (Whalley, 2013b; Evans, 2005; Mendlowicz, 2005) suggesting these are markers of an inherited vulnerability. However, these studies have often been conducted on younger relatives who are at high-risk for developing the disorder and are not yet passed the period of maximum population risk. The findings may relate to prodromal features and illness development as these individuals may become unwell. Although some studies have looked in multiplex families (Glahn, 2010) none have specifically paired each patient to their sibling and carefully phenotyped the siblings to ensure they were entirely well, without a mental illness.

In order to address the issues discussed above, the current study design paired bipolar 1 patients with their healthy siblings. The siblings were relatively unlikely to develop BD as they are an older cohort (mean age 45 years) and have passed the period of maximum population risk. They were also beyond the age at which their ill sibling developed the disorder. This offers a powerful opportunity to investigate a variety of cognitive domains, personality and temperament factors that are known to be altered in BD and to assess

whether their siblings share some of these deficits suggesting trait effects or whether they are specific to the patients in which case they are likely to be state effects (including medication effects). The design of the study also allowed for the identification of potential resilience factors if siblings and patients are at extremes of a measure while controls remain intermediate. Therefore this design limits the risk of future illness in the first degree relative participants. In particular, the novel aspect of this study is the pairing of individual patients with bipolar to their own healthy sibling, to minimise potential variance between the groups by virtue of greater shared environmental and genetic factors.

In this chapter, the objectives were to investigate behavioural differences between groups that relate to BD in the following domains; mood symptoms and impulsivity, temperament and personality factors, and cognitive measures including Intelligence Quotient (IQ), processing speed, set-shifting, reaction time tasks related to reward and response inhibition, and facial emotion recognition.

2.2.1 Hypotheses

- i) Siblings will experience more sub-syndromal symptoms than controls.
- ii) Trait effects will be demonstrated with processing speed (DSST), set-shifting (ID/ED), and facial emotion recognition (Ekman 70). Siblings will demonstrate behavioural deficits in these tasks in between to a greater degree than controls and to a lesser degree than their bipolar relatives.
- iii) State effects where patients score significantly more than controls and their siblings will be demonstrated with neuroticism, cyclothymia and extraversion, impulsivity (BIS), sensitivity to reward, response inhibition (SSRT) and the reaction time task (CCRTT).

2.3 Methods

2.3.1 Recruitment

Individuals diagnosed with Bipolar 1 Disorder (BD1) were identified through psychiatrists' caseloads across Scotland. A diagnosis of BD1, and euthymia in the bipolar proband, were confirmed using the Structural Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) (First, 2002). These subjects also identified a sibling aged 30-55 years not suffering from a mood disorder or major mental illness as they were less likely to develop BD in the future or be prodromal for BD at assessment. Only one proband-sibling pair was recruited from each family. Where there was more than one healthy sibling, the sibling closest in age or who was able to attend was recruited. Healthy volunteers with no personal or family history of BD or family history of mood disorder in their first degree relatives were recruited from the social networks of participants and the local community. Exclusion criteria for the study were major neurological disorder, a history of substance dependence, learning disability or any history of head injury that included loss of consciousness, and any contraindications to fMRI. A total of 25 bipolar-sibling pairs and 27 controls provided suitable clinical and neuropsychological data. All participants provided written informed consent. The study was approved by the local research ethics committee.

2.3.2 Assessment

2.3.2.1 Assessment of psychiatric symptoms and disorder

All participants were interviewed by an experienced psychiatrist (JS). Diagnoses were confirmed using the Structural Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) (First, 2002). Clinical symptoms were assessed using the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), the Young Mania Rating Scale (YMRS) (Young, 1978) and the Positive and Negative Symptoms Scale (PANSS) (Kay, 1987). Self-assessment questionnaires were completed including the Temps-A (temperament) (Akiskal, 2005a), the Neo Five Factor Inventory (personality) (Scandell, 2000), Barratt Impulsiveness Scale (impulsivity) (Patton, 1995), the Sensitivity to reward and punishment questionnaire and

the Childhood Trauma Questionnaire (including emotional, sexual and physical questions) (Berstein, 1997) (See Table 2.1).

Questionnaire	Description
Temps-A	A widely used 39-item self-report questionnaire that measures five factors of temperament (cyclothymia, depression, irritability, hyperthymia and anxiety). Items are rated "yes" or "no".
Neo Five Factor Inventory	This 60-item self-report questionnaire measures five personality dimensions (neuroticism, extraversion, openness to experience, agreeableness and conscientiousness). Items are rated on a five point scale from "strongly disagree" to "strongly agree".
Barratt Impulsiveness Scale	The BIS-11A is 21-item self-report inventory that measures impulsivity as a trait encompassing three domains: attentional impulsivity (intolerance for complexity and persistence); motor impulsivity (tendency to act without forethought); and non-planning impulsivity (lack of a sense of the future). Items are rated from 1 (absent) to 4 (most extreme). BIS-11A total scores for healthy individuals generally range between 50 and 60.
Sensitivity to reward & punishment questionnaire	This 48 item self-report questionnaire incorporates two scales: sensitivity to punishment (24 items) and sensitivity to reward (24 items). Items are rated "yes" or "no".
Childhood Trauma Questionnaire	A 28 item self-report questionnaire validated for screening for a history of abuse and neglect. Items are rated on a five point scale from "Never true" to "Very often true".

Table 2.1: Descriptive table of questionnaires used.

2.3.2.2 Assessment of neuropsychological tests

All participants completed paper and pen tasks including the National Adult Reading Test (NART) (Nelson, 1982), the forward and backward Digit Span (short term memory), the matrix reasoning, similarities, vocabulary, and block design subtests of the Weschler Abbreviated Scale of Intelligence (WASI) (Weschler, 1999) and the Digit Symbol Substitution Test which measures psychomotor performance. Additional laptop-based tasks included the Stop signal reaction time task, the Cued reinforcement reaction time task (Cools, 2002), Intra-dimensional/ Extra-dimensional shift test and the Ekman 70. Details of each computer-based task are below. All tasks have previously been used in Bipolar populations and have been validated and considered reliable.

2.3.2.2.1 Digit Symbol Substitution Test (DSST)

1	2	3	4	5	6	7	8	9
^	=	○	×	□	⌌	⊥	+	

3	6	1	9	5	4	8	3	9	7	2	5	6	3	4	1	9
○	⌌	^														

Figure 2.1: DSST coding bar (above) and sample test (below).

This paper and pen test of psychomotor speed consists of a set of digit-symbol pairs presented at the top of the page. Under each digit, participants have to fill in the related symbol as quickly as possible (see 2.1). The score is calculated by the number of correct pairs completed in 90 seconds.

2.3.2.2.2 Stop signal reaction time task (Aron, 2005)

This is a task that aims to measure the reaction time taken to inhibit a task that has already started. Participants will see a single arrow in the centre of the screen pointing left or right and their task is to press the appropriate arrow key on the keyboard (Go trial). If a beep occurs, they are to try to withhold their response (Stop trial). Left and right arrows are presented for up to 1s in equal numbers and counterbalanced with stop trials. A quarter of all trials are stop trials when a 900hz tone sounds for 500ms at various delays (100, 150, 200, 250ms) after the arrow is presented. Successful inhibition shortens the next stop trial delay by 50ms and an unsuccessful inhibition lengthens the next stop trial delay by 50ms. There are 4 different staircases sampling stop signal delays at different time points. There are a total of 96 go trials and 32 stop trials. Participants are asked to respond as fast as they can. The stop signal reaction time (SSRT) is estimated by subtracting the average stop signal delay (SSD) from the median successful reaction time. The average SSD is computed by taking the last 12 values from all the staircases after 50% converge

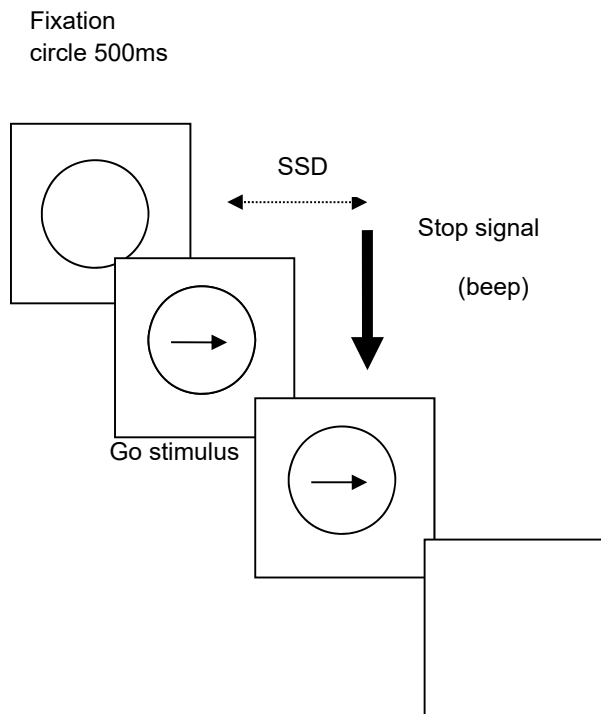


Figure 2.2: Stop signal reaction time task. This diagram represents a single trial. Participants are asked to respond as fast as possible to a left or right pointed arrow with a left or right button press respectively. In this example, there is a right button press. On a minority of trials, the stop-signal beep sounds at the stop-signal delay, signalling for the participant to not press (inhibit) the arrow button.

2.3.2.2.3 Cued reinforcement reaction time task (CRRTT)

In this simple choice reaction time task speeding to responses is seen after the presentation of coloured cues which signal higher probabilities of a reward in healthy participants. Initially these cues (a coloured rectangle around the task) have no obvious meaning and are therefore neutral but over the course of the task they become associated with increased likelihood of a reward (in the form of a smiley face, points and a positive noise) and this stimulates adaptation to the reward in the participant who responds with great effort (speed).

Specifically on each trial participants perform a rapid 'odd one out' judgement by choosing which of three shapes is different (see 2.3). A coloured rectangle precedes and remains around the three shapes and acts as a cue signalling the likelihood that a correct response would be followed by a reward. The reinforcement probabilities for the different colours are 10, 50 and 90%. Fifty-six trials occur with 18 of each contingency. Participants had to press buttons '1', '2' or '3' on the keyboard with their dominant hand to signal their choices which were immediately followed with feedback of a yellow happy face, a yellow sad face and a points score of 1 or 100 points depending on reaction time.

Reaction time thresholds were determined for each participant during the two practice blocks of 20 trials where there were no cues or feedback. The mean reaction time (mean RT) and standard deviation (SD) were used to compute a threshold for reward delivery in the main task (mean RT – SD).

Incorrect trials were excluded from the analyses. Reaction times and accuracy at the various levels of reward were analysed using pairwise t-tests or MWU where appropriate.

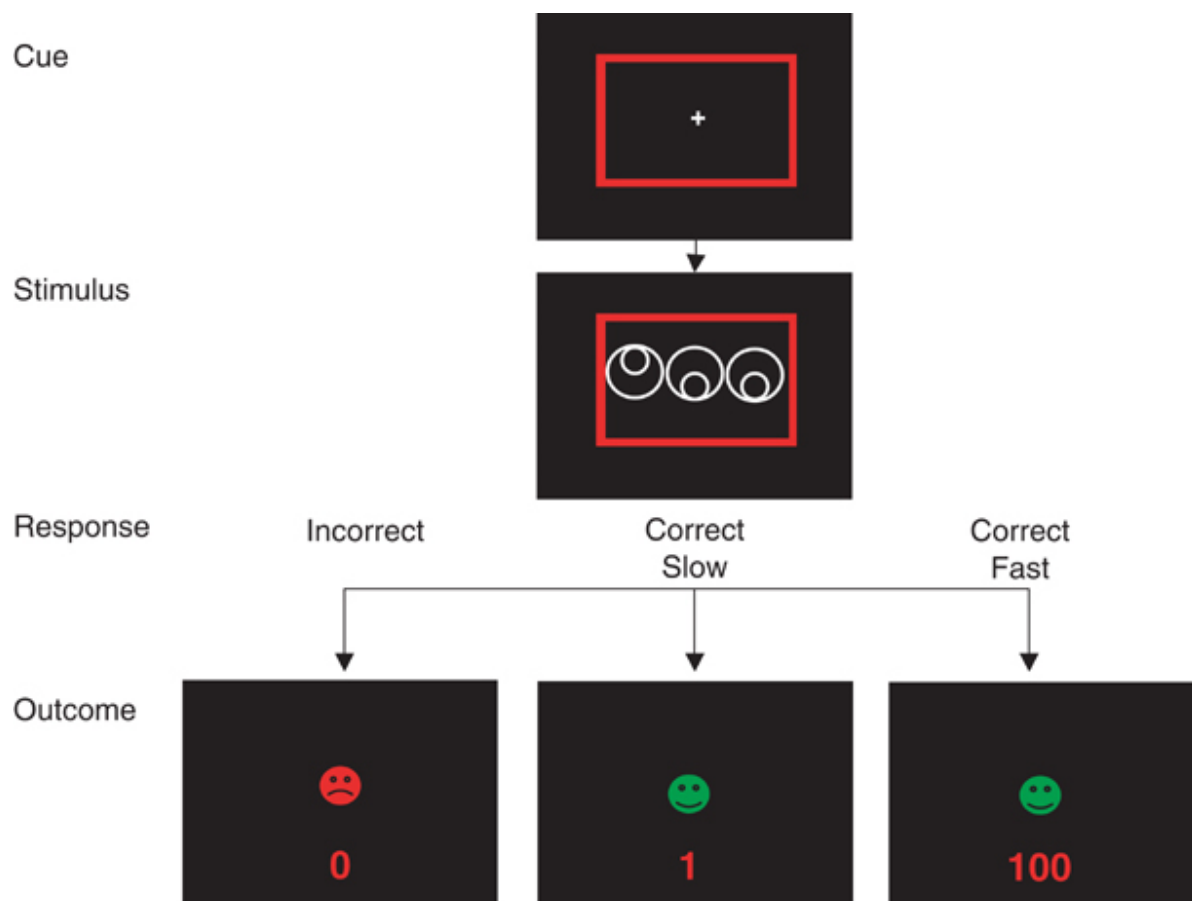


Figure 2.3: Cued reinforcement reaction time task. As described above, participants will see a plus sign followed by a coloured rectangle inside which are 3 double-circle images. They are expected to choose the odd one out from the 3 images and press respective buttons on a laptop. The following screen explains the outcome which will either be incorrect, correct but slower than their reaction time threshold determined on their initial trial or correct and faster than their reaction time threshold.

2.3.2.2.4 Intra-dimensional/ Extra-dimensional shift test (ID/ED)

Derived from the Wisconsin Card Sorting Test (Haaland, 1987), the ID/ED involves visual discrimination and attentional set formation. The two different dimensions used are pink-filled shapes and white lines. Simple stimuli consist of one of those dimensions presented in two different forms and the participant has to choose which of the forms is correct. Compound stimuli consist of both dimensions presented together with one form overlapping the other.

The task begins with simple stimuli and the participant must learn which one is correct (simple discrimination). After each choice, by touching the stimulus on the computer screen, feedback is given. Correct choices result in the word 'correct' in green with a ring tone while incorrect choices result in the word 'wrong' in red with a low negative tone. After 6 correct responses, the contingencies change and the previous correct form becomes incorrect (simple reversal). Distracting stimuli, in the form of the other previously unseen dimension, are then added creating compound discrimination stages and then reversal. After this has been learnt (which always requires 6 consecutively correct responses), there is an intra-dimensional shift where new exemplars of the 2 dimensions are introduced but the relevant dimension is unchanged. Finally there's an extra-dimensional shift and reversal (see 2.4). If at any stage the participant fails to attain 6 consecutive correct trials then after 50 trials the test terminates.

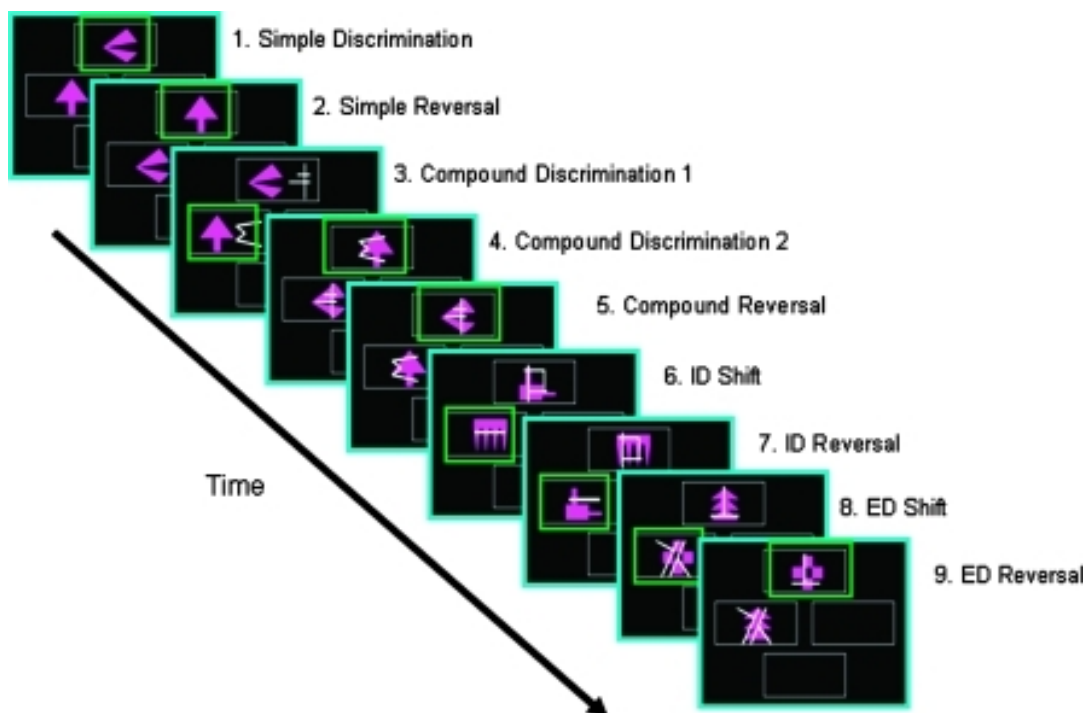


Figure 2.4: IDED task design (described in detail above).

2.3.2.2.5 Ekman 70

The Ekman 70 Faces Test uses photographs from the Ekman and Friesen series of Pictures of Facial Affect, which has been the most widely used and validated series of photographs in facial expression research. From this series, the faces of 10 actors (6 female, 4 male) were chosen, each displaying six basic emotions (happiness, sadness, disgust, fear, surprise and anger) as well as neutral expressions. The Ekman 70 Faces Test is used to assess recognition of facial expressions of basic emotions. The maximum test score indicating best performance is 70 for all seven emotions and 10 for each basic emotion.

There was a practice of the 10 facial expressions. A mouse was used to choose one of the seven labels of different expressions which were visible across the bottom of the screen. Faces were presented for 5s and then disappeared from view. However time for the response was unlimited. Accuracy and reaction time were recorded.

2.3.2.3 Statistical analysis

All data were analysed using SPSS v19.0. Initial group comparisons were conducted using standard ANOVA approach where appropriate. Subsequent pairwise comparisons were performed to determine the origin of these differences. Independent sample t-tests or chi-squared were used when appropriate unless otherwise stated. For any significant differences between paired groups, appropriate clinical covariates were included that were significantly different for that pair. The statistical threshold was $p < 0.05$. Bonferroni corrections for multiple comparisons were performed within each task, where appropriate.

Mann Whitney Tests were conducted to assess the between group differences as the data were not normally distributed. Subsequently Spearman's correlation was performed to determine whether group differences were correlated with symptom scores. All patients were taking medications. There was not enough power to determine differences between medication types due to the small sample size.

2.4 Results

2.4.1 Demographic characteristics of the study groups

Demographic data was available on 25 patient-sibling pairs and 27 controls (see Table 2.2). All participants were in their early to mid-forties. There were more female participants in each group and most were right handed. Parental employment as a proxy for parental socio-economic status was more likely to be non-manual. Alcohol consumption averaged 6-8 units per week and 4-5 cigarettes per day. There were no significant differences between the groups for any of these factors.

2.4.2 Clinical characteristics of the study groups

Patients scored significantly higher than controls on all clinical ratings including the PANSS but only differed significantly from their siblings for depression and mania scores (see Table 2.2). The patients had an average age of onset of their illness of 26.9 years with an illness duration of 18.6 years (SD 6.9 years). During that time they had experienced on average 12 episodes of mania (mean 12.4, SD 16.9) and 11 of depression (mean 11.0, SD 13.8). Seventy-six percent (76.2%) had experienced a psychotic episode in the past although none were psychotic at the time of assessment. Lithium was prescribed to 66.7% of patients and 61.9% were prescribed an antipsychotic (with average chlorpromazine equivalent doses of 204.6 mg (SD 262.9mg)) at assessment and 42.9% were also prescribed an antidepressant.

Self-assessment questionnaires demonstrated greater neuroticism, cyclothymia, non-planning impulsiveness, total impulsivity and sensitivity to punishment in the patients than either siblings or controls. (see Table 2.3). Patients were less extraverted and conscientious than controls and both patients and siblings were less open than controls. Depression (Temps-A) scores, motor impulsiveness and attentional impulsiveness were greater in patients than siblings but not controls. There were no differences between the groups related to the Childhood Trauma Questionnaire.

Table 2.2: Demographic and clinical data.

	BD N=25	Sibs N=25	Controls N=27	ANOVA (F/X², p)	CvBD (X², p)	C vSibs (X², p)	BD v Sibs (X², p)
Age in yrs Mean (SD)	46.2 (4.8)	45.7 (5.1)	43.7 (4.9)	2.0, 0.14			
Gender % male	37.0	44.0	40.7	0.26, 0.88			
Parental SES % manual occ.	44.0	44.0	48.1	0.47, 0.79			
Handedness % R, other	74.1	92.0	85.2	4.67, 0.32			
Alcohol per week Units mean (SD)	7.6 (19.0)	6.0 (8.1)	7.2 (8.8)	0.11, 0.89			
Cigarettes/day Mean (SD)	3.8 (6.9)	5.1 (7.8)	1.8 (5.0)	1.7, 0.19			
HAM-D median (IQR)	6.0 (8.0)	1.0 (3.0)	1.0 (3.0)	48.6, <0.01	20.9, <0.01	1.2 (0.27)	11.9, <0.01
YMRS median (IQR)	1.0 (3.0)	0.0 (0.0)	0.0 (0.0)	24.0, 0.09	16.8, <0.01	1.7 (0.19)	12.6, <0.01
Psychosis total median (IQR)	7 (1)	7 (0)	7 (0)		8.0, 0.02	0.5, 0.50	3.6, 0.06
Neurosis total median (IQR)	7 (0)	7 (0)	7 (0)		6.4, 0.04	0.00, 1.00	3.1, 0.08
General total median (IQR)	21 (12)	19 (5)	18 (3)		10.7, <0.01	2.7, 0.10	3.6, 0.06

Table 2.3: Self-assessment questionnaires' results

	Bipolar (n=25)	Sibling (n=25)	Contro l (n=27)	Significance (MWU, p value)		
				BD vs Con	Sib vs Con	BD vs Sib
Personality (NEO-FFI)						
Neuroticism	30 (21)	15 (13)	17 (12)	160.0, <0.01	298.0, 0.50	123.5, <0.01
Extraversion	24 (10)	28 (7)	30 (10)	180.0, <0.01	257.5, 0.14	229.5, 0.11
Openness	28 (17.5)	27 (5.5)	33 (9)	217.0, 0.03	180.5, <0.01	297.5, 0.77
Agreeableness	32 (12.5)	35 (4)	33 (7)	318.5, 0.73	263.0, 0.17	238.5, 0.15
Conscientiousness	30 (11.5)	32 (7.5)	36 (7)	163.0, <0.01	259.0, 0.15	218.5, 0.07
Temperament (TEMPS-A)						
Cyclothymia	5 (6)	0 (1.5)	0 (2)	107.5, <0.01	301.5, 0.44	82.5, <0.01
Depression	0 (3)	0 (0)	0 (1)	254.5, 0.09	281.0, 0.17	197.0, <0.01
Irritability	0 (3)	0 (1)	0 (1)	280.0, 0.24	326.0, 0.81	253.0, 0.20
Hyperthymia	0 (3.5)	2 (3)	1 (2)	304.0, 0.53	320.5, 0.75	273.0, 0.43
Anxiety	0 (1)	0 (1)	0 (1)	300.0, 0.43	311.0, 0.58	299.5, 0.78
Barratt Impulsiveness Scale						
Motor impulsiveness	23 (8.5)	20 (3.5)	21 (4)	241.0, 0.08	271.0, 0.22	173.5, <0.01
Non-planning impulsiveness	29 (8)	22 (7.5)	23 (6)	140.0, <0.01	302.5, 0.52	160.5, <0.01
Attentional Impulsiveness	17 (10)	12 (4)	14 (5)	239.5, 0.07	268.5, 0.20	171.0, <0.01
BIS total	69 (13)	57 (12.5)	59 (10)	159.5, <0.01	312, 0.64	132.5, <0.01
Sensitivity to Reward & Punishment						
Reward	5 (8.5)	4 (6)	7 (5)	323.0, 0.79	272.5, 0.23	272.0, 0.43
Punishment	14 (14.5)	6 (6)	5 (8)	183.5, <0.01	283.0, 0.32	185.5, 0.01
Childhood Trauma Questionnaire						
Total	43 (39.75)	40 (14.5)	35 (24)	226.5, 0.07	306.5, 0.57	245.0, 0.27

2.4.3 Neuropsychological results

The groups did not differ on premorbid IQ measured by the NART. However, controls scored higher than patients or siblings on both verbal and full-scale IQ and higher than patients on performance IQ measured by the WASI (see Table 2.4). Controls also

performed significantly better than patients on the backward digit span, a test of working memory. Processing speed, measured by the DSST was also faster in controls than either patients or siblings. There were no significant differences between patients and their siblings on any neuropsychological measurement.

Table 2.4: Neuropsychological results including premorbid and current IQ, digit span and digit symbol substitution test.

	BD N=25	Sibs N=25	Controls N=27	ANOVA (F, p)	CvBD (F/X², p)	C vSibs (F/X², p)	BD v Sibs (F/X², p)
NART IQ Mean (SD)	112.4 (7.2)	111.9 (8.1)	115.4 (4.5)	2.13, 0.13			
Full-scale IQ Mean (SD)	103.0 (13.5)	106.4 (15.4)	116.4 (10.3)	7.52, <0.01	1.0, <0.01	5.0,<0. 01	1.2, 0.62
Performance IQ, Mean (SD)	102.2 (15.3)	109.7 (15.3)	116.5 (9.3)	7.56, <0.01	5.1, <0.01	5.8, 0.06	0.01, 0.15
Verbal IQ Mean (SD)	102.8 (11.1)	101.6 (14.0)	112.6 (12.5)	6.17, <0.01	0.9, <0.01	0.3,<0. 01	1.9, 0.52
Forward Digit Span Mean (SD)	6.6 (1.3)	6.7 (1.0)	6.8 (1.0)	0.27, 0.76			
Backward Digit Span Mean (SD)	4.4 (1.1)	4.9 (1.3)	5.4 (0.7)	5.99, <0.01	3.2 <0.01	2.0, 0.08	0.01, 0.17
DSST (90secs) Mean (SD)	42.2 (10.7)	47.5 (12.7)	59.6 (7.4)	19.6, <0.01	4.6, <0.01	5.7,<0. 01	0.2, 0.16

2.4.3.1 Stop signal reaction time task

Patients were significantly slower to stop during this task than either siblings or controls (see Table 2.5).

Table 2.5: SSRTT & CRRTT. The CRRTT results are given for reaction time and accuracy of performance in relation to the probability of receiving a reward.

		Participants			Significance (f/MWU, p)		
		Bipolar n=25	Siblings n=25	Controls n=25	BD vs Con	Sib vs Con	BD vs Sib
Cued reinforcement reaction time task (CRRTT)							
Mean RT	Low prob of reward	1087 (178)	1021 (204)	999 (181)	0.65, 0.09	0.00, 0.69	0.36, 0.23
	Mid prob of reward	1092 (181)	986 (209)	1001 (176)	0.33, 0.08	0.21, 0.79	0.76, 0.06
	High prob of reward	1113 (190)	1022 (205)	994 (166)	0.61, 0.02	1.5, 0.59	0.19, 0.11
Mean Accuracy	Low prob of reward	87 (15)	93 (14)	100 (7)	149, <0.01	227, 0.08	211, 0.07
	Mid prob of reward	87 (14)	93 (17)	94 (13)	169, <0.01	261, 0.30	214.5, 0.08
	High prob of reward	93 (9)	93 (10)	94 (18)	190, 0.03	229, 0.10	272.5, 0.58
% trials > 1 SD slower than subject's mean	Low prob of reward	60.1 (23.2)	59.8 (21.1)	73.0 (19.2)	3.48, 0.04	0.31, 0.03	1.41, 0.96
	Mid prob of reward	62.3 (24.9)	57.9 (23.4)	70.3 (21.6)	0.37, 0.23	0.01, 0.06	0.37, 0.53
	High prob of reward	60.6 (19.4)	57.5 (18.6)	72.7 (20.5)	0.82, 0.04	0.56, <0.01	0.06, 0.57
% trials > 1 SD faster than subject's mean	Low prob of reward	26.9 (24.4)	31.7 (21.2)	20.2 (18.3)	5.60, 0.28	0.11, 0.05	2.74, 0.47
	Mid prob of reward	24.2 (23.1)	33.3 (21.7)	22.9 (22.8)	0.13, 0.84	0.23, 0.10	0.00, 0.16
	High prob of reward	27.7 (22.4)	32.5 (19.1)	21.0 (20.2)	0.10, 0.28	0.24, 0.04	0.01, 0.42
Stop Signal Reaction Time Task							
SSRT		291.1 (79.3)	218.0 (37.4)	227.8 (58.4)	3.63, <0.01	3.85, 0.48	15.88, <0.01

2.4.3.2 Cued Reinforcement Reaction Time Task

The patients' reaction time was significantly slower than controls to the events that offered the highest probability of a reward, when reaction time would be expected to be fastest. In fact the raw data suggests that the patients' reaction times slowed rather than speeded up to the greater rewarding events. Patients were also significantly less accurate than controls at all levels of reward.(see Table 2.5).

2.4.3.3 IDED

Patients made significantly more errors overall than controls (see Table 2.6). There were no specific set-shifting, attention shifting or pattern recognition differences between the groups.

Table 2.6: IDED results of total performance only.

	BD N=24	Sibs N=24	Controls N=27	CvBD (MWU, p)	C vSibs (MWU, p)	BD v Sibs (MWU, p)
Total stages	9 (2)	9 (2)	9 (2)	259.5, 0.15	310.0, 0.99	221.5, 0.17
Total trials	83.5 (35.75)	87.0 (30.0)	73.0 (29.0)	266.5, 0.28	230.5, 0.12	258.5, 0.71
Total errors	23 (11.75)	19 (22.0)	13 (15)	215.5, 0.04	225.5, 0.10	259.5, 0.73

2.4.3.4 Ekman 70

Patients labelled less sad faces correctly than siblings (MWU=178, $p<0.01$) or controls (MWU=178, $p=0.01$). However this result did not sustain correction for multiple comparisons. Patients and siblings had slower reaction times to faces displaying disgust (patients: MWU=165, $p<0.01$, siblings: MWU=165, $p=0.01$), fear (patients MWU=148, $p<0.01$ and siblings: MWU=160, $p<0.01$), sadness (patients: MWU=149, $p<0.01$, siblings: MWU=133, $p<0.01$) and surprise (patients: MWU=161, $p<0.01$, siblings: MWU=158, $p<0.01$) than controls (see Table 2.7). All but disgust remained significant after correcting for multiple comparisons.

Table 2.7: Ekman 70 results of accuracy and reaction time of facial emotion recognition.

	BD N=25	Sibs N=25	Controls N=23	ANOVA (F, p)	CvBD (MWU, p)	C vSibs (MWU, p)	BD v Sibs (MWU, p)
Accuracy %, Median (IQR)							
Anger	73 (27)	64 (23)	64 (27)	1.50, 0.47	277, 0.65	252, 0.45	263, 0.23
Disgust	64 (43)	73 (19)	73 (18)	1.51, 0.47	245, 0.27	251, 0.44	288, 0.48
Fear	73 (41)	64 (41)	82 (18)	2.80, 0.25	223, 0.12	223, 0.18	318, 0.89
Happy	100 (0)	100 (0)	100 (9)	0.33, 0.85	282, 0.63	270, 0.62	325, 1.0
Neutral	91 (8)	91 (13)	91 (12)	0.62, 0.74	263, 0.44	269, 0.68	305, 0.69
Sadness	68 (24)	82 (22)	82 (27)	9.53, <0.01	178, 0.01	285, 0.96	178, <0.01
Surprise	86 (32)	91 (18)	91 (19)	1.70, 0.43	246, 0.27	281, 0.89	267, 0.26
Reaction Time (ms), Mean (SD)							
Anger	3840 (1038)	3807 (909)	3817 (1100)	0.04, 0.98	292, 0.89	277, 0.83	323, 0.97
Disgust	3638 (1401)	3344 (863)	2691 (899)	9.01, 0.01	165, <0.01	165, 0.01	313, 0.82
Fear	3955 (1933)	3383 (653)	2906 (644)	10.85, <0.01	148, <0.01	160, <0.01	294, 0.56
Happy	2163 (1049)	1995 (433)	1812 (485)	1.59, 0.45	250, 0.33	231, 0.24	310, 0.78
Neutral	2678 (871)	2901 (1003)	2451 (864)	3.01, 0.22	250, 0.33	202, 0.08	288, 0.49
Sadness	3544 (1018)	3474 (668)	2757 (809)	12.86, <0.01	149, <0.01	133, <0.01	295, 0.57
Surprise	3331 (1082)	3290 (797)	2714 (803)	9.79, <0.01	161, <0.01	158, <0.01	310, 0.78

2.4.4 Correlations with symptoms scores

Neuroticism, cyclothymia, depression and sensitivity to punishment all correlated positively with depression scores measured by HAM-D both within the patient group and across all groups. Extraversion and conscientiousness correlated negatively with

depression scores. Mania scores correlated positively with neuroticism, openness, cyclothymia, depression, non-planning impulsiveness and sensitivity to punishment and negatively with conscientiousness (see Table 2.8).

There were no correlations between any significant behavioural/ cognitive results and symptom scores using the HAM-D and YMRS.

Table 2.8: Correlations of temperament, personality, impulsivity and reward measures with symptom scores.

	Spearman's rho, p			
	Within group			Across groups
	Bipolar (n=25)	Sibling (n=25)	Control (n=27)	
Correlation with HAM-D				
Temperament (TEMPS-A)				
Neuroticism	0.66, <0.01	NS	0.39, 0.05	0.53, <0.01
Extraversion	-0.48, 0.02	NS	NS	-0.48, <0.01
Conscientiousness	NS	NS	NS	-0.32, <0.01
Personality (NEO-FFI)				
Cyclothymia	0.73, <0.01	NS	NS	0.52, <0.01
Depression	0.64, <0.01	NS	NS	0.42, <0.01
Sensitivity to reward & punishment				
Sensitivity to punishment	0.69, <0.01	NS	NS	0.45, <0.01
Correlation with YMRS				
Temperament (TEMPS-A)				
Neuroticism	0.41, 0.04	NS	NS	0.31, <0.01
Openness	0.50, 0.01	NS	NS	NS
Conscientiousness	NS	NS	NS	-0.30, <0.01
Personality (NEO-FFI)				
Cyclothymia	0.50, 0.01	NS	NS	0.43, <0.01
Depression	0.49, 0.01	NS	NS	0.39, <0.01
Barratt Impulsiveness Scale (BIS)				
Non-planning impulsiveness	NS	NS	NS	0.22, 0.05
Sensitivity to reward & punishment				
Sensitivity to punishment	0.45, 0.03	NS	NS	0.27, 0.02

Table 2.9: Correlations of cognitive measures with each other and with symptom scores

	Spearman's rho, p			
	Within group			Across groups
	Bipolar (n=25)	Sibling (n=25)	Control (n=27)	
Correlation with processing speed (DSST)				
SSRT	NS	NS	NS	-0.27, 0.02
BIS total	NS	NS	NS	-0.31, <0.01
BDS	NS	NS	NS	0.37, <0.01
HAM-D	NS	NS	NS	-0.28, 0.02
Cyclothymia	NS	NS	NS	-0.27, 0.02
Acc Fear	NS	NS	NS	0.24, 0.04
Acc sadness	NS	NS	NS	0.26, 0.03
Correlation with response inhibition (SSRT)				
BDS	NS	NS	NS	-0.29, 0.01
Acc sadness	NS	-0.40, 0.05	NS	-0.29, 0.01
DSST	NS	NS	NS	-0.27, 0.02
Correlation with working memory (BDS)				
DSST	NS	NS	NS	0.37, <0.01
SSRT	NS	NS	NS	-0.29, 0.01
Acc disgust	0.41, 0.05	NS	NS	0.29, 0.01
Acc sadness	NS	NS	NS	0.23, 0.05
Neuroticism	NS	NS	NS	-0.27, 0.02
Cyclothymia	NS	NS	NS	-0.31, <0.01
Correlations with Impulsivity (BIS)				
DSST	NS	NS	NS	-0.31, <0.01
YMRS	0.47, 0.02	NS	NS	0.37, <0.01
Acc sadness	NS	NS	-0.50, 0.02	-0.30, 0.01
Neuroticism	0.68, <0.01	0.49, 0.01	0.42, 0.03	0.61, <0.01
Cyclothymia	0.68, <0.01	NS	0.38, 0.05	0.62, <0.01
SR	0.43, 0.03	NS	0.47, 0.01	0.38, <0.01
SP	0.43, 0.03	0.47, 0.02	NS	0.48, <0.01

Acc - accuracy

2.5 Discussion

Processing speed, working memory and possibly lower intelligence represent trait-related measures of BD. Measures of personality (neuroticism and extraversion), temperament (cyclothymia) and impulsivity (non-planning impulsiveness) are state-related findings in this sample and may represent resilience factors in this cohort of siblings.

2.5.1 Intelligence

Although premorbid IQ did not differ between the groups, patients and their siblings had lower scores compared to healthy participants on almost all aspects of current intelligence measured using the 4 subsets of the WASI. Prospective studies have demonstrated subtle deficits in executive function in at risk adolescents using the Wisconsin Card Sort Test (Meyer, 2004) and in healthy male conscripts (mean age 19 years) using visuo-spatial reasoning (Tihonen, 2005) who have subsequently developed BD. The siblings in this study are passed the period of greatest risk of developing the disorder, suggesting that the decreasing of IQ over time may represent underlying vulnerability but other features are needed to confer illness. Additionally, hospitalisation with BD has been associated with premorbid low IQ and for only a minority of high IQ men (Gale, 2013). However, once diagnosed, there is substantial evidence that neurocognitive impairments are associated with duration and course of illness (Zubieta, 2001; Robinson, 2006).

2.5.2 Executive function

Executive function deficits have been reported consistently in BD (Bora, 2009; Robinson, 2006; Arts, 2008). This study found greater impairments in response inhibition and set-shifting in patients than either siblings or controls, consistent with meta-analytic results (Robinson, 2006) but contradicting another meta-analysis (Bora, 2009) that promotes prolonged latency of response inhibition and set-shifting but not processing speed as candidate endophenotypes. Bora and colleagues included 45 studies of euthymic bipolar patients and 17 studies of relatives and found intact psychomotor processing in relatives, citing treatment effects in patients as the cause of their psychomotor slowness. Ventral

and dorsal prefrontal cortices, including the right inferior frontal cortex and its subcortical connections (Rubia, 2003) have been implicated in response inhibition (Blumber, 2003) and set shifting (Monchi, 2001). These regions demonstrate pathology key to BD (Phillips, 2008). Again it may be that these siblings represent a different group to the more studied first degree relatives who are often younger and more at risk of developing BD or MDD. The effects found only in patients may relate to their medications, however in such a small cohort this is difficult to confirm.

In this study, processing speed was slower in both patients and siblings in keeping with the literature suggesting this as an endophenotype for BD (Glahn, 2010) and challenging the potential confounding effects of antipsychotic medications. However there have been four cohorts of first-degree relatives whose psychomotor speed has remained intact (Kieseppa, 2005; McIntosh, 2005). Deficits in this cognitive domain relate to neuronal efficiency (Rypma, 2006) (faster performing individuals show less neural activity) and are likely to impact on most neuropsychological investigations, although covarying for them may eliminate the group effects, suggesting that processing speed may be an important cognitive process that underpins bipolar disorder and subsequent cognitive deficits.

Working memory assessed using the Backward Digit Span also demonstrated deficits in the patients and a trend towards poorer performance in the siblings lending support for its endophenotypic status (Bora, 2009; Ferrier, 2004) . Functional MRI experiments of working memory indicate that the brain networks involved include prefrontal, temporal and parietal regions (Robinson, 2009). Memory impairments have been found consistently in patients (Robinson, 2006) and inconsistently in relatives (Glahn, 2010; Arts, 2008).

2.5.3 Personality & Temperament

Patients rated themselves higher on neuroticism and cyclothymia and lower on extraversion than their siblings or the healthy controls in keeping with previous findings (Akiskal, 2005b; Jylha, 2010). Neuroticism and cyclothymia correlated positively with both depression and mania scores and extraversion correlated negatively with depression scores across all groups and within the patient group confirming these features of personality and temperament have a relationship to symptoms although the direction of the association is undetermined. Our group has found higher neuroticism and cyclothymia scores in young first degree relatives of BD individuals in a longitudinal study (Whalley, 2011). These scores subsequently separated those high-risk individuals who developed depression from those who remained well, confirming these as features of vulnerability, prodrome and illness (Whalley, 2013b).

2.5.4 Impulsivity, Reward & Punishment

Impulsivity is a complex construct. However, its association with a variety of symptoms including suicidality in BD (Swann, 2005; Swann, 2009a) has driven research into this behavioural domain. Models include reward-based impulsivity, with an inability to delay response for a reward, and the inability to evaluate a stimulus adequately before responding, encompassing deficits in attention and behavioural disinhibition. Increased impulsivity worsens clinical prognosis in BD (Jimenez, 2012). It is of interest that a recent paper described an association between impulsivity in BD and genetic variability at glycogen synthetase kinase-3 β (GSK3 β) the isoenzyme of which is inhibited by lithium and mediates serotonergic function (Jimenez, 2014).

Patients rated themselves with greater impulsivity than their siblings in all domains with a trend towards significance compared to controls for motor and attentional impulsivity. Non-planning impulsiveness was significantly greater in patients than their siblings or controls. In fact, patients scored highest on all impulsivity measures and siblings scored lowest with controls scoring intermediately. Euthymic BD has been associated with

greater impulsivity (Henna, 2013). In keeping with clinical findings and some studies (Swann, 2009b; Swann, 2003) of impulsivity as a feature of mania, this measure correlated with mania scores, in contrast to other studies where impulsivity was independent of mood state (Strakowski, 2010). Decreases in impulsivity measures in the healthy siblings may be an adaptation that relates to resilience and protects them from expressing the illness. However one important limitation of the interpretation of these results is that anxiety was not measured in these participants and has a strong association with impulsivity (Moeller, 2001).

Sensitivity to punishment was greater in the patients than either siblings or controls and correlated with both depressed and manic symptoms confirming this domain as a state-related feature of BD. This subtle finding has been demonstrated using the Iowa Gambling Task, where BD patients with higher depressive scores chose the least risky deck of cards to potentially avoid punishments (Adida, 2011). Patients did not differ in their sensitivity to reward compared to the other groups as one might have expected and this may be due to the clinical states of the patients who had very few manic symptoms at examination.

Patients' reaction time to events that offered the highest probability of a reward (CRRTT) was significantly slower than controls, as was their response inhibition (SSRTT). Psychomotor slowing can be a result of both medication and depressive symptomatology (Goodwin, 1990; Dantchev, 1998). Patients were also less accurate than controls across the reinforcement reaction time task, irrespective of the probability of reward. This may be a feature of their illness and represent a lack of concentration or attention. There appear to be a number of issues with the results from this task suggesting that it was not sensitive to reward processing in these cohorts. There was no clear speeding of reaction time to greater probabilities of reward as one would expect especially in controls. Additionally, data confirming the percentage of trials that were one standard deviation from the subject's mean reaction time (which were derived prior to the main task)

suggests that the controls' reaction times were faster prior to the main task. Therefore, the controls may have experienced ceiling effects, limiting the performance differences between the groups.

2.5.5 Set shifting and reversal learning

Bipolar patients made more errors overall on the ID/ED than controls but not in any specific domain of the task and therefore did not demonstrate the perseverative errors seen in more symptomatic patients (McGrath, 1997; Coffman, 1990). Again these may be due to medications as these results did not correlate with symptom measures. The deficits seen in relatives (Bora, 2009; Linke, 2012) were not present in our sample and may relate more to prodromal features than underlying vulnerability.

2.5.6 Facial emotion labelling

Patients labelled less sad faces correctly than siblings or controls. Patients and siblings had slower reaction times to faces displaying disgust, fear, sadness and surprise than controls. This may be a consequence of slower processing speed. Difficulty labelling sadness may be a subtle feature of subclinical symptoms as state-related labelling impairments have been demonstrated previously (Harmer, 2002).

2.5.7 Confounds

The impact of psychotropic medication on cognitive dysfunction has been assessed in previous studies by investigating euthymic medication-free bipolar subjects and comparing them with those taking mood stabilizers. No differences were found (Goswami, 2010; Joffe, 1989). However other medications, especially antipsychotics, and the complex effects of polypharmacy have not been quantified. All the BD patients in this sample were taking some medication. There would not be enough power to demonstrate differences between those prescribed and not prescribed either antipsychotics or antidepressants. Issues around adherence would also be relevant (NICE clinical guideline

(CG76) January 2009: Medicines adherence: Involving patients in decisions about prescribed medicines and supporting adherence), rendering any findings questionable.

2.5.8 Limitations

Cohort sizes were small for neuropsychological investigations. Although each sibling-pair was asked about their family tree, shared paternity has not been confirmed. Not all patients were euthymic at the time of assessment however the range of symptom scores has enabled state-related correlations. Ceiling effects in the controls may have impacted on the reward reaction time task.

2.5.9 Summary

Trait-related findings in these cohorts support previous findings of deficits in processing speed, working memory and decreasing intelligence. Our data do not confirm response inhibition and set-shifting as candidate endophenotypes, however support previous findings of processing speed as an endophenotype. Personality and temperament measures associated with BD were only marked in patients and correlated with symptoms. The sibling group present differently to many first degree relatives from previous studies, demonstrating less of the vulnerability markers from the literature. This may be due to their unique presentation both in terms of their age and relationship to risk but also as they have not developed a mood disorder, depression or BD, suggesting that the lack of vulnerability may relate more to resilience.

3 Chapter 3:

Experiment 2: A functional magnetic resonance imaging comparison of individuals with Bipolar Disorder, their siblings and controls examining facial emotion processing.

3.1 Abstract

The neural circuitry that underpins facial emotion processing is known to be disrupted in BD. This study sought to test whether dysfunctions with this network were present in BD and whether they related to genetic vulnerability to illness or adaptive resilience. Twenty-five bipolar I patients each with their unaffected sibling, were compared to 24 healthy age and gender-matched controls using an implicit and explicit facial emotion processing task during event-related functional MRI. Data were analysed using pairwise comparisons at whole brain level. In patients compared to controls, implicit facial emotion processing was associated with lingual gyrus and insula over-activations and explicit emotion processing elicited fusiform under-activations in patients compared with controls. These findings are likely to represent correlates of disease expression. Posterior cingulate over-activations and putamen and cerebellar under-activity in siblings compared to controls, and parietal under-activations in siblings compared to their ill relatives, may represent adaptive responses associated with resilience.

3.2 Introduction

The prevailing model of bipolar disorder describes an imbalance between cortical and subcortical neural circuitry such that reduced dorsolateral prefrontal and orbito-frontal activation is associated with disinhibition of limbic structures such as the amygdala and striatum (Sheline, 2003; Strakowski, 2005). One interpretation of these data is that there are impairments in higher level cognitive abilities that monitor and assess base or innate emotion processing of the amygdala or that an overactive limbic system is overriding cortical regions. This results in behaviours that are unrestrained or unchecked and would be in keeping with some of the features of bipolar disorder, such as mania, disinhibition and anhedonia.

Facial identification remains intact in BD while determining the emotional valence of an expression has been demonstrated to be impaired in a number of studies (Brotman 2008; Bozikas, 2006; Getz, 2003; Lembke, 2002; Verderman, 2012) although findings are conflicting (Robinson, 2015) Impairments have been demonstrated in all phases of the illness. However, certain mental states have shown consistent deficits in the labelling of specific emotions. Positive and negative biases exist during mania and depression respectively (Murphy, 1999), although the relationship to symptoms seems less strong in mania. Findings are less consistent in euthymic patients with some studies reporting no deficits (Robinson, 2015) although fear labelling has been impaired. There have been very few behavioural studies conducted with adult first degree relatives of BD patients however our own data of young adult first degree relatives of BD patients (The Bipolar Family Study) did not demonstrate an underlying vulnerability related to facial emotion processing (as discussed in Chapter 1).

There is a substantial literature on human face processing using functional magnetic resonance imaging. The neural circuitry that underpins these processes is known to be disrupted in BD and includes the ventromedial and dorsolateral prefrontal cortex, orbito-frontal cortex, the anterior cingulate cortex, fusiform gyrus, inferior temporal gyrus,

occipital gyrus, amygdala, ventral striatum, insular, hippocampus and the dorsomedial nucleus of thalamus (Gur, 2002; Fusar-Poli, 2009; Hulvershorn, 2012). Amygdala activation has been most consistently associated with emotion processing especially with fear (Adolphs, 1994) but also happy and sad expressions (Fusar-Poli, 2009). Disgusted and angry faces are associated with insula activation (Harmer, 2002). Unaffected first degree relatives also show hyper-activations in the medial prefrontal cortex, putamen and amygdala when implicitly viewing either fearful or happy faces compared to neutral faces (Surguladze, 2010) .

The majority of studies have employed implicit facial affect labelling paradigms which reveal greater involvement of subcortical regions (Critchley, 2000; Hariri, 2003). The addition of explicit affect labelling in an event-related design enables more detailed investigations of the prefrontal cortical aspects of affect processing as these involve more complex judgments requiring appraisal and higher order functions. Stronger recruitment of face processing regions e.g. fusiform gyrus (Habel, 2007) has also been demonstrated with explicit paradigms in controls.

In this chapter, the objectives were to assess both implicit and explicit processing of happy, neutral and fearful facial expressions in euthymic bipolar individuals and their unaffected matched siblings. The selection of euthymic patients for this study is based on literature suggesting more stable and repeatable neural activations and further minimises differences between the groups driven by state-related factors such as clinical symptoms. Happy and fearful expressions have been most widely used previously and therefore enable robust neural activation hypotheses. An event related design that incorporates all three expressions (happy, fearful and neutral) and both responses (implicit and explicit) will facilitate comparisons of all elements of facial processing. Explicit responses will allow both evaluation of emotion recognition during the task and the assessment of the neural correlates of executive function which, in attentional tasks, have been shown to be altered in first degree relatives (Drapier, 2008) . The addition of siblings of the bipolar individuals

who were passed the age of greatest risk of developing the disorder and who did not experience any form of mood disorder offered the opportunity to investigate features of familial vulnerability, endophenotypic features and resilience in the absence of illness and medication, as well as state-related effects associated with symptoms.

3.2.1 Hypotheses:

- i. There will be no differences in performance between the groups (in accordance with typical functional imaging task design criteria whereby all individuals including patients can perform the task at a desired threshold level of accuracy (here specified as >75%) to avoid subsequent interpretative complications).
- ii. Based on previous literature described above, Bipolar patients will under-activate cortical regions and over-activate subcortical/limbic regions, to both implicit and explicit facial expressions of both happy and fearful faces when compared to healthy controls. Fearful faces are likely to elicit greater group differences. Unaffected siblings will lie intermediate in between patients and controls.
- iii. There will be greater cortical deficits for the explicit task which typically in healthy individuals recruits a greater degree of cortical processing.

3.2.2 Additional explanations:

- i. Where patients' brain activations differentiated them from controls and their siblings, these changes will be considered as correlates of disease expression.
- ii. Where siblings' brain activity is shared with their BD relatives and differentiates both groups from controls, this would reflect genetic predisposition to the disorder.
- iii. Where siblings' brain activations differentiated them from controls and/or their BD relative, or controls activations were intermediate between the siblings and patients, this may represent adaptive responses associated with resilience.

3.3 Methods

3.3.1 Recruitment and clinical assessments of participants

Recruitment and clinical assessments were as described in chapter 2. A total of 25 bipolar-sibling pairs and 24 controls provided suitable fMRI data as one control was unable to participate due to poor visual acuity that could not be corrected with the visual aids we had available.

3.3.2 Experimental paradigm: Implicit & explicit facial emotion processing task

The Ekman Faces Task was event-related and used photographs from the Ekman and Friesen series of Pictures of Facial Affect. The faces of 9 actors (5 female, 4 male) were chosen, each displaying one of three expressions (happiness, fear or neutral). A face was displayed in the centre of the screen and the participant had to press a left or right thumb button that corresponded to the words on the bottom left or right positions on the screen which asked either for a judgment about the gender ('male' or 'female') of the face or an explicit judgment about whether the face was 'emotional' or 'not emotional'. The same stimuli were used in both conditions. There was one run with 108 trials in total. Each expression was presented twice for each condition. Each stimulus was presented for 1500ms within a trial with a mean duration of 3500ms (1000ms jitter). There were 4 counterbalanced versions of the task commencing either with i) a neutral face and a gender judgement; ii) a neutral face and an emotion judgement; iii) an emotional face and a gender judgement or iv) an emotional face and an emotion judgement.

3.3.2.1 In-scanner behaviour

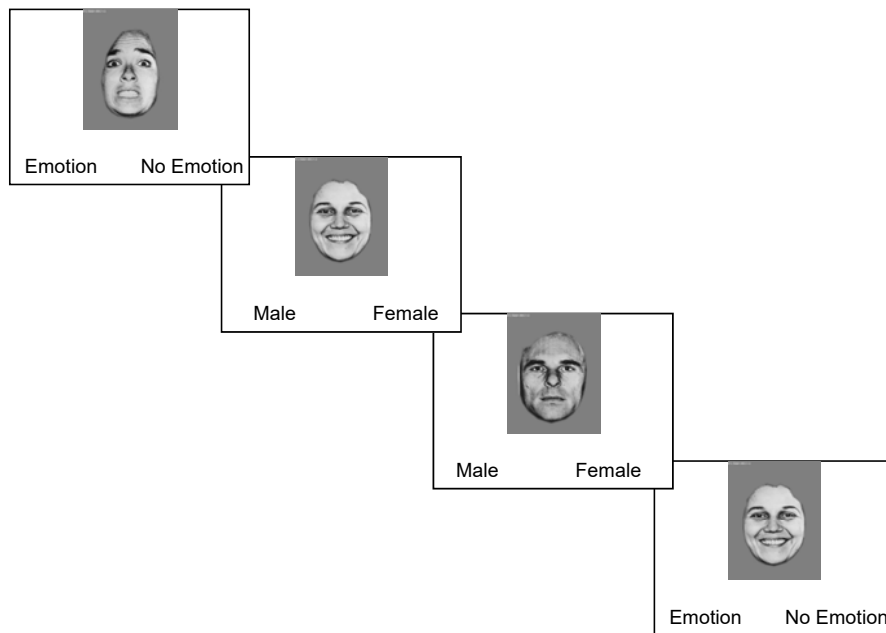
Reaction times and accuracy for each condition (either gender or emotion judgement) were calculated for each group for each emotional condition. Means/medians and variance are specified within table 3.2. Analysis between the groups was conducted using ANOVA in SPSS followed by pairwise comparison (using Mann Whitney U tests where appropriate) in SPSS. Similar to the imaging analysis the prime contrasts were for i) implicit versus neutral conditions, ii) explicit versus neutral conditions, and iii) implicit

versus explicit emotions, primarily using fearful and happy faces separately and then combining the emotions to enable a more powerful analysis.

3.3.2.2 Image acquisition

Imaging was carried out at the Scottish Brain Imaging Research Centre (SBIRC) on a GE 1.5 T Signa scanner (GE Medical, Milwaukee, USA). The functional imaging protocol consisted of axial gradient-echo planar images (EPI) (TR/TE = 2000/40ms; matrix = 64 x 64; field of view (fov) = 24 cm) acquired continually during each of the experimental paradigms. Twenty seven contiguous 5 mm slices were acquired within each TR period. Each EPI acquisition was run for 230 volumes. The T1 sequence yielded 180 contiguous 1.2 mm coronal slices (matrix = 192 x 192; fov = 24 cm; flip angle 8°).

Figure 3.1: Implicit & explicit facial emotion processing task demonstrating an explicit choice of an emotional face requiring a choice of ‘emotion’ or ‘no emotion’ (top), an implicit choice (gender) to an emotional face (second image), an implicit choice to a neutral face (third image) and finally, another explicit, emotional choice to an emotional face.



3.3.2.3 Image processing

EPI and T1 images were reconstructed into NIFTI format (Mayo Foundation, Rochester, MN, USA) using DICOM convert functions available in SPM8 (Statistical Parametric Mapping; <http://www.fil.ion.ucl.ac.uk/spm/>) running in Matlab (The MathWorks, Natick, MA, USA). To assess data quality reconstructed images were examined using ‘Art Repair’ software (<http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm>). There were no scans with excessive movement over the selected threshold for exclusion which was more than one voxel over a TR period. EPI images were realigned to the mean functional image

using a two-pass procedure to correct for movement throughout the period of acquisition. The structural (source) and functional (reference) image were then co-registered and the anatomical image was then segmented, creating grey and white matter images. Spatial normalisation parameters generated from the previous step were then used to normalise at 2 mm³ the realigned functional EPI data. Finally, the realigned and normalised images were smoothed with a 6x6x6 mm full width half maximum (FWHM) Gaussian filter.

3.3.2.4 Image analyses

First level statistical analysis was performed using the general linear model approach in SPM8. Three different pairwise analyses were conducted to investigate different hypotheses. First level analyses were conducted differently according to the specific groups contained in each pairwise comparison. This was to account for the fact that the unaffected relatives and bipolar proband were paired (within a family), yet the control samples were unrelated to either the unaffected relative or patients' sample, resulting in differences in variance between groups due to differences in relatedness.

3.3.2.4.1 Control comparisons: Patients versus healthy controls or siblings versus healthy controls:

At the individual subject level the data was modelled with seven conditions (explicit or implicit happy, explicit or implicit fear, explicit or implicit neutral and baseline) each by a boxcar convolved with a synthetic haemodynamic response function. Estimates of the subject's movement during the scan were entered as 'covariates of no interest'. Contrast images were generated for each participant for the contrasts of interest (explicit or implicit happy vs neutral, fear vs neutral) representing pair-wise comparisons of parameter estimates for the conditions. These contrast images per subject were then entered into a second-level analysis.

3.3.2.4.2 Patients versus siblings:

At the individual subject level each bipolar patient and their related sibling were modelled together each by a boxcar convolved with a synthetic haemodynamic response function in order to acknowledge the reduced variance of familiarity in these groups. Estimates of the subject's movement during the scan were entered as 'covariates of no interest'. Contrast images were generated for each pair for all the contrasts of interest (implicit versus explicit by happy versus neutral, fear versus neutral,) representing pair-wise comparisons of parameter estimates for the conditions. These contrast images per pair were then entered into a second-level analysis. Based on the hypotheses, the prime contrasts of interest were: i) implicit versus neutral, ii) explicit versus neutral, and iii) implicit versus explicit emotions primarily using fearful and happy faces separately and then combining the emotions to enable a more powerful analysis.

3.3.2.5 Second level analysis

3.3.2.5.1 Patients versus healthy controls or siblings versus healthy controls:

Contrast images were entered into a pairwise F or T test in SPM8 comparing either patients vs controls or siblings vs controls. The model was used to examine condition effects, and overall group effects.

3.3.2.5.2 Patients versus siblings:

Contrast images *per pair* of related family members as generated above were then entered into a second-level analysis to examine condition and group effects.

Based on the hypotheses, the prime contrasts of interest were: i) implicit versus neutral, ii) explicit versus neutral, and iii) implicit versus explicit emotions primarily using fearful and happy faces separately and then combining the emotions to enable a more powerful analysis.

Statistical maps were thresholded at a level of $p < 0.005$ (uncorrected) and regions were considered significant at a cluster level, with family-wise error correction (FWE), of $p < 0.05$. All coordinates are quoted in Montreal Neurological Institute (MNI) convention (<http://www.mni.mcgill.ca>) and images are overlaid onto standard brain in MNI space using Mango software package (<http://ric.uthscsa.edu/mango>). Based on the prior hypothesis, small volume corrections were applied for the amygdala created using the WFU PickAtlas (Maldjian, 2003; Tzourio-Mazoyer, 2002) .

Post hoc analyses to investigate the activation differences in all three groups were performed by extracting significant clusters using a 4mm sphere and performing statistical analyses in SPSS 19 including correlation analyses between extracted clusters and symptom scores within relevant groups using Spearman's Rho and Pearson's correlation coefficient. Differences originated from pairwise comparisons where the design matrix did not include the third group to avoid bias in interpretation of the group that was excluded.

3.4 Results

3.4.1 Participant characteristics

Twenty-five patient-sibling pairs and 24 controls were analysed. Demographic and clinical results are summarised in Table 3.1. There were no differences between the groups in age, gender, parental occupation, premorbid IQ and handedness. Patients had higher depression (HAM-D) and mania (YMRS) ratings than both siblings and controls. Self-reported neuroticism and cyclothymia were also greater in patients than either siblings or controls. Extraversion showed the inverse pattern, with patients scoring significantly lower than controls.

Table 3.1: Demographic and clinical results including age, gender, premorbid IQ, parental occupation as a proxy for socio-economic status, depression and mania scores and relevant personality and temperament factors.

	Bipolar patients N=25	Siblings N=25	Controls N=24	BD v C (F/X ² , p)	Sibs v C (F/X ² , p)	BD v Sibs (F/X ² , p)
Age in yrs Mean (SD)	45.6 (5.0)	45.2 (5.1)	43.0 (5.1)	NS	NS	NS
Gender % male	36.0	44.0	41.7	NS	NS	NS
Handedness % R, other	84.0	96.0	83.3	NS	NS	NS
Parental SES % manual occupation	56	56	52	NS	NS	NS
NART IQ Mean (SD)	113.2 (6.8)	111.9 (8.1)	115.4 (4.5)	NS	NS	NS
HAM-D median (IQR)	6 (8)	1 (8)	2 (2)	97.5, <0.01	NS	136.0, <0.01
YMRS median (IQR)	0 (4)	0 (2)	0 (2)	192.0, <0.01	NS	171.5, <0.01
Neuroticism median (IQR)	30 (21)	15 (13)	16.5 (13)	131.5, <0.01	NS	123.5, <0.01
Extraversion median (IQR)	24 (10)	28 (7)	31 (9)	153.5, <0.01	NS	NS
Cyclothymia median (IQR)	5 (9)	0 (2)	0 (2)	92.0, <0.01	NS	82.5, <0.01

3.4.2 In-scanner performance

There were no differences between the groups related to accuracy for assessing either the gender or emotionality of the faces viewed in the scanner. Bipolar patients had slower reaction times when they viewed implicit fearful faces than controls ($f=0.82$, $p=0.05$) see Table 3.2.

Table 3.2: In-scanner performance of reaction time and task accuracy.

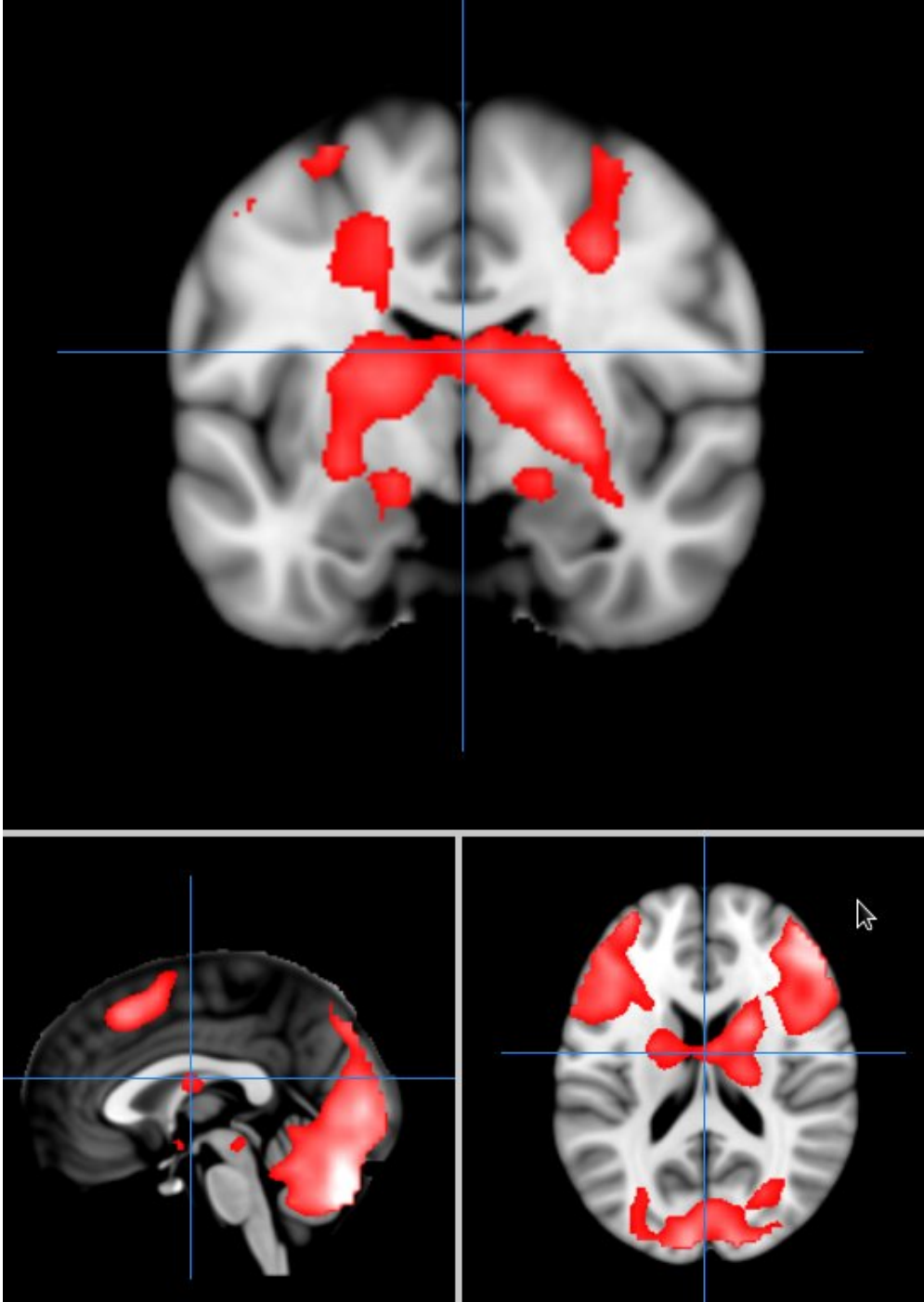
		Bipolar patients N=25	Siblings N=25	Controls N=24	BD v C (F/X ² , p)	Sibs v C (F/X ² , p)	BD v Sibs (F/X ² , p)
Reaction Time (ms) mean (SD)							
Implicit	Neutral	1196 (228)	1165 (116)	1077 (176)	NS	NS	NS
	Fear	1253 (239)	1195 (138)	1092 (173)	0.82, 0.05	NS	NS
	Happiness	1178 (229)	1121 (131)	1041 (153)	NS	NS	NS
Explicit	Neutral	1438 (258)	1380 (176)	1338 (265)	NS	NS	NS
	Fear	1420 (282)	1309 (187)	1293 (189)	NS	NS	NS
	Happiness	1325 (220)	1256 (261)	1211 (187)	NS	NS	NS
Accuracy (%) median (IQR)							
Implicit	Neutral	89 (15)	91 (9)	94 (10)	NS	NS	NS
	Fear	90 (9)	89 (10)	92 (9)	NS	NS	NS
	Happiness	89 (12)	95 (7)	96 (7)	NS	NS	NS
Explicit	Neutral	72 (28)	81 (13)	82 (14)	NS	NS	NS
	Fear	87 (13)	82 (16)	87 (13)	NS	NS	NS
	Happiness	78 (30)	90 (11)	92 (7)	NS	NS	NS

3.4.3 Task-activated regions (Figure 3.2)

Bilateral amygdala, occipital (visual) cortices and frontal regions were activated during the task, demonstrating appropriate responses in controls.

Figure 3.2: Activation map of fear greater than neutral faces in control group only. The figure demonstrates activation for the contrast of fear versus neutral facial stimuli for both implicit and explicit conditions combined, within healthy controls only. This image demonstrates significant activation in bilateral amygdala, lateral prefrontal regions, occipital regions. Image thresholded consistent with analysis thresholds in main text. For

all such figures images are overlaid onto standard brain in MNI space using Mango software package (<http://ric.uthscsa.edu/mango>).



3.4.3.1 Patient vs Control Comparison (see Table 3.3)

Table 3.3: BD vs Controls: regions of significant differences between the groups including within group correlations with relevant symptom, personality and temperament scores.

Contrast	P _{FWE} value	KE	Z	Co-ords	Region	Correlation with Ham-D, YMRS, Neuroticism, Extraversion, Cyclothymia (Pearsons, p)	
						BD	Con
						Within Group	
						BD	Con
BD > Con:							
Imp Fear > Neutral (p<0.001)	0.035	90	3.93	-12 -79 -8	L Lingual Gyrus	NS	-0.438, 0.03 (Extra)
Imp Emotion > Neutral (p<0.001)	0.052	87	3.91	42 2 4	R Insula	NS	0.375, 0.07 (Extra)
Con > BD:							
Exp > Imp Fear (p<0.005)	0.045	259	3.62	27 -70 -5	R Fusiform/ Lingual Gyrus	NS	NS

3.4.3.1.1 Implicit fear versus neutral

Patients demonstrated greater activations than controls in the left lingual gyrus when viewing implicit fearful faces in comparison to neutral faces. This result correlated with negatively with extraversion (P=-0.438, p=0.03) scores within the control groups but demonstrated no association within the patient group (see Figure 3.3).

Greater amygdala activations were present in patients than controls during implicit facial processing but only at lower thresholds.

3.4.3.1.2 Implicit happiness versus neutral

There were no significant differences using this contrast.

3.4.3.1.3 Implicit emotion versus neutral

There were no further significant results for the contrast of implicit fear versus neutral. Therefore, in order to increase power, implicit processing of both emotions (fear and happy) were combined and compared to implicit neutral faces. Patients demonstrated greater activations in the insula to implicit emotional faces compared to neutral faces. There were no correlations with symptoms, personality or temperament scores suggesting that this was not a state effect (see Figure 3.4).

3.4.3.1.4 Explicit versus implicit fear

Patients demonstrated reduced activations than controls in the right fusiform/lingual gyrus to explicit greater than implicit fear. There were no correlations with symptoms personality or temperament scores suggesting that this was not a state effect (see Figure 3.5).

3.4.3.1.5 Explicit versus implicit happiness

There were no significant differences using this contrast.

Using extracted data, siblings activations appear intermediate between patients and controls for all significant contrasts.

Figure 3.3: Extracted lingual gyrus activation (4mm radius sphere centred on -12 -79 -8) with standard error bars from the contrast implicit fear greater than neutral faces, bipolar patients greater than controls. (1 = BD, 2 = siblings, 3 = controls).

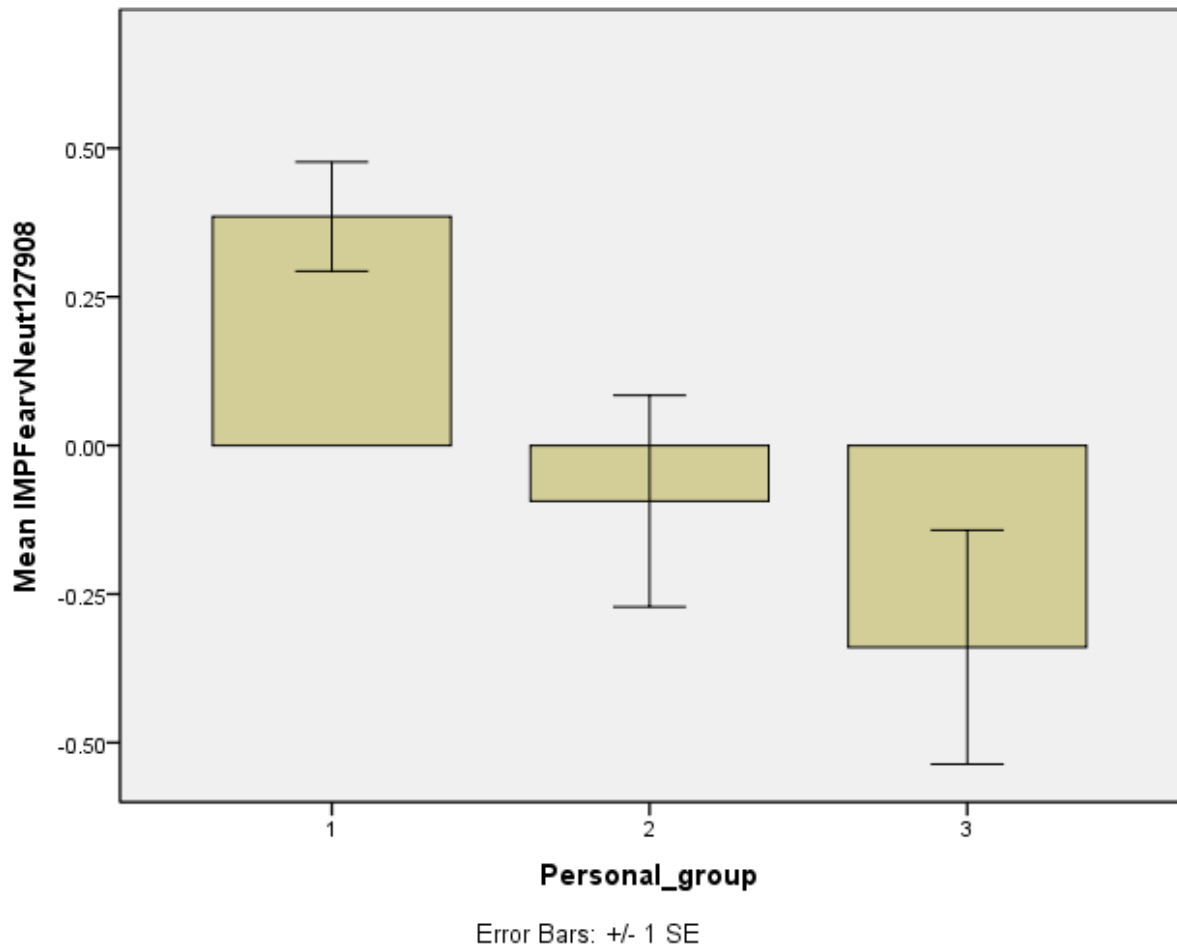


Figure 3.4: Extracted insula activation (4mm radius sphere centred on 42 2 4) with standard error bars from the contrast implicit emotion greater than neutral faces, bipolar patients greater than controls. (1 = BD, 2 = siblings, 3 = controls).

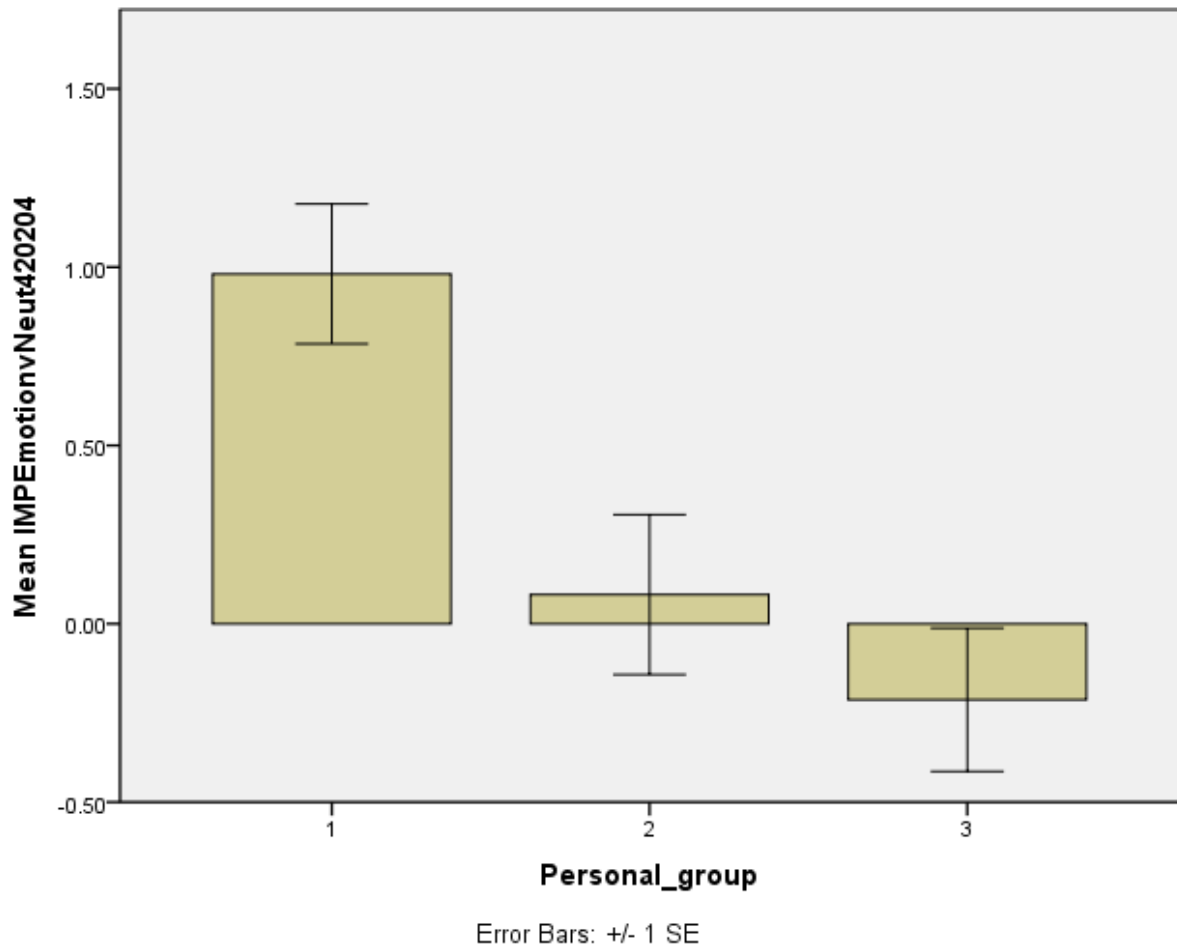
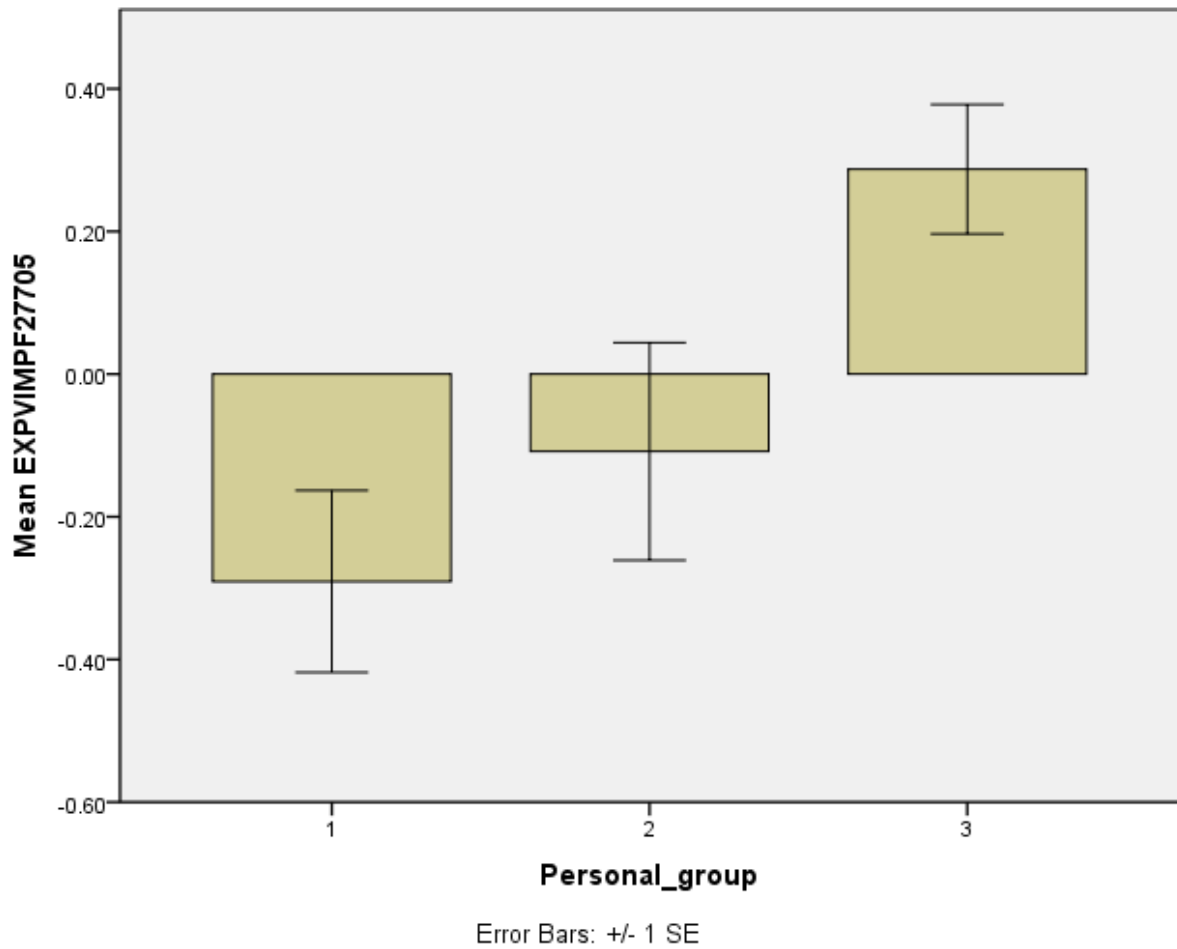


Figure 3.5: Extracted fusiform activation (4mm radius sphere centred on 27 -70 -5) with standard error bars from the contrast explicit fearful greater than implicit fearful faces, controls greater than bipolar patients. (1 = BD, 2 = siblings, 3 = controls).



3.4.3.2 Siblings vs Control Comparison (see Table 3.4)

Table 3.4: Sibs vs Controls: regions of significant differences between the groups

There were no significant within group correlation results.

Contrast	P _{FWE} value	KE	Z	Co-ords	Region
Siblings >Con (threshold p<0.005):					
Exp> Imp Happy	0.034	251	3.69	9 -55 16	R Posterior Cingulate
Con > Siblings (threshold p<0.005):					
Imp Happy > Neutral	0.003	412	4.10	-27 -22 10	L Putamen/ Lentiform
	0.023	266	3.89	-6 -73 -29	L Cerebellum

3.4.3.2.1 Implicit fear versus neutral or Explicit fear versus neutral or Explicit versus implicit fear

The processing of fearful faces did not reveal any significant differences in activations between siblings and controls.

3.4.3.2.2 Implicit happiness versus neutral

Siblings demonstrated reduced activations to implicit happy compared with neutral faces in the putamen and cerebellum. Extracted data suggests that the patients' activations were intermediate between their siblings and controls in both regions (see Figures 3.7 & 3.8).

3.4.3.2.3 Explicit versus implicit happiness

Siblings demonstrated greater activations in the posterior cingulate during explicit compared to implicit events that involved happy faces (see Figure 3.6). Extracted data suggests that the patients' activations were similar to controls.

Figure 3.6: Extracted Posterior Cingulate activation (4mm radius sphere centred on 9 -55 16) with standard error bars from the contrast explicit greater than implicit happy faces, siblings greater than controls. (1 = BD, 2 = siblings, 3 = controls).

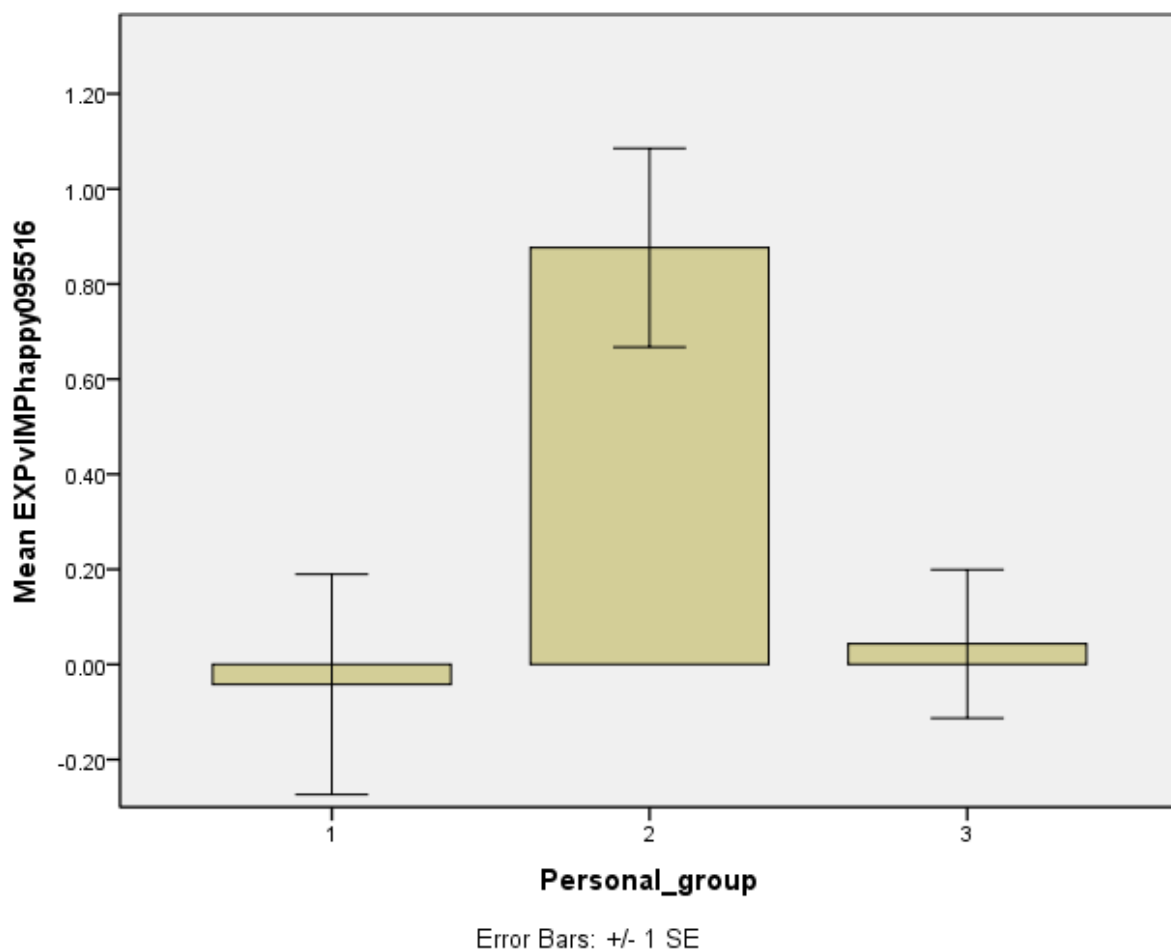


Figure 3.7: Extracted Putamen activation (4mm radius sphere centred on -27 -22 10) with standard error bars from the contrast implicit happy greater than neutral faces, controls greater than siblings. (1 = BD, 2 = siblings, 3 = controls).

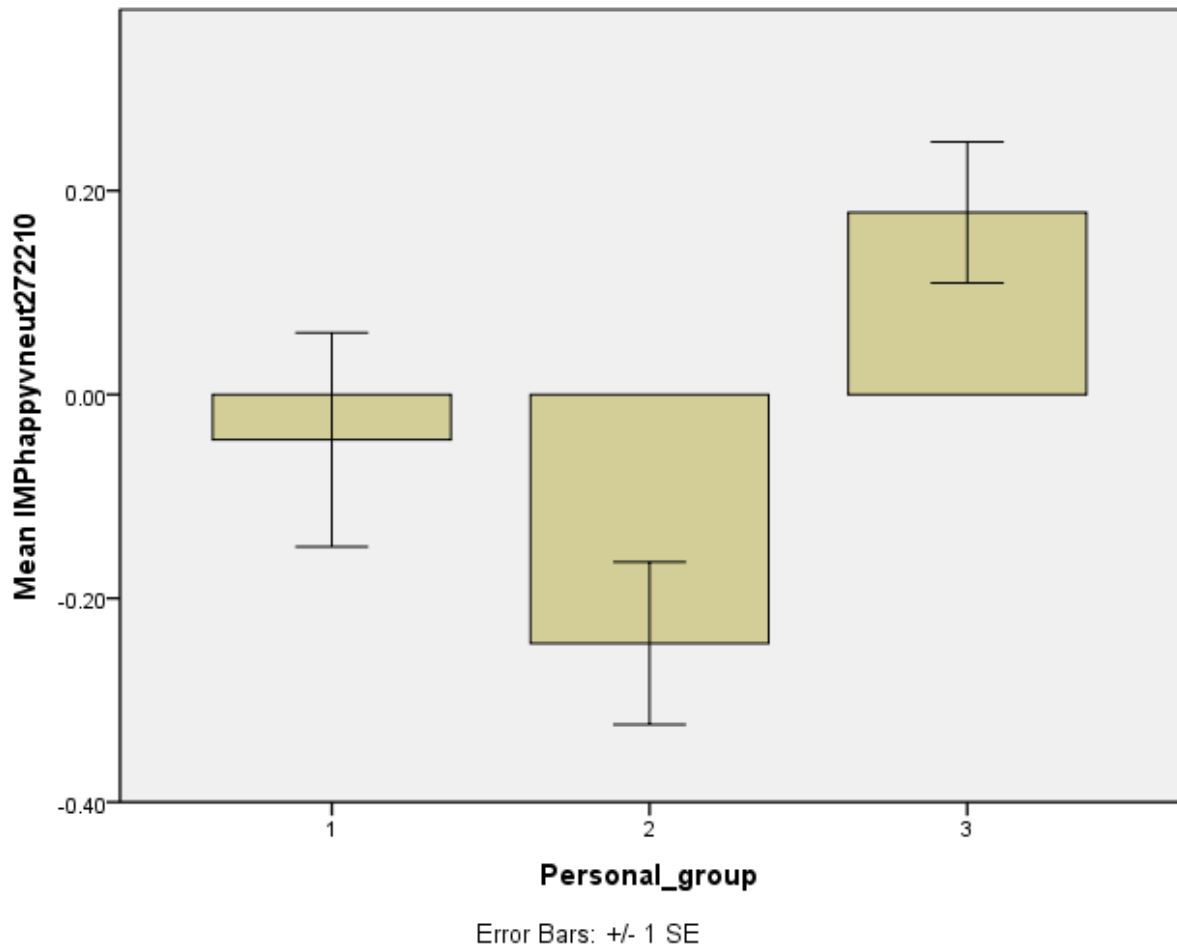
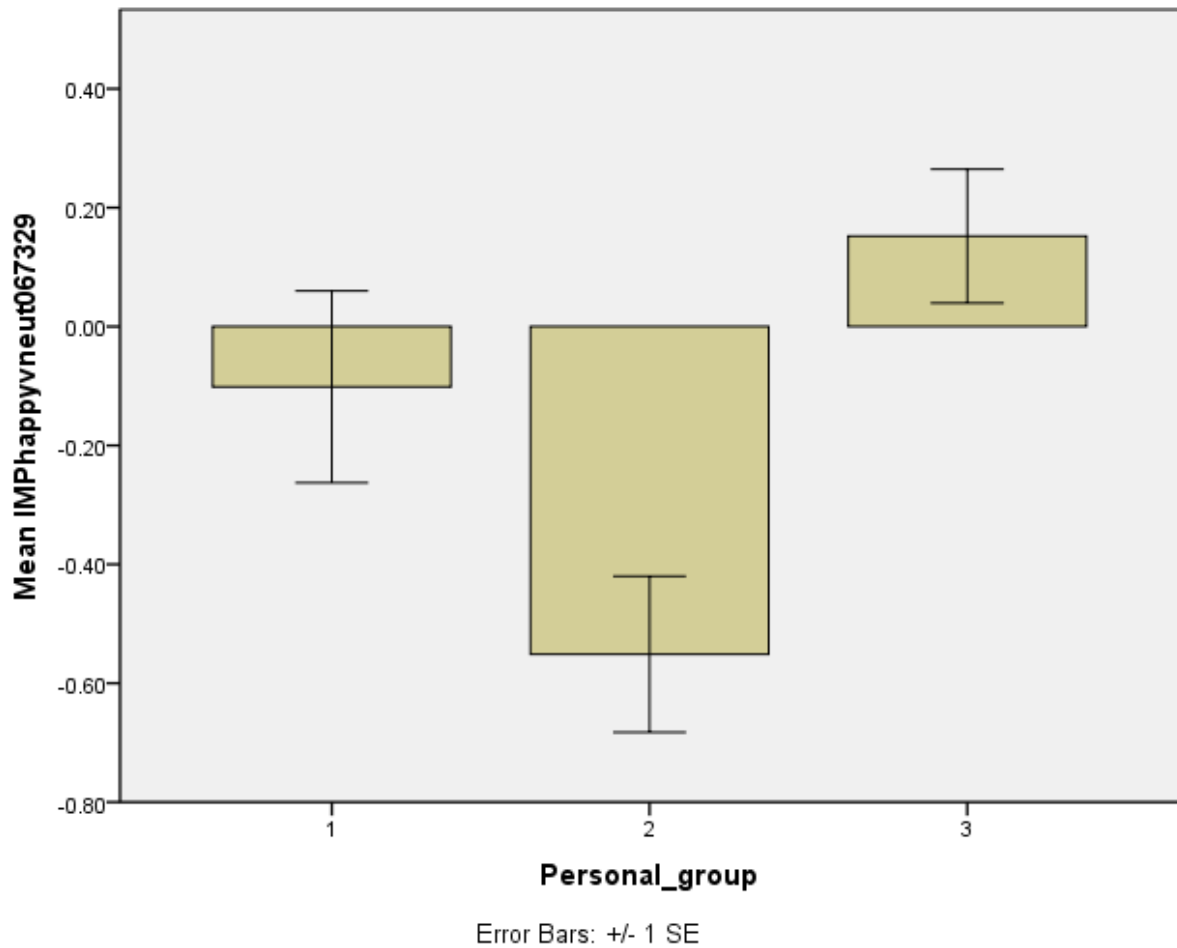


Figure 3.8: Extracted Cerebellum activation (4mm radius sphere centred on -6 -73 -29) with standard error bars from the contrast implicit happy greater than neutral faces, controls greater than siblings. (1 = BD, 2 = siblings, 3 = controls).



3.4.3.3 Patient vs Sibling Comparison

Table 3.5: BD vs Siblings: regions of significant differences between the groups.

There were no significant within group correlation results.

P_{FWE} value	KE	Z	Co-ords	Region
Full factorial vs Neutral: All Implicit > Explicit (threshold p<0.005):				
0.002	619	4.01	-6 -73 7	L Lingual Gyrus
0.014	403	3.48	-24 -61 49	L Superior Parietal Lobe

3.4.3.3.1 Implicit fear/ happiness versus neutral or Explicit fear/ happiness versus neutral or Explicit versus implicit fear/ happiness

The processing of fearful or happy faces alone did not reveal any significant differences in activations between patients and their siblings.

3.4.3.3.2 Implicit emotion versus neutral

When the emotions (fear and happy) were combined, bipolar individuals showed greater activations than their siblings in the left lingual gyrus during the implicit emotion judgments compared to explicit emotion judgments (see table 3.5 and figure 3.9). Extracted data demonstrated intermediate deactivations in controls.

3.4.3.3.3 Implicit versus explicit emotion

Bipolar individuals demonstrated hyper-activation while their siblings showed hypo-activation in the left superior parietal lobe during the implicit emotion judgments compared to explicit emotion judgments (see table 3.5 and figure 3.10). Extracted data demonstrated intermediate deactivations in controls. Both sets of results did not correlate

with symptom, personality or temperament scores suggesting that they were not state effects.

Figure 3.9: Extracted lingual gyrus activation (4mm radius sphere centred on -6 -73 7) with standard error bars from the contrast all implicit greater than explicit faces, comparing bipolar patients and their siblings. (1 = BD, 2 = siblings, 3 = controls).

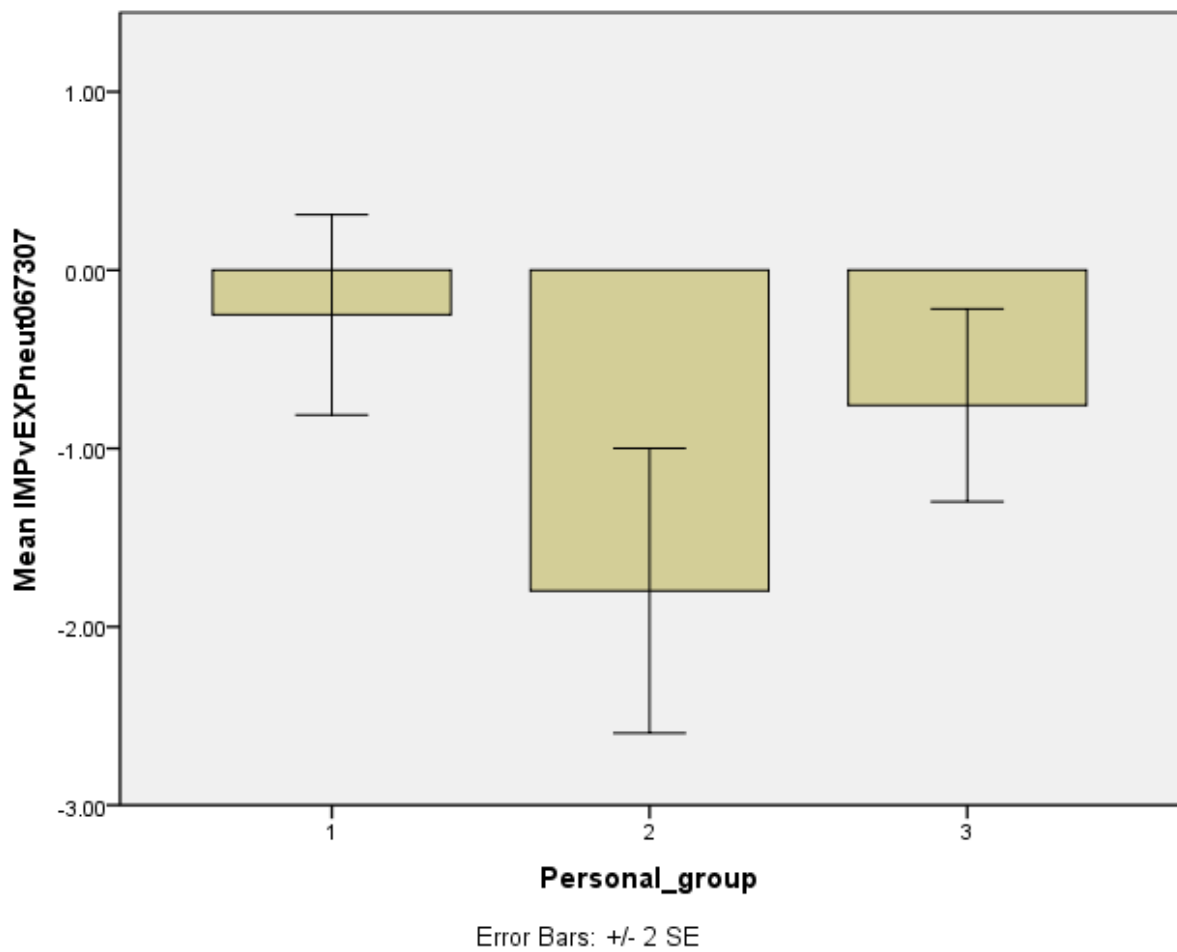
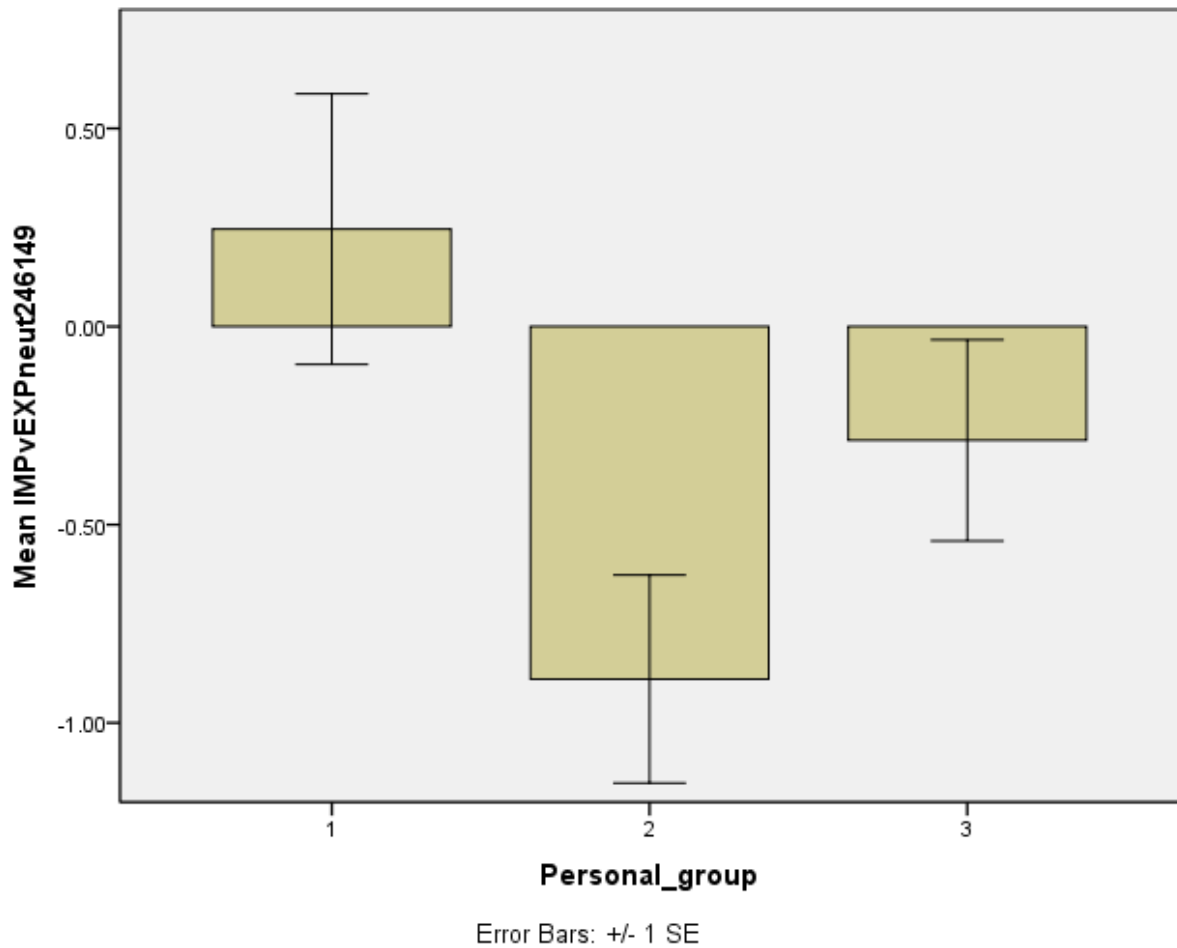


Figure 3.10: Extracted Superior Parietal Lobe activation (4mm radius sphere centred on -24 -61 49) with standard error bars from the contrast all implicit greater than explicit faces, comparing bipolar patients and their siblings. (1 = BD, 2 = siblings, 3 = controls).



3.5 Discussion

This study has identified significant neural activity that differentiates BD from controls and their siblings, and additionally, siblings from controls in regions implicated in BD (Strakowski, 2012; Phillips, 2008). These regions are part of the affective (insula, cingulate cortex, putamen, lingual gyrus) and facial processing network (fusiform gyrus).

The main findings demonstrate that implicit facial emotion processing has elicited greater lingual gyrus activations in bipolar individuals than in siblings or controls, implicating this regional activity as a correlate of disease expression. Additionally, implicit facial emotion processing elicited greater insula activation in bipolar patients compared to controls. Explicit emotion processing demonstrated reduced fusiform activation in bipolar patients compared to controls, supporting the hypothesis of cortical deficits in patients during explicit processing.

Adaptive responses associated with resilience were elicited with both implicit and explicit processing. Siblings demonstrated reduced putamen and cerebellum activations compared to controls and reduced superior parietal activation compared with their bipolar relatives with implicit emotion processing. In contrast to their ill relatives, siblings demonstrated greater (cortical) posterior cingulate activations compared to controls with explicit processing.

3.5.1 Correlates of disease expression:

Lingual gyrus activations: This occipital region is involved in the encoding of complex images and has direct connections with limbic regions such as the amygdala. Activated by emotional imagery, a meta-analysis of 1600 healthy subjects from 105 studies found bilateral lingual activations elicited across all facial stimuli (Fusar Poli 2009). Therefore the present findings support the view that greater activity in this region relates to early, innate subcortical processing of emotion. It may be that the reduction in prefrontal cortical

top-down control, established in the literature, contributes to the hyper-activation of this region compared with healthy individuals.

When compared to siblings, lingual activations were greater for all implicit compared to all explicit events which would suggest that the cognitive load required for labelling emotions (during the explicit events) may have dampened the lingual response to a greater degree in patients compared to their siblings. There were no behavioural differences in labelling accuracy or reaction time to explicit events between the groups implicating more subtle differences in task execution that did not impact on performance. Extracted data demonstrated controls' activations as intermediate between patients and their siblings, possibly supporting a hypothesis of resilience within the siblings. It may be that siblings' lingual activations showed less variance than their ill relatives between implicit and explicit processing and this may represent a neural mechanism of resilience.

The result in comparison to controls related to implicit fearful facial expressions when compared to neutral expressions. A positive trend activation in lingual gyrus has been demonstrated previously in control subjects (n=63) to fearful greater than neutral faces (Radua, 2010). There is a strong literature implicating the amygdala in fear processing, again suggesting a direct relationship between amygdala and lingual regions. Similar findings in controls suggest that the effect has a similar trajectory in controls and patients but may just be of greater magnitude in patients. The extracted values for this contrast (implicit fear versus neutral) correlated positively with depression scores and negatively with extraversion scores across the groups. Therefore these over-activations to fearful expressions may be state-dependant.

Insula activation: Implicit emotion (happy and fearful) compared to neutral processing elicited greater activations in this region in bipolar patients than controls. This activation correlated positively with measures of state (depression and mania scores) and trait

(neuroticism and cyclothymia) liability across the groups but not within any individual group. The insula is multifunctional and engaged in attentional switches, autonomic response regulation and viscerosception (Menon, 2010). It is also implicated in emotion processing and regulation (Phillips, 2003), and the subjective experience of emotion and self-reflection (Beauregard, 2006). It has extensive anatomical and effective connectivity with the amygdala, anterior cingulate cortex and ventrolateral prefrontal cortex (Nagai, 2007; Stein, 2007). We have found greater insula activations that correlated with trait liability to BD in young individuals at high-risk due to familial bipolar who later develop depression (Whalley, 2013b). Greater activations to fearful and happy faces have been demonstrated in bipolar I patients (Surguladze, 2010), and to sad faces during mania (Lennox, 2004). The insula is part of a network involved in salience processing (Sridharan, 2008). This finding may reflect a greater emphasis on emotional stimuli in bipolar individuals that contributes to greater symptomatology and trait features. There were no significant differences in activations in this region in siblings compared to the other groups in contrast to the literature (Fusar-Poli, 2012), which contributes to growing evidence of this cohort presenting with greater resilience than other at risk groups in the literature.

Fusiform activations: Explicit facial processing of fear elicited greater reduction in fusiform activations in patients than controls compared to implicit processing. There were no associations with state or trait measures. The fusiform is critical for face processing including facial identity recognition (Hoffman, 2000), social communication (Haxby, 2002) and eye contact (George, 2001). This finding is in keeping with the literature on explicit face processing in healthy cohorts and with fear processing (Fusar-Poli, 2009; Vuilleumier, 2004). Reduced fusiform activity to facial emotions has also been found in young bipolar spectrum patients (Perlman, 2014).

3.5.2 Adaptive responses associated with resilience:

Here, the regions where siblings' activations differed significantly from their ill relatives and where controls activations were intermediate between siblings and patients are discussed in keeping with the hypotheses.

Putamen activation: Implicit happy compared to neutral faces elicited hypo-activations in putamen and cerebellum in siblings compared to controls. The putamen is part of the network involved in cognitive control and emotion regulation and is implicated in attention allocation and cognitive interference mediation along with the anterior cingulate cortex (Bush, 2000), as well as motivational processes (Kober, 2008). The literature is small and inconsistent regarding functional findings in putamen in emotion processing in BD. Similar activation patterns in putamen have been shown in hypomanic bipolar patients in response to positive affect (Malhi, 2004), during an Emotional Stroop Test (Malhi, 2005) and in patients during implicit facial processing (Brotman, 2014). However contrasting putamen hyper-activation have also been demonstrated to happy faces in patients and to fearful faces in relatives (Surguladze, 2010). Patients in this study demonstrated no significant activations in putamen, which may relate to sample size limiting the detection of differences. Behavioural studies have demonstrated that individuals with greater extraversion scores are more motivated towards increasing their happiness than those with lower extraversion (Tamir, 2009). Higher extraversion scores, especially in controls, may be explained in part by their greater motivational activity during happy emotion processing. The siblings' reduced activations suggest that happy facial processing elicits less attentional and motivational activity than controls in this region.

Cerebellar activation: Cerebellar under-activations in siblings when compared to controls were elicited by implicit happy facial processing. The cerebellum has anatomic and functional connections to the PFC and limbic structures and communicates with the monoamine-producing brainstem nuclei which supply the cerebrum and limbic system (Konarski, 2005). Therefore cerebellar activity has both direct and indirect effects on the

cognitive processing of emotion via cortical association areas and effects on emotional experience and regulation from limbic structures (Villanueva, 2012). Cerebellar activity has been demonstrated in response to different emotions (Reiman, 1997; Sacchetti, 2002) and cerebellar lesions have resulted in emotional blunting (Levisohn, 2000). However, the literature is sparse, especially in relatives of BD patients. Structurally, increases in cerebellar volumes in a high risk cohort have been associated with resilience by the authors as the finding was not present in patients or controls (Kempton, 2009). Functional cerebellar abnormalities have mainly been associated with illness course in patients (Strakowski, 2005). In contrast to our finding in siblings, cerebellar over-activations to happy faces have been found in depressed adolescents with BD (Diler, 2013). Our relatives were not depressed and constituted a larger sample (n=25) compared to the study of adolescents (n=10). Patients' activations appear intermediate between siblings and controls and there were no associations with trait or state measures. It may be that the patients were relatively well and so did not activate this region significantly. Due to the limited literature it is difficult to comment on the relevance of this finding.

Posterior cingulate activations: Explicit facial processing of happiness elicited greater posterior cingulate activations in siblings than controls compared to implicit processing. Interestingly, extracted data showed that the patient's activation were similar to controls. This finding correlated positively with depression and negatively with extraversion scores across the groups. The PCC has connections to the hippocampus and visual parietal cortex involved in memory and spatial functions respectively (Rolls, 2015) and is implicated in self-referential activity (Brewer, 2013) as well as the default mode network. It may be that siblings are recruiting this region to enhance their spatial episodic memory or are involved in cognitive processing where they are referring to their own experience to inform the task. PCC under-activity have been shown in PET studies with the induction of negative emotions in euthymic bipolar patients, with depressed patients (Kruger, 2004) and in paediatric BD when viewing angry faces (Deveney, 2015). Symptom correlations that influence brain function, although sub-threshold regarding clinical diagnosis, may

have important prognostic implications. They may be predictive of future mood episodes (Marangell, 2004). Although patients in the present study do not demonstrate any alterations in activations when compared directly to controls, our positive correlation with depressive symptoms opposes these mood congruent decreases in activity suggested in the literature.

Superior parietal activation: Siblings demonstrated hypo-activation in this region compared to their ill relatives during the viewing of implicit as opposed to explicit facial processing. This region is involved in maintaining attention to visual information and is important for sensorimotor integration by maintaining an internal representation of the body's state (Wolpert, 1998). In this study, there were no correlations with state or trait measures. This result may represent a functional resilience in the siblings as the controls' activations appear intermediate between the patients and their siblings. Participants were asked to label the gender of the face during implicit processing. It may be that the siblings had less need to attend to the faces in detail in order to determine gender than their ill relatives. Or possibly the BD cohort demonstrated a stronger engagement of attention towards more salient facial stimuli (Pessoa, 2002).

3.5.3 In relation to the stated hypotheses:

We have demonstrated over-activations in BD in regions directly linked to amygdala such as the lingual gyrus and insula elicited by implicit facial emotion processing and under-activity in cortical regions in the fusiform gyrus with explicit processing in keeping with prediction. Altered brain function in these regions is likely to represent correlates of disease expression especially those that were associated with symptoms.

Resilience (only in terms of functional imaging correlates of clinical status) may be represented by siblings' hypo-activations in lingual and parietal regions that differed significantly from their ill relatives and where controls activations were intermediate between siblings and patients. Additionally, regions that differentiated siblings from controls (posterior cingulate, putamen, cerebellum) and were not altered in patients may

be conceived as adaptive. Resilience has been discussed in detail in chapter 1. If resilience were in fact a consequence of low genetic burden in relatives then the expectation would be of minimal disruption in brain function and the siblings' activations would appear similar to controls. The regional differences presented here could be viewed as adaptive responses to abnormalities related to genetic predisposition (Frangou, 2012). Healthy siblings may be recruiting additional neural resources or demonstrating reallocation of processing to other regions (Frangou, 2012). Although passed the age of greatest risk of developing BD, the relatives' diagnostic status still has the potential to change. Therefore, these findings require replication and longitudinal studies may offer greater insights into resilience factors.

We did not find the decreases in prefrontal cortical function that are consistently associated with emotion processing. These more subtle differences may be more prominent in future connectivity analyses where the circuitry rather than discrete regions will be investigated.

3.5.4 Limitations

We did not find significant amygdala activations to fearful stimuli at an appropriate threshold in our cohorts and this may be due to the majority of patients being euthymic or an issue of sample size. There have been studies of emotion perception or regulation tasks that have found no amygdala abnormalities in euthymia (Hassel, 2008; Malhi, 2007; Robinson, 2008). Using a motor inhibition task, Kaladjian and colleagues (Kaladjian, 2009) demonstrated decreased amygdala responsiveness between mania and remission. These studies suggest the effect may be related to state or treatment.

The sample size and difficulties related to the analyses in SPM (described below) may also have contributed to the limited findings and the possibility of false positive findings.

Analyses were conducted with pairwise comparisons in SPM as there is no function to account for the paired relationships between patients and their well siblings. It is expected that future analysis packages will enable brain imaging statistics to account for familial relationships.

Another limitation for consideration relates to movement artefacts. We set a priori maximum threshold standardly applied to functional imaging (ref heather/Liana). We also controlled for movement during preprocessing and included the 6 movement parameters as regressors in the analysis however, we cannot exclude the possibility that there may be remaining confounds at the group comparison level relating to movement that cannot be excluded.

We also note that we have implemented an initial uncorrected cluster threshold of $p < 0.005$ and subsequently corrected for multiple comparisons, however, the standard SPM threshold is typically $p < 0.001$. Therefore, our threshold may introduce a small number of false positive findings.

All our BD patients were taking some medication. There would not be enough power to demonstrate differences between those prescribed and not prescribed either antipsychotics or antidepressants. In addition, the cross-sectional nature of this study does not enable the exclusion of the major drug types, including lithium and antipsychotics, as potential confounding factors.

3.5.5 Future Directions

Connectivity analyses would enable investigation of the functional networks involved in facial emotion processing in more detail and possibly offer greater insights into how the regions highlighted in this study interact within the network.

Longitudinal studies in high risk cohorts would enable greater understanding of the relationships between clinical symptoms and brain function. Is disease expression associated with a failure to maintain adaptive changes?

Characterising the biological underpinnings of resilience using both imaging and cellular level mechanisms (such as the dysfunctional glucocorticoid receptor signalling²⁵⁰) may provide quantitative measures that could improve diagnosis and earlier intervention. Biomarkers would also enable greater stratification in patients, offering another avenue for the tailoring of treatments.

3.5.6 Summary

In the present study, implicit facial emotion processing was associated with lingual gyrus and insula over-activations in patients compared to controls, while explicit emotion processing elicited fusiform under-activations in patients compared with controls. All these findings are likely to represent correlates of disease expression.

Over-activation in posterior cingulate and hypo-activations in putamen and cerebellar activity in siblings compared to controls, and parietal hypo-activations in siblings compared to their ill relatives, may represent adaptive responses associated with resilience.

4 Chapter 4:

Experiment 3: A functional magnetic resonance imaging comparison of Instrumental reward learning in individuals with Bipolar Disorder, their siblings and controls.

4.1 Abstract

Abnormalities of reward processing and decision-making are core features of bipolar I disorder (BD). These processes are closely linked with fronto-striatal and midbrain circuitry. The study sought to test whether dysfunctions of these pathways were present in BD and whether they were related to genetic vulnerability to illness. Twenty-one bipolar I patients each with their unaffected sibling, were compared to 22 healthy age and gender-matched controls using an instrumental reward-learning task during event-related functional MRI paradigm. Data were analysed across the wholebrain and using two a priori region of interest analyses; i) ventral striatum/midbrain and ii) prefrontal cortex (PFC). Ventral striatum over-activation in association with the difference between observed and expected rewarding outcomes (the prediction error) was demonstrated in individuals with BD compared to controls. Reduced prefrontal activations were seen in the patient and sibling groups compared to controls in association with the learning of the value of the conditioned stimulus. These findings suggest that ventral striatal over-activations represent a correlate of the expression of BD while prefrontal deactivations in reward related circuitry underlie the genetic vulnerability to BD.

4.2 Introduction

An increased sensitivity to reward cues (Harmon-Jones, 2008) leading to greater motivation towards the pursuit of rewarding experiences has been proposed to underlie symptoms of mania. Conversely, insensitivity to rewarding cues has been associated with anhedonia and depression (Huys, 2013). Although these features do not explain all presentations of BD, especially mixed affective states, they highlight the importance of investigating reward circuitry in BD. The symptoms of mania can be understood as excessive pleasure-seeking and goal-directed activities with unrealistically high expectations of success. ICD 10 describes 'behaviour that is foolhardy or reckless and whose risks the individual does not recognise'. Depressive symptoms could also be considered as a deficit of reward or motivation. It is these symptoms that represent dysfunctions of reward processing and warrant investigation using paradigms that address this circuitry.

Reinforcement learning, a form of instrumental conditioning, enables the investigation of learning about rewards (and punishments). Investigation of reward learning allows for sensitivity to the cues themselves (the immediate hedonic experience and the cognitive processing of their value (Larkin, 2007; Lee, 2007)) as well as exploring the adaptations of behaviour through the learning of the difference between the predicted value of future rewards and their actual value. This difference is known as reward prediction error (PE). Midbrain and striatal dopaminergic activity and the subcortical and cortical circuitry linked to them are clearly associated with reinforcement learning as explained in chapter 1. However the complexity of this system is just beginning to be fully understood (Garrison, 2013).

The investigation of reward learning is relevant in bipolar disorder as the resultant effects on cortico-striatal plasticity may represent a mediating mechanism underlying the core symptoms of BD that relate to mood and drive (Schultz, 1997). Reinforcement learning is strongly associated with dopamine signalling and much of the relevant neural circuitry

(ventral and dorsal striatum, cingulate cortex and medial prefrontal cortices (Basten, 2010; Abe, 2011; Heekeren, 2008; Heekeren, 2006; Kim, 2012)) is also implicated in BD. Dopaminergic pathways are fundamental to the core symptoms of bipolar disorder. For example, dopaminomimetics can be associated with mania (Sultzer, 1989). Drugs of abuse such as cocaine are euphorogenic. Manic patients benefit from antipsychotic medications which mostly target dopaminergic systems (Perlis, 2006). These same medications also act as successful mood stabilisers, although this may relate to their additional pharmacological effects, beyond dopamine receptor blockade. Pharmacological agents such as lithium and valproate are also known to act on dopamine transmission (Cousins, 2009). DA manipulations affect mood (Tremblay, 2002). Drugs which maintain intrasynaptic dopamine levels are antidepressant (Berton, 2006), while agents that deplete dopamine, such as reserpine, are depressogenic. The severity of depression correlates with the magnitude of amphetamine-induced reward and the reduction in concentration of dopamine metabolites in cerebrospinal fluid.

The objectives of this chapter were to apply reinforcement reward learning to investigate the neurobiology of BD, offering the opportunity to enhance our knowledge of the neural mechanisms underpinning the disorder. Prediction-error modelling could potentially relate these to the activity of a specific neurotransmitter, dopamine (as discussed in Chapter 1). It may be that prediction error signalling is aberrant and is not invoked appropriately, for instance over-activity in the striatum at the point of prediction error rather than an expected decrease which would explain the behaviours that continue without apparent recognition for the risks or consequences. Additionally, this paradigm could be used to address the higher order cognitive aspects of goal-directed behaviour as the learning of the changing value attributed to a given stimuli can also be modelled. It may be that if prefrontal, top-down, executive control is reduced, this will also contribute to subcortical over- activity. Although this system is likely to be bi-directional, these simple models allow an initial investigation of the circuitry in this population.

The addition of siblings of the bipolar individuals who were passed the age of greatest risk of developing the disorder and who did not experience any form of mood disorder offered the opportunity to investigate features of familial vulnerability, endophenotypic features and resilience in the absence of illness and medication, as well as state-related effects associated with symptoms.

4.2.1 Hypotheses:

- i) There will be no differences in performance between the groups.
- ii) Regions associated with PE (ventral striatum/midbrain) will demonstrate greater recruitment of BOLD in BD mediating unrealistic goal attainment behaviour and motivational drive.
- iii) Regions associated with value learning (PFC) will demonstrate reduced recruitment of BOLD in BD representing inadequate executive control and, potentially, as a consequence of the changes in subcortical activity.

4.2.2 Additional explanations:

- d) Where siblings' brain activity is shared with their BD relatives and differentiates both groups from controls this would reflect genetic predisposition to the disorder.
- e) Where siblings' brain activations differentiated them from controls and/or their BD relatives, or controls' activations were intermediate between the siblings and patients, this may represent adaptive responses associated with resilience.
- f) Where patients' brain activations differentiated them from controls and their siblings, these changes will be considered as correlates of disease expression.

4.3 Methods

4.3.1 Recruitment and clinical assessments

Recruitment and clinical assessments were as described in chapter 2. A total of 21 bipolar-sibling pairs and 22 controls provided suitable fMRI data. Three bipolar patients, 1 sibling and 2 controls did not perform the task adequately and stated that they had not understood the instructions after the scanning session. One control was unable to participate due to poor visual acuity that could not be corrected with the visual aids we had available.

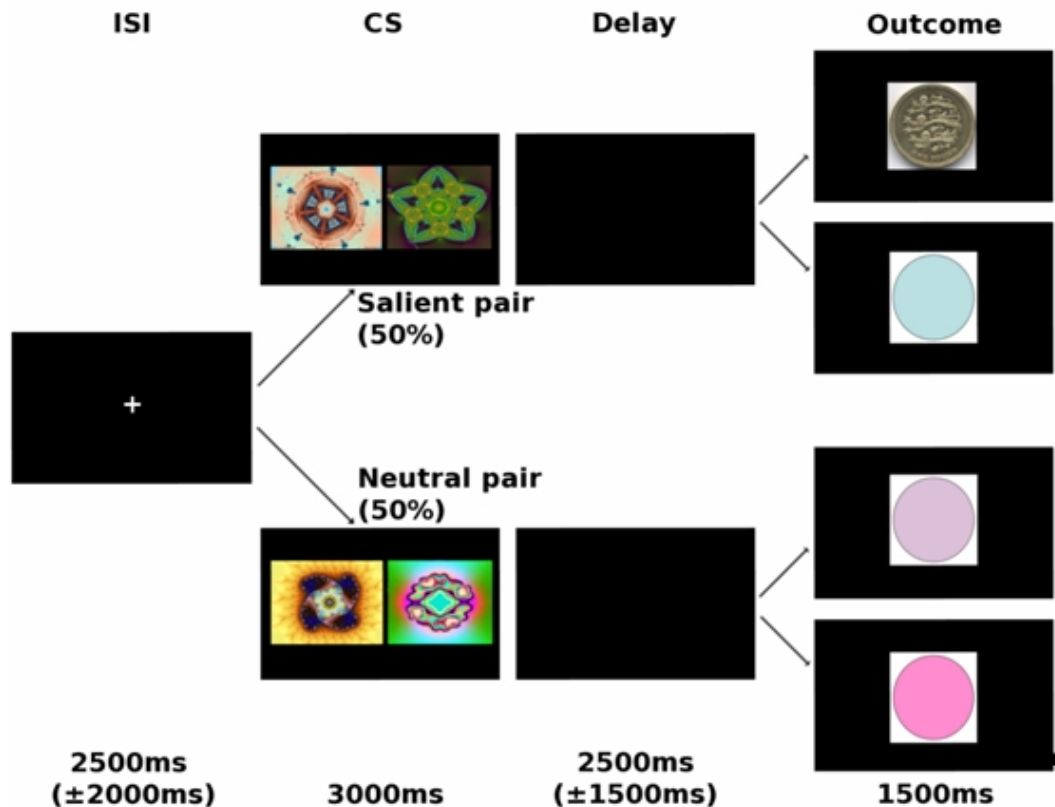
4.3.2 Experimental paradigm: The reinforcement reward learning task

The reinforcement reward-learning task involved monetary gains that required choosing between two visual stimuli. This adaptation of the reward-learning task by Murray and colleagues (Murray, 2008) was designed so that the learner must discover which actions will yield the most reward through trial and error. There were two trial types (salient and neutral) each involving a different pair of visual stimuli (fractals rather than coloured blocks used in Murray's task). Within the salient pair, one stimulus (the conditioned stimulus, $CS_{s, high}$) had a high probability of providing a reward, the other, a lower probability ($CS_{s, low}$); these probabilities changed over the course of the experiment. The neutral pair of stimuli were known as $CS_{N, a}$ and $CS_{N, b}$. Neither could be considered "high" or "low" due to their lack of association with any rewarding outcome. For both the salient and neutral pairs, eight blocks of five trials were presented, randomly interleaved, a total of 80 trials. For the first two blocks, the $CS_{s, high}$ had 100% probability of reward, and $CS_{s, low}$ 0%. For blocks three and four, $CS_{s, high}$ dropped to 80% rewarding, and $CS_{s, low}$ increased to 20%. For the final four blocks, $CS_{s, high}$ decreased further to 60%, and $CS_{s, low}$ became 40%. This schedule allowed participants to learn the contingencies in the early stages, but introduced surprising mismatches between their learned expectations and actual outcomes as the experiment progressed. The inclusion of neutral trials disguised the conceptually blocked nature of the shifting probabilities. The task is summarised in Figure 4.1.

4.3.2.1 Task Description

Each trial began with the presentation of a fixation cross (duration varied between 500ms and 4500ms). The visual stimuli were then presented for 3000ms, during which the participant chose one of the pair via a button press corresponding to the side of the screen on which the chosen stimulus was located. After an imposed delay between the CS and feedback (between 1000ms and 4000ms), the outcome, which was either an image of a £1 coin, or a plain coloured disc of equivalent size, was displayed. Feedback remained onscreen for 1500ms before the next trial began (Figure 4.1). The inter-trial interval was jittered to optimise the power with which salient versus neutral activation differences could be detected. The delay between stimuli presentation and outcome was jittered to allow for the disambiguation of CS- and outcome-related activations. Written instructions were presented before commencement of the task. Participants did not receive the money they won. However, they were unaware that this would be the outcome while performing the task. This was due to funding and philosophical issues within the department at the time.

Figure 4.1: Instrumental reward-learning task design as participants experienced the task in the scanner (described in detail above).



4.3.2.2 Participant Instructions

In this game you will see two coloured blocks on the screen. You have to choose the left-hand one or the right-hand one. Depending on which block you choose, the computer will then give you feedback, which may be a picture of a £1 coin (this means you win), or a neutral picture, or nothing at all. At first you will not know which block to choose, so you have to guess, but by the end you will have learned, through trial and error, which to choose. Finally, the computer will add up all the £1's. Remember to keep trying all the way through as that way you will win the most money.

4.3.2.3 Reinforcement learning algorithm

A standard Q learning reinforcement algorithm was fitted to each participant's behavioural choices. Q learning is a computational method that encapsulates two functions: learning the contingencies between states, actions and outcomes; and applying this knowledge to

choose the most rewarding actions. It has previously been shown to provide a good account for functional data during instrumental conditioning (Sutton, 1998). To determine the Q value of a given stimulus when next encountered, the model estimates the value of that stimulus during the previous encounter and updates that knowledge by accounting for the mismatch between that estimation of value and the actual outcome of the previous trial (the prediction error (PE)). Here the model attempted to learn the Q values associated with choosing $CS_{s, high}$ and $CS_{s, low}$ (No learning of the values of $CS_{N, a}$ or $CS_{N, b}$ took place due to their lack of rewarded reinforcement). The expected value of $CS_{s, high}$ ($Q[CS_{s, high}](t + 1)$) for the next trial was updated according to the rule:

$$Q[CS_{s, high}](t + 1) = Q[CS_{s, high}](t) + (\alpha * \delta(t))$$

Where $\delta(t)$ is:

$$\delta(t) = R(t) - Q[CS_{s, high}](t)$$

Otherwise known as the prediction error (δ), that is the mismatch between the current estimation of the value of $CS_{s, high}$, and the actual outcome of the trial $R(t)$. The learning rate (α) is the rate at which the individual adapts their choices as they gain information about the stimuli. Rewarding outcomes were encoded as $R(t) = 1$, and all other outcomes as $R(t) = 0$. These learned values were then used to decide which CS was the most appropriate to use, using a Softmax function:

$$P(C_t = [CS_{s, high}]) = \frac{e^{Q[CS_{s, high}](t) / \beta}}{e^{Q[CS_{s, high}](t) / \beta} + e^{Q[CS_{s, low}](t) / \beta}}$$

Here, β is the temperature of learning, that is, the degree to which a difference between the value of the stimuli, $Q[CS_{s, high}](t)$ and $Q[CS_{s, low}](t)$ whether they are more or less rewarding, biases an individual's choice of stimulus: a higher β leads to more random, exploratory decisions. $CS_{s, high}(t)$ and $CS_{s, low}(t)$ were both used to calculate $\delta [CS_{s, high}](t)$ and $\delta [CS_{s, low}](t)$. This model was then fit to each participant's combination of choices

and outcomes, using maximum likelihood estimation on the model's negative log likelihood, where α and β were free parameters. Q values were initialised at zero. The estimation was repeated with 1000 initialisation points to reduce the risk of falling into a local minimum. In order to generate sets of fMRI regressors representing the prediction error at both the choice and outcome moments for each participant, the median values of these parameters across all participants were combined with each participant's behavioural responses.

Learning rate and temperature information can provide insights into how peoples' learning styles differ. Higher learning rate suggests greater leaps made at each step of learning, contingencies are identified sooner, or if excessive, lead to consistent "overshooting" of the target. Learning temperature is an estimate of consistency, how capable the person is of staying with 'the best' strategy, rather than exploring alternative options. Higher learning temperature could be said to represent a more erratic learning style.

Table 4.1: Explanatory key of parameters for Q value modelling.

Parameter	Description
Prediction Error (δ or PE)	the mismatch between the estimation of value and the actual outcome of the previous trial
Q value (of a stimulus) (Q)	the value of that stimulus during the previous encounter updated by accounting for the mismatch between that estimation of value and the actual outcome of the previous trial
A (learning rate) (α)	the rate at which the individual adapts their choices as they gain information about the stimuli

B (learning temperature) (β)	the degree to which a difference between the value of the stimulus biases the choice of stimulus
--------------------------------------	--

For each participant, the model estimated which α and β pair provided the best fit for their actual actions, given the outcomes they experienced, where fit was determined using the negative log likelihood of the chosen actions. The α and β parameters obtained for each subject were correlated with their symptom measures. Group differences for α , β and reactions times were assessed with ANOVAs, and the number of pounds won with the Kruskal-Wallis test. In order to compare all groups with an appropriate means of representing the data, a single parameter set (α/β) was estimated for the whole study sample by concatenating the behavioural choices and outcomes for all participants and applying the model. A trial-by-trial sequence of PEs and Q values for each participant were generated, determined by their behavioural choices (O'Docherty, 2007) , using a model where α and β had been set to these sample-optimised values, and the actions and outcome were entered as those actually performed by the participant at the time of scanning. PE and Q value regressors were used to modulate the onsets of outcome and CS respectively.

4.3.2.4 Image acquisition

Imaging was carried out at the Brain Imaging Research Centre (BIRC) for Scotland on a GE 1.5 T Signa scanner (GE Medical, Milwaukee, USA). The functional imaging protocol consisted of axial gradient-echo planar images (EPI) (TR/TE = 2000/40 ms; matrix = 64 x 64; field of view (fov) = 24 cm) acquired continually during the experimental paradigm. Twenty seven contiguous 5 mm slices were acquired within each TR (2s). There was one session and the EPI acquisition was run for 386 volumes, giving a total fMRI scan time of 12m 52s. The first four volumes were discarded to avoid T1-weighted saturation effects. The T1 sequence yielded 128 coronal slices (inversion time, 600 ms; echo time, 3.4 ms; flip angle = 15°; fov = 22 cm; slice thickness = 1.7 mm; matrix = 256x192).

4.3.2.5 Image processing

The EPI and T1 images were reconstructed into nifti format (Mayo Foundation, Rochester, MN, USA) using DICOM convert functions available in SPM8 (Statistical Parametric Mapping: The Wellcome Department of Cognitive Neurology and collaborators, Institute of Neurology, London) running in Matlab (The MathWorks, Natick, MA, USA). Images were pre-processed using standard protocols available in SPM8. All EPI images were realigned to the mean volume in the series. The functional images were then normalised according to standard co-registration procedures using the individual's structural scan. Finally, all realigned and normalised images were smoothed with an 8x8x8 mm full width half maximum (FWHM) Gaussian filter and resampled at an isotropic resolution of 3mm. Data were also high-pass filtered at 128s, and serial correlations estimated using a first-order autoregressive model.

4.3.2.6 Image analyses

At the first-level, two analyses were carried out: (a) each participant's PE regressor was used to parametrically modulate the outcome phase of salient trials, and (b) each Q value regressor parametrically modulated the onset of CS_S stimuli. The onsets of CS_N and their associated outcomes and motion parameters were included as nuisance regressors. A T contrast image representing each parametric modulation was taken forward into a series of second-level, random effects analyses.

Since a considerable amount is known about the neural basis of PE through experimental animal and human studies, we focussed on task related regions (the ventral striatum/midbrain for PE analyses and DLPFC, vmPFC/mOFC for the Q value analyses) and conducted a hypothesis-based investigation of activations within those regions. The main effect of PE across groups was assessed using a one-way ANOVA. One-sample F-tests examined PE effects within each group individually. Significance was assessed at whole-brain level, using an uncorrected threshold of $p < 0.005$, then corrected for multiple comparisons according to family-wise error (FWE) at $p_{FWE} < 0.05$.

An a priori ventral striatum/midbrain ROI was applied to the PE analysis. This region of interest (ROI) consisted of the union between Brodmann–defined substantia nigra and a 10mm diameter sphere located at 0, -20, -10 MNI (Murray, 2008; Romaniuk, 2010) and the inferior half of a union between the AAL-defined caudate nucleus and putamen, with the cutoff being $z = -3$ MNI (Romaniuk, 2010) using the WFU Pickatlas.

A PFC ROI was applied to the Q value analyses, defined by regions consistently associated with value encoding and decision-making. It comprised three 15mm radius spheres centred on DLPFC (-23 29 37 and -13 44 35), vmPFC/mOFC (-4 60 -6).

For both analyses, activation was considered significant if the voxel height exceeded a corrected threshold of $p_{FWE} < 0.05$ within the relevant ROI.

For each cluster of significant voxels in hypothesised regions, the first eigenvariate of the data was extracted for pairwise mixed regression analyses to compare the unrelated groups (patients versus controls and siblings versus controls) with family added as a random factor in a mixed-effects ANOVA analysis to take account of the non-independence of patients and sibling pairs (as this was not possible in SPM). In order to account for the effects of symptoms, we repeated our analyses including the HAM-D and YMRS scores as covariates. Where the group differences remained significant, we concluded that symptoms did not mediate or confound the relationship with brain activation. In situations where the group differences became non-significant, we then conducted a test of the association between symptom and brain activation. A significant association between symptom and brain activation was then taken as evidence that the between-group differences were mediated by symptoms and not by differences in genetic liability alone. All analyses were repeated for the encoding of value. In order to investigate the relationship between PE and Q value, a correlation analysis was performed using extracted data from regions demonstrating significant group differences, although connectivity analyses would be preferable in the future.

4.3.2.7 Potential confounders

The potential confounding effects of medication and history of psychotic, manic and depressive episodes were investigated using extracted data for the main analyses of interest. Within the patient group, cohorts were compared if they were prescribed or not prescribed: i) lithium, ii) antidepressants or iii) antipsychotics at the time of assessment. The relationship of task-related activation to chlorpromazine equivalent doses of prescribed antipsychotic medication was also investigated using extracted data.

4.4 Results

4.4.1 Participant characteristics

Twenty-one patient-sibling pairs and 22 controls were analysed. Demographic and clinical results are summarised in Table 4.1. There were no significant differences between the groups in age, gender, parental occupation, premorbid IQ and handedness. Patients had higher depression (HAM-D) and mania (YMRS) ratings than both siblings and controls. Self-reported neuroticism, cyclothymia and impulsivity (BIS) were also greater in patients than either siblings or controls. Extraversion showed the inverse pattern, with lowest ratings in patients. Other than a trend towards greater depression ratings, the siblings displayed no significant differences when compared with the control group.

Within the patient group, mean illness duration was 18.6 years (SD 6.9 years), 76.2% had experienced a psychotic episode, and they averaged 12 lifetime episodes of mania (mean 12.4, SD 16.9) and 11 episodes of depression (mean 11.0, SD 13.8). Lithium was prescribed to 66.7% of patients and 61.9% were prescribed an antipsychotic at assessment and 42.9% were also prescribed an antidepressant.

Table 4.2: Demographic and clinical measures.

	BD N=21	Sibs N=21	Controls N=22	BD v Con	Sib v Con	BD v Sib (F/X², p)
Age in yrs Mean (SD)	45.4 (5.0)	45.2 (5.3)	44.0 (5.0)	0.03, 0.37	0.38, 0.48	0.18, 0.89
Gender % male	38.1	52.4	50.0	0.62, 0.43	0.02, 0.88	0.87, 0.54
Parental SES % manual occupation	61.9	61.9	45.5	1.36, 0.51	1.36, 0.51	0.00, 0.60
Handedness % R, other	80.0	95.0	86.4	1.38, 0.51	1.98, 0.37	2.06, 0.36
NART IQ Mean (SD)	113.6 (7.2)	112.7 (7.9)	115.5 (5.0)	7.06, 0.14	10.12, 0.07	0.33, 0.57
HAM-D median (IQR)	7 (7)	3 (3)	2 (2)	62.5, <0.01	155.5, 0.06	92, <0.01
YMRS median (IQR)	2 (5)	0 (0)	0 (0)	127, <0.01	200, 0.18	101.5, <0.01
Neuroticism median (IQR)	34 (20)	16 (13)	17 (15)	88.5, <0.01	208.5, 0.58	72, <0.01
Extraversion median (IQR)	23 (7.5)	26 (7.5)	30.5 (10.25)	99.5, <0.01	173.5, 0.16	142, 0.05
Cyclothymia median (IQR)	6 (8.5)	0 (1.5)	0 (2.25)	46.5, <0.01	202.5, 0.42	26, <0.01
BIS total median (IQR)	70 (25.5)	55 (12)	60 (19.75)	99, <0.01	175.5, 0.18	64.5, <0.01

4.4.2 Performance

4.4.2.1 Behavioural results from the within scanner reinforcement reward learning task.

Learning rate, learning temperature, reaction times (RT) for both CS_S and CS_N trials and the number of pounds won did not differ between groups (see Table 4.3). However it

appears that the controls won less pounds overall and this may relate to their lower learning rate and higher temperature scores, suggesting that they were more erratic in their learning. This may have been due to motivational differences between the groups. The optimal learning rate and learning temperature parameters were estimated for the whole sample as 0.42 and 0.27 respectively.

Table 4.3: Behavioural results from the reinforcement reward learning task.

	Patients Mean (SD)	Siblings Mean (SD)	Controls Mean (SD)	ANOVA F/X², p
Learning rate	0.40 (0.31)	0.41 (0.31)	0.33 (0.33)	0.44, 0.64
Learning temperature	0.30 (0.28)	0.27 (0.23)	0.36 (0.35)	0.54, 0.58
Pounds won	24.7 (3.4)	25.3 (3.2)	21.9 (5.3)	2.78, 0.07
Reaction Time (salient CS)	1220 (254)	1195 (311)	1245 (309)	0.16, 0.86
Reaction Time (neutral CS)	1547 (285)	1611 (242)	1576 (380)	0.22, 0.80

4.4.2.2 Reinforcement learning model regressors

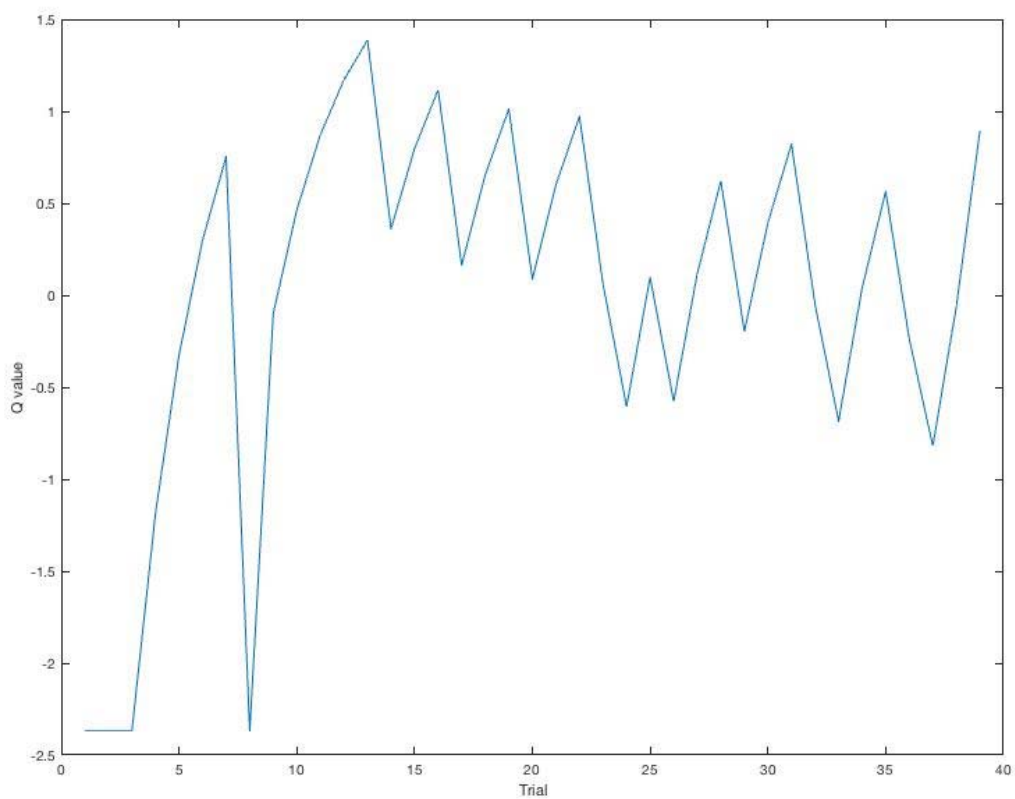


Figure 4.2: Example of the reinforcement learning model's estimated Q values per trial for one participant.

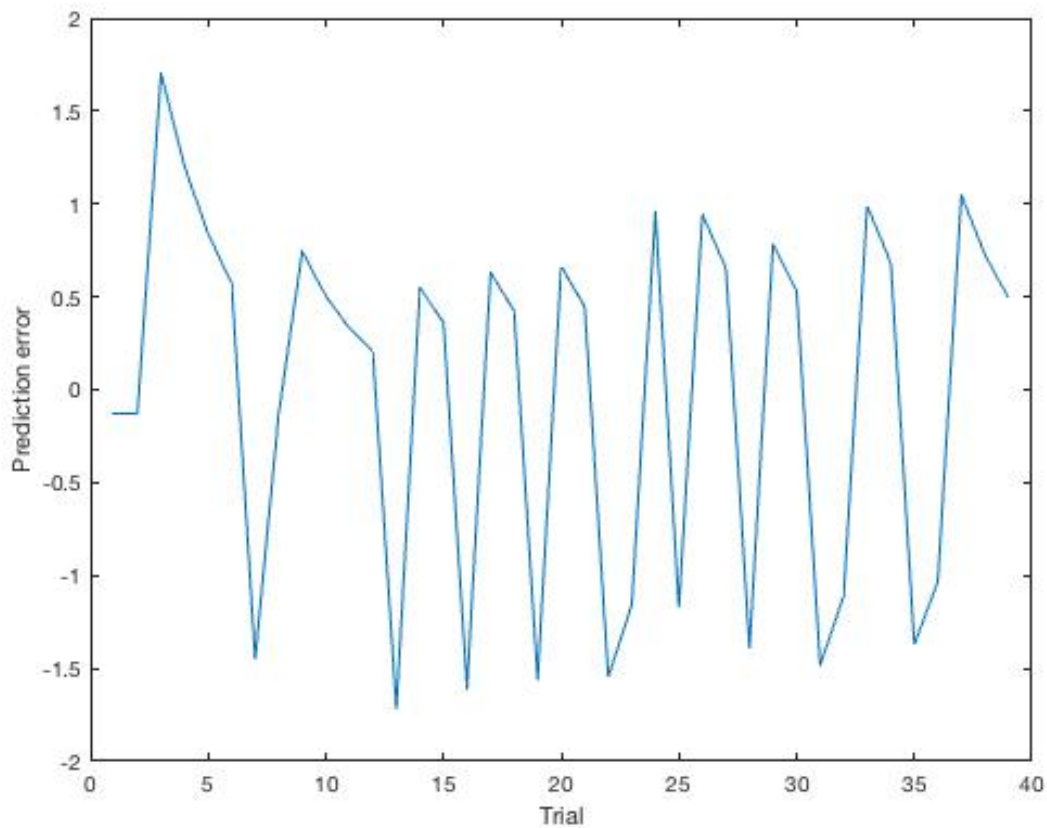


Figure 4.3: Prediction error model output per trial for one participant.

The regressors output by the computational model were convolved with a canonical haemodynamic response function (HRF) within SPM prior to being used to regress the fMRI data.

4.4.3 Imaging results

4.4.3.1 Prediction error results

4.4.3.1.1 Main effect of condition: PE across groups

When the three groups were analysed together, reward PE was associated with over-activity in the left ventral striatum within the striatum/midbrain ROI and at whole brain level bilaterally in the right ventral striatum and occipital lobes (Table 4.4, Figure 4.4a).

Table 4.4: Imaging results for PE and Q value (*ROI results, # Negative relationship)

P_{FWE} value	Peak size T	Z	Co-ords	Region
Main effect of PE across all groups:				
<0.001*	5.91	5.11	-21 -1 -11	L Ventral Striatum ROI
0.014	5.43	4.75	21 -1 -14	R Ventral Striatum
<0.001	11.99	6.20	-27 -94 -2	L Occipital Lobe
<0.001	11.39	6.13	30 -91 -5	R Occipital Lobe
Main effect of PE within groups:				
Controls:				
0.002	8.02	5.37	-42 -64 -20	R Occipital Lobe
0.011	6.85	4.91	-27 -97 -2	L Occipital Lobe
0.028	6.34	4.69	-12 -97 -8	Occipital Lobe
Patients:				
0.025*	4.58	3.74	3 5 -5	Ventral Striatum ROI (Nucleus accumbens)
0.035*	4.40	3.64	-24 -4 -8	L Ventral Striatum ROI
0.001	8.68	5.53	-15 -94 -5	L Occipital Lobe
0.004	7.79	5.23	33 -88 -8	R Occipital Lobe
0.004	7.78	5.22	-24 -94 -2	L Occipital Lobe
Siblings:				
0.001	8.26	5.39	-24 -94 -2	L Occipital Lobe
<0.001	9.06	5.65	33 -91 -5	R Occipital Lobe
Main effect of Q value across all groups:				
0.003#	5.89	5.09	0 32 40	R Medial Frontal Gyrus
0.006#	5.72	4.97	54 -52 37	R Posterior Parietal Lobe
Main effect of Q value within groups:				
Patients:				
0.006*#	6.41	4.67	-3 26 40	L Prefrontal Cortex ROI (Medial Frontal Gyrus)
Siblings:				
0.01*#	5.93	4.45	-3 38 34	L Prefrontal Cortex ROI (Medial Frontal Gyrus)
Between group comparison of Q value: Patients < Controls				
0.044*	3.89	3.57	-27 41 43	L Prefrontal Cortex ROI (DLPFC)

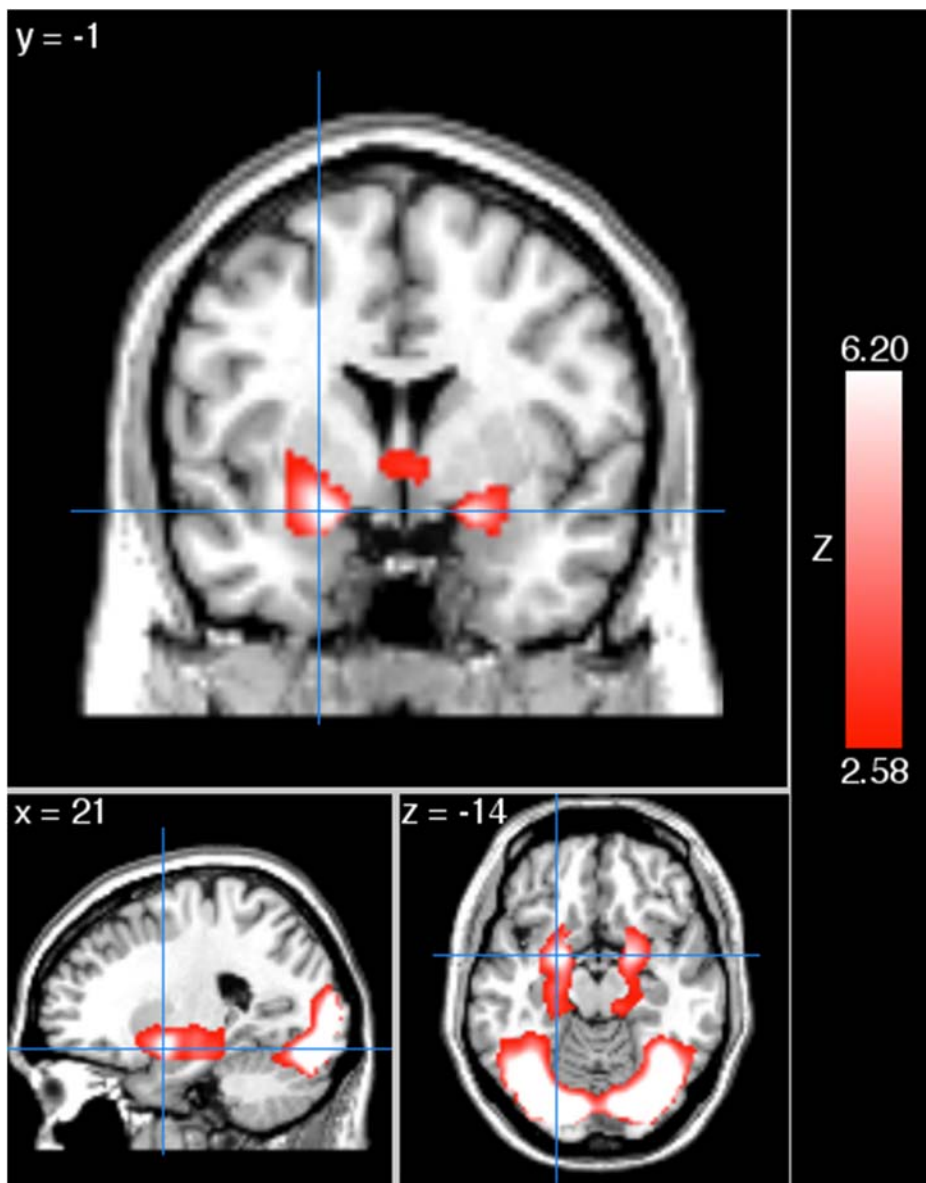


Figure 4.4a: The main effect of prediction error across groups.

4.4.3.1.2 Between group comparisons of PE

Using extracted data from the whole brain ventral striatal peak voxel, reward PE signalling was associated with a significant over-activity in patients compared to controls ($T=5.88$,

p=0.02) that remained when symptoms scores (T=5.91, p=0.02) and lifetime history of psychosis (T=7.68, p<0.01) were included as covariates. There was a trend in the same direction between patients and their siblings (T=3.74, p=0.07). Siblings' activations were not significantly different from controls in direct comparisons (Figure 4.4b).

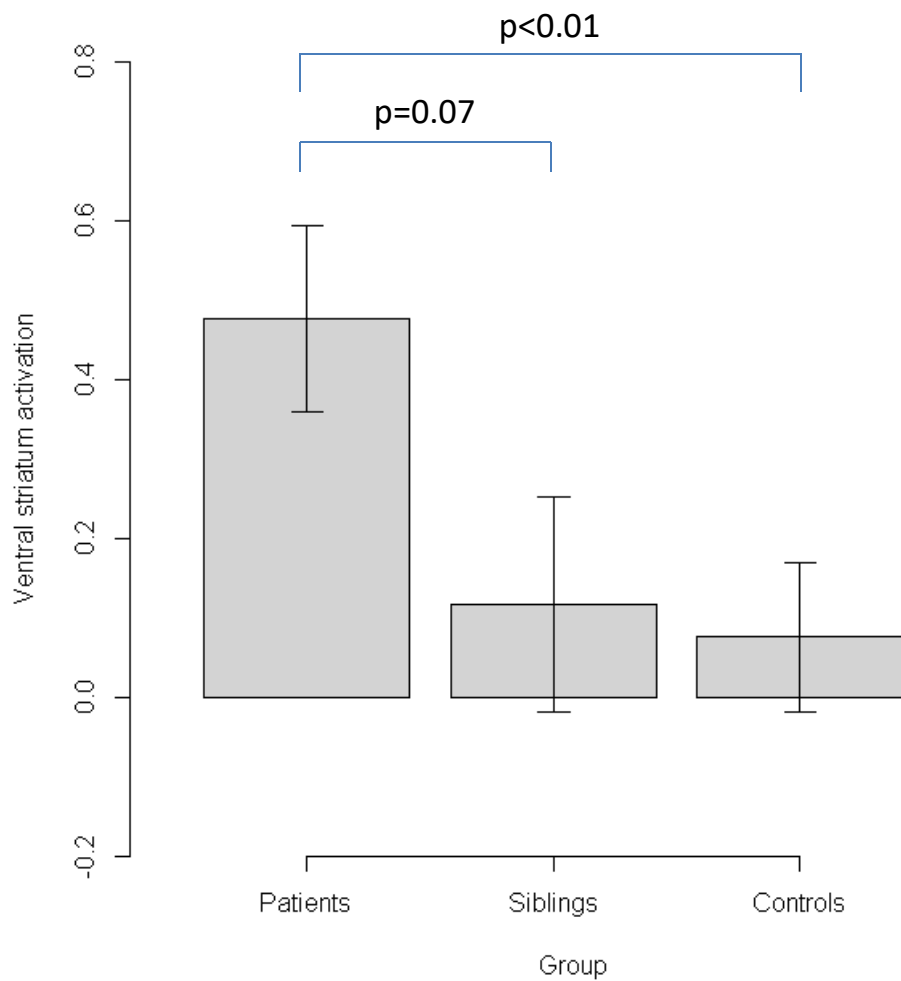


Figure 4.4b: Extracted PE activation from ventral striatum (3mm radius sphere centred on 21 -1 -14) with standard deviations. Extractions were drawn from the second level analysis, which was composed of first level T contrast estimates of PE.

4.4.3.1.3 Group x condition interactions

There were no group by PE interactions.

4.4.3.2 Q value results:

4.4.3.2.1 Main effect of condition:

When the three groups were analysed together, representation of Q value learning was associated with deactivations in bilateral medial frontal and right supramarginal gyri at whole brain level (see Figure 4.5a).

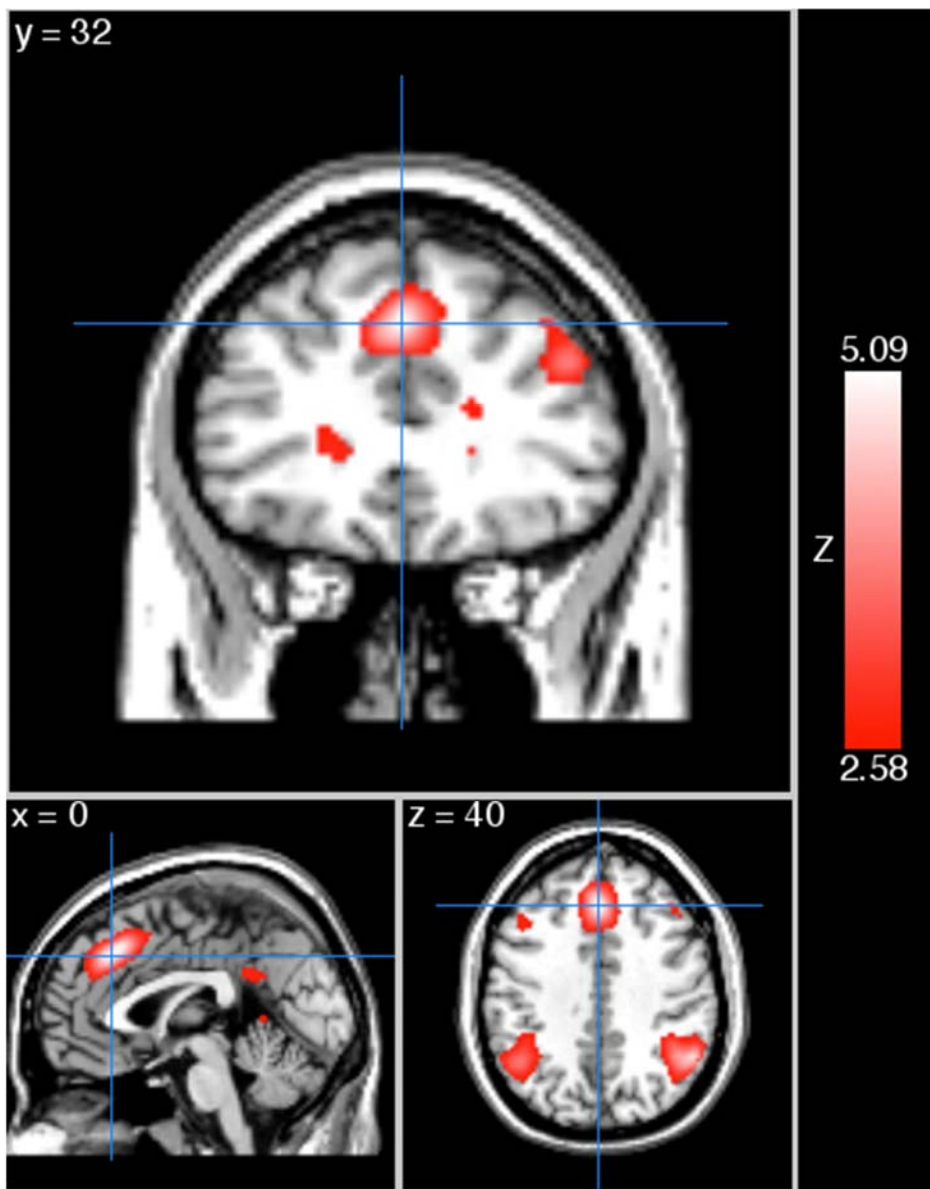


Figure 4.5a: The main effect of Q value encoding across groups.

4.4.3.2.2 Activation within each group: Q value

Controls: There were no significant regional activations associated with Q value in the control sample.

Patients and Siblings: The medial frontal activation fell within the Q value ROI, and was reduced in both patients and siblings (see Figures 4.5a and 4.5b).

4.4.3.2.3 Between group comparison of Q value

Paired t-tests using extracted data from the whole brain medial frontal gyrus result for Q value showed significantly decreased activation in patients compared with controls ($F=7.15$, $p<0.01$) that could be accounted for by differences in depressive symptomatology (model with HAM-D: $F<0.01$, $p=0.97$). Siblings' activations demonstrated a trend deactivation compared to controls ($F=3.73$, $p=0.06$) but not their ill relatives. HAM-D scores correlated negatively with the extracted values across all groups (Spearman's $\rho=-0.36$, $p<0.01$) and within the patient group alone (Spearman's $\rho=-0.63$, $p<0.01$). Parameter estimates showed that siblings' activations appear intermediate although siblings did not differ significantly from controls or patients (Figure 4.5b).

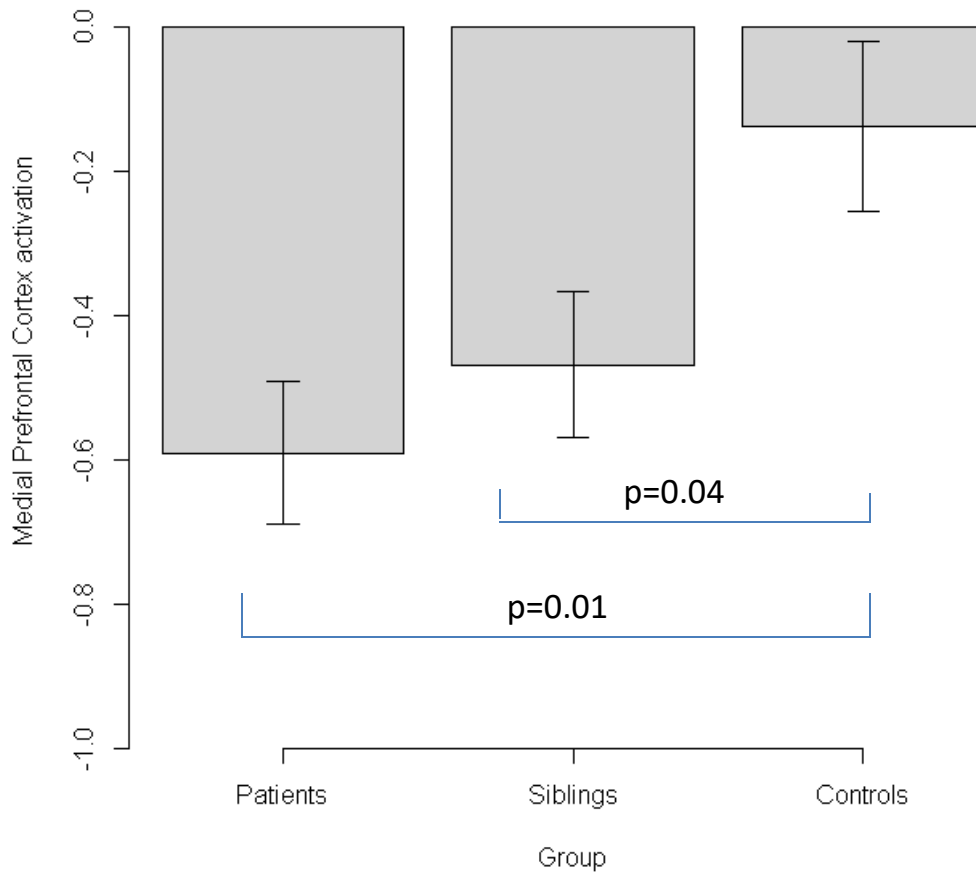


Figure 4.5b: Extracted medial prefrontal activation encoding Q value (3mm radius sphere centred on 0 32 40) with standard deviations. Extractions were drawn from the second level analysis, which was composed of first level T contrast estimates of Q value.

Q value encoding was associated with under-activation within left DLPFC in patients compared with controls which remained significant when symptom scores were included as covariates ($T=6.91$, $p=0.01$). Parameter estimates for this peak voxel showed that siblings had an intermediate degree of activation, which significantly differed from controls using paired t-tests from the extracted data ($T=9.14$, $p<0.01$) and with symptom scores included as covariates ($T=4.60$, $p=0.04$).

4.4.3.2.4 Group x condition interaction:

There were no group by Q value interactions.

4.4.3.3 Analyses of potential confounding factors

There were no differences between patients who were or were not prescribed lithium, antidepressants or antipsychotics. The number of previous episodes of mania or depression did not associate with any of the extracted values.

4.5 Discussion

In support of the a priori hypotheses, we found that PE is associated with ventral striatal over-activations in patients compared to controls. Siblings' activations were similar to controls suggesting that this abnormality may relate more to features of the illness than a familial predisposition. Secondly, we found that the value attributed to a stimulus as the task progressed was associated with PFC under-activations in BD and their siblings compared to controls, supporting the hypothesis that these abnormalities may underpin the neurobiology of genetic risk for Bipolar Disorder.

The reinforcement learning task used and Q value analysis are standard techniques for investigating reward processing. There were no significant performance differences between the groups and a standardized set of in-scanner behavioural parameters were used for analyses.

BD is a condition characterised by unrealistic expectations of success and disrupted reward-learning. Exaggerated PE signals in the striatum are likely to reflect both abnormal error-related reward-learning and lead to an enhanced motivational response to the conditioned stimulus or a greater recruitment in striatal regions to achieve the same level of performance. Similar striatal over-activations have been reported in manic (Ablner, 2008) and euthymic patients (Mason, 2014). Others have found ventral putamen over-activity present in BD but not siblings, in keeping with this study's results. These exaggerated PE signals have therefore been demonstrated across all states in BD; in euthymia and mania. While most of the cohort was euthymic, some met criteria for depression, although these signals were not associated with symptom severity in the current cohort. Thus, this abnormality of PE signalling could provide a neurobiological basis for the characteristic symptoms of BD, although it is not specific to any state. For instance, the symptoms of mania where risky behaviour continues in the face of negative consequences may be due to inappropriate striatal activity inaccurately indicating rewards. This results in a lack of updating of learning and excessive motivation towards

a specific goal. Greater salience for errors could also explain depressive symptomatology where enhanced processing of negative stimuli (such as errors) and experiences that are sustained rather than short-term could lead to excessive dampening of emotional reactivity. Additionally, failure of sensory data to propagate to DLPFC may lead to a lack of emotional attenuation and contextual information (Hamilton, 2013), maintaining the negative bias. Compatible with this hypothesis, individuals experiencing depression (Fusar-Poli, 2009) and bipolar patients with anhedonia (Liverant, 2014; Pizzagalli, 2008b) fail to develop a response bias towards rewarding stimuli during reinforcement paradigms (Pizzagalli, 2008a). These features while present may not reach clinical threshold until the circuitry is impacted in other ways, for instance a reduction in prefrontal regulation, which initiates the symptomatic presentations. We have previously reported over-activations in VS to a non-emotional, verbal fluency task in patients (McIntosh, 2008) and correlated with depression scores in young healthy adults and high-risk relatives (Whalley, 2011). Blumberg and colleagues reported a similar positive association between depressive symptoms and striatal activations (Blumberg, 2003). The lack of striatal pathology in siblings in this study may represent a lack of depressive symptoms or signify resilience as these particular siblings did not experience mood disorders and were passed the period of greatest risk.

This study found that the value attributed to a stimulus as the task progressed was associated with medial PFC under-activations in BD and their siblings compared to controls. There are two main circuits involved in reward learning; the orbitofrontal-limbic circuit (involved in reward and aversion) and the medial prefrontal, medial and posterior cingulate circuit (involved in introspective functions; mood, emotion and visceral reactions). Here medial prefrontal gyrus activations were reduced in BD to the learning of value. Activation of this region is associated with the monitoring of actions (Amodio, 2006) and errors and social processing (Koban, 2014). Neuropathological changes to this region and its network could be undermining the regulation of hedonic and affective processing (Savitz, 2014). In this study, depression rating scores correlated negatively with the extracted values across all groups and within the bipolar group alone, suggesting that this

effect may be mediated by depressive symptoms providing more direct evidence of the relationship between reward circuitry and the symptoms of BD.

The finding of under-activation in the DLPFC, a region with projections to the medial prefrontal network and strongly associated with decision-making, reward planning and action (Ichihara-Takeda, 2008) was not associated with symptoms. Mason and colleagues reported similar results in euthymic BD individuals (Mason, 2014). However their task used a range of rewarding values and so they demonstrated BD patients preferentially activating DLPFC to low-probability, more risky rewards while controls activated DLPFC to high probability rewards, in pursuit of longer term goals. This evidence supports the hypothesis that DLPFC fails to suppress behaviours that offer immediate reward in favour of longer term goals in BD. Siblings' activations also decreased significantly compared to controls although appeared intermediate between the other groups, supporting the hypothesis of aberrant DLPFC activity being associated with underlying vulnerability to BD. It may be that trait increases in impulsivity found in BD patients and to a lesser degree in their siblings may be explained by these findings.

Although Linke and colleagues (Linke, 2012) conducted a reversal learning reward study with first degree relatives, no previous functional MRI studies have compared patients with their own siblings directly (Linke, 2012). The sample was chosen in order to reduce variance as there would be greater shared genetic and environmental influence for both groups. However, issues regarding statistical power due to sample size, low signal, symptoms being measured at a single time point and other concerns regarding the cross-sectional nature of this study must all be acknowledged (Button, 2013). This study did not find increases in orbitofrontal cortical activity that have been reported previously during reward anticipation in mania (Bermppohl, 2010), euthymia (Linke, 2012; Nusslock, 2012) and relatives (Linke, 2012) . The primary reason is likely to be related to difference in task design, analysis and possibly power. None of these functional tasks modelled reward processing using temporal difference modelling which assesses trial by trial effects,

offering a more sophisticated, computational analytical approach that attempts to model learning as it occurs. Linke and colleagues used a different type of task; reversal learning where the contingencies being compared were very different to that used here.

The correlation between the extracted data in PFC and ventral striatum/midbrain regions supports the hypotheses that ventral striatum-PFC circuits are implicated in associative learning that underlie the representation of expectancies while ventral networks represent motivational value (Frank, 2011; Schultz, 2006). Dynamic changes in striatal dopamine firing are thought to update PFC representations as both striatum and PFC are primary targets of dopamine projections. Poorer representation of behaviourally relevant information in these regions may relate less satisfactory information to the reward processing network, diminishing the quality of resultant decision making.

Abnormalities of PE have previously been demonstrated in schizophrenia. BD and schizophrenia share symptoms, genetic architecture and reward processing abnormalities (Gold, 2008; Berman, 2010). Aberrant striatal PE may represent a convergent abnormality in the brain and contribute to the development of abnormal associations that lead to the irrational beliefs seen in psychosis, as well as mood symptoms. However, subtle differences in reward processing and motivation networks may influence the resulting phenotypic expression. Psychotic symptoms have been associated with PE in schizophrenia (Murray, 2008). Seventy-six percent of our BD patients had a psychotic episode within their lifetime. None were psychotic at the time of scanning. We found no associations between lifetime psychotic symptoms and the extracted data. Regarding mood symptoms, there was no correlation between extracted data for the ventral striatum and HAM-D and YMRS scores. However, mood symptoms at the time of scanning affected the learning of value in the medial frontal gyrus, suggesting these activation differences may underpin depressed mood in both affected and unaffected subjects.

4.5.1 Limitations

Methodological limitations of the sample and clinical assessments

The sample size is small compared to more recent studies. Cross-sectional studies are unable to account for future development of illness. As a result, some well siblings in this study may eventually develop bipolar disorder or depression. Additionally, symptoms and therefore diagnosis or lack of diagnosis is determined by subjective accounts of participants' past experiences.

The inclusion of medicated participants only in the BD cohort is a potential limitation as disentangling medication and illness effects is particularly challenging. The post-hoc analyses conducted, and the inclusion of unmedicated siblings suggest that prescribed medication cannot better account for the findings reported. Although the possibility that the striatal result was not due to medication could not be ruled out, this finding has been demonstrated in several studies previously.

Methodological limitations of model fitting and estimation

The task immediately separated CS high and CS low and although the weighting of presentation reached 60% and 40% respectively, they did not cross over. As a result, there was little information to estimate learning rate. A future study would ensure full crossover of CS high and low to enable this estimation.

The learning rate and temperature parameters were averaged across the entire sample. As there were 21 patient-sibling pairs (totalling 42 individuals), the estimation of these parameters may have been subject to bias, given that control participants were relatively under-represented at 22 individuals. This could result in a poorer model fit for control

participants, affecting group contrast comparisons examining the computational model regressors.

Methodological limitations of the imaging technology

There is an ongoing debate about statistical power in small studies and especially those using functional imaging (Button, 2013). Whilst functional MRI is a useful tool for measuring neural systems activity in vivo, it cannot measure dopamine activity directly. Dopamine receptors are found on some micro-vessels in the brain and so BOLD signal may reflect both the release of DA and the direct vascular mechanisms.

The modulation of striatal plasticity is extremely complex. D1, adenosine, acetylcholine and NMDA (glutamatergic) receptors in the VS have all been implicated in striatal long term potentiation (LTP), an important component in strengthening the stimulus-response associations in this region (Lovinger, 2010). Elevated VS dopamine has been associated with the symptoms of mania however, glutamatergic receptor activation stimulates dopamine release in the striatum and elevated glutamate levels have been associated with depression and mixed states in BD (Jun, 2014). The complexity of pathology in VS and its circuitry suggests that very subtle changes may alter learning, understanding and regulation with a variety of mechanisms. Neuroimaging can highlight broad differences in levels of oxygenation of regions but cannot account directly for the aetiology of those presentations.

4.5.2 Future Directions

Dynamic causal modelling of this data would enable us to explore the direction of effects in reward processing. Analyses of specific symptoms of BD using the mathematical formulation of reward learning would facilitate a more detailed understanding of their neurobiology (Huys, 2013). Future studies could specifically target dopamine and other neurotransmitter systems involved in reward-learning using molecular imaging.

Investigating the neuroimaging findings in association with the severity of symptoms using a dimensional approach, especially those objective and self-report measures that reflected emotional and behavioural dysregulation and differentiated the groups (see chapter 2: Ham-D, YMRS, neuroticism, cyclothymia, extraversion, non-planning impulsiveness and total impulsivity score) would potentially capture more specific information about the underlying neural mechanisms (Bebko, 2014; Insel, 2010).

4.5.3 Summary

PE signalling is associated with ventral striatal over-activations in BD compared to controls. Siblings' activations were similar to controls suggesting that this abnormality may relate more to features of the illness than a familial predisposition. Secondly, this study found that the learning of the value attributed to a stimulus was associated with PFC under-activations in BD and their siblings compared to controls, supporting the hypothesis that these abnormalities may underpin the neurobiology of genetic risk for Bipolar Disorder.

5 Chapter 5: Discussion

5.1 Summary of research question and methods

In order to further develop our understanding of the pathology of bipolar disorder, a unique cohort of discordant sibling pairs was recruited; individuals with Bipolar Disorder I who each had a healthy sibling who was passed the age of greatest risk for developing the disorder, and a set of healthy controls matched for age, premorbid IQ and socioeconomic status. Functional magnetic resonance imaging techniques were implemented to research the neural correlates of vulnerability, illness and resilience in BD. It was hypothesised that findings in siblings that were intermediate between controls and patients demonstrated vulnerability markers, as quantitative traits. This method would address concerns about the heterogenous influence of i) symptoms, ii) the pathology of disease progression and iii) medications in the patient group as the siblings were free of all these factors but due to shared environment and genetic influences they demonstrated similar but weaker differences in comparison to their relatives. Although it was not possible to discriminate between the genetic and shared environmental influence, this research paradigm also offered an opportunity to study the neural correlates of resilience represented by the sibling cohort.

An instrumental reward learning task targeted the circuitry underpinning reward processing and bipolar disorder. Analytic techniques were employed to model dopamine-related learning and prediction error. It was hypothesised that reward related regions associated with prediction error such as the striatum would be over activated in individuals with BD, mediating unrealistic goal attainment behaviour and motivational drive. Prefrontal cortical regions associated with value learning would demonstrate under-activations in BD representing inadequate top-down control either underlying or, potentially, as a consequence of the changes in subcortical activity.

Additionally, a facial emotion processing task was chosen to assess prefrontal and subcortical function. Here it was hypothesised that Bipolar patients would under-activate

cortical regions and over-activate subcortical/limbic regions, to both implicit and explicit facial expressions of both happy and fearful faces when compared to healthy controls. Also there would be greater cortical deficits for the explicit task which typically in healthy individuals recruits a greater degree of fronto-temporal cortical processing to label the emotions.

5.2 Summary of findings

To the best of the author's knowledge this is the first study to examine the functional correlates of reward and facial emotion processing in a cohort of patients with BDI who were recruited each with a healthy sibling who was passed the age of greatest risk for the development of BD. Additionally, by virtue of having no mood disorder history by an average age of 45 years, these siblings appear to represent a particularly resilient group.

Neuropsychological testing revealed trait-related deficits in processing speed, working memory and decreasing intelligence, with slower processing speed representing an endophenotype. However other candidate endophenotypes from the literature (response inhibition and set-shifting (Bora, 2009)) were not supported by this study as the siblings did not demonstrate deficits. Greater openness represented a trait personality feature although it correlated with manic symptoms in the patient group. As this is a self-report measure, it is possible that it represents a state effect in patients but due to the environmental influence of being a sibling of a bipolar individual, siblings view themselves as more open. Personality and temperament measures associated with BD (increased neuroticism, extraversion, cyclothymia and impulsiveness) were only significantly greater in patients than controls and correlated with symptoms. Previous studies have associated these measures with familial risk for BD and found correlations with structural and functional brain changes in high-risk cohorts (Sprooten, 2011; Whalley, 2013a; Whalley, 2011). The striking lack of concordance with those findings in this study points to the siblings representing a uniquely robust group or this study representing an older cohort. They may additionally have been protected from the disorder in part by their personality

and temperament characteristics which do not correlate with greater risk of illness development. It maybe that the factors that have lead to the development of those characteristics endow additional pathological resilience.

Reaction time for i) response inhibition, ii) to cued rewards, and iii) set-shifting errors were all increased in patients but not their relatives. These could be effects of medication or illness combined with slower processing speed. Deficits in labelling sad facial expressions were also state-related and have correlated with symptoms in patients in previous studies (Harmer, 2002) although not here.

Reward processing using functional MRI revealed illness-related ventral striatal over-activation associated with PE signalling, supporting previous studies of reward (as discussed in Chapters 1 and 4). PFC deactivations related to the learning of the value attributed to a stimulus were associated with familial susceptibility for BD and correlated with depressive symptoms. PET studies have also demonstrated i) impaired learning of new verbal information associated with hypoactivation of DLPFC in euthymic patients (Deckersbach, 2006) and ii) sadness induction that elicited reduced OFC activity in euthymic patients and unaffected siblings (Kruger, 2006). However the latter study found reduced medial PFC activity in patients but over-activity in siblings suggesting this as a potential resilience effect.

These findings concur with a model of impaired prefrontal modulation of limbic networks that underpins BD (Langan, 2009). However, these results suggest that the cognitive, top-down modulation may be a trait feature, or intermediate phenotype, while the clinical illness is apparent only when the regulation of limbic regions becomes more significantly impaired, leading to increased responsiveness of these emotion regulation regions.

The mechanisms underpinning the fMRI differences between well siblings and patients are highly complex. Invoking translational techniques to explore the cellular mechanisms may begin to explain BOLD signal differences. Rodent models of depression (using a social defeat stress paradigm) have demonstrated a normal firing rate of VTA dopamine neurons in resilient animals and an increased rate in susceptible animals, similar to our findings. However, both groups experienced induction of hyperpolarisation-activated cation current which increases the intrinsic excitability of these neurons. Therefore the resilient mice were likely to exhibit an additional counteracting ionic mechanism which normalises the firing rate. Microarray analyses identified increased mRNA encoding K⁺ channel subunits in the resilient mice which were shown to functionally occlude the increased current when induced (Russo, 2012). This finding demonstrates an adaptive mechanism that normalises functioning, resulting in resilience in the context of a depressive paradigm. Therefore the limbic dysregulation by patients may not simply be a feature of clinical disease as the limbic regulation demonstrated by the siblings in this study may represent a biological adaptive effect of resilience that at present we are unable to examine directly.

Table 5.1: Summary of findings

Domain	Result	Research Tool
Trait Effects (present in siblings and patients)		
Personality	↓ openness	NEO FFI
Neuropsychology	↓ processing speed	Digit Symbol Substitution Test (90secs)
	↓ working memory	Backward Digit Span
	↓ Intelligence	WASI full scale IQ (& verbal IQ)
MRI tasks		
Value attributed to stimulus (Q)	↓ PFC activations	Reward fMRI task
State Effects (present only in patients)		
Personality	↑ neuroticism ↑ extraversion ↓ conscientiousness	NEO FFI
Temperament	↑ cyclothymia	TEMPS-A
Impulsivity	↑ Non-planning impulsiveness	Barratt Impulsiveness Scale
Reaction Time	↑ reaction time to rewards	Cued Reaction Time Task
Response Inhibition	↑ stop signal reaction time	Stop Signal Reaction Time Task
Set Shifting	↑ Errors	IDED
Facial emotion labelling	↓ Sadness labelling	Ekman Faces
MRI tasks		
Facial Emotion Reaction Time	↑ reaction time to implicit fearful faces	Implicit/Explicit facial emotion processing fMRI task
Activations to Implicit Fear	↑ Left Lingual Gyrus	
Activations to explicit > Implicit fear	↓ Right fusiform/lingual gyrus	
Activation to Implicit Fear + Happiness	↑ Right Insula	
Prediction Error	↑ ventral striatal activations	Reward fMRI task
Adaptive responses associated with resilience		
Implicit happiness (Sibs vs Con)	↓ Left Putamen ↓ left Cerebellar	Implicit/Explicit facial emotion processing fMRI task
Explicit > Implicit happiness (Sibs vs Con)	↑ Right Posterior cingulate	
Implicit>Explicit (Sibs vs BD)	↓ Left Superior parietal	

The facial emotion paradigm associated disease expression with lingual gyrus and insula over-activations during implicit emotion processing. These regions are involved in facial expression recognition (Kitada, 2010) and attentional shifting (Rutter, 1987) respectively. Both may have increased activity due to their direct connections to limbic regions which are also over-active in BD, potentially due to the reduced prefrontal, top down control. Disease expression was also associated with reduced fusiform activations during explicit emotion processing in keeping with previous studies of BD. This region is important for the perception and recognition of faces as part of a network of brain areas required for facial emotion recognition.

Adaptive responses associated with resilience were demonstrated with posterior cingulate over-activations (a region involved in emotional salience (Maddock, 2003)) and activated as part of the default mode network during planning (Leech, 2014)) and putamen (involved in category learning (Ell, 2006)), cerebellar (cognitive functions include attention and learning (Wolf, 2009)) and superior parietal hypo-activations (attentional processing (Wolpert, 1998)). These regional differences may represent mechanisms that counteract maladaptive changes that are seen in susceptible individuals.

5.3 The healthy sibling group

The sibling group present differently to many first-degree relative cohorts from previous studies, demonstrating less of the vulnerability markers from the literature. This may be due to their unique presentation both in terms of their age and relationship to risk but also as they have not developed a mood disorder, depression or BD, suggesting that the lack of vulnerability may relate more to resilience.

Understanding the pathological features of resilience offers similar opportunities to defining the neural correlates for risk and vulnerability. Both contribute to a greater knowledge of the neurobiological mechanisms that maintain and effect health in those with more vulnerability factors for a specific disease. In the future, it may prove possible to isolate genetic pathways associated with BD using resilient as well as vulnerable cohorts. Biomarkers of resilience would enable clinicians to offer more accurate prognoses and interventions for those at risk without resilient markers. These might include teaching or training at-risk individuals to develop adaptive strategies and/or more directly enhancing neuroendocrine and other biological mechanisms that promote adaptive coping.

There are huge challenges associated with research into resilience. For instance, defining resilience is controversial and complex. Relief from symptoms in the context of greater risk and vulnerability often contributes to the definition but does not clearly point to factors that should be measured. Additionally, resilience may be just one of several constructs that reduce vulnerability. From a psychological perspective, other protective factors include hardiness, adjustment, good fit between child and environment, the buffering of environment by important adults in the child's life.

In this study, resilience was described as neural activations that differed between siblings and their ill relatives where controls appeared intermediate, inferring that the siblings had adapted their functioning in ways that were contrary to their relative's brain activity. Additionally, resilience was implied by activations that separated siblings from controls with the caveat that these differences were not in the same direction as their ill relations. In the latter cases, the assumption is that adaptations from healthy control functioning may be necessary to prevent the development of illness. In other words, the siblings are processing information or emotion differently in order to overcome their greater tendency to illness. All these postulates require greater investigation in larger, prospective cohorts for validation.

5.4 Limitations of the work

5.4.1 The participants

The sibling cohort was recruited specifically as a group with reduced risk of developing BD. However, they appear to be a group that has rarely been investigated in the literature resulting in a limitation of comparison data. Comorbidities such as alcohol and illicit drug use were assessed, although, other psychiatric and medical comorbidities were not included. Additionally, bipolar disorder may develop at any time in adult life and so this cross-sectional design does not account for future development of illness by the siblings who remain at greater risk than the controls. Interpretation of their functional data was

also challenging, in part due to the limitations of pairwise comparisons with a three group sample.

The sample size was small in comparison to more recent studies. Extended family structure regarding illness and resilience (for instance, the size of each sibship, parental illness or wellbeing, the likely genetic loading of risk related to other family members) was not accounted for in this study.

5.4.2 The methods

Temperamental characteristics that may have enabled resilience e.g. characteristics that elicited positive, caring responses from a variety of people, skills/values that lead to efficient use of abilities, realistic goals and plans (Rutter, 1987) were not tested.

Regarding the functional faces task, the inclusion of two relevant emotions (happy and fearful) in BD in addition to neutral faces and implicit and explicit judgements allowed for investigation of a greater number of brain regions with robust a priori hypotheses. However, the number of different contrasts for analyses also limited the power to find differences between the groups. It might have been beneficial to limit the design to implicit judgements only for more robust analyses of sub-cortical functioning between the three groups.

From a clinical perspective, a unique and interesting set of siblings were recruited whose specific clinical characteristics enabled the investigation of familial hypotheses with greater power. However, statistical analyses were limited to pairwise comparisons for all functional data in order to use the relatedness information as there was no clear strategy for incorporating this field in SPM when additionally including healthy controls. This has limited interpretation of the results as the direct three group comparisons could not be

undertaken with the relatedness factor included. Due to the increasing emphasis on genetic research and the recruitment of extended families, it is expected that future analysis packages will enable brain imaging statistics to account for familial relationships e.g. ASReml. One caveat is that these generally employ techniques such as maximum likelihood estimation based on iterative methods that rely on large sample sizes which are rarely available in imaging studies.

The inclusion of medicated participants only in the BD cohort is a potential limitation to the current study as disentangling medication and illness effects is particularly challenging. Medications could only be addressed by comparing those with and without specific categories of psychotropic drugs. Due to the cross-sectional nature of the study this could not account for each individual's medication history. The sample size would also limit any interpretation as there was unlikely to be enough power to detect differences related to medication effects. However, the post-hoc analyses conducted, and the inclusion of unmedicated siblings suggest that prescribed medication cannot better account for the findings reported. Results that demonstrated similar effects in patients and siblings were most likely to relate to shared familial and genetic aetiology rather than illness-related effects such as medications or chronicity of symptoms.

5.5 Future directions

Functional connectivity analyses using dynamic causal modelling of both paradigms would enable us to explore the direction of effects and investigate the functional networks relevant to facial emotion processing and reward learning. Subsequent exploration of the structure-function relationship combined with genetic profiling would begin to highlight more specific biological pathways. These techniques are likely to offer greater explanation of the potential resilience-associated brain activations observed in this study.

Longitudinal studies of resilience would be useful to ensure that those defined as resilient by virtue of never developing BD were followed up and retained healthy clinical status. Additionally, adaptations associated with age, illness phase, chronicity, symptom dimensions and variability, medications, life events and psychological impacts could be assessed.

'Big data' studies of similar cohorts and families that include genetic data, beginning with polygene scores and leading to genetic pathway analyses might enable much more targeted molecular research in the future.

Characterising the biological underpinnings of resilience using both imaging and cellular level mechanisms may provide quantitative measures that could improve diagnosis and earlier intervention. Biomarkers would also enable greater stratification in patients, offering another avenue for the tailoring of treatments.

Animal studies would tender models that represent circuit-level synaptic changes that cannot be distinguished using fMRI BOLD signalling. BOLD activations do not specify whether the neuronal recruitment of blood oxygen is to inhibitory or excitatory cells or even whether these are neuronal, glial or related to other cells. For instance, optogenetic stimulation of rodent medial PFC neurons with channel rhodopsin promoted resilience to social defeat stress (Covington, 2011). This resilience is likely to be mediated via glutamatergic microcircuitry (Russo, 2012) .

5.6 Conclusion

This study has demonstrated illness-associated over-activations in limbic and closely associated cortical regions elicited by reward learning and facial emotion processing and

under-activations in the facial processing region. Prefrontal cortical deactivations elicited by reward learning correlated with depressive symptoms and represented vulnerability to bipolar disorder. Adaptive neural correlates were demonstrated in various brain regions and may represent biomarkers of resilience. This initial study into resilience highlights the opportunities to develop this field, offering another avenue to improving our understanding of bipolar disorder, potentially through more accurate prognostic indicators and for using functional MRI biomarkers to measure the benefits (or lack of benefit) of specific interventions.

6 References

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