

# **Emotional processing and bipolar disorder**

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**Thesis submitted for the degree of**

**Doctor of Philosophy**

**Department of Psychiatry**

**The University of Oxford**

**Trinity Term 2010**

## **Abstract**

The aetiology of bipolar disorder remains unclear and investigation to date has focussed largely on bipolar patients. Whilst ultimately of huge value, such studies may also be confounded by current mood or experience of repeated illness episodes or current or past medication; using at-risk samples may bypass some of these problems. The current research therefore assessed the efficacy of the Mood Disorder Questionnaire (MDQ) as a screening tool for vulnerability to bipolar disorder. The MDQ was used with two sets of criteria to identify two sub-groups of medication-naïve young bipolar phenotype subjects who were at risk for bipolar disorder by virtue of experience of mood elevation. Analysis of data from the Student Stress Survey was carried out to characterise the bipolar phenotype. Compared to a control group with no experience of mood elevation, the two bipolar phenotype sub-groups showed a gradient of prevalence of bipolar diagnosis and associated co-morbidity. Behavioural and functional magnetic resonance imaging (fMRI) techniques were employed to investigate emotional processing, decision-making, and sleep and circadian rhythmicity in bipolar phenotype students. Analyses revealed that positive emotional processing biases, disrupted decision-making, and increased activity during sleep were associated with the bipolar phenotype and, therefore, may represent vulnerability markers for bipolar disorder. Finally, a psychopharmacological investigation of quetiapine, which stabilises mood, was carried out in healthy volunteers. One-week quetiapine administration resulted in biases away from both positive and negative emotional stimuli (i.e. a mood-stabilising effect), reduced discrimination between different magnitudes of gains and losses during risky decision-making (consistent with an antidepressant effect), and increased sleep duration. In sum, this research has developed our understanding of vulnerability markers associated with the bipolar phenotype and provided a first step towards uncovering the psychological mechanisms through which quetiapine's clinical effects may be mediated.

## Acknowledgments

I would like to thank my excellent supervisors Dr Catherine Harmer and Prof Guy Goodwin for their fantastic support throughout my DPhil. I pass on my immense gratitude to Catherine for all her comments and suggestions, which were crucial in getting to the final version of this thesis and for her unending positivity and encouragement during my time in Oxford. I thank Guy for his optimism and good humour in response to the challenges of manuscript submissions and job-hunting!

Thanks go to my collaborator Dr Katharina Wulff for her time and effort in setting up the actigraphy study, for all her help in the early days of analysis, and for her patience during my confusion over clock changes. I would like to thank my collaborator Dr Robert Rogers for his help with the decision-making paradigms and for his great enthusiasm about the quetiapine results. He really showed me that a few exciting results can really lift one's spirits and spur on writing up. I would like to acknowledge Dr Rebecca Chandler for her collaboration with the screening interviews.

I would like to thank Pete Champion for his endless support and for reminding me to keep chipping away at the thesis when it seemed too daunting a prospect to complete. Thanks go to Ben Britton for the competition that has driven me to completing my DPhil on time. I would like to thank Nancy Rawlings, Lizzie Parsons, and Dr Poornima Kumar for being excellent office mates and for helping to keep me sane! Thanks to Poornima for her help with the imaging analysis in the face of an ever-nearing abstract submission deadline, and for reminding me to keep setting my standards high. I would also like to thank Dr Susannah Murphy for her help with imaging analysis and for all her support and advice over the last year.

Finally, I would like to acknowledge the Medical Research Council for my studentship, without which this research would not have been able to be carried out.

## **Declaration**

Some parts of this thesis have been published or submitted for publication:

### **Chapter 2**

Rock, P. L., Chandler, R. A., Harmer, C. J., Rogers, R. D., & Goodwin, G. M. (manuscript submitted). The common bipolar phenotype in young people.

### **Chapter 3**

Rock, P. L., Goodwin, G. M., & Harmer, C. J. (2010). The common adolescent bipolar phenotype shows positive biases in emotional processing. *Bipolar Disorders*, *12*(6), 606-615.

Rock, P. L., Goodwin, G. M., & Harmer, C. J. (manuscript in preparation). Mood elevation and neural responses during the emotional Stroop task.

### **Chapter 6**

Rock, P. L., Harmer, C. J., McTavish, S. F. B., Goodwin, G. M., & Rogers, R. D. (manuscript in preparation). The effects of quetiapine on risky decision-making.

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# **1 Research background**

## **1.1 Bipolar disorder**

### **1.1.1 Introduction to bipolar disorder**

Bipolar disorder is an affective disorder that is characterised by episodes of depression and mania interspersed with periods of relative recovery during euthymia. This debilitating and lifelong disease affects not only mood but also the domains of decision-making, attention, sleep and energy, motivation, pleasure, and appetite.

According to the World Health Organization (WHO), bipolar disorder is the sixth leading cause of disability worldwide as measured by years of life lived with a disability (Lopez & Murray, 1998). The estimated lifetime prevalence of bipolar disorder ranges from 0.3% - 1.5% worldwide when DSM-IV-TR (Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Text Revision) (American Psychiatric Association, 2000) criteria for bipolar I disorder are used (Merikangas, et al., 2007; Weissman, et al., 1996).

### **1.1.2 Diagnostic criteria**

A diagnosis of bipolar I disorder requires the experience of a manic episode with or without a depressive episode. According to the DSM-IV-TR criteria, a manic episode is defined as a period of elated, expansive, or irritable mood with three (or four if mood is irritable) out of seven concurrent mood-elevation symptoms that are neither attributable to a medical illness nor induced pharmacologically. The manic episode must last at least a week and be associated with functional impairment or must result

in hospitalisation. Mood-elevation symptoms capture feelings of grandiosity, reduced need for sleep, increased talkativeness, racing thoughts, distractibility, increased activity, and reckless behaviour. The age of onset of bipolar I disorder appears to peak in sub-groups of patients at around 20, 30 and 40 years of age (Bellivier, et al., 2003; Pavuluri, Birmaher, & Naylor, 2005; Perlis, et al., 2004).

A diagnosis of DSM-IV-TR bipolar II disorder requires the experience of both hypomanic and major depressive episodes. Lifetime prevalence estimates for bipolar II disorder are about 1% (Angst, 1998; Merikangas, et al., 2007). A hypomanic episode is one that does not reach threshold for a manic episode because it persists for less than a week, does not result in functional impairment, and is not associated with delusional ideas, but does persist for at least four days. The DSM-IV-TR criteria for a major depressive episode are low mood for most of the day nearly every day or loss of interest in most things for a period lasting at least two weeks. Furthermore, criteria require experience of at least three concurrent symptoms of depression that are neither attributable to medical illness or bereavement nor induced pharmacologically. These symptoms of depression must have affected the patient nearly every day and include decreased or increased appetite, difficulty sleeping, slowed movement/speech or feelings of restlessness, feeling tired and without energy, feeling worthless or guilty, difficulty concentrating or making decisions, and thoughts about self-harm or suicide.

### **1.1.3 Bipolar spectrum disorder**

The last two decades have seen emerging interest in bipolar spectrum disorder (Akiskal, et al., 2000; Angst, et al., 2003), which includes bipolar not otherwise specified (NOS) in addition to bipolar I disorder and bipolar II disorder in its

definition. Bipolar NOS describes a softer type of bipolar disorder and may be characterised by hypomania alone or hypomanic symptoms with minor depression, dysthymia or recurrent brief depression (which do not reach threshold for a major depressive episode). A recent study of a large adult sample from the United States estimated the lifetime prevalence for bipolar spectrum disorder to be 4.5% (Merikangas, et al., 2007). A similar high rate (5.3%) of bipolar spectrum disorder was also seen in a sample of young subjects from the Oregon Adolescent Depression Project (Lewinsohn, Shankman, Gau, & Klein, 2004). These figures are concerning because longitudinal research indicates that 15.8% of adolescents and young adults with bipolar NOS convert to bipolar II disorder (hypomania and major depression) (Beesdo, et al., 2009). However, recent research has revealed that hypomanic experience during adolescence may be part of a common adolescent bipolar phenotype and translation to bipolar disorder occurs in only a minority of cases (Tijssen, et al., 2010) (and see **Chapter 2**).

#### **1.1.4 Misdiagnosis and delayed diagnosis**

Patients with bipolar disorder frequently receive an incorrect initial diagnosis of major depression (Ghaemi, Sachs, Chiou, Pandurangi, & Goodwin, 1999) for a number of reasons. Firstly, most patients with bipolar disorder present to their clinician with an episode of depression and infrequently report previous periods of mood elevation (Hirschfeld, 2010). Correspondingly, recent research has found that between 28% (Hantouche, et al., 1998) and 49% (Benazzi, 1997) of patients with major depression were actually suffering from bipolar II disorder.

Secondly, mood-elevation symptoms are not often recognised as problematic, particularly when expressed as hypomania rather than mania (Cassano, et al., 1999). Indeed, even when symptoms of mood elevation are reported, the minimum duration required for a diagnosis of hypomania is four days, which is longer than the typical duration of an episode of mood elevation (Altshuler, et al., 1995).

Thirdly, high rates of anxiety and substance misuse co-morbidities (Freeman, Freeman, & McElroy, 2002; Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Merikangas, et al., 2007; Simon, et al., 2004) may contribute to misdiagnosis. Furthermore, the presence of co-morbidities can worsen treatment response and clinical outcome. For example, alcohol and drug misuse has been found to reduce treatment adherence and confound diagnosis (Strakowski, DelBello, Fleck, & Arndt, 2000).

A recent survey revealed that one third of bipolar patients waited at least 10 years before receiving their first accurate diagnosis of bipolar disorder (Hirschfeld, Lewis, & Vornik, 2003; Lish, Dime-Meenan, Whybrow, Price, & Hirschfeld, 1994). Delays in correct diagnosis result in delays in treatment with mood stabilisers and can lead to inappropriate treatment with unopposed antidepressants (Perlis, 2005), which may worsen clinical outcome by precipitating a switch to mania or inducing rapid-cycling (Ghaemi, Boiman, & Goodwin, 2000). Furthermore, the efficacy of mood stabilisers has been found to be reduced if treatment is initiated in patients who have already had several illness episodes (Swann, Bowden, Calabrese, Dilsaver, & Morris, 1999, 2000). Therefore, it is important for patients presenting with major depression to be assessed for bipolar disorder. The use of a self-report screening tool such as the Mood

Disorder Questionnaire (Hirschfeld, et al., 2000b) is one such way to assess for bipolar disorder.

### 1.1.5 The Mood Disorder Questionnaire

The Mood Disorder Questionnaire (MDQ) (Hirschfeld, et al., 2000b) is a self-report screening tool that targets the mood-elevation symptoms that contribute to a diagnosis of (hypo-) mania (Table 1.1).

**Table 1.1** The Mood Disorder Questionnaire (MDQ) (Hirschfeld, et al., 2000b).

1.	Has there ever been a period of time when you were not your usual self and...	Yes	No
	...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	<input type="checkbox"/>	<input type="checkbox"/>
	...you were so irritable that you shouted at people or started fights or arguments?	<input type="checkbox"/>	<input type="checkbox"/>
	...you felt much more self-confident than usual?	<input type="checkbox"/>	<input type="checkbox"/>
	...you got much less sleep than usual and found you didn't really miss it?	<input type="checkbox"/>	<input type="checkbox"/>
	...you were much more talkative or spoke much faster than usual?	<input type="checkbox"/>	<input type="checkbox"/>
	...thoughts raced through your head or you couldn't slow your mind down?	<input type="checkbox"/>	<input type="checkbox"/>
	...you were so easily distracted by things around you that you had trouble concentrating or staying on track?	<input type="checkbox"/>	<input type="checkbox"/>
	...you had much more energy than usual?	<input type="checkbox"/>	<input type="checkbox"/>
	...you were much more active or did many more things than usual?	<input type="checkbox"/>	<input type="checkbox"/>
	...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	<input type="checkbox"/>	<input type="checkbox"/>
	...you were much more interested in sex than usual?	<input type="checkbox"/>	<input type="checkbox"/>
	...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	<input type="checkbox"/>	<input type="checkbox"/>
	...spending money got you or your family into trouble	<input type="checkbox"/>	<input type="checkbox"/>
2.	If you checked YES to more than 1 of the above, have several of these ever happened during the same period of time? <i>Please circle one response only.</i>		
	Yes	No	
3.	How much of a problem did any of these cause you – like being unable to work; having family, money or legal troubles; getting into arguments or fights? <i>Please circle one response only.</i>		
	No problem	Minor problem	Moderate problem
			Serious problem

Experience of mood elevation is predictive of future episodes of depression as well as bipolar disorder (Lewinsohn, Seeley, & Klein, 2003). Furthermore, high scores on the MDQ have been found to be associated with increased probability of diagnosis of bipolar disorder (Hirschfeld, et al., 2000b). For example, when used with validated screening criteria ( $\geq 7$  mood-elevation symptoms and endorsement of the co-occurrence and problematic nature of symptoms), the MDQ had a high sensitivity for

detecting bipolar disorder (0.73) and a very good specificity (0.90) for screening out those without bipolar disorder in a psychiatric sample (Hirschfeld, et al., 2000b). Therefore, criteria for what will be described as a 'probable bipolar' diagnosis require experience of at least seven of the 13 mood-elevation symptoms and endorsement of the co-occurrence and problematic nature of the symptoms (Hirschfeld, et al., 2000b).

## **1.2 The Student Stress Survey**

The University of Oxford Student Stress Survey is an online screening questionnaire that assesses psychological health. Undergraduate students from 26 colleges within the University were invited to participate online via an email link during the first term of their fresher year. Those students who took part were then invited to complete follow-up surveys during the first term of their second and third years. Between 2004 and 2008, 2591 students completed the survey, with 50% completing the follow-up survey in their second year and 38% completing the survey in their third year. In addition to the MDQ, a number of validated questionnaires and other questions were included in the survey to assess: neuroticism and depression, family factors, life experience, substance misuse and gambling, and general health.

### **1.3 Emotional processing**

#### **1.3.1 Mood dysregulation in bipolar disorder**

Symptoms of bipolar disorder, such as mania, depression, and mood lability, are thought to be a consequence of abnormal processing of emotional stimuli. Disruption of two neural circuits, a ventral system and a dorsal system, has been proposed to underlie mood dysregulation, which in turn may underpin the affective symptoms of bipolar disorder (Phillips, 2006). The ventral system includes the amygdala, insula, ventral striatum, ventral anterior cingulate cortex (ACC), ventrolateral prefrontal cortex (VLPFC), and orbitofrontal cortex (OFC), which are thought to be involved in the identification of the emotional significance of a stimulus and the production of affective states (Phillips, Drevets, Rauch, & Lane, 2003a). The dorsal system includes the dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), dorsal ACC, and hippocampus, which are thought to integrate emotional input with cognitive processes and play a regulatory role in emotional processing. For example, it has been hypothesised that mood lability may arise as a consequence of experiencing emotions at inappropriately high intensities and an inability to regulate mood, both of which can be accounted for by emotional processing abnormalities (Phillips, Drevets, Rauch, & Lane, 2003b).

#### **1.3.2 Emotional processing biases in bipolar disorder**

The experience of emotions with inappropriate intensities may be considered in terms of emotional processing biases within a cognitive psychological framework. Cognitive psychological theories emphasise the importance of negative biases in the interpretation of, and memory for, emotional stimuli in depression (Beck, Shaw, &

Emery, 1979). Consistent with these theories, depressed bipolar patients have been found to be more likely to misinterpret facial expressions and show a negative bias compared to healthy controls. For example, studies of depressed bipolar patients have revealed impaired recognition of both happy and sad facial expressions (Rubinow & Post, 1992). Negative biases in emotional processing have also been found in depressed patients during a task employing self-referent emotional word stimuli rather than faces (Lyon, Startup, & Bentall, 1999; Murphy, et al., 1999). Experimental evidence from manic bipolar patients is less clear-cut and biases towards both negative (Lyon, et al., 1999; Murphy, et al., 1999) and positive (Murphy, et al., 1999) emotional material have been recorded in patients suffering from acute mania.

The existence of emotional processing biases during mood episodes may be unsurprising, but there are some reports of their persistence in periods of remission. For example, in facial expression recognition tasks, euthymic bipolar patients showed facilitated recognition of disgusted facial expressions (Harmer, Grayson, & Goodwin, 2002) and impaired recognition of fearful (Yurgelun-Todd, et al., 2000) and surprised facial expressions (Summers, Papadopoulou, Bruno, Cipolotti, & Ron, 2006).

### **1.3.3 The emotional test battery**

Emotional processing can be assessed behaviourally using the emotional test battery, which is comprised of a number of tasks that have been shown to be sensitive to antidepressant treatment in healthy volunteers (Harmer, Shelley, Cowen, & Goodwin, 2004; Harmer, Hill, Taylor, Cowen, & Goodwin, 2003), vulnerability to depression (Chan, Goodwin, & Harmer, 2007; Mannie, Bristow, Harmer, & Cowen, 2007), and bipolar illness (Harmer, Grayson, & Goodwin, 2002). This battery includes the

following tasks: facial expression recognition, emotional categorisation, emotional recall memory, emotional recognition memory, emotion-potentiated startle, and an attentional vigilance word dot-probe. Increased processing of positive vs. negative stimuli has been recorded following a single-dose of the noradrenergic reuptake inhibitor (NRI) reboxetine (Harmer, et al., 2003) and seven-day treatment with the antidepressants mirtazapine (Arnone, Horder, Cowen, & Harmer, 2008), citalopram and reboxetine (Harmer, et al., 2004). On the other hand, the opposite pattern has been found in subjects at risk for depression by virtue of high neuroticism (N) (Chan, et al., 2007). However, a single dose of the selective serotonin reuptake inhibitor (SSRI) citalopram was found to increase processing of fear (Browning, Reid, Cowen, Goodwin, & Harmer, 2007), demonstrating the differences in effects of single-dose and seven-day treatment with the SSRI citalopram.

#### **1.3.4 The facial expression matching task**

The facial expression matching task has been used to investigate neural processing of fearful and happy facial stimuli and was designed to activate both the amygdala and regulatory areas including the DLPFC (Drabant, McRae, Manuck, Hariri, & Gross, 2009; Hariri, et al., 2005). This task has been found to be sensitive to previous history of depression as well as antidepressant treatment. Indeed, patients recovered from depression were found to have increased activation of bilateral DLPFC and right caudate to fearful faces relative to healthy controls (Norbury, Selvaraj, Taylor, Harmer, & Cowen, 2009). Furthermore, short-term treatment with the SSRI citalopram increased amygdala activation to happy faces in healthy volunteers (Norbury, Taylor, et al., 2009). Finally, consistent with the use of facial stimuli,

activation of the fusiform face area has been recorded in response to fearful vs. happy faces in placebo-treated healthy volunteers (Norbury, Taylor, et al., 2009).

### **1.3.5 The emotional counting Stroop**

Abnormalities in emotional processing have also been recorded using the emotional counting Stroop in bipolar patients. The emotional counting Stroop is a variant of the counting Stroop that has been designed to recruit the rostral ‘affective’ subdivision of the ACC (rACC) (Whalen, et al., 1998). In this task, the emotional salience of word stimuli competes with the cognitive demand to count the number of words being presented. An fMRI study employing the emotional counting Stroop in healthy volunteers revealed deactivation of the rACC to neutral words compared to a fixation baseline, which has been proposed to reflect active inhibition of this limbic region in order to allocate resources towards effective cognitive performance (Whalen, et al., 1998). Whalen and colleagues also found greater activation to negative words vs. neutral words, which they proposed was related to the continued capacity of the rACC to monitor emotionally-salient information.

Furthermore, disorder-specific processing has been found in the rACC in patients performing the emotional Stroop task. For example, increased rACC activation to sad words in depressed patients (Mitterschiffthaler, et al., 2008) and to phobia-related words in specific animal phobic patients (Britton, Gold, Deckersbach, & Rauch, 2009) has been recorded during emotional Stroop paradigms. In an emotional colour word Stroop, medicated euthymic bipolar patients showed reduced cortical and sub-cortical activation, including in the left amygdala and left ventral prefrontal cortex (VPFC), to emotional stimuli (Malhi, Lagopoulos, Sachdev, Ivanovski, & Shnier,

2005). In a non-emotional colour word Stroop, reduced activation of the right dorsal ACC and increased activation of the DLPFC during interference trials was recorded in medicated bipolar I patients (Gruber, Rogowska, & Yurgelun-Todd, 2004). Gruber and colleagues proposed that enhanced DLPFC responses were necessary in order to compensate for abnormal ACC activation during the interference trials.

### **1.3.6 Attentional vigilance faces dot-probe**

The attentional vigilance faces dot-probe was designed to assess attentional bias to threat. This task has been found to be sensitive to treatment with the SSRI citalopram, which resulted in reduced attentional vigilance towards masked fearful faces, but not sensitive to treatment with the NRI reboxetine relative to placebo (Murphy, Yiend, Lester, Cowen, & Harmer, 2009). Furthermore, a single dose of the anxiolytic diazepam increased attentional vigilance towards masked happy faces relative to placebo (Murphy, Downham, Cowen, & Harmer, 2008).

### **1.3.7 Physiological response to emotional stimuli**

The emotion-potentiated startle is part of the emotional test battery described above and is used to assess physiological reactivity via measurement of eye-blink magnitude to a burst of white noise presented during different emotion conditions (positive, negative, neutral). This task has been found to be sensitive to administration of antidepressants and anxiolytics in healthy volunteers. For example, reduced startle magnitude across all emotion conditions was recorded following a single dose of the anxiolytic diazepam (Murphy, et al., 2008) or the antidepressant mirtazapine (Arnone, et al., 2008). Seven-day treatment with the SSRI citalopram (Harmer, Shelley, Cowen, & Goodwin, 2004) or the antidepressant agomelatine (Harmer, et al., 2010)

has been associated with reduced startle amplitude for the negative condition in particular, i.e. reduced reactivity to negative stimuli. On the other hand, a single dose of the SSRI citalopram increased startle amplitudes across all emotions (Browning, et al., 2007), consistent with the differential effects of single-dose and seven-day treatment with citalopram described earlier. Meanwhile, no changes in startle reactivity were recorded following one-week treatment with the NRI reboxetine (Harmer, et al., 2004), suggesting that modulation of startle responses may rely on modulation of serotonin activity. Furthermore, subjects at risk of depression by virtue of high neuroticism (N) did not differ from controls in terms of startle eye-blink magnitude (Chan, et al., 2007).

## **1.4 Decision-making**

### **1.4.1 Normative (rational) decision-making**

Successful decision-making under conditions of uncertainty relies upon the ability to weigh up the good and bad possible outcomes in light of the likelihood of occurrence of each outcome. Models of rational, or normative, decision-making propose that an optimal choice is the one with the maximal expected value, based on the sum of its gains and losses, each weighted by their probability of occurrence (Shafir & Tversky, 1995).

### **1.4.2 Non-normative (irrational) decision-making**

Although human decision-making often conforms to normative (rational) models described above, non-normative (irrational) decision-making sometimes occurs. Such decision-making is described as non-normative because two options with equal expected values are not chosen equally often.

One example of non-normative decision-making is the 'reflection effect' and can be assessed with the risky decision-making task described below. Confronted with a choice between a certain gain and a 50/50 gamble to win twice that gain or to win nothing (i.e. with an identical expected value), decision-makers typically choose the guaranteed gain and show risk aversion. On the other hand, confronted with a choice between a certain loss and a 50/50 gamble to lose twice that loss or to lose nothing (i.e. with an identical expected value), decision-makers typically choose to gamble and behave in a risk-seeking manner. The reflection effect describes the tendency of decision-makers to show risk-averse behaviour when a decision is framed in terms of

gains, but show risk-seeking behaviour when a decision is framed in terms of losses. It should be noted, however, that a choice framed in terms of gains (gains only) does not have the same expected value as a choice framed in terms of losses (losses only); this is not the case for the framing effect described below.

The second example of non-normative decision-making is the framing effect and this can be assessed with the framed risky-choice task described below. Decisions can often be framed in more than one way and this can have an effect on the actions of a decision-maker. The framing effect is best demonstrated by the Asian disease problem, which was described by Tversky & Kahneman (Tversky & Kahneman, 1981). In this dilemma, decision-makers are asked to choose between two programmes that may be used to combat an unusual Asian disease that is expected to kill 600 people. The first choice is between Programme A and Programme B. If Programme A is adopted, 200 people will be saved (expected outcome: 200 saved and 400 lost). If Programme B is adopted, there is a 1/3 probability that 600 people will be saved and 2/3 probability that no people will be saved (expected outcome 200 saved and 400 lost). For these two programmes (A and B) that are framed in a positive manner, i.e. in terms of saving people, the majority (72%) of decision-makers behave in a risk-averse manner and choose the certain outcome (Programme A). On the other hand, the two programmes can be framed in a negative manner, i.e. in terms of people being allowed to die. Thus, if Programme C is adopted, 400 people will die (expected outcome 200 saved and 400 lost) and if Programme D is adopted there is a 1/3 probability that nobody will die and a 2/3 probability that 600 people will die (expected outcome 200 saved and 400 lost). For these two programmes (C and D) that are framed in a negative manner, i.e. in terms of letting people die, the majority (78%)

of decision-makers behave in a risk-seeking manner and choose Programme D. The framing effect describes the change from a preference for the guaranteed choice (risk averse) in positively framed choices to a preference for the risky gamble (risk seeking) in negatively framed choices. The framing effect is different from the reflection effect described above because all programmes (A-D) have an expected outcome of saving 200 of the 600 people and letting 400 people die.

### **1.4.3 Cognitive dysfunction in bipolar disorder**

Symptoms of bipolar disorder, including risky behaviour during mania, are thought to result from abnormal cognitive processing within bipolar disorder. Bipolar patients, particularly during the manic phase, show impaired performance on attentional tasks and tasks involving cognitive flexibility. For example, manic bipolar patients have been found to show increased interference on the colour-word Stroop and impaired performance during the intra-dimensional/extra-dimensional attentional set-shifting task, indicating reduced attention and cognitive flexibility (Clark, Iversen, & Goodwin, 2001).

As described above, the DLPFC and dorsal regions of the ACC play an important role in integrating cognitive processes with emotional processes in order to regulate emotion (Phillips, et al., 2003a) and are found to be disrupted in bipolar disorder (Phillips, et al., 2003b). Additionally, the VPFC (including the OFC) has been implicated in cognitive dysfunction in bipolar disorder (Keener & Phillips, 2007). Accordingly, structural neuroimaging studies have revealed reduced volumes of these regions in bipolar patients (Lopez-Larson, DelBello, Zimmerman, Schwiers, & Strakowski, 2002). Such findings have been complemented by functional

neuroimaging studies that have revealed altered activation of these prefrontal regions during performance of decision-making and cognitive interference tasks during not only bipolar mania, but also during bipolar depression and remission. In a recent study employing the colour-word Stroop in manic, depressed, and euthymic bipolar patients, Blumberg and colleagues (2003) revealed that manic patients showed attenuated neural responses in the right VPFC and depressed patients showed increased neural responses in the left VPFC compared to euthymic patients. The same study showed that bipolar patients demonstrated decreased activation of the rostral left VPFC independent of mood state relative to controls (Blumberg, et al., 2003). Additionally, a separate study recorded decreased dorsal ACC activation in depressed bipolar patients compared to controls during the colour-word Stroop task (Marchand, et al., 2007).

#### **1.4.4 Risky decision-making in bipolar disorder**

Effective decision-making depends upon intactness of the neural circuitry involved in emotional processing and cognitive function, including the OFC (Bechara, Tranel, Damasio, & Damasio, 1996), ACC (Bush, et al., 2002), and ventral striatum (including the nucleus accumbens) (Knutson, Taylor, Kaufman, Peterson, & Glover, 2005), which have been found to be disrupted in bipolar disorder (Keener & Phillips, 2007; Phillips, et al., 2003b). Accordingly, decision-making in bipolar disorder is problematic and may be reflected in symptoms such as increased risk taking, excessive spending, and gambling behaviour.

Consistent with reports of altered emotional processing and cognitive function, abnormal risky decision-making has been recorded in bipolar patients both

behaviourally and neurally. For example, compared to controls, manic bipolar patients were found to more frequently select cards from the risky decks during incentive decision-making in the Iowa Gambling Task (Adida, et al., 2008). Furthermore, reduced activation of VPFc and dorsal prefrontal cortex (DPFC) was recorded in euthymic bipolar patients during the Iowa Gambling Task (Frangou, Kington, Raymont, & Shergill, 2008). Depressed bipolar patients were found to make suboptimal choices during a risky decision-making task (Rubinsztein, Michael, Underwood, Tempest, & Sahakian, 2006). Use of the same task with concurrent positron emission tomography (PET) revealed increased left dorsal ACC activation and reduced activation of the inferior frontal gyrus in manic patients compared to controls (Rubinsztein, et al., 2001).

#### **1.4.5 Intra-dimensional/extra-dimensional attentional set-shifting task**

The intra-dimensional/extra-dimensional attentional set-shifting task assesses cognitive flexibility during reversal learning, intra-dimensional set shifting, and extra-dimensional set shifting. Manic patients have been found to show reduced cognitive flexibility during reversal learning and extra-dimensional set-shifting blocks of the intra-dimensional/extra-dimensional set-shifting task (Clark, et al., 2001). This impairment was also recorded during the extra-dimensional set-shifting block in a study recently carried out in depressed bipolar patients (Rubinsztein, et al., 2006).

#### **1.4.6 Risky decision-making task**

The risky decision-making task has been designed to investigate how decision-makers combine information about gains and losses when choosing between actions associated with uncertain outcomes and to assess the reflection effect described above

(Rogers, et al., 2004; Rogers, et al., 2003; Rogers, Wakeley, Robson, Bhagwagar, & Makela, 2007). Research implementing this risky decision-making task has revealed that performance on the task is sensitive to manipulation of monoamine function (see Psychopharmacological effects on decision-making below).

#### **1.4.7 Framed risky-choice task**

Framing of decisions has been found to affect risk preference during decision-making as described above (Tversky & Kahneman, 1981). For example, positively-framed choices tend to be associated with risk aversion whilst negatively-framed choices are associated with risk-seeking behaviour (Tversky & Kahneman, 1981). Alterations in patterns of decision-making in positively-framed and negatively-framed conditions have been recorded in euthymic bipolar patients when making risky choices under conditions of uncertainty. The framed risky-choice task has been designed to assess sensitivity to framing during decision-making under conditions of uncertainty (Chandler, Wakeley, Goodwin, & Rogers, 2009). For example, a recent study employing the framed risky-choice task revealed that previously undiagnosed and euthymic bipolar patients showed an attenuated sensitivity to framing of dilemmas compared to controls, suggesting that changes in decision-making are not limited to mood episodes (Chandler, Wakeley, Goodwin, & Rogers, 2009).

## **1.5 Sleep**

### **1.5.1 Sleep and circadian rhythms**

Sleep is a highly complex series of physiological and behavioural states and shows specific patterns of neurological activity (Foster & Wulff, 2005). Sleep consists of 70-90 minute cycles beginning with stages 1-4 of non-rapid eye movement (non-REM), followed by a rapid eye movement (REM) sleep stage (Foster & Wulff, 2005).

Sleep is regulated by an interaction between a homeostatic system and a circadian system. The homeostatic system represents a wake-dependent build-up of sleep pressure, which increases during wakefulness and is alleviated with sleep (Borbely & Achermann, 1999; Dijk & von Schantz, 2005). The homeostatic system therefore maintains the duration and intensity of sleep (Wulff, Porcheret, Cussans, & Foster, 2009). On the other hand, the circadian system generates an approximately 24-hour rhythm of wakefulness and sleep propensity. The circadian system also determines the timing of sleep as well as other biological rhythms, including those affecting melatonin levels (Arendt, 1997), cortisol levels (Weitzman, Boyar, Kapen, & Hellman, 1975), body temperature (Waterhouse, et al., 2005), mental performance (McNair, Lorr, & Droppleman, 1971), and mood (Boivin, et al., 1997).

Circadian rhythm is coordinated by suprachiasmatic nuclei within the anterior hypothalamus that show endogenous rhythmicity (R. Y. Moore & Silver, 1998; Schwartz, 1991). However, intrinsic circadian rhythm in humans is slightly longer than 24 hours, and environmental zeitgebers (time cues), such as the light-dark cycle,

and social zeitgebers (e.g. interaction with other family members, weekends, and shift work) are involved in entrainment to a 24-hour cycle (Duffy & Czeisler, 2009).

## **1.5.2 Sleep and circadian rhythm disruption in bipolar disorder**

### ***1.5.2.1 Sleep and circadian rhythm disruption***

Sleep disturbance is associated with impaired quality of life, which results in negative effects in psychosocial, occupational, and health areas (Ancoli-Israel & Roth, 1999). Evidence of sleep disruption in bipolar disorder comes from studies of sleep and circadian rhythms during mood episodes and euthymia, studies assessing the effects of sleep deprivation, and the effectiveness of psychosocial therapy (Harvey, Schmidt, Scarna, Semler, & Goodwin, 2005), which will be discussed in the following sections.

### ***1.5.2.2 Evidence of disrupted sleep and circadian rhythms during mood episodes and euthymia***

Abnormal sleep-wake patterns and disrupted circadian rhythms are frequently recorded in psychiatric disorders, including bipolar disorder, schizophrenia, anxiety disorders, and seasonal affective disorder (Wulff, Gatti, Wettstein, & Foster, 2010; Wulff, et al., 2009). Sleep disruption is an intrinsic clinical feature of all phases of bipolar disorder, with patients experiencing insomnia or hypersomnia during depressive episodes and reduced need for sleep during (hypo-) manic episodes. For example, a recent review by Harvey (2008) found that 23% - 78% of depressed patients had experienced hypersomnia, 58% - 60% of depressed patients had experienced difficulty falling asleep, and 69% - 99% of manic patients had experienced reduced need for sleep. Furthermore, sleep disturbance or circadian

instability are seen in approximately two thirds of bipolar patients between episodes (Harvey, et al., 2005), with euthymic bipolar patients showing reduced daytime activity (Harvey, et al., 2005) and greater fragmentation of sleep-wake rhythm and reduced inter-daily stability (Jones, Hare, & Evershed, 2005). However, many studies that recorded sleep and circadian rhythm disruption in euthymic bipolar patients have been subject to medication confounds. This has been addressed by a recent study in medication-naïve euthymic bipolar subjects which recorded reduced inter-daily stability and reduced relative amplitude (driven by increased activity during least active five hours of sleep) (Chandler, Wulff, Foster, & Goodwin, 2008). Meanwhile, it is still not known whether such an effect is dependent on experience of serious illness episodes or if it may represent a vulnerability marker associated with the bipolar phenotype.

#### ***1.5.2.3 Effects of sleep deprivation***

Further support for the involvement of sleep disruption in mood episodes in bipolar disorder comes from studies assessing sleep deprivation in the treatment of the disorder. For example, experimentally-induced sleep deprivation has been found to induce (hypo-) mania in bipolar patients (Wu & Bunney, 1990) and to be an effective treatment for bipolar depression (Wirz-Justice & Van den Hoofdakker, 1999).

#### ***1.5.2.4 Effectiveness of psychosocial therapy***

Psychosocial therapies for bipolar disorder were developed in response to findings of disrupted sleep and circadian rhythm and sensitivity to sleep deprivation in bipolar disorder. These therapies, for example social rhythm therapy, focus on maintaining a regular daily routine and consistent sleep-wake patterns, and have been found to be

effective adjuncts to pharmacological treatments for bipolar disorder (Frank, Swartz, & Kupfer, 2000).

### **1.5.3 Investigating sleep and circadian rhythms**

Wrist actigraphy is a non-invasive technique that can be used to monitor rest-activity patterns continuously and to determine characteristics of circadian rhythm. An actometer, e.g. the Actiwatch® (Cambridge Neurotechnology Ltd, UK), is worn like a normal wristwatch and measures movement. Actigraphy relies on piezoelectric sensors to measure acceleration, which can be integrated to generate an output linked to the amplitude of movement. Light levels are recorded in addition to movement. A diary is used to record bedtime, wake time, naps, and other activities, such as showering, during which the Actiwatch® is removed. The diary is additionally important in order to differentiate between sleep and sedentary activities such as reading, which is not possible with the actigraph alone. Furthermore, information from the diary is used to edit the actigraph for periods when the Actiwatch® is not worn. Therefore, in combination with diary records, actigraphy can give a reliable assessment of rest-activity patterns over extended periods of days or weeks.

Questionnaires such as the Morningness-Eveningness questionnaire (Horne & Ostberg, 1976) can be used to assess diurnal (day/night) preference, i.e. “morningness” or “eveningness”. Responses can be used in classification of chronotype, including extreme morning type, moderate morning type, neither type, moderate evening type, and extreme evening type. Higher scores on the Morningness-Eveningness questionnaire are associated with a greater degree of morningness, which is associated with earlier waking and bedtime, whilst eveningness is associated with

later waking and bedtimes. A score of 16-30 represents extreme evening type, 31-41 represents moderate evening type, 42-58 represents neither type, 59-69 represents moderate morning type, and 70-86 represents extreme morning type in student-aged subjects (Horne & Ostberg, 1976). Chronotype determined with the Morningness-Eveningness questionnaire has been found to correlate well with biological measures of circadian rhythm (Duffy, Rimmer, & Czeisler, 2001).

## **1.6 Advantages of studying an at-risk group**

Inconsistencies in the literature regarding the psychological and neural abnormalities in bipolar disorder may have arisen as a consequent of the heterogeneous nature of the study population. Investigation of patients with bipolar disorder is subject to effects of current mood state, for example during mania and depression. Even during euthymia there may be subtle mood effects and, more importantly, medication confounds which are almost inevitable when studying a severe psychiatric disorder. Moreover, there may be great variability in the number and severity of previous illness episodes. Although this may be addressed in part by studying first-episode bipolar disorder, these patients may not in fact be experiencing their first episode owing to frequent misdiagnosis and delayed diagnosis of bipolar disorder (Bowden, 2001).

Studies in at-risk groups enable the investigation of emotional processing, decision-making, and sleep and circadian rhythmicity to take place in the absence of state-dependent mood changes, scar effects of repeated mood episodes, or the effects of medications. A continuum approach is increasingly being applied in the investigation of subclinical psychiatric disorders in the search for vulnerability markers associated with these disorders. For example, never-depressed students with high neuroticism (N), which is a vulnerability marker for major depression, showed negative biases in emotional processing and memory (Chan, et al., 2007). Furthermore, young people at risk for major depression by virtue of having a depressed biological parent showed altered rACC functioning during the emotional counting Stroop, despite an absence of recorded negative biases in emotional processing and memory (Mannie, et al., 2008).

## **1.7 Pharmacological treatment**

### **1.7.1 Pharmacological treatment for bipolar disorder**

Recent advances in psychiatric research, with their emphases on randomised controlled trials and systematic meta-analyses, have resulted in evidence-based guidelines to aid clinicians in the treatment of bipolar disorder (Goodwin, 2009). These guidelines recommend lithium as a first-line maintenance monotherapy because it effectively prevents manic relapse and has shown some efficacy in the prevention of depressive episodes (Geddes, Burgess, Hawton, Jamison, & Goodwin, 2004; Goodwin & Geddes, 2003). Furthermore, lithium administration is associated with reduced risk of suicide (Baldessarini, et al., 2006), which is particularly common in patients with mood disorders (Harris & Barraclough, 1997). However, lithium treatment is limited by its narrow therapeutic range (0.5-1.4mmol/l) and adverse side effects (e.g. weight gain, excessive thirst, and long-term effects on the thyroid and kidney), which require regular blood serum level monitoring and may result in treatment non-adherence (Burgess, et al., 2001). If lithium monotherapy is ineffective or not well tolerated, alternative or adjunctive pharmacological treatments will be implemented, for example mood-stabilising anticonvulsants (valproate, carbamazepine, and lamotrigine) or atypical antipsychotics (quetiapine, olanzapine, and aripiprazole) (Goodwin, 2009).

### **1.7.2 Pharmacology of quetiapine**

Quetiapine was developed as an atypical antipsychotic and shows dual antagonism at dopaminergic D<sub>2</sub> receptors and serotonergic 5-HT<sub>2A</sub> receptors. It is effective in the treatment of bipolar mania (Bowden, et al., 2005; Langosch, et al., 2008; Sajatovic,

Calabrese, & Mullen, 2008) as a result of its antagonism at dopaminergic D<sub>2</sub> receptors (Harrison-Read, 2009) (Gefvert, et al., 2001; Kapur, et al., 2000). Its active metabolite, norquetiapine, adds to the overall pharmacological profile of quetiapine and may contribute to quetiapine's efficacy in the stabilisation of mood from depressive bipolar episodes (Goldstein, Nyberg, & Brecher, 2008). Norquetiapine acts as an antagonist at dopaminergic D<sub>2</sub> receptors and serotonergic 5-HT<sub>2C</sub> receptors, acts as a partial agonist at serotonergic 5-HT<sub>1A</sub> receptors, and blocks the noradrenaline transporter (Goldstein, et al., 2008), thereby acting as a noradrenaline reuptake inhibitor. Together, the actions of quetiapine and norquetiapine on serotonin receptors (increasing serotonin levels) and the noradrenaline reuptake transporter (increasing noradrenaline levels) are thought to be responsible for the mood improvements associated quetiapine administration in bipolar depression (Goldstein, et al., 2008). For example, quetiapine has been shown to be an effective monotherapy in the treatment of bipolar depression (Calabrese, et al., 2005; Endicott, Paulsson, Gustafsson, Schioler, & Hassan, 2008; Endicott, Rajagopalan, Minkwitz, Macfadden, & Group, 2007) and, importantly, does not appear to increase the risk of switching to mania (Thase, 2008). Quetiapine is also recommended as a mood-stabilising maintenance treatment for bipolar disorder owing to its ability to protect against relapse of both manic and depressive symptoms (Goodwin, 2009). Finally, since quetiapine has a low affinity for, and fast dissociation from, D<sub>2</sub> receptors, it has a very low propensity for the extrapyramidal effects that are frequently associated with typical antipsychotics (Kapur & Remington, 2001; Kapur & Seeman, 2000, 2001).

### **1.7.3 Pharmacological research**

#### ***1.7.3.1 Psychopharmacological effects on emotional processing***

To date, psychopharmacological studies of emotional processing have focussed on investigating the effects of antidepressants used to treat unipolar depression. Studies in healthy volunteers have revealed that facial expression identification is affected by administration of antidepressants. Short-term administration of the SSRI citalopram and the NRI reboxetine has been found to increase recognition of happy facial expressions and reduce recognition of negative facial expressions (e.g. anger, fear, and disgust) (Harmer, et al., 2004; Harmer, et al., 2003). Furthermore, antidepressant treatment is associated with facilitated categorisation of, and memory for, positive vs. negative self-referent personality characteristic words (Harmer, et al., 2004; Harmer, et al., 2003). Such findings suggest that the therapeutic effects of antidepressants may be mediated through positive emotional processing biases, which redress the negative biases recoded in depression (Harmer, et al., 2003).

Differential effects on threat processing have been recorded for different classes of antidepressants (SSRIs and NRIs) using the emotion-potentiated startle and the attentional vigilance faces dot-probe as described above. For example, diminished startle responsivity and attentional vigilance to fearful faces was recorded in healthy volunteers receiving citalopram, but not in those receiving reboxetine (Harmer, et al., 2004; Murphy, Yiend, et al., 2009). These findings suggest that citalopram may redress attentional biases towards threatening stimuli, which is consistent with cognitive psychological theories of anxiety (MacLeod, Rutherford, Campbell,

Ebsworthy, & Holker, 2002) and relevant to its clinical use in the treatment of anxiety.

### ***1.7.3.2 Psychopharmacological effects on decision-making***

Psychopharmacological studies of decision-making have shown that the processing of reward-related cues, punishment-related cues, and modulation of non-normative decision-making is influenced by modulation of serotonin and dopamine levels in healthy volunteers. Thus, tryptophan depletion, which lowers serotonin activity (Moore, et al., 2000), reduced attention towards information about possible gains, implying that serotonin may play a role in the processing of reward cues whilst deliberating between risky choices (Rogers, et al., 2003). On the other hand, tryptophan supplementation was associated with modulation of non-normative decision-making (reduced loss aversion) and altered combination of information about small gains and small losses (Murphy, Longhitano, et al., 2009). Together, these findings suggest that serotonin may modulate non-normative features of decision-making and the processing of reward cues during risky choice. On the other hand, reduced dopamine activity was associated with impaired discrimination between large and small possible losses, without diminution of the reflection effect, implying that dopamine may play a role in the processing of punishment cues whilst deliberating between risky choices (Scarna, McTavish, Cowen, Goodwin, & Rogers, 2005).

### ***1.7.3.3 Pharmacological effects on sleep and circadian rhythms***

Pharmacological studies employing actigraphy have shown that antidepressant treatments that improved sleep and circadian rhythmicity also facilitated mood

improvement in depressed patients. This was demonstrated by a recent study comparing the novel antidepressant agomelatine, which acts as an agonist at melatonergic MT<sub>1</sub> and MT<sub>2</sub> receptors and as an antagonist at serotonergic 5-HT<sub>2C</sub> receptors, with a control antidepressant (sertraline) (Kasper, et al., 2010). Agomelatine was associated with greater improvements in circadian relative amplitude, increased sleep efficiency, increased sleep latency, and better mood improvement over six weeks relative to the control antidepressant (Kasper, et al., 2010). Therefore, the ability to redress disrupted sleep and circadian rhythms may represent a key property of pharmacological treatments for mood disorders.

#### ***1.7.3.4 Pharmacological effects of quetiapine***

To date, investigation of the psychopharmacological effects of quetiapine on emotional processing and decision-making in healthy volunteers has been limited. However, quetiapine administration has been found to ameliorate (i) previously impaired recognition of surprised and angry (but not fearful) faces in patients with schizophrenia (three-week administration; mean dose 413.5 ± 165.6 mg per day) (Cabral-Calderin, et al., 2010) and (ii) cognitive dysfunction in early psychosis as assessed by the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) Neurocognitive Battery (R. S. Keefe, et al., 2006) (over 12 weeks; mean dose 506 ± 215 mg per day) (R. S. E. Keefe, et al., 2007). Furthermore, 8-week treatment with quetiapine (200mg – 800mg per day) in patients with schizophrenia was found to improve both social competence and neuropsychological performance assessed by the Social Skills performance Assessment (Patterson, Moscona, McKibbin, Davidson, & Jeste, 2001), the Penn Emotional Acuity Test (Erwin, et al., 1992), the Rey Auditory Learning Test (Rey, 1964), and in terms of verbal fluency.

A single dose (25mg or 100mg) of quetiapine has been found to increase sleep time, sleep efficiency and subjective sleep quality in healthy volunteers, which may relate to its clinical efficacy (Cohrs, et al., 2004). Furthermore, adjunctive quetiapine administration in patients with unipolar or bipolar depression increased duration of non-REM sleep, decreased the total time in REM sleep, whilst not significantly affecting sleep efficiency (Gedge, Lazowski, Murray, Jokic, & Milev, 2010).

## **1.8 Thesis aims and chapter summary**

### **1.8.1 Thesis aims**

This thesis aims to characterise the bipolar phenotype and investigate the behavioural and neural changes in emotional processing and decision-making as well as physiological changes in sleep and circadian rhythmicity that may underlie vulnerability to bipolar disorder. The psychopharmacological effects of the atypical antipsychotic quetiapine were also assessed with the aim of increasing understanding of its psychological mechanisms of action.

### **1.8.2 Chapter summary**

#### ***1.8.2.1 Chapter 2: Characterising high scores on the Mood Disorder Questionnaire and the bipolar phenotype***

Chapter 2 characterised the Mood Disorder Questionnaire (MDQ) and looked in detail at its efficacy as a screening tool for mood disorder including bipolar disorder. The chapter begins with analysis of a cohort of undergraduate students who took part in the University of Oxford Student Stress Survey. Prevalence of bipolar diagnosis, experience of different mood-elevation symptoms, and levels of associated co-morbidity were assessed for three groups that were designated based on MDQ scores: a group screening as probable bipolar (seven or more items plus problems), a group screening as threshold bipolar (seven symptoms alone), and a control group who scored zero on the MDQ.

### ***1.8.2.2 Chapter 3: Emotional processing and the bipolar phenotype***

Chapter 3 is the first experimental chapter and deals with emotional processing in undergraduate students with either high or low scores on the MDQ, i.e. a bipolar phenotype group and a control group. The emotional test battery described previously was completed by participants outside the scanner. A facial expression matching task and an emotional counting Stroop were performed in the scanner with concurrent fMRI to explore the neural correlates of emotional processing in the bipolar phenotype.

### ***1.8.2.3 Chapter 4: Decision-making and the bipolar phenotype***

Chapter 4 explores decision-making and cognitive flexibility in the bipolar phenotype group and the control group described in Chapter 3. A framed risky-choice task and the intra-dimensional/extra-dimensional attentional set-shifting task were completed outside the scanner. A risky decision-making task was performed in the scanner with concurrent fMRI.

### ***1.8.2.4 Chapter 5: Sleep and circadian rhythms and the bipolar phenotype***

Chapter 5 details the use of actigraphy to assess sleep and circadian rhythms in the group of bipolar phenotype students and the group of controls described in Chapter 3.

### ***1.8.2.5 Chapter 6: The effect of quetiapine on emotional processing, decision-making, and sleep and circadian rhythms in healthy volunteers***

Chapter 6 investigates the effects of one-week quetiapine administration in healthy volunteers in a non-imaging study using behavioural assessments optimised in Chapters 3 to 5 in addition to one new task. The emotional test battery (Chapter 3)

and the risky decision-making task (Chapter 4) were completed. Sleep and circadian rhythms were assessed using actigraphy (Chapter 5) for one week pre-drug and for one week during drug administration. An attentional vigilance faces dot-probe was also included in the test battery.

#### ***1.8.2.6 Chapter 7: General discussion***

Chapter 7 presents a general discussion of the outcomes of Chapter 2 to Chapter 6. This chapter includes a summary of findings and their implications as well as a discussion of limitations and possibilities for further work.

## **2 Characterising high scores on the Mood Disorder**

### **Questionnaire and the bipolar phenotype**

#### **2.1 Introduction**

This chapter will investigate undergraduate students who have completed a battery of online questionnaires assessing psychological health as part of the University of Oxford Student Stress Survey. Survey responses were collected to assess experience of mood elevation and co-morbidities that may be common even within subthreshold bipolar disorder (Lewinsohn, et al., 2004).

As part of the Student Stress Survey, participants completed the Mood Disorder Questionnaire (MDQ) (Hirschfeld, et al., 2000b) to screen for previous experience of mood elevation which may be associated with increased likelihood of bipolar diagnosis (Beesdo, et al., 2009; Hirschfeld, et al., 2000b; Lewinsohn, et al., 2003). However, recent research has suggested that (hypo-) manic experience during adolescence is a frequent phenomenon that is characteristic of a common adolescent bipolar phenotype for which conversion to bipolar disorder occurs in only a minority of cases (Tijssen, et al., 2010). The implication of this finding is that there is a relatively common bipolar phenotype in late teenage development (defined by hypomanic experience) that is a risk factor for mood disorder. Moreover, there is scope for a continuum approach in psychological or neurobiological studies so as to include sub-syndromal symptom experience as well as categorical bipolar disorder. Indeed, 'bipolar disorder' defined by clinical interview in a population not seeking help for their psychiatric symptoms may be regarded more as the severe end of the risk continuum than an established life-time condition. This may be the case because

the rates of mood disorder in population samples at age 20-30 appear higher than those recorded later in life (compare (Beesdo, et al., 2009) with (Merikangas, et al., 2007)).

## **2.2 Aim**

The aim of this chapter is to detect symptoms of mood elevation in a student population and to better define a bipolar phenotype common in young people. The hypomanic symptom profiles of students satisfying screening criteria for the probable bipolar syndrome (at least seven mood-elevation symptoms plus problems) and threshold bipolar students (at least seven symptoms alone) were characterised. Furthermore, associated psychological vulnerabilities and prevalence of DSM-IV-TR bipolar disorder (I, II, or NOS) within these groups and a group of controls (zero symptoms) were assessed.

### **2.3 Methods 1: Student Stress Survey**

Questionnaire responses of 1202 students who satisfied criteria for the probable bipolar group (seven or more items plus problems, N=106), the threshold bipolar group (seven or more items alone, N=459), or the asymptomatic control group (scoring zero items, N=637) were analysed. Together with MDQ symptom items, information was collected on neuroticism and depression, family factors, life experiences, substance misuse and gambling, and general health.

#### **2.3.1 Neuroticism and depression**

Eysenck's Personality Questionnaire (Eysenck, Eysenck, & Barrett, 1985) was included as a measure of neuroticism (maximum score = 15). The 12-item General Health Questionnaire (GHQ) (Goldberg, 1992) provided an indication of current psychological distress. GHQ responses were scored using a binary system (0-0-1-1; maximum score = 12); a cut-off of three items was used for GHQ-12 "caseness" (Goldberg & Williams, 1988). When scores on the GHQ exceeded this cut-off, the nine-item Patient Health Questionnaire (PHQ) was used to probe for current depressive episodes (threshold score = 15; maximum score = 27) (Kroenke, Spitzer, & Williams, 2001). Previous history of depression was also assessed.

#### **2.3.2 Family factors**

The Student Stress Survey included questions asking whether the student had had a happy or unhappy family environment whilst growing up, and if the student had any family history of mood disorder, in particular, bipolar disorder.

### **2.3.3 Life experiences**

Students were asked to indicate if they had experienced any significant losses within the last six months or if things had been going “really well”.

### **2.3.4 Substance misuse and gambling**

The CAGE questionnaire (Mayfield, McLeod, & Hall, 1974) for alcohol dependency was included (threshold score = 2; maximum score = 4). The Student Stress Survey also included questions about subjective concern with alcohol and drug use, gambling frequency, and online gambling.

### **2.3.5 General health**

Simple questions about current and past health problems and use of medications were also included.

## 2.4 Methods 2: Interview

In collaboration with Rebecca A Chandler (RAC), participants were recruited and interviewed with the Mini International Neuropsychiatric Interview – Plus (MINI-Plus) (Sheehan, et al., 1998) to screen for DSM-IV-TR diagnoses of bipolar I, II, or not otherwise specified (NOS) and other psychiatric disorders. MINI-Plus administration and diagnosis training was completed by both RAC and PLR and, furthermore, MINI-Plus diagnoses were corroborated by one psychiatrist (Guy M. Goodwin) to minimise differences in classification between raters. Participants were selected based on their responses to the MDQ and reached criteria for the probable bipolar group (seven or more items plus problems, N=21 of which PLR: N=7 and RAC: N=14), the threshold bipolar group (seven or more items alone, N=71 of which PLR: N=22 and RAC: N=49), or the zero symptoms group (N=43 of which PLR: N=17 and RAC: N=26).

The positive predictive value of the MDQ for bipolar diagnosis was calculated for the probable bipolar and threshold bipolar sub-groups using the following equation: Positive predictive value = true positives / (true positives + false positives). A true positive occurred when a participant screened positively on the MDQ and also had a DSM-IV-TR diagnosis of bipolar I, II, or NOS. A false positive occurred when a participant screened positively on the MDQ but did not have a DSM-IV-TR bipolar diagnosis.

## **2.5 Methods 3: Statistical analyses**

All data were analysed with SPSS statistical software (Version 16.0 for Mac, SPSS Inc.) to test for differences between students in the probable bipolar, threshold bipolar, and zero-symptoms groups. Questionnaire scores were analysed using one-way ANOVAs (two-tailed) to test for differences between groups. In the case of a significant main effect of group, post-hoc *t* tests were carried out. Chi-square tests were used to analyse dichotomous data for differences between groups. Chi-square tests were also used to investigate the different MDQ mood-elevation symptoms that had been experienced by the probable bipolar and threshold bipolar groups. A significance threshold of  $p < 0.05$  was used for all analyses.

## 2.6 Results 1: Mood-elevation symptoms in the probable bipolar and threshold bipolar groups

Prevalence of different symptoms of mood elevation is shown for the probable bipolar (at least seven symptoms and endorsement of the co-occurrence and problematic nature of symptoms) and threshold bipolar (at least seven symptoms, but no reported problems) groups in Table 2.1. Total symptom scores were on average only one item higher in the probable bipolar group who endorsed symptom co-occurrence and problems.

**Table 2.1** MDQ symptoms score and prevalence of mood-elevation symptoms.

	Probable bipolar (N=106)	Threshold bipolar (N=459)	Difference	Significance
MDQ symptoms score	9.65 (1.94)	8.48 (1.47)	1.17	$t=6.938, p<0.001$
Frequency of individual symptoms	%	%	Difference (%)	
<b>Marked differences</b>				
Hyper behaviour leading to trouble	<b>81</b>	50	31	$\chi^2=33.182, p<0.001$
Risk-taking behaviour	<b>82</b>	58	24	$\chi^2=21.724, p<0.001$
Irritability leading to shouting	<b>79</b>	56	23	$\chi^2=20.136, p<0.001$
Irresponsible spending	<b>27</b>	7	20	$\chi^2=37.163, p<0.001$
<b>Slight differences</b>				
Racing thoughts	<b>85</b>	73	12	$\chi^2=6.566, p=0.010$
Distractibility	<b>90</b>	80	10	$\chi^2=5.808, p=0.016$
<b>Minor or no differences</b>				
Increased interest in sex	70	64	6	$\chi^2=1.080, p=0.299$
Increased talkativeness	80	75	5	$\chi^2=1.295, p=0.255$
Increased sociability	61	61	0	$\chi^2=0.004, p=0.952$
Increased confidence	84	85	-1	$\chi^2=0.041, p=0.840$
Decreased need for sleep	68	69	-1	$\chi^2=0.074, p=0.785$
Increased energy	85	88	-3	$\chi^2=0.649, p=0.421$
Increased activity	73	<b>83</b>	-10	$\chi^2=5.453, p=0.020$

Values represent mean (SD) for MDQ symptoms score. Cells highlighted in bold represent those frequencies that are significantly higher than expected ( $p<0.05$ ).  $df=563$  for MDQ symptoms score or  $df=1$  for other variables.

A cluster of behavioural symptoms was particularly frequently endorsed in the probable bipolar group who had experienced co-occurring symptoms and problematic

outcomes. The probable bipolar group showed a frequency difference of more than 20% for items capturing hyper behaviour, risk-taking, irritability, and irresponsible spending (Table 2.1). By contrast, core subjective symptoms of mood elevation (e.g. increased energy and activity, decreased need for sleep) were endorsed almost equally often in the two high MDQ sub-groups, with intermediate exceptions of racing thoughts and distractibility.

## 2.7 Results 2: Associated vulnerability

### 2.7.1 Neuroticism and depression

Neuroticism score on the Eysenck Personality Questionnaire (EPQ-N score) was significantly affected by group ( $F(2,1199)=124.772$ ,  $p<0.001$ ) (Table 2.3). Specifically, students in the probable bipolar group ( $9.42 \pm 3.48$ ) had relatively higher EPQ-N scores than those in the threshold bipolar group ( $8.10 \pm 3.54$ ) ( $t=3.497$ ,  $df=563$ ,  $p=0.001$ ). Students in both the probable bipolar group ( $t=11.747$ ,  $df=741$ ,  $p<0.001$ ) and the threshold bipolar group ( $t=13.349$ ,  $df=1094$ ,  $p<0.001$ ) had substantially higher scores than those in the zero-symptoms group ( $5.31 \pm 3.32$ ).

GHQ scores were analysed using a threshold score of 3 out of 12 as an indication of current caseness. Even with this liberal definition, caseness frequency was significantly affected by group ( $\chi^2=56.343$ ,  $df=2$ ,  $p<0.001$ ) (Table 2.3). The probable bipolar group had the highest frequency of students reaching the GHQ threshold (76%, mean score =  $5.65 \pm 3.56$ ), followed by the threshold bipolar group (59%, mean score =  $4.00 \pm 3.16$ ), and the zero-symptoms group (43%, mean score =  $2.98 \pm 3.05$ ).

The frequencies of current and past depressive episodes were estimated by taking PHQ scores over a threshold score of 15 (out of 27). The frequency of occurrence of students scoring above this threshold was significantly different by group for both current PHQ ( $\chi^2=64.082$ ,  $df=2$ ,  $p<0.001$ ) and past PHQ ( $\chi^2=101.212$ ,  $df=2$ ,  $p<0.001$ ) (Table 2.3). The frequencies of students scoring above threshold for current and past PHQ were substantially elevated for the probable bipolar group (32% and 54%

respectively), followed by the threshold bipolar group (10% and 21% respectively) and the zero-symptoms group (4% and 9% respectively). Thus the probable bipolar sample were six times more likely to report a current or past probable DSM-IV episode of depression than the non-bipolar controls and two to three times more likely than the threshold bipolar group.

### **2.7.2 Family factors**

The frequency of not experiencing a ‘usually happy family’ whilst growing up was significantly affected by group ( $\chi^2=19.314$ ,  $df=2$ ,  $p<0.001$ ) (Table 2.3). In particular, the probable bipolar group had the highest frequency of experience of an unhappy family (33%), followed by the threshold bipolar group (25%) and the zero-symptoms group (17%).

The frequency of occurrence of a family history of mood disorder appeared also to be significantly affected by group ( $\chi^2=39.828$ ,  $df=2$ ,  $p<0.001$ ) (Table 2.3). The probable bipolar group had the highest frequency of occurrence of familial depression (55%), followed by the threshold bipolar group (32%), then by the zero-symptoms group (25%). The frequency of occurrence of parental mood disorder followed the same pattern by group ( $\chi^2=11.095$ ,  $df=2$ ,  $p=0.004$ ); the probable bipolar group had the highest rate (31%), followed by the threshold bipolar group (17%) and the zero-symptoms group (16%). The frequency of occurrence of familial bipolar disorder as reported by survey was not significantly affected by group ( $\chi^2=0.244$ ,  $df=2$ ,  $p=0.885$ ) (see Table 2.3, but see below for the contrasting result from the interviewed sample).

### **2.7.3 Life experiences**

The frequency of occurrence of at least one significant loss or disappointment in the last six months was significantly affected by group ( $\chi^2=48.375$ ,  $df=2$ ,  $p<0.001$ ) (Table 2.3). Perhaps unexpectedly, the control group had the highest frequency of occurrence of significant losses (77%), followed by the threshold bipolar group (64%) and the probable bipolar group (47%). The frequency of experience of things going really well was affected reciprocally by group ( $\chi^2=60.438$ ,  $df=2$ ,  $p<0.001$ ). The probable bipolar group had the highest frequency (23%), followed by the threshold bipolar group (9%) and the zero-symptoms group (3%).

### **2.7.4 Substance misuse and gambling**

CAGE scores were analysed using a threshold of 2 out of 4 to identify those students at increased risk of alcohol dependency. Group had a significant effect on the frequency of students scoring above this threshold ( $\chi^2=136.877$ ,  $df=2$ ,  $p<0.001$ ) (Table 2.3). The probable bipolar group had the highest frequency of students scoring above the CAGE threshold (35%), followed by the threshold bipolar group (23%) and by the zero-symptoms group (6%).

The frequency of being concerned by their own alcohol or drug usage followed the same pattern by group ( $\chi^2=41.315$ ,  $df=2$ ,  $p<0.001$ ) (Table 2.3). The probable bipolar group had the highest frequency of occurrence of concern with alcohol or drugs (18%), followed by the threshold bipolar group (9%), then by the zero-symptoms group (3%), i.e. at about 50% the CAGE rates.

The frequency of students who gamble several times a month was low but significantly modulated by group ( $\chi^2=7.201$ ,  $df=2$ ,  $p=0.027$ ) (Table 2.3). Both probable bipolar (6%) and threshold bipolar groups had high frequencies of students who gambled several times a month (7%), compared to the zero-symptoms group (3%).

The frequency of students who had gambled online was significantly affected by group ( $\chi^2=16.613$ ,  $df=2$ ,  $p<0.001$ ) (Table 2.3). The probable bipolar group had the highest frequency (15%), followed by the threshold bipolar group (7%), then by the zero-symptoms group (2%).

### **2.7.5 General health**

The frequency of occurrence of health problems was significantly affected by group ( $\chi^2=33.417$ ,  $df=2$ ,  $p<0.001$ ) (Table 2.3). In particular, the probable bipolar group had the highest frequency of occurrence of health problems (28%), followed by the threshold bipolar group (13%), then by the zero-symptoms group (8%). There was a very low incidence of use of medications such as antidepressants, antipsychotics, and lithium. Group had a significant effect on the frequency of use of such medications ( $\chi^2=16.782$ ,  $df=2$ ,  $p<0.001$ ) (Table 2.3). In particular, the probable bipolar group had the highest frequency of use (6%), followed by the threshold bipolar group (2%) and the zero-symptoms group (0.4%).

**Table 2.3** Student Stress Survey questionnaire scores for the three MDQ groups.

	Probable bipolar (N=106)	Threshold bipolar (N=459)	Zero- symptoms (N=637)	Significance
<b>Neuroticism and depression</b>				
EPQ-N	9.42 (3.48)	8.10 (3.54)	5.31 (3.32)	$F=124.772, p<0.001$
GHQ-12 caseness ( $\geq 3$ )	76	59	43	$\chi^2=56.343, p<0.001$
Current PHQ $\geq 15$	32	10	4	$\chi^2=71.771, p<0.001$
Past PHQ $\geq 15$	54	21	9	$\chi^2=104.613, p<0.001$
<b>Family factors</b>				
Unhappy family	33	25	17	$\chi^2=17.538, p<0.001$
Familial mood disorder	56	32	25	$\chi^2=42.542, p<0.001$
Parental depression	31	17	16	$\chi^2=10.396, p=0.006$
Familial bipolar disorder	16	19	18	$\chi^2=0.635, p=0.728$
<b>Life experiences</b>				
Significant losses	47	64	77	$\chi^2=46.616, p<0.001$
Things going really well	23	9	3	$\chi^2=60.239, p<0.001$
<b>Substance misuse/gambling</b>				
CAGE $\geq 2$	34	22	6	$\chi^2=90.110, p<0.001$
Concerned about alcohol/drugs	18	9	3	$\chi^2=42.881, p<0.001$
Gambles several times a month	6	7	3	$\chi^2=7.020, p=0.030$
Gambles online	13	8	2	$\chi^2=17.340, p<0.001$
<b>General health</b>				
Health problems	28	14	8	$\chi^2=36.596, p<0.001$
Medications	6	2	0.4	$\chi^2=16.782, p<0.001$

Values represent means (standard deviations) for EPQ-N and % for other variables.  $df=2,1199$  for EPQ-N or  $df=2$  for other variables. Ns are reduced to 80, 345 & 499 for current PHQ, past PHQ, medications, parental depression, and to 48, 217, 318 for gambles several times a month or gambles online as these were added to the survey in 2005 and 2006 respectively.

## 2.8 Results 3: Interview data (positive predictive value in collaboration with Rebecca A Chandler)

Demographic characteristics and results of a psychiatric interview with the MINI-Plus are shown in **Table 2.5**.

**Table 2.5** Interview sample: prevalence of DSM-IV-TR bipolar diagnosis, co-morbidities, and family history of mood disorder.

Number (%) in sample	Probable bipolar (N=21)	Threshold bipolar (N=71)	Zero-symptoms (N=43)	Significance
DSM-IV-TR bipolar I, II, NOS	13 (62)	24 (34)	0 (0)	$\chi^2=30.255, p<0.001$
DSM-IV-TR bipolar I	1 (5)	0 (0)	0 (0)	$\chi^2=5.469, p=0.065$
DSM-IV-TR bipolar II	8 (38)	12 (17)	0 (0)	$\chi^2=16.742, p<0.001$
DSM-IV-TR bipolar NOS	4 (19)	12 (17)	0 (0)	$\chi^2=8.555, p=0.014$
DSM-IV-TR unipolar depression	1 (5)	5 (7)	3 (7)	$\chi^2=0.145, p=0.930$
DSM-IV anxiety co-morbidity	7 (33)	9 (13)	0 (0)	$\chi^2=15.103, p=0.001$
DSM-IV bulimia nervosa	1 (5)	2 (3)	0 (0)	$\chi^2=1.716, p=0.424$
DSM-IV alcohol dependence/abuse	1 (5)	7(10)	1 (2)	$\chi^2=2.588, p=0.274$
DSM-IV substance dependence/abuse	2 (10)	1 (1)	0 (0)	$\chi^2=6.346, p=0.042$
Family history of mood disorder	15 (75)	11 (17)	4 (10)	$\chi^2=29.154, p<0.001$
Family history of bipolar disorder	4 (20)	1 (1)	0 (0)	$\chi^2=17.538, p<0.001$

Anxiety co-morbidities include generalised anxiety disorder, specific phobia, obsessive-compulsive disorder, social phobia, agoraphobia, and panic disorder.  $df=2$  for all Chi-square analyses. <sup>a</sup> Probable bipolar: N=20; threshold bipolar: N=65; zero-symptoms: N=40.

These interviews revealed a generally good agreement between interview and questionnaire estimates of bipolar experience. Thus, there were no bipolar diagnoses in the zero-symptoms group, confirming that the specificity of the MDQ is optimal for controls. As expected, a score of seven symptoms on the MDQ, i.e. a high MDQ score, predicted an increased rate of DSM-IV-TR bipolar diagnosis (bipolar I, II, NOS) at interview. In the probable bipolar group, the prevalence of bipolar diagnosis was 62% and in the threshold bipolar group the rate was 34%. These figures, if representative, translate into a total sample prevalence of 8.8% for all bipolar

diagnoses, of whom approximately half will have bipolar II disorder. Direct interview produced more plausible estimates of family history of mood or bipolar disorder than is possible in a questionnaire and showed much higher rates in the probable bipolar sample.

## **2.9 Discussion and conclusion**

### **2.9.1 Summary of findings**

The MDQ showed a high positive predictive value for DSM-IV-TR bipolar diagnosis when used with full validated screening criteria in the probable bipolar group (seven or more items plus problems) (62%) and a moderate positive predictive value when used with threshold bipolar criteria (seven items alone) (34%). No students in the zero-symptoms group had a bipolar diagnosis.

There was a cluster of behavioural mood-elevation symptoms that occurred particularly frequently in the probable bipolar group and which were therefore associated with endorsement of the co-occurrence and problematic nature of symptoms. These mood-elevation symptoms included hyper behaviour, risk-taking, irritability, and irresponsible spending. The probable bipolar group had a very high degree of associated vulnerability, including high levels of neuroticism, feeling of depression, family history of mood disorder, substance misuse and gambling, and general health problems. The threshold bipolar group shared these associated vulnerabilities, but to a lesser extent.

### **2.9.2 Discussion of results**

This study confirmed high rates of bipolar experience in the student sample. From the 2591 respondents to the online Student Stress Survey, there were 565 (22%) who scored at least seven mood-elevation symptoms on the self-report MDQ and were in the high MDQ group. Within the high MDQ group, there were high rates of bipolar experience in both the probable bipolar and threshold bipolar sub-groups. Probable

bipolar criteria on the MDQ gave a high positive predictive value (62%) for DSM-IV-TR bipolar diagnosis. Furthermore, there was still a moderate positive predictive value when the MDQ was used with threshold bipolar criteria (34%), indicating that the MDQ may be a useful screening tool for bipolar disorder even when used with threshold bipolar criteria. Although the use of less stringent screening criteria will naturally result in a higher false positive rate, screening for both probable bipolar and threshold bipolar subjects may be invaluable in identifying bipolar phenotype subjects who form part of a continuum of vulnerability for bipolar disorder and who might otherwise be missed.

Behavioural items such as hyper behaviour, risk-taking, irritability leading to shouting, and irresponsible spending were more common in those students endorsing additional MDQ items that indicated co-occurring symptoms and symptom-related problems (described here as the probable bipolar group). On the other hand, core subjective symptoms of mood elevation were equally common in the two high MDQ sub-groups (probable bipolar and threshold bipolar groups). The absence of a significant difference in core symptoms (increased activity, energy, confidence, sociability, talkativeness, interest in sex, and decreased need for sleep) is compatible with a continuum of mood-elevation experience in this young population and confirms the existence of a common bipolar phenotype in late adolescence that can be readily identified either by interview or by on line self-report (as here).

Co-morbidity also offers important support for the conclusion that the phenotype may be properly regarded as bipolar. In general, co-morbidity was elevated in both high MDQ sub-groups (probable bipolar and threshold bipolar) compared with

asymptomatic controls. However, there were higher levels of co-morbidity in the probable bipolar group than the threshold bipolar group. This was true for neuroticism (Eysenck, et al., 1985) and caseness on the General Health Questionnaire (Goldberg, 1992), which are associated with vulnerability for depression. Consistent with this, high-scoring students were more likely to have had a depressive episode, as assessed with the Patient Health Questionnaire (Kroenke, et al., 2001). Furthermore, scores of two or more items on the CAGE questionnaire, which have been shown predict alcoholism (sensitivity = 81%, specificity = 89%; psychiatric sample) (Mayfield, et al., 1974), behaved similarly, as did more frequent gambling behaviour. Perhaps more surprisingly, this pattern was also seen for reports of physical health problems. An association between general medical conditions and established bipolar I disorder is well accepted (Perron, et al., 2009), but the present association may imply common mechanisms of vulnerability acting much earlier in life and in apparently milder conditions. One possibility may be via immune mechanisms, which have attracted speculation previously in this context (McEwen, 2003; Spurrell & Creed, 1993).

For the bipolar phenotype groups, there was an increased incidence of perception of things going really well and decreased incidence of significant losses in the last six months. However, it remained unknown whether these differences may have been associated with positive interpretative biases; this was therefore investigated in the next chapter.

If, as the self-report data suggest, mood-elevation experience is both relatively common and on a continuum of severity, the cut applied by DSM-IV-TR to diagnose bipolar II disorder may be rather arbitrary. Indeed, this study provided evidence that it

may be more valuable to consider bipolar disorder as a spectrum and to study bipolar phenotype subjects. This is particularly the case with adolescent subjects since it is clear that, apart from methodological uncertainties related to interviewing/self-report, mood-elevation symptoms (and presumably DSM-IV-TR diagnoses) may not persist in this age group when sampled repeatedly (Tijssen, et al., 2010).

### **2.9.3 Limitations**

Firstly, surveys have limitations and this is illustrated by the failure to distinguish increased rates of familial mood disorder; all groups endorsed this item at rather high rates. This is entirely contrary to expectations based on strong evidence for a genetic component of bipolar disorder (Angst, Frey, Lohmeyer, & Zerbin-Rudin, 1980; Craddock & Jones, 1999; F. K. Goodwin & Jamison, 1990). Indeed the estimates of family history of bipolar disorder obtained at interview in this sample were more plausible.

Secondly, a more fundamental question is the extent to which endorsement of symptoms of mood elevation is a real measure of psychopathology. However, the comorbidity with anxiety, depression, alcohol misuse, gambling and physical illness all echo the established illness phenotype in bipolar disorder (Kessler, et al., 2007) and suggest that a valid cluster of psychopathology is associated with the experience of mood elevation. Furthermore, there was a gradient of prevalence of DSM-IV-TR bipolar diagnosis across the probable bipolar (62%), threshold bipolar (34%), and control (0%) groups.

Finally, direct interview is traditionally treated as a benchmark for diagnosis, but it is also known to be vulnerable to the experience of the interviewer and the instrument employed. For example, this has been found to lead to differences in rates of bipolar diagnosis in the same sample (Regeer, et al., 2004). In any case, the extrapolated rate of disorder in the whole sample is around 4.5% for bipolar II diagnosis, and directly interviewed teenage population samples may give comparable rates. For example, in the German Early Developmental Stages of Psychopathology (EDSP) study, the estimated cumulative incidences of mutually exclusive mood disorder categories up to age 33 was 4.0% for bipolar disorder (major depression plus mania or hypomania), 1.5% for unipolar mania, and 3.6% for unipolar hypomania (Beesdo, et al., 2009).

#### **2.9.4 Conclusion**

In conclusion, these findings support the hypothesis that symptoms of mood-elevation are a common adolescent phenomenon. The MDQ is a valuable screening tool for the bipolar phenotype when used with either full or threshold bipolar criteria. This is supported by symptom profiles determined at interview and also gradients of increased risk of co-morbidity for neuroticism, substance misuse, and even poor physical health across probable bipolar, threshold bipolar, and zero symptoms groups. The transition to more severe disorder remains poorly understood and is an important target for future study. However, the bipolar phenotype is an easily identified risk factor for mood disorder which is of potential interest in understanding psychopathology, treatment, and prevention.

**Chapters 3, 4, and 5** will investigate emotional processing, decision-making, and sleep and circadian rhythms in bipolar phenotype subjects who have experienced

seven or more MDQ items with or without problems (i.e. both probable bipolar and threshold bipolar subjects). Given that the bipolar phenotype shares common features with bipolar disorder, the approach of studying bipolar phenotype subjects will be used to investigate psychological (emotional processing and decision-making) and physiological (sleep and circadian rhythm) factors relevant to bipolar disorder.

## 3 Emotional processing and the bipolar phenotype

### 3.1 Introduction

In **Chapter 2**, the Mood Disorder Questionnaire (MDQ) (Hirschfeld, et al., 2000b) was used with full probable bipolar criteria (seven items plus problems) and threshold bipolar criteria (seven items alone) to identify high-scoring students with experience of mood elevation. Results from **Chapter 2** revealed that the MDQ is a useful screening tool for bipolar disorder, even when used with less stringent threshold bipolar criteria. Specifically, the threshold bipolar group had a moderate prevalence of bipolar diagnosis and intermediate levels of associated vulnerability compared to the probable bipolar (full criteria) group. These findings provide evidence in support of a continuum approach to bipolar disorder and emphasise the need for further study of the bipolar phenotype.

**Chapter 2** reported that the bipolar phenotype, including probable bipolar and threshold bipolar groups, is associated with increased levels of neuroticism and depression in addition to the mood-elevation symptoms that were identified during screening with the MDQ. Therefore, this chapter investigates emotional processing in undergraduate students scoring highly on the MDQ, who satisfied full or threshold bipolar criteria and therefore formed part of the bipolar phenotype. A battery of behavioural tasks, including facial expression recognition, emotional categorisation, emotional memory, emotion-potentiated startle, and an attentional vigilance word dot-probe, was used to investigate emotional processing in bipolar phenotype participants and controls. Furthermore, a facial expression matching task and an emotional

counting Stroop task were completed in the scanner with concurrent fMRI to investigate the neural activity associated with emotional processing in these groups.

### 3.2 Aim

This chapter investigates emotional processing in a group of medication-naïve and previously undiagnosed high MDQ students with the aim of uncovering putative vulnerability markers associated with the bipolar phenotype. Biases in emotional processing and their neural substrates were assessed using a battery of tasks previously found to be sensitive to depression, vulnerability for depression, and antidepressant drug action (Harmer, et al., 2004). Since bipolar phenotype participants were recruited on the basis of mood-elevation experience, it was hypothesised that these subjects would show positive biases in emotional processing. In addition to predictions about biased emotional processing, it was hypothesised that altered neural activity would be recorded in bipolar phenotype participants in key brain regions involved in emotional processing and regulation (as described under Mood dysregulation in bipolar disorder in **Chapter 1**). Therefore, it was postulated that positive biases in emotional processing would be associated with diminished neural responses to negatively-valenced stimuli in brain regions that constitute the ventral system, which is involved in encoding the salience of emotional information, for example the amygdalae and rostral anterior cingulate cortex (rACC). Furthermore, positive biases may also be associated with increased neural responses to negatively-valenced stimuli in brain regions that form part of the dorsal system, which is involved in emotion regulation, for example the dorsolateral prefrontal cortex (DLPFC).

### **3.3 Methods 1: Participant characteristics**

#### **3.3.1 Participants for behavioural tasks**

Participants were recruited through the University of Oxford Student Stress Survey and had completed the MDQ online. Sixty-two undergraduate students (31 female, 31 male) with either high or low scores on the Mood Disorder Questionnaire (MDQ) (Hirschfeld, et al., 2000b) gave their written informed consent to participate in the study, which was approved by Oxfordshire Research Ethics Committee (REC 05/Q1606/174). Thirty-two participants (17 female, 15 male) were in the bipolar phenotype group by virtue of high scores on the MDQ (mean MDQ score  $\pm$  standard deviation =  $8.8 \pm 1.4$ , range = 7-12). Thirty participants (14 female, 16 male) were in the control group by virtue of low scores on the MDQ (mean MDQ score  $\pm$  standard deviation =  $0.6 \pm 0.9$ , range = 0-3).

#### **3.3.2 Participants for functional imaging tasks (sub-sample)**

A sub-sample of these participants, 44 right-handed participants (22 female, 22 male), also completed the functional imaging tasks. Twenty-two participants (11 female, 11 male) were in the bipolar phenotype group (mean MDQ score  $\pm$  standard deviation =  $8.6 \pm 1.5$ , range = 7-12). Twenty-two participants (11 female, 11 male) were in the control group (mean MDQ score  $\pm$  standard deviation =  $0.6 \pm 0.9$ , range = 0-3). These participants were screened to exclude those with contraindications to MRI examination (e.g. metal in body, claustrophobia).

### **3.3.3 Psychiatric and medical screening**

The Mini International Neuropsychiatric Interview-Plus (MINI-Plus) (Sheehan, et al., 1998) was used to screen participants for current or prior psychiatric disorder, including any history of alcohol or other substance abuse. MINI-Plus criteria were used to identify cases of bipolar I, bipolar II, and bipolar not otherwise specified (NOS). In addition to possible diagnoses of major depression and/or (hypo-) mania, acceptable co-morbidities for bipolar phenotype participants included generalised anxiety disorder (GAD), panic disorder, agoraphobia, social phobia, and specific phobia on the condition that the co-morbidity did not interfere with participation. Control participants were screened to exclude any current or prior psychiatric disorder. Where clinical judgement indicated an absence of functional impairment, participants endorsing sufficient criteria to receive a liberal MINI-Plus alcohol dependence diagnosis were not excluded.

All participants were screened to exclude those with history of significant medical disorder, pregnancy and lactation, current usage of any medication other than contraception, and any history of antidepressant, mood stabiliser, or antipsychotic use.

### **3.3.4 Demographic information**

Verbal IQ and full-scale IQ were assessed using the National Adult Reading Test (NART) (Nelson, 1982) and Wechsler Abbreviated Scale of Intelligence (WASI- vocabulary and matrices sub-scales) (Wechsler, 1999) respectively.

Details of family history of mood disorder, including bipolar disorder, were sought. Participants with a family history of schizophrenia were not included, and control participants were excluded if they had a family history of bipolar disorder.

### **3.3.5 Characterisation of subjective mood and personality characteristics**

To assess mood and personality characteristics, participants were interviewed with the 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) and also completed the following questionnaires: Eysenck Personality Questionnaire-neuroticism sub-scale (EPQ-An) (Eysenck & Eysenck, 1975), State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, & Lushene, 1970), Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), Befindlichkeit Scale of Mood and Energy (BfS) (von Zerssen, Strian, & Schwarz, 1974), Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988), and 100mm Visual Analogue Scales (VAS) for the following variables: happy, sad, irritable, anxious, interested in others, content, and talkative.

## **3.4 Methods 2: Behavioural tasks**

### **3.4.1 The emotional test battery**

The emotional test battery was developed to assess aspects of cognitive processing relevant to depression and anxiety. Tasks from this battery targeted processing of emotional stimuli, memory for emotionally-valenced stimuli, and attentional biases. The emotional test battery included facial expression recognition, emotional categorisation, incidental emotional recall memory, emotional recognition memory, emotion-potentiated startle, and an attentional vigilance word dot-probe.

### **3.4.2 Facial expression recognition**

#### ***3.4.2.1 Stimuli***

Pictures of faces representing six basic emotions (anger, disgust, fear, happiness, sadness, and surprise) were taken from Ekman & Friesen (Ekman & Friesen, 1976). These were morphed between two standard images: 0% (neutral) and 100% (full emotion) in 10% steps. Four examples (drawn from a pool of ten individuals) of each emotion at each intensity (10% to 100%) were presented, giving a total of 240 emotional stimuli. Each of the ten faces was also presented in a neutral expression, giving a total of 250 stimuli presentations.

#### ***3.4.2.2 Procedure***

The facial stimuli were presented on a computer screen (in a random order) for 500 ms and replaced by a blank screen. Participants made their responses by pressing a labelled key (ang, disg, fea, hap, sad, surp, neut) on the keyboard. Each participant

was asked to respond as quickly and accurately as possible. Percentage accuracy, reaction times for correct choices, and misclassifications were recorded in this task. As response tendency may confound accuracy and misclassification data, a signal detection analysis was performed (Green & Swets, 1966; Grier, 1971). This assessed target sensitivity ( $d'$ ; from 0 to 1), which is an index of the perceptual discriminability of target stimuli from noise, and response bias ( $\beta$ ; from -1 to +1), with lower scores indicating a greater tendency to respond regardless of whether a target is present (see Statistical analyses).

### **3.4.3 Emotional categorisation**

#### ***3.4.3.1 Stimuli***

Sixty personality characteristics were selected to be extremely agreeable (e.g. cheerful, honest, optimistic) or disagreeable (e.g. domineering, untidy, hostile) and were taken from Anderson (Anderson, 1968). Personality characteristics were matched in terms of word length and ratings of frequency and meaningfulness.

#### ***3.4.3.2 Procedure***

Personality characteristic stimuli were presented on a computer screen (in a random order) for 500 ms and replaced with a blank screen. Participants were asked to categorise the personality characteristic as likeable or dislikeable by pressing a labelled key (like, dislike) as quickly and accurately as possible. Specifically, they were asked to imagine whether they would be pleased or upset if they heard someone referring to them as possessing the personality characteristic, so that the judgement

was in part self-referent. Percentage accuracy and reaction times for correct identifications were recorded in this task.

### **3.4.4 Emotional memory**

#### ***3.4.4.1 Procedure for recall memory***

Immediately after completion of the emotional categorisation task participants were given two minutes in which to recall and write down as many of the personality characteristics as possible. This task therefore allowed the assessment of incidental memory for positive and negative characteristics. The numbers of positive and negative words recalled were computed allowing calculation of the number of hits and intrusions. The percentage of positive hits/intrusions out of the total number of hits/intrusions was calculated in this task.

#### ***3.4.4.2 Stimuli and procedure for recognition memory***

Following recall assessment, emotional recognition memory was assessed by asking participants to respond with 'familiar' or 'novel' to 60 previously presented targets (30 positive, 30 negative) and 60 matched distractors (30 positive, 30 negative). Stimuli were presented on a computer screen (in a random order) until the participant made a response. Percentage accuracy, reaction times for correct identifications, and false alarms (when the participant responded 'familiar' to a distractor) were recorded in this task. As with facial expression recognition data, signal detection analyses were also carried out with emotional recognition results (see Statistical Analyses).

### **3.4.5 Emotion-potentiated startle**

#### ***3.4.5.1 Stimuli***

Pictures from the International Affective Picture System (Lang, Bradley, & Cuthbert, 1998) were used to elicit positive, neutral, or negative emotions. These stimuli had been rated and selected in order that the positive and negative pictures were similar in terms of arousal ratings, but opposite in valence, whereas the neutral pictures were low on arousal and average on valence (Larson, Ruffalo, Nietert, & Davidson, 2000). Stimuli were presented for 13s (inter-trial interval: mean = 13s, range = 11-15s) on a computer screen. Pictures were presented in two blocks in a fixed pseudo-random order with the constraint that no two pictures of the same type (positive, neutral, negative) were presented successively.

#### ***3.4.5.2 Procedure and recording***

The eye-blink component of the startle response was recorded from the orbicularis oculi using electromyography (EMG; EMG startle response system, San Diego Instruments, San Diego, CA, USA). Acoustic probes were 50-ms, 95-dB bursts of white noise with a nearly instantaneous rise time (generated through the noise generator and amplifier of the EMG startle response system). Probes were delivered binaurally through headphones at 1.5s, 4.5s, or 7.5s after picture onset (Larson, et al., 2000). Within each block of 21 pictures, probes were delivered during five pictures of each trial type (positive, neutral, negative). To limit expectation, two trials per valence per block did not contain startle probes, and three probes per block were given during the inter-trial interval. The task began with an introductory set of nine neutral pictures and nine startle probes (two of which were within the inter-trial

interval). These habituation trials were included to orient participants to the procedure and to reduce inter-participant variability in startle response that was not due to the emotion potentiation.

EMG signals were filtered (low cut-off: 0.5hz; high cut-off: 100Hz), rectified, and smoothed using a 5-ms filter window. Eye-blink reflex magnitudes in microvolts were calculated by subtracting the amount of integrated EMG at reflex onset from the peak amplitude maximum amount of integrated EMG between 20 ms and 120 ms after probe onset. Trials with no perceptible eye-blink reflex were assigned a magnitude of zero and included in the analysis. Eye-blink reflexes with an excessive noise during the 20-ms pre-startle baseline period were excluded.

The raw data were analysed to provide assessment of baseline differences for each of the valence conditions. The data were then  $z$ -transformed within each participant to assess the potentiation effects independently from more general changes in startle amplitude. Immediately after the emotion-potentiated startle task participants were asked to view the pictures again and rate each one for arousal and valence on a ten-point scale.

### **3.4.6 Attentional vigilance word dot-probe**

#### ***3.4.6.1 Stimuli***

Two types of emotional words were used in this task: 60 socially threatening negative words and 60 positive words. Each emotional word was paired with a matched neutral word. Another 60 neutral-neutral word pairs were given as fillers.

### **3.4.6.2 Procedure**

Preceded by a fixation cross (500 ms), a word pair was presented on the screen with one word at the top and the other word at the bottom. The emotional words appeared at the top and bottom position with equal frequency. In the unmasked condition the word pair was presented for 500 ms, whereas in the masked condition the word pair appeared for 14 ms followed by the display (186 ms) of a mask. After that, a probe (one or two stars) appeared in the position of one of the preceding words. Participants were asked to indicate the number of stars by pressing a labelled (1, 2) key on the keyboard. Accuracy and reaction time were recorded. Attentional vigilance reaction times were calculated for both types of emotional word by subtracting the mean reaction time for congruent trials (probe and emotional word appeared in same position) from the reaction time for incongruent trials (probe appeared in position opposite to emotional word) (for correct responses only).

### **3.5 Methods 3: Functional imaging tasks**

#### **3.5.1 Facial expression matching**

##### ***3.5.1.1 Stimuli***

For the emotional blocks, facial stimuli were fearful or happy faces and were derived from a standard set of pictures of facial affect (Matsumoto & Eckman, 1988). For the sensorimotor control blocks, geometric shape stimuli were rectangles that were horizontally or vertically oriented.

##### ***3.5.1.2 Procedure***

Participants completed a perceptual task involving the matching of fearful and happy facial expressions with concurrent fMRI. There were four 30-s blocks of fearful facial expression matching, which alternated with four 30-s blocks of happy facial expression matching, i.e. a block design. Each block consisted of six trials, presented sequentially for 5s. The order of presentation was counterbalanced across participants and between groups. The eight emotional task blocks were preceded by, interleaved with, and followed by nine 30-s blocks of a sensorimotor shape orientation matching task. During the emotional matching task blocks, participants viewed a trio of faces presented in a triangular configuration. Participants selected one of the two bottom faces (probes) that expressed the same emotion as the top (target) face (via an MRI-compatible keypad). During the sensorimotor control task blocks, participants viewed a trio of rectangles presented in a triangular configuration. Participants selected one of the bottom two rectangles that matched the orientation (either vertical or horizontal) of the target shape. Stimuli were presented on a personal computer using E-Prime

(version 1.2, Psychology Software Tools Inc., Pittsburgh, Philadelphia, USA) and projected onto an opaque screen at the foot of the scanner bore, which participants viewed using angled mirrors. Both accuracy and reaction times were recorded by E-Prime.

### **3.5.2 Emotional counting Stroop**

#### ***3.5.2.1 Stimuli***

Word stimuli were drawn from a larger pool used in previous research examining depression and anxiety (Mathews, Mogg, May, & Eysenck, 1989). Words were selected to be neutral (e.g. mileage, molecule), socially threatening (e.g. worthless, inferior), physically threatening (e.g. fatal, accident), or positive (e.g. generous, achievement). Words were matched in terms of word length, frequency, and imageability (see [www.psy.uwa.edu.au/mrcdatabase/uwa\\_mrc.htm](http://www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm)).

#### ***3.5.2.2 Procedure***

Participants performed a modified version of the emotional Stroop called the ‘name the number of words’ task, i.e. an emotional counting Stroop (Whalen, et al., 1998), with concurrent fMRI. Participants completed one run of the task with a total of 160 words being presented across 16 blocks, i.e. a block design. Four 10-word blocks of each stimulus type were presented in a pseudo-random order and interspersed with 20-s blocks of fixation, free of stimulus (no motor response), which acted as baseline. Presentation of the four conditions was counterbalanced across participants and between the two groups. Participants completed ten trials during each presentation block (stimulus presentation = 1500 ms, inter-trial interval = 500 ms). For each trial,

participants viewed between one and four identical copies of the word and were instructed to indicate (via an MRI-compatible keypad) the number of words presented. Stimuli were presented on a personal computer using E-Prime (version 1.2, Psychology Software Tools Inc., Pittsburgh, Philadelphia, USA) and projected onto an opaque screen at the foot of the scanner bore, which participants viewed using angled mirrors. Both accuracy and reaction times were recorded by E-Prime.

### **3.5.3 Image acquisition**

Imaging data for the facial expression matching task and the emotional counting Stroop task were collected using a Siemens Magnetom Trio TIM 3-Tesla scanner located at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR). Functional magnetic resonance imaging (fMRI) consisted of 45  $T_2^*$ -weighted echo-planar image (EPI) slices (repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle =  $87^\circ$ , matrix = 64 x 64, 3mm isotropic voxels) for both tasks. The first two EPI volumes were discarded to avoid  $T_1$  equilibration effects. To facilitate later co-registration of the fMRI data into standard space, a  $T_1$ -weighted structural image was also acquired (TR = 2040 ms, TE = 4.7 ms, flip angle =  $8^\circ$ , matrix = 192 x 192, 1mm isotropic voxels) for each participant.

### **3.5.4 fMRI data analyses**

fMRI data were pre-processed and analysed using freely available software tools within FMRIB's (Oxford Centre for Functional MRI of the Brain) Software Library (FSL, version 4.1.1) (Smith, et al., 2004). Pre-processing included within-subject image realignment (Jenkinson, Bannister, Brady, & Smith, 2002), non-brain removal

(Smith, 2002), and spatial smoothing using a Gaussian kernel (5mm full-width-half-maximum). The time series was high-pass filtered (to a maximum of 0.008Hz).

Analyses of data from individual participants were computed using a general linear model with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). For the facial expression matching task, two explanatory variables were modelled: 'fearful faces' and 'happy faces'. For the emotional counting Stroop task, four explanatory variables were modelled: 'neutral words', 'socially threatening words', 'physically threatening words', and 'positive words'. Socially threatening and physically threatening blocks were combined to generate a 'negative' category. The explanatory variables were modelled by convolving each emotion block with a haemodynamic response function, using a variant of a  $\gamma$  function (i.e. normalisation of the probability density function of the  $\gamma$  function) with a standard deviation of 3s and a mean lag of 6s. In addition, temporal derivatives were included in the model as covariates of no interest to increase statistical sensitivity.

Individual participants' data were combined at a group level using a full mixed-effects analysis (Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). This mixed-effects approach enabled generalisation of the results beyond the sample of participants tested. Characterising between-group differences on task-specific brain activity may be confounded by the possibility that changes in activation are actually produced by shifting baseline rather than by a change in the brain response to the task itself. With this in mind, all comparisons reported here directly contrasted emotion blocks, for example fearful faces vs. happy faces or negative words vs. neutral words, rather than using an underspecified low-level baseline condition. Significant

activations were identified using cluster-based thresholding of statistical images with a height threshold of  $Z > 2.3$  with a spatial extent threshold of  $p < 0.05$ , whole-brain corrected for multiple comparisons at the cluster level. Cluster-based thresholding using Gaussian random field theory (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994) is an alternative to voxel-based correction and may be more sensitive to activation under conditions in which one can assume multiple contiguous activated voxels (Forman, et al., 1995). Brain areas with significant activation were localised using Montreal Neurological Institute (MNI) coordinates. For those regions when a significant group x emotion interaction was identified, percentage blood oxygenation level-dependent (BOLD) signal change for each contrast was calculated in order to identify the profile of the group effect. In the emotional counting Stroop task, BOLD signal change measurements for socially threatening words and physically threatening words were explored separately.

### **3.5.5 Region-of-interest analyses**

#### ***3.5.5.1 Facial expression matching task***

Regions of interest (ROI) were defined a priori based on regions implicated in emotional processing, in particular the facial expression matching task, and found to be disrupted in bipolar disorder (see **Chapter 1**). ROI were defined for each participant for the left and right amygdalae were generated using a robust model-based segmentation/registration tool (Patenaude, Smith, Kennedy, & Jenkinson, 2008) implemented within FSL. Group structural ROI were defined within FSL based on the Harvard-Oxford cortical structural atlas for the left and right fusiform face area (temporal occipital fusiform cortex) (<http://www.fmrib.ox.ac.uk/fsl/>). Mean parameter

estimates for each explanatory variable, for each participant, across the entire ROIs (left and right amygdala and fusiform face area separately), were extracted and converted to percent signal change.

### ***3.5.5.2 Emotional counting Stroop task***

A group structural ROI for the rostral section of the ACC (rACC) was defined within FSL using the Harvard-Oxford cortical structural atlas with a further condition that the y-coordinate was greater than 30 (Bush, Luu, & Posner, 2000). This area was based on a priori findings that the rostral ACC is activated by the emotional counting Stroop task (Whalen, et al., 1998) and has been found to show disorder-specific processing (Britton, et al., 2009; Mitterschiffthaler, et al., 2008). Mean parameter estimates for each explanatory variable, for each participant, across the entire ROI, were extracted and converted to percent BOLD signal change.

## 3.6 Methods 4: Statistical analyses

### 3.6.1 Statistical analyses

Baseline demographic and participant characteristics were analysed using univariate analyses of variance (ANOVA) with group and gender as between-subjects factors. One-sample *t* tests were used for comparisons with a test value. All other measures, including extracted percent BOLD signal change, were analysed using repeated-measures analyses of variance (ANOVAs) with group (bipolar phenotype vs. controls) and gender as between-subjects factors and emotion as the within-subjects factor. Laterality (left, right) was included as a within-subjects factor in repeated-measures analyses of variance for extracted percent BOLD signal change when appropriate. Significant interactions were followed up with univariate ANOVAs with group and gender as fixed factors. All statistical analyses were performed using SPSS (version 16.0 for Mac, SPSS Inc.). A significance threshold of  $p < 0.05$  was used for all analyses.

### 3.6.2 Signal detection analyses

Target sensitivity ( $d'$ ) and response bias ( $\beta$ ) were calculated for facial expression recognition and emotional recognition data according to equations described by Grier (1971):

$$\text{Target sensitivity } (d') = 0.5 + [(y - x)(1 + y - x) / 4y(1 - x)]$$

$$\text{Response bias } (\beta) = [y(1 - y) - x(1 - x)] / [y(1 - y) + x(1 - x)]$$

$x$  = probability of a false alarm

= number of false alarms / number of distractors

$y$  = probability of an accurate response

= number of accurate responses / number of targets

Target sensitivity ( $d'$ ) takes values between 0 and 1, and higher  $d'$  values are associated with better target sensitivity. Response bias ( $\beta$ ) takes values between -1 and +1, and higher  $\beta$  values are associated with a conservative response style, i.e. fewer false alarms.

## 3.7 Results 1: Behavioural tasks

### 3.7.1 Participant characteristics

#### 3.7.1.1 Demographics

The two groups were well matched for age (bipolar phenotype vs. controls: mean  $\pm$  standard deviation = 20.2  $\pm$  1.0 years vs. 20.7  $\pm$  1.6 years), gender, verbal IQ (117.4  $\pm$  5.4 vs. 118.0  $\pm$  4.4), and full-scale IQ (129.3  $\pm$  6.3 vs. 128.4  $\pm$  5.5).

#### 3.7.1.2 Subjective mood and personality characteristics

All participants were euthymic (HAM-D  $\leq$  8 and YMRS  $\leq$  8) during testing, although bipolar phenotype participants had marginally higher depression and mania rating scores (Table 3.1).

**Table 3.1** Subjective mood and personality characteristics of participants who completed behavioural tasks.

	Bipolar phenotype N=32	Control N=30	Significance <i>df</i> =1,58
Mood Disorder Questionnaire	8.8 (1.4)	0.6 (0.9)	-
EPQ neuroticism	8.8 (3.0)	5.4 (2.8)	$F=20.464, p<0.001$
Hamilton Depression Rating Scale	2.9 (2.3)	1.7 (1.8)	$F=4.642, p=0.035$
Young Mania Rating Scale	3.1 (2.7)	1.5 (1.5)	$F=8.654, p=0.005$
Befindlichkeit Scale	25.8 (20.3)	13.3 (12.1)	$F=8.460, p=0.005$
Beck Depression Inventory	7.9 (5.7)	2.9 (4.0)	$F=16.834, p<0.001$
State Anxiety Inventory	18.7 (5.8)	15.4 (3.8)	$F=8.244, p=0.006$
Trait Anxiety Inventory	21.8 (6.2)	16.7 (3.9)	$F=15.262, p<0.001$
State Positive Affect Schedule	31.8 (7.5)	33.2 (4.9)	$F=0.676, p=0.414$
State Negative Affect Schedule	13.7 (2.9)	13.1 (3.6)	$F=0.632, p=0.430$
Trait Positive Affect Schedule	31.8 (5.8)	34.9 (4.3)	$F=6.028, p=0.017$
Trait Negative Affect Schedule	16.1 (4.9)	13.7 (3.0)	$F=5.276, p=0.025$
Visual Analogue Scales:			
Happy	67.9 (16.3)	72.7 (14.5)	$F=1.478, p=0.229$
Sad	24.1 (21.1)	12.1 (11.6)	$F=7.140, p=0.010$
Irritable	28.0 (22.4)	17.5 (15.8)	$F=4.705, p=0.034$
Anxious	29.7 (23.0)	27.4 (21.4)	$F=0.160, p=0.691$
Interested in others	72.2 (17.3)	73.0 (16.9)	$F=0.129, p=0.721$
Content	69.1 (23.3)	78.3 (16.0)	$F=3.505, p=0.066$
Talkative	62.2 (20.4)	64.7 (17.4)	$F=0.262, p=0.611$

Values represent means (standard deviations).

Bipolar phenotype participants had significantly higher trait and state levels of depressive mood and anxiety as well as neuroticism, and lower levels of positive mood and energy (Table 3.1).

### ***3.7.1.3 Bipolar diagnoses and co-morbidities***

Of the bipolar phenotype participants, the following DSM-IV-TR diagnoses were made: 7 bipolar II, 5 bipolar NOS, and 3 major depressive disorder. The following anxiety co-morbidities were present in the bipolar phenotype group: 1 case of generalised anxiety disorder, 2 cases of lifetime panic disorder, and 4 cases of agoraphobia. There were 8 (5) cases of lifetime (current) alcohol dependence in the bipolar phenotype group and 4 (2) cases in the control group; clinical judgement was used to include these participants owing to lack of functional impairment. All main results remained unchanged when those students with a diagnosis of bipolar II or NOS, major depressive disorder, or anxiety or alcohol dependence co-morbidities were excluded.

### ***3.7.1.4 Family history of mood disorder***

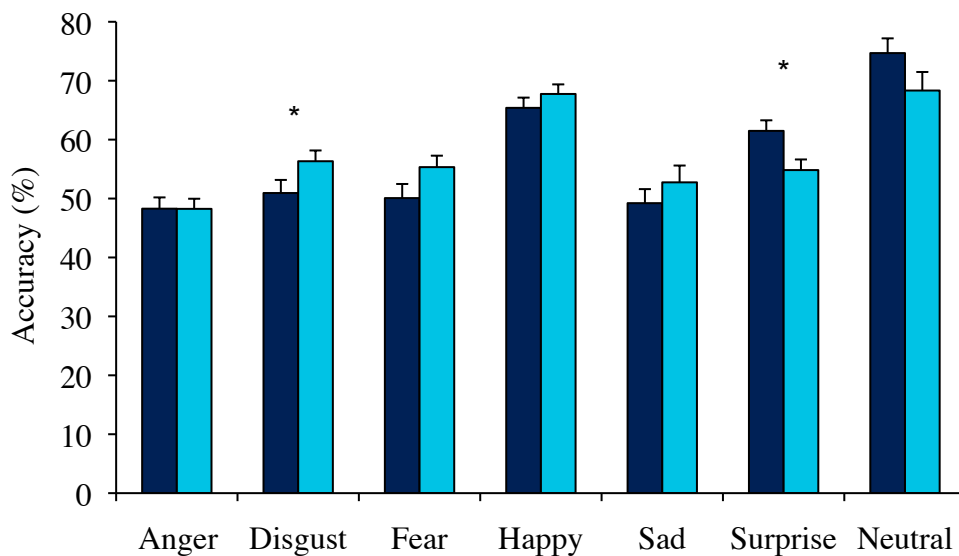
Family history data were missing for eight of the 32 participants in the bipolar phenotype group and eight of the 30 participants in the control group. For bipolar phenotype participants for whom family history data were available, 25% (6 people) endorsed a family history of mood disorder of which 4% (1 person) endorsed a family history of bipolar disorder, 17% (4 people) endorsed a family history of major depressive disorder, and 4% (1 person) endorsed a family history of both depression and anxiety disorder. For control participants, 23% (5 people) endorsed a family

history of mood disorder, all of whom had a family history of major depressive disorder and not bipolar disorder or anxiety disorder.

### 3.7.2 Facial expression recognition

#### 3.7.2.1 Accuracy

There was a significant main effect of emotion ( $F(6,348)=31.714, p<0.001$ ), indicating that percentage accuracy was affected by the emotion of the facial expression being recognised. There was a significant group x emotion interaction ( $F(6,348)=2.889, p=0.009$ ), reflecting differential effects of emotion on accuracy of facial expression recognition across the two groups (Figure 3.1).



**Figure 3.1** Accuracy of facial expression recognition across different emotions for bipolar phenotype group (dark bars) and control group (light bars). Error bars represent standard error of the mean (SEM) (\*  $p<0.05$  for comparison between bipolar phenotype group and controls).

Post-hoc analyses revealed that bipolar phenotype participants were significantly better at recognising surprised faces ( $F(1,58)=6.469, p=0.014$ ) and worse at

recognising disgusted faces ( $F(1,58)=4.196, p=0.045$ ) in the absence of differences in recognition of other basic emotions (all  $p$  values  $> 0.1$ ). There was no group x emotion x gender interaction ( $F(6,348)=0.845, p=0.536$ ). The bipolar phenotype group responded with an average accuracy of  $57.2 \pm 4.7 \%$  and the control group responded with an average accuracy of  $57.7 \pm 5.4 \%$ ; there was no main effect of group ( $F(1,58)=0.556, p=0.459$ ).

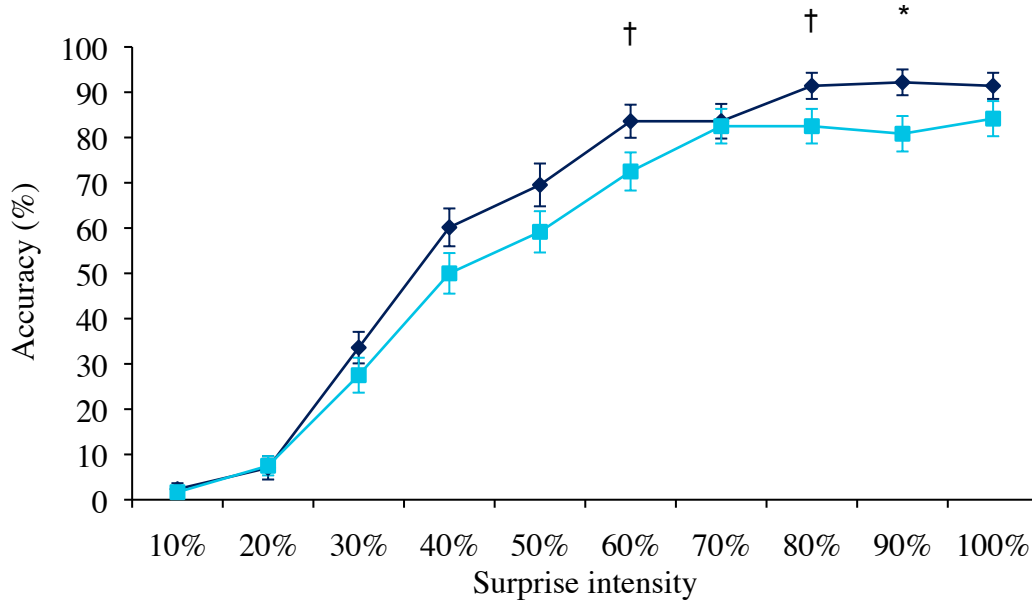
### **3.7.2.2 Reaction time**

There was a significant main effect of emotion ( $F(6,348)=14.087, p<0.001$ ), indicating that reaction time was affected by the emotion of the facial expression being recognised. There was no group x emotion interaction ( $F(6,348)=1.691, p=0.122$ ) or group x emotion x gender interaction ( $F(6,348)=0.393, p=0.884$ ) for reaction time for facial expression recognition. However, exploratory analyses revealed that bipolar phenotype participants were significantly faster to recognise surprised faces than controls ( $F(1,58)=6.137, p=0.016$ ), in the absence of group differences for reaction time to recognise other facial expressions (all  $p$  values  $> 0.1$ ). The bipolar phenotype group responded with an average reaction time of  $1773 \pm 277$  ms and the control group responded with an average reaction time of  $1791 \pm 263$  ms; there was no main effect of group ( $F(1,58)=0.019, p=0.891$ ).

### **3.7.2.3 Accuracy across intensities**

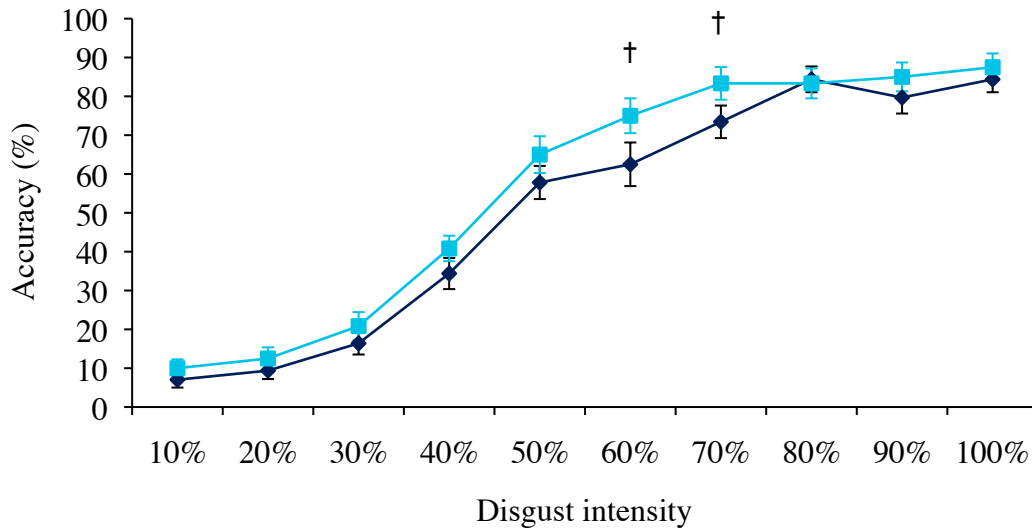
Since bipolar phenotype participants showed significantly better accuracy for the recognition of surprised facial expressions and significantly worse recognition of disgusted facial expression compared to controls, analysis of accuracy across emotional intensities (10% to 100%) was carried out for these emotions. For surprised

facial expressions, bipolar phenotype participants showed significantly better recognition at 90% intensity ( $F(1,58)=5.199, p=0.026$ ), with a trend towards better recognition at 60% intensity ( $F(1,58)=3.702, p=0.059$ ) and at 80% intensity ( $F(1,58)=3.508, p=0.066$ ) (Figure 3.3).



**Figure 3.3** Accuracy of recognition of surprised facial expressions across different intensities for bipolar phenotype group (dark diamonds) and control group (light squares). Error bars represent SEM (\*  $p<0.05$ , †  $p<0.1$  for comparison between bipolar phenotype group and controls).

For disgusted facial expressions, bipolar phenotype participants showed a trend towards worse recognition at 60% intensity ( $F(1,58)=3.887, p=0.054$ ) and at 70% intensity ( $F(1,58)=3.466, p=0.068$ ) (Figure 3.5).



**Figure 3.5** Accuracy of recognition of disgusted facial expressions across different intensities for bipolar phenotype group (dark diamonds) and control group (light squares). Error bars represent SEM (†  $p < 0.1$  for comparison between bipolar phenotype group and controls).

### 3.7.2.4 Misclassifications

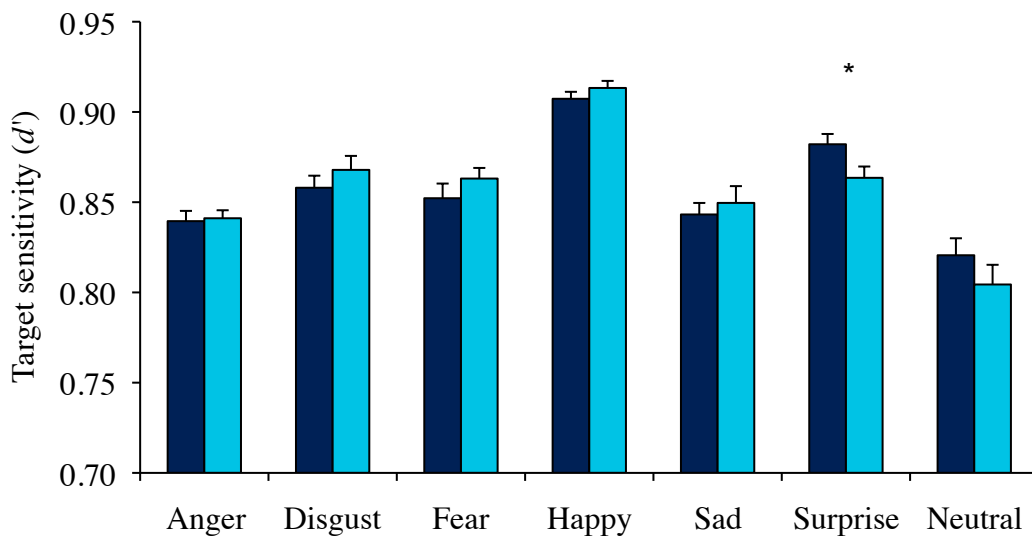
There was a significant main effect of emotion ( $F(6,348)=400.119$ ,  $p < 0.001$ ), indicating that the number of misclassifications was significantly affected by facial expression. Out of a total of 250 trials, only ten facial expressions were neutral. Since lower intensities of emotional faces (e.g. 10% anger, 20% disgust etc.) are hard to discriminate as showing an emotion, both groups showed very high rates of misclassification as neutral, i.e. indicating that the face was neutral when it was in fact a different facial expression. Bipolar phenotype participants made an average of  $66.8 \pm 15.9$  misclassifications as neutral and control participants made an average of  $60.0 \pm 15.8$  misclassifications as neutral from the 250 trials. There was a trend towards a group x emotion interaction ( $F(6,348)=2.048$ ,  $p=0.059$ ), reflecting differential effects of emotion on frequency of misclassification across the two groups. Post-hoc analyses revealed that bipolar phenotype participants showed a trend towards a greater rate of misclassification as neutral ( $F(1,58)=3.037$ ,  $p=0.087$ ) in the absence of other group

differences in misclassification rate for the other individual emotions (all  $p$  values > 0.1). There was no group x emotion x gender interaction ( $F(6,348)=0.968, p=0.447$ ) or main effect of group ( $F(1,58)=1.833, p=0.181$ ).

### 3.7.2.5 Signal detection

#### 3.7.2.5.1 Target sensitivity ( $d'$ )

There was a significant main effect of emotion ( $F(6,348)=45.727, p<0.001$ ), indicating that target sensitivity ( $d'$ ) was affected by the emotion of the facial expression being recognised. There was a trend towards a group x emotion interaction for target sensitivity ( $d'$ ) ( $F(6,348)=1.919, p=0.077$ ), reflecting differential effects of emotion on target sensitivity ( $d'$ ) across the two groups (Figure 3.7).



**Figure 3.7** Target sensitivity ( $d'$ ) across emotions for bipolar phenotype group (dark bars) and control group (light bars). Error bars represent SEM (\*  $p<0.05$  for comparison between bipolar phenotype group and controls).

Post-hoc analyses revealed that the bipolar phenotype group showed significantly better target sensitivity ( $d'$ ) for surprised faces ( $F(1,58)=4.552, p=0.037$ ) compared to controls. There was no group x emotion x gender interaction ( $F(6,348)=1.068, p=0.381$ ) or main effect of group ( $F(1,58)=0.074, p=0.787$ ).

#### 3.7.2.5.2 *Response bias ( $\beta$ )*

There was a significant main effect of emotion ( $F(6,336)=75.587, p<0.001$ ), indicating that response bias ( $\beta$ ) was affected by the emotion of the facial expression being recognised. However, there was no group x emotion interaction ( $F(6,336)=0.986, p=0.434$ ), group x emotion x gender interaction ( $F(6,336)=0.618, p=0.716$ ), or main effect of group ( $F(1,56)=0.018, p=0.894$ ) for response bias ( $\beta$ ).

### 3.7.3 Emotional categorisation

#### 3.7.3.1 *Accuracy*

There was no main effect of word valence ( $F(1,58)=1.539, p=0.220$ ), indicating that the accuracy of categorisation of positive 'likeable' personality characteristics did not differ from that of negative 'dislikeable' personality characteristics. There was no group x word valence interaction ( $F(1,58)=0.032, p=0.858$ ) or group x word valence x gender interaction ( $F(1,58)=0.236, p=0.629$ ) for accuracy of emotional categorisation. Both groups performed this task with high accuracy and there was no main effect of group ( $F(1,58)=1.531, p=0.221$ ). The bipolar phenotype group responded with an average accuracy of  $96.9 \pm 3.1 \%$  and the control group responded with an average accuracy of  $95.0 \pm 7.3 \%$ .

### **3.7.3.2 Reaction time**

There was no main effect of word valence ( $F(1,58)=1.177, p=0.282$ ), indicating that reaction time to categorise positive personality characteristics did not significantly differ from reaction time to categorise negative personality characteristics. There was no group x word valence interaction ( $F(1,58)=0.961, p=0.331$ ) or group x word valence x gender interaction ( $F(1,58)=0.070, p=0.792$ ) for reaction time for emotional categorisation. The bipolar phenotype group responded with an average reaction time of  $1089 \pm 196$  ms and the control group responded with an average reaction time of  $1161 \pm 216$  ms; there was no main effect of group ( $F(1,58)=1.621, p=0.208$ ).

## **3.7.4 Incidental emotional recall memory**

### **3.7.4.1 True recall**

Participants from both groups performed well on this task and there was no main effect of group on the mean number of words correctly recalled ( $F(1,58)=0.310, p=0.580$ ). Bipolar phenotype participants correctly recalled on average  $14.1 \pm 4.2$  personality characteristics and control participants correctly recalled on average  $14.6 \pm 4.5$  personality characteristics. More correctly recalled words were positive than negative for the bipolar phenotype group ( $t(31)=2.430, p=0.021$ ) and there was a trend towards this pattern in the control group ( $t(29)=2.012, p=0.054$ ). Percentage of positive correctly recalled words was not affected by group ( $F(1,58)=0.028, p=0.868$ ) and there was no group x gender interaction ( $F(1,58)=0.200, p=0.657$ ).

### **3.7.4.2 False intrusions**

False intrusions were recorded for only 37 participants (19 bipolar phenotype and 18 controls). There were very few false intrusions and there was no main effect of group on the number of false intrusions ( $F(1,58)=0.358, p=0.552$ ). The bipolar phenotype group recorded on average  $1.0 \pm 1.1$  false intrusions and the control group recorded on average  $1.3 \pm 1.5$  false intrusions. More false intrusions were positive than negative for the bipolar phenotype group ( $t(18)=2.518, p=0.021$ ), but there was no such effect for the control group ( $t(17)=1.651, p=0.117$ ). However, percentage of positive false intrusions was not significantly affected by group ( $F(1,33)=0.354, p=0.556$ ) and there was no group x gender interaction ( $F(1,33)=0.178, p=0.676$ ).

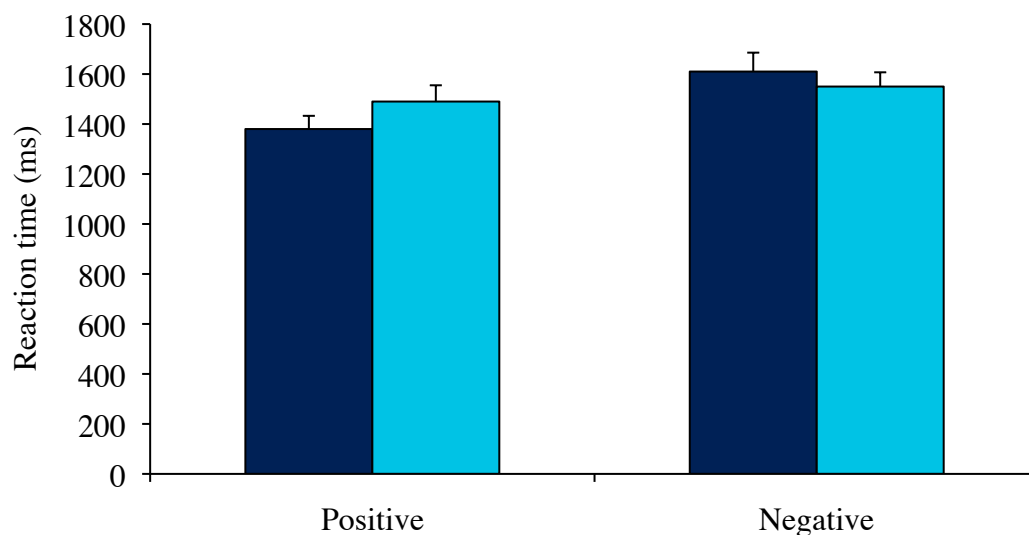
## **3.7.5 Emotional recognition memory**

### **3.7.5.1 Accuracy**

There was a significant main effect of word valence on emotional recognition accuracy ( $F(1,58)=57.439, p<0.001$ ). More positive than negative personality characteristics were correctly recognised by both the bipolar phenotype group ( $t(31)=6.425, p<0.001$ ) and the control group ( $t(29)=4.328, p<0.001$ ). There was no group x word valence interaction ( $F(1,58)=1.034, p=0.314$ ) or group x word valence x gender interaction ( $F(1,58)=1.630, p=0.207$ ). Both groups performed this task with a high accuracy. The bipolar phenotype group responded with an average accuracy of  $85.5 \pm 8.2 \%$  and the control group responded with an average accuracy of  $83.4 \pm 10.2 \%$ ; there was no main effect of group ( $F(1,58)=0.614, p=0.437$ ).

### 3.7.5.2 Reaction time

There was a significant main effect of word valence ( $F(1,58)=17.055, p<0.001$ ), with faster recognition of positive compared to negative personality characteristics. Furthermore, there was a significant group x word valence interaction ( $F(1,58)=6.344, p=0.015$ ), and the bipolar phenotype group showed enhanced recognition speed for positive vs. negative personality characteristics compared to controls (Figure 3.9).



**Figure 3.9** Reaction time to recognise positive and negative personality characteristics for bipolar phenotype group (dark bars) and control group (light bars). Error bars represent SEM.

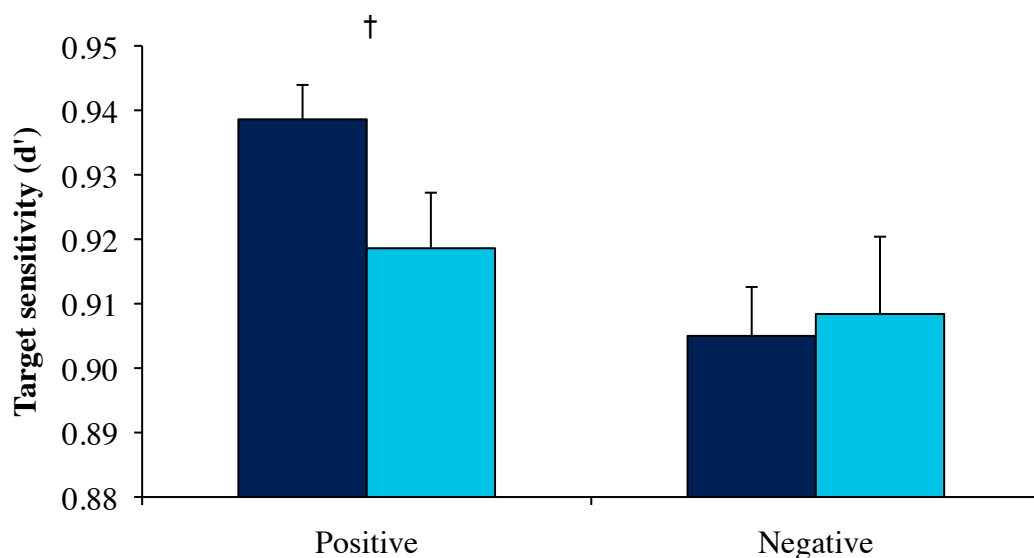
However, post-hoc analyses revealed that there was no group difference in reaction time to recognise positive ( $F(1,58)=1.616, p=0.209$ ) or negative ( $F(1,58)=0.649, p=0.424$ ) personality characteristics. There was no group x word valence x gender interaction ( $F(1,58)=0.150, p=0.700$ ). The bipolar phenotype group responded with an average reaction time of  $1494 \pm 334$  ms and the control group responded with an average reaction time of  $1521 \pm 312$  ms; there was no main effect of group ( $F(1,58)=0.037, p=0.847$ ).

### 3.7.5.3 Signal detection

#### 3.7.5.3.1 Target sensitivity ( $d'$ )

There was a significant main effect of word valence ( $F(1,58)=12.310, p=0.001$ ), with greater target sensitivity ( $d'$ ) to positive than negative personality characteristics.

There was a trend towards a group x word valence interaction for target sensitivity ( $d'$ ) ( $F(1,58)=3.495, p=0.067$ ), and the bipolar phenotype group showed enhanced target sensitivity ( $d'$ ) to positive vs. negative personality characteristics compared to controls (Figure 3.11).



**Figure 3.11** Target sensitivity to positive and negative personality characteristics for bipolar phenotype group (dark bars) and control group (light bars). Error bars represent SEM (†  $p<0.1$  for comparison between bipolar phenotype group and controls).

Post-hoc analyses revealed that bipolar phenotype participants showed a trend towards greater target sensitivity ( $d'$ ) for positive personality characteristics ( $F(1,58)=3.619, p=0.062$ ) in the absence of a group difference for negative

personality characteristics ( $F(1,58)=0.125, p=0.725$ ). There was no group x word valence x gender interaction ( $F(1,58)=0.140, p=0.709$ ) or main effect of group ( $F(1,58)=0.440, p=0.510$ ).

#### *3.7.5.3.2 Response bias ( $\beta$ )*

There was no main effect of word valence ( $F(1,58)=0.098, p=0.756$ ), indicating that response bias ( $\beta$ ) was not affected by the type of personality characteristic being recognised. There was no group x word valence interaction ( $F(1,58)=1.169, p=0.284$ ), group x word valence x gender interaction ( $F(1,58)=0.135, p=0.715$ ), or main effect of group ( $F(1,58)=1.318, p=0.256$ ) for response bias ( $\beta$ ).

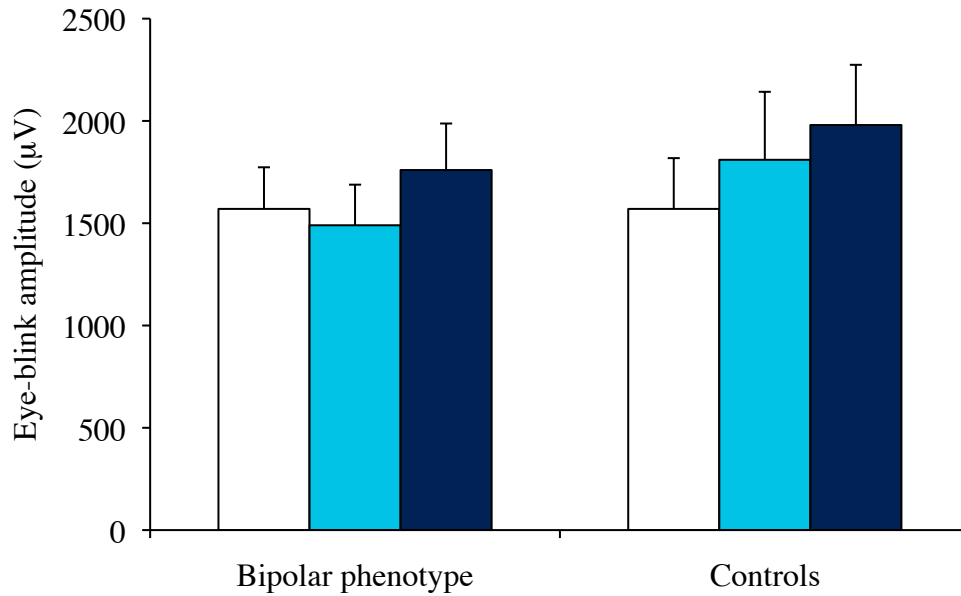
### **3.7.6 Emotion-potentiated startle**

#### *3.7.6.1 Excluded participants*

Of the 32 bipolar phenotype participants, eight were excluded from analysis because of equipment/signal failure or because they displayed a startle response on fewer than 25% of trials. Of the 30 control participants, seven were excluded.

#### *3.7.6.2 Raw startle amplitudes*

Raw startle eye-blink amplitudes were significantly affected by emotion condition (positive, neutral, negative) ( $F(2,86)=8.884, p<0.001$ ), with potentiation of eye-blink responses being shown during negative picture presentation compared with both positive ( $t(46)=4.120, p<0.001$ ) and neutral ( $t(46)=2.916, p=0.005$ ) picture presentation (Figure 3.13).

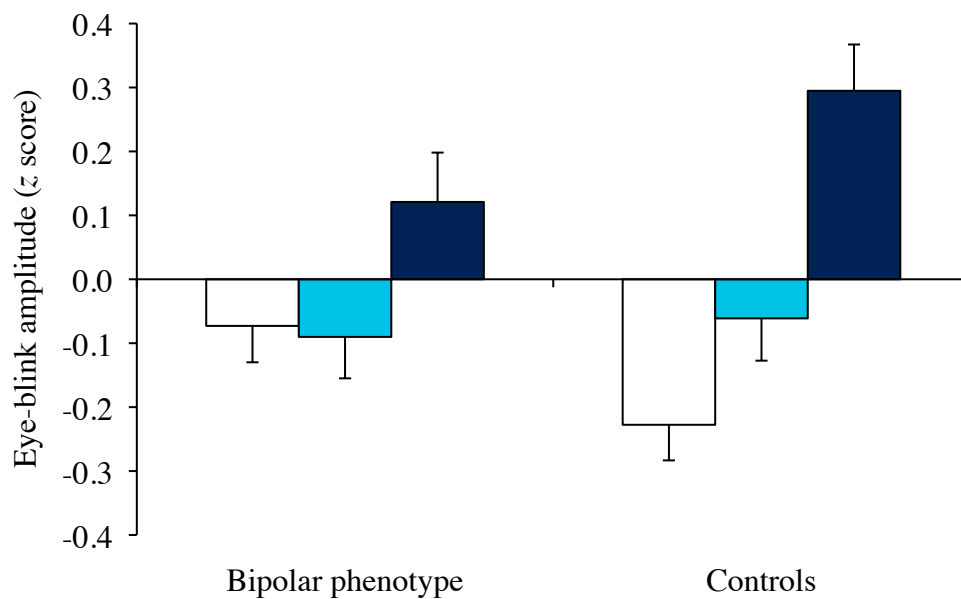


**Figure 3.13** Raw startle eye-blink responses for positive (white), neutral (light), and negative (dark) emotion conditions. Error bars represent SEM.

There was a weak trend towards a group x emotion condition interaction ( $F(2,86)=2.338, p=0.103$ ). Exploratory analyses revealed that the bipolar phenotype group showed attenuated startle responses to the negative and neutral conditions compared to the positive condition ( $F(1,43)=4.718, p=0.035$ ), in the absence of group differences for negative compared to neutral and positive conditions ( $F(1,43)=0.249, p=0.620$ ) or for negative and positive conditions compared to neutral condition ( $F(1,43)=2.330, p=0.134$ ). Meanwhile, there were no group differences in raw startle eye-blink amplitude to positive ( $F(1,43)=0.015, p=0.902$ ), neutral ( $F(1,43)=0.839, p=0.365$ ), or negative ( $F(1,43)=0.500, p=0.483$ ) emotion conditions. There was no group x emotion condition x gender interaction ( $F(2,86)=0.819, p=0.444$ ) or main effect of group ( $F(1,43)=0.393, p=0.534$ ).

### 3.7.6.3 Z-transformed startle data

Z-transformed startle responses were also affected by emotion condition ( $F(2,86)=11.702$ ,  $p<0.001$ ), with potentiation of eye-blink responses being shown during negative picture presentation compared with both positive ( $t(46)=4.380$ ,  $p<0.001$ ) and neutral ( $t(46)=3.142$ ,  $p=0.003$ ) picture presentation (Figure 3.15).



**Figure 3.15** Z-transformed startle eye-blink responses for positive (white), neutral (light), and negative (dark) emotion conditions. Error bars represent SEM.

The group x emotion condition interaction did not appear to be significant ( $F(2,86)=2.089$ ,  $p=0.130$ ), but exploratory analyses revealed that the bipolar phenotype group showed a trend towards enhanced Z-transformed startle responses during the positive condition ( $F(1,43)=3.797$ ,  $p=0.058$ ) and showed significantly attenuated Z-transformed startle responses during negative and neutral conditions ( $F(1,32)=5.296$ ,  $p=0.026$ ). There was no group x emotion condition x gender interaction ( $F(2,86)=1.648$ ,  $p=0.199$ ), or main effect of group ( $F(1,43)=0.464$ ,  $p=0.500$ ).

### **3.7.7 Attentional vigilance word dot-probe**

#### **3.7.7.1 Missing data**

Data from one bipolar phenotype participant were missing for the attentional vigilance word dot-probe task.

#### **3.7.7.2 Attentional vigilance reaction time**

##### *3.7.7.2.1 Unmasked condition*

There was no effect of word valence ( $F(1,57)=0.904$ ,  $p=0.346$ ), indicating that attentional vigilance reaction time did not differ between positive-neutral and negative-neutral words pairs in the unmasked condition. There was no group x word valence interaction ( $F(1,57)=0.063$ ,  $p=0.802$ ), group x word valence x gender interaction ( $F(1,57)=0.031$ ,  $p=0.860$ ), or main effect of group ( $F(1,57)=0.069$ ,  $p=0.793$ ).

##### *3.7.7.2.2 Masked condition*

There was no effect of word valence ( $F(1,57)=0.762$ ,  $p=0.387$ ), indicating that attentional vigilance reaction time did not differ between positive-neutral and negative-neutral words pairs in the masked condition. There was no group x word valence interaction ( $F(1,57)=0.389$ ,  $p=0.536$ ), group x word valence x gender interaction ( $F(1,57)=2.277$ ,  $p=0.137$ ), or main effect of group ( $F(1,57)=0.017$ ,  $p=0.896$ ).

There was no group x word valence x masking interaction ( $F(1,57)=0.372, p=0.544$ ) or group x word valence x masking x gender interaction ( $F(1,57)=1.432, p=0.236$ ).

### **3.7.8 Exclusion of participants with a bipolar diagnosis**

To assess whether group differences may have been related to bipolar diagnosis, analyses were performed excluding seven participants with a diagnosis of bipolar II and five participants with a diagnosis of bipolar NOS.

For the facial expression recognition task, the group x emotion interaction remained significant for accuracy of recognition ( $F(6,276)=2.801, p=0.012$ ). However, there was also a trend for a group x emotion interaction for reaction time ( $F(6,276)=2.094, p=0.054$ ). As before, the bipolar phenotype group showed a trend towards increased accuracy of recognition for surprised faces ( $F(1,46)=3.889, p=0.055$ ) and significantly reduced accuracy of recognition of disgusted faces ( $F(1,46)=6.948, p=0.011$ ). However, bipolar phenotype participants also showed significantly reduced accuracy of recognition for fearful faces ( $F(1,46)=6.971, p=0.011$ ). As before, bipolar phenotype participants showed significantly faster recognition of surprised faces ( $F(1,46)=4.976, p=0.031$ ). However, the bipolar phenotype group also showed a trend towards slower recognition of disgusted faces ( $F(1,46)=3.564, p=0.065$ ). The group x emotion interaction for target sensitivity ( $d'$ ) no longer reached significance ( $F(6,276)=1.438, p=0.200$ ).

The group x emotion interaction for emotional recognition reaction time remained significant ( $F(1,46)=4.075, p=0.049$ ).

There was no longer a trend towards a group x emotion interaction for startle amplitude (raw:  $F(2,68)=2.127$ ,  $p=0.127$ ; Z-transformed:  $F(2,68)=0.915$ ,  $p=0.406$ ), which may be accounted for reduced statistical power as a result of N=15 in the bipolar phenotype group and N=23 in the control group.

## 3.8 Results 2: Functional imaging tasks

### 3.8.1 Participant characteristics

#### 3.8.1.1 Demographics

The sub-sample of participants that completed the functional imaging tasks were also well matched for age ( $20.2 \pm 1.0$  vs.  $20.6 \pm 1.4$  years), gender, verbal IQ ( $118.6 \pm 4.3$  vs.  $119.3 \pm 3.5$ ), and full-scale IQ ( $131.0 \pm 6.0$  vs.  $130.2 \pm 4.2$ ) across the two groups.

**Table 3.3** Subjective mood and personality characteristics of sub-sample of participants who completed functional imaging tasks.

	Bipolar phenotype N=22	Control N=22	Significance <i>df</i> =1,40
Mood Disorder Questionnaire	8.6 (1.5)	0.6 (0.9)	-
EPQ neuroticism	8.3 (3.2)	5.2 (2.9)	$F=10.743, p=0.002$
Hamilton Depression Rating Scale	2.4 (2.4)	1.9 (1.8)	$F=0.707, p=0.405$
Young Mania Rating Scale	3.4 (2.9)	1.3 (1.4)	$F=9.934, p=0.003$
Befindlichkeit Scale	26.6 (23.3)	10.1 (7.9)	$F=9.537, p=0.004$
Beck Depression Inventory	7.7 (6.1)	2.3 (3.0)	$F=14.077, p=0.001$
State Anxiety Inventory	19.6 (6.1)	15.1 (4.2)	$F=8.269, p=0.006$
Trait Anxiety Inventory	21.1 (6.2)	16.2 (3.6)	$F=10.177, p=0.003$
State Positive Affect Schedule	32.0 (8.5)	34.1 (4.9)	$F=0.927, p=0.341$
State Negative Affect Schedule	13.8 (3.1)	12.9 (3.5)	$F=0.717, p=0.402$
Trait Positive Affect Schedule	31.9 (6.1)	35.1 (4.2)	$F=4.096, p=0.050$
Trait Negative Affect Schedule	16.0 (5.0)	13.7 (2.9)	$F=3.345, p=0.075$
Visual Analogue Scales:			
Happy	69.0 (17.0)	74.6 (15.0)	$F=1.453, p=0.235$
Sad	23.1 (22.0)	12.0 (11.7)	$F=4.236, p=0.046$
Irritable	31.2 (24.4)	15.9 (13.5)	$F=6.425, p=0.015$
Anxious	24.7 (21.9)	23.9 (18.8)	$F=0.017, p=0.897$
Interested in others	72.2 (18.5)	75.9 (17.8)	$F=0.479, p=0.493$
Content	72.6 (24.1)	79.4 (17.1)	$F=1.159, p=0.288$
Talkative	64.3 (21.2)	66.2 (18.9)	$F=0.090, p=0.765$

Values represent means (standard deviations).

#### 3.8.1.2 Subjective mood and personality characteristics

As in the full sample, bipolar phenotype participants had marginally higher depression and mania rating scores and showed significantly higher trait and state

levels of depressive mood and anxiety as well as neuroticism, and lower levels of positive mood and energy (Table 3.3).

### ***3.8.1.3 Bipolar diagnoses and co-morbidities***

Of the bipolar phenotype participants, the following DSM-IV-TR diagnoses were made: 2 bipolar II, 3 bipolar NOS, and 3 major depressive disorder. The following anxiety co-morbidities were present in the bipolar phenotype group: 1 case of generalised anxiety disorder, 2 cases of lifetime panic disorder, and 2 cases of agoraphobia. There were 6 (3) cases of lifetime (current) alcohol dependence in the bipolar phenotype group and 2 (1) cases in the control group; clinical judgement was used to include these participants owing to lack of functional impairment. Again, all main results remained unchanged when those students with a diagnosis of bipolar II or NOS, major depressive disorder, or anxiety or alcohol dependence co-morbidities were excluded.

### ***3.8.1.4 Family history of mood disorder***

Family history data were missing for five of the 22 participants in the bipolar phenotype group and six of the 22 participants in the control group. For bipolar phenotype participants for whom family history data were available, 29% (5 people) endorsed a family history of mood disorder of which 6% (1 person) endorsed a family history of bipolar disorder, 18% (3 people) endorsed a family history of major depressive disorder, and 6% (1 person) endorsed a family history of both depression and anxiety disorder. For control participants, 13% (2 people) endorsed a family history of mood disorder, both of whom gave a family history of major depressive disorder.

### 3.8.2 Facial expression matching

#### 3.8.2.1 Accuracy

Bipolar phenotype participants responded with an average accuracy of  $91.5 \pm 7.6\%$  and control participants responded with an average accuracy of  $93.2 \pm 1.6\%$ ; there was no main effect of group ( $F(1,40)=1.030, p=0.316$ ). There was a main effect of emotion ( $F(2,80)=1136.446, p<0.001$ ), indicating that accuracy differed for matching of happy and fearful faces (Table 3.4).

**Table 3.4** Behavioural responses in the facial expression matching task.

	Bipolar phenotype N=22	Controls N=22
Accuracy		
Fear (%)	85.0 (7.3)	86.9 (2.3)
Happy (%)	97.9 (8.1)	99.4 (1.5)
Reaction time		
Fear (ms)	1918 (360)	2014 (499)
Happy (ms)	1527 (361)	1564 (365)

Values represent means (standard deviations).

Accuracy was better for matching of happy facial expressions compared to fearful facial expressions both for bipolar phenotype participants ( $t(21)=21.203, p<0.001$ ) and for control participants ( $t(21)=26.325, p<0.001$ ). There was no group x emotion interaction ( $F(2,80)=0.253, p=0.618$ ). There was a trend towards a group x emotion x gender interaction ( $F(2,80)=4.051, p=0.051$ ). For female participants, there was a weak trend towards a group x emotion interaction ( $F(1,20)=2.907, p=0.104$ ). Post-hoc analyses revealed that bipolar phenotype participants ( $85.6 \pm 2.9$ ) had significantly reduced accuracy for matching fearful faces compared to controls ( $87.9 \pm 1.3$ ) ( $F(1,20)=5.806, p=0.026$ ), in the absence of a group difference for happy faces

( $F(1,20)=0.200, p=0.660$ ). For male participants, there was no group x emotion interaction ( $F(1,20)=1.250, p=0.277$ ).

### **3.8.2.2 Reaction time**

There was a main effect of emotion on reaction time for matching facial expressions ( $F(1,40)=159.548, p<0.001$ ). Reaction times were slower for fearful faces compared to happy faces for both bipolar phenotype participants ( $t(21)=8.212, p<0.001$ ) and control participants ( $t(21)=9.103, p<0.001$ ) (Table 3.4). There was no group x emotion interaction ( $F(1,40)=0.764, p=0.387$ ) or group x emotion x gender interaction ( $F(1,40)=0.005, p=0.942$ ). Bipolar phenotype participants responded with an average reaction time of  $1722 \pm 343$  ms and control participants responded with an average reaction time of  $1789 \pm 421$  ms; there was no main effect of group ( $F(1,37)=0.536, p=0.469$ ).

### **3.8.2.3 Functional MRI results: ROI**

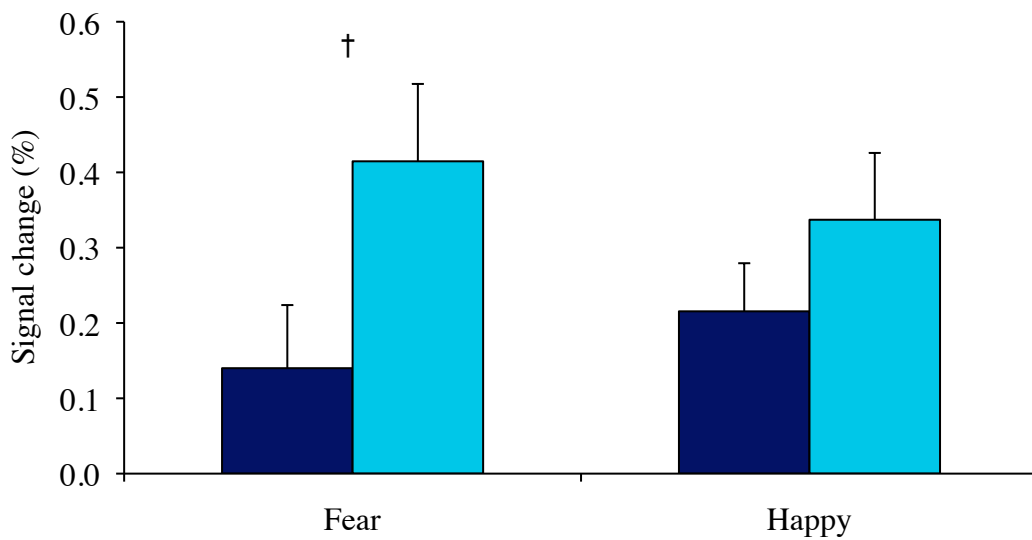
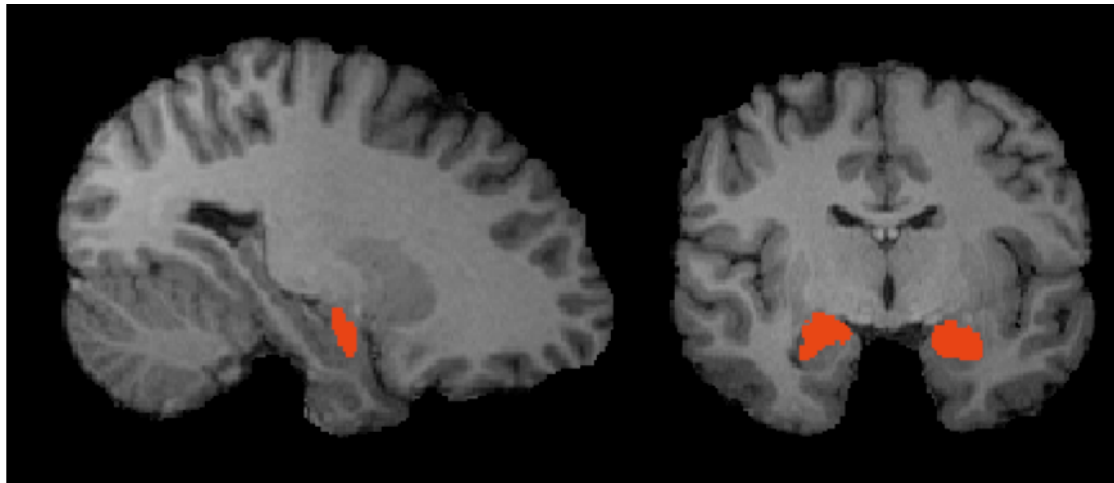
#### **3.8.2.3.1 Bilateral amygdalae ROI**

Both groups showed significant activation to fearful faces (bipolar phenotype:  $t(21)=3.766, p=0.001$ ; controls:  $t(21)=3.167, p=0.005$ ) and happy faces (bipolar phenotype:  $t(21)=3.153, p=0.005$ ; controls:  $t(21)=3.535, p=0.002$ ) in the bilateral amygdalae. There was no main effect of emotion on percentage BOLD signal change in the bilateral amygdalae ( $F(1,40)=0.688, p=0.412$ ), indicating that activation to fearful faces did not differ significantly from activation to happy faces. There was no group x emotion interaction ( $F(1,40)=0.788, p=0.380$ ), group x emotion x laterality interaction ( $F(1,40)=0.102, p=0.751$ ), group x emotion x laterality x gender

interaction ( $F(1,40)=0.562, p=0.458$ ), or main effect of group ( $F(1,40)=0.742, p=0.394$ ). However, there was a trend towards a group x emotion x gender interaction ( $F(1,40)=3.990, p=0.053$ ).

For female participants, there was no group x emotion interaction ( $F(1,20)=2.085, p=0.164$ ) or group x emotion x laterality interaction ( $F(1,20)=0.578, p=0.456$ ). There was a trend towards a main effect of group ( $F(1,20)=3.284, p=0.085$ ), with bipolar phenotype participants showing reduced percentage BOLD signal change relative to controls. Exploratory analyses revealed that bipolar phenotype participants showed a trend towards reduced percentage BOLD signal change to fearful faces ( $F(1,20)=4.292, p=0.051$ ), but not to happy faces ( $F(1,20)=1.236, p=0.279$ ) in the bilateral amygdalae (Figure 3.17).

For male participants, there was no group x emotion interaction ( $F(1,20)=2.442, p=0.134$ ), group x emotion x laterality interaction ( $F(1,20)=0.091, p=0.766$ ), or main effect of group ( $F(1,20)=0.160, p=0.694$ ).



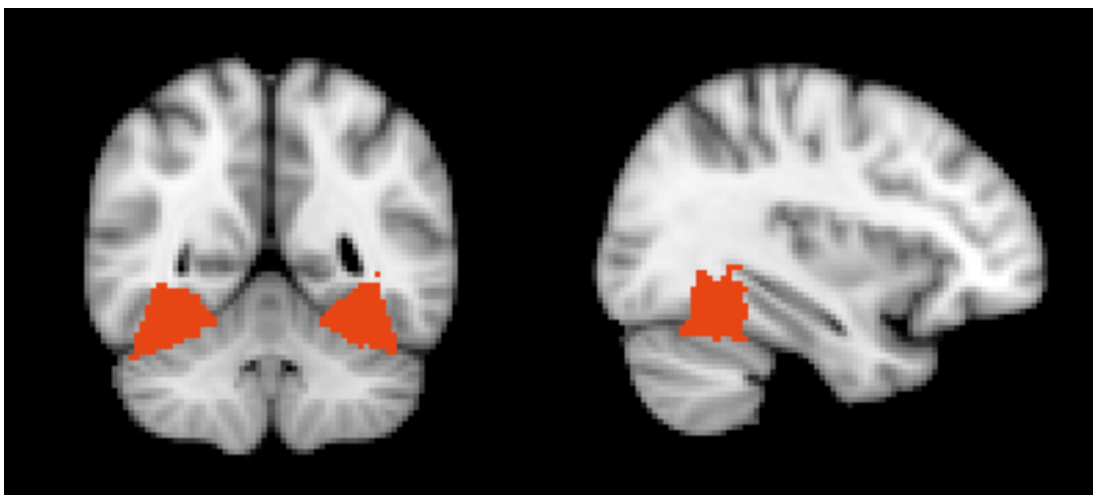
**Figure 3.17** Top: Sagittal and coronal images depicting segmented structural ROI for the bilateral amygdalae from a representative subject. Bottom: Bilateral amygdala responses to fearful and happy faces in female bipolar phenotype participants (dark bars) and female control participants (light bars). Error bars represent SEM (†  $p < 0.1$  for comparison between bipolar phenotype group and controls).

### 3.8.2.3.2 Fusiform face area ROI

Both groups showed significant activation to fearful faces (bipolar phenotype:  $t(21)=11.898$ ,  $p < 0.001$ ; controls:  $t(21)=8.755$ ,  $p < 0.001$ ) and happy faces (bipolar phenotype:  $t(21)=10.822$ ,  $p < 0.001$ ; controls:  $t(21)=7.757$ ,  $p < 0.001$ ) in the left fusiform face area and to fearful faces (bipolar phenotype:  $t(21)=10.844$ ,  $p < 0.001$ ; controls:  $t(21)=10.734$ ,  $p < 0.001$ ) and happy faces (bipolar phenotype:  $t(21)=9.858$ ,

$p < 0.001$ ; controls:  $t(21) = 10.878$ ,  $p < 0.001$ ) in the right fusiform face area (for image of structural ROI, see Figure 3.19).

There was a main effect of emotion on percentage BOLD signal change in the bilateral fusiform face area ( $F(1,40) = 23.121$ ,  $p < 0.001$ ), with significantly greater activation to fearful than happy faces. There was no group x emotion interaction ( $F(1,40) = 0.614$ ,  $p = 0.438$ ), group x emotion x laterality interaction ( $F(1,40) = 0.607$ ,  $p = 0.441$ ), group x emotion x gender interaction ( $F(1,40) = 0.624$ ,  $p = 0.434$ ), or main effect of group ( $F(1,40) = 0.116$ ,  $p = 0.735$ ).



**Figure 3.19** Coronal and sagittal images depicting the fusiform face area structural region of interest

### **3.8.2.4 Functional MRI results: Whole brain analysis**

#### **3.8.2.4.1 Main effect of task (control participants)**

Control participants showed significant activation of a neural network including bilateral amygdalae, hippocampi, thalami, fusiform gyri, inferior frontal gyri, middle frontal gyri, superior frontal gyri, precentral gyri, paracingulate gyri, lingual gyri, and

(lateral) occipital cortices in response to fearful and happy facial expressions (Table 3.6) (cluster-based thresholding with height threshold of  $Z > 2.3$  and whole-brain corrected spatial extent threshold of  $p < 0.05$ ).

**Table 3.6** Peak cluster activation in brain regions of significantly increased BOLD response for control participants in the facial expression matching task.

Brain region	Cluster size (voxels)	Z value	Coordinates <sup>a</sup>		
			x	y	Z
<b>Fear</b>					
Occipital cortex	29279	7.30	14	-102	-2
Middle frontal gyrus	5469	5.75	50	26	28
Precentral gyrus	4489	5.61	-36	6	28
Paracingulate gyrus	1131	5.41	-6	10	52
Superior parietal lobule	620	4.83	-26	-58	40
Cerebellum	367	5.79	-28	-72	-50
<b>Happy</b>					
Occipital cortex	25456	7.36	14	-102	-2
Precentral gyrus	3071	5.08	38	6	32
Precentral gyrus	2094	4.35	-36	8	26
Frontal pole	565	3.76	44	60	-2
Superior frontal gyrus	434	3.51	4	24	60
<b>Fear vs. happy</b>					
Middle frontal gyrus	1306	4.55	40	22	24
Supramarginal gyrus	1290	4.72	-32	-50	38
Lateral occipital cortex (right superior)	1252	4.66	32	-66	44
Lateral occipital cortex (right inferior)	982	3.70	48	-68	-6
Lateral occipital cortex (left inferior)	861	3.64	-34	-78	8
Cerebellum	766	3.76	-6	-70	-22
Precentral gyrus	647	3.76	-58	8	36
Frontal orbital cortex	421	4.08	-34	34	-2
<b>Happy vs. fear</b>					
Frontal pole	620	3.70	-2	64	0

Brain region refers to peak voxel (other regions included in cluster). <sup>a</sup> Montreal Neurological Institute (MNI) coordinates (x, y, z) refer to peak activation within each cluster identified, thresholded at  $Z > 2.3$  and  $p < 0.05$  corrected.

#### 3.8.2.4.2 Group x emotion interaction

There were no significant group x emotion interactions (cluster-based thresholding with height threshold of  $Z > 2.3$  and whole-brain corrected spatial extent threshold of  $p < 0.05$ ).

### 3.8.3 Emotional counting Stroop

#### 3.8.3.1 Behavioural data

##### 3.8.3.1.1 Accuracy

Bipolar phenotype participants responded with an average accuracy of  $96.4 \pm 7.2 \%$  and control participants responded with an average accuracy of  $97.8 \pm 2.8 \%$ ; there was no main effect of group on accuracy ( $F(1,40)=0.741, p=0.395$ ) (Table 3.8). There was no main effect of emotion ( $F(3,120)=0.594, p=0.620$ ), group x word valence interaction ( $F(3,120)=0.385, p=0.764$ ), or group x word valence x gender interaction ( $F(3,120)=0.295, p=0.829$ ).

**Table 3.8** Behavioural responses in the emotional counting Stroop task.

	Bipolar phenotype N=22	Controls N=22
Accuracy		
Neutral (%)	96.5 (8.4)	97.5 (3.1)
Social threat (%)	96.1 (8.4)	98.4 (2.4)
Physical threat (%)	96.0 (7.4)	97.4 (6.7)
Positive (%)	97.0 (5.5)	98.1 (2.4)
Reaction time		
Neutral (ms)	7724 (78)	7207 (108)
Social threat (ms)	7770 (102)	7123 (103)
Physical threat (ms)	7849 (95)	7222 (101)
Positive (ms)	7659 (87)	7156 (105)

Values represent means (standard deviations).

##### 3.8.3.1.2 Reaction time

There was no main effect of emotion ( $F(3,120)=1.320, p=0.271$ ), group x emotion interaction ( $F(3,120)=0.624, p=0.601$ ), or group x emotion x gender interaction ( $F(3,120)=0.897, p=0.445$ ). There was a trend towards a main effect of group ( $F(1,40)=3.933, p=0.054$ ), with bipolar phenotype participants ( $775 \pm 87$  ms) responding more slowly than control participants ( $718 \pm 101$  ms) (Table 3.8). Since

there was a trend towards a main effect of group on reaction time, mean reaction time was included as a covariate of no interest in subsequent functional MRI analyses.

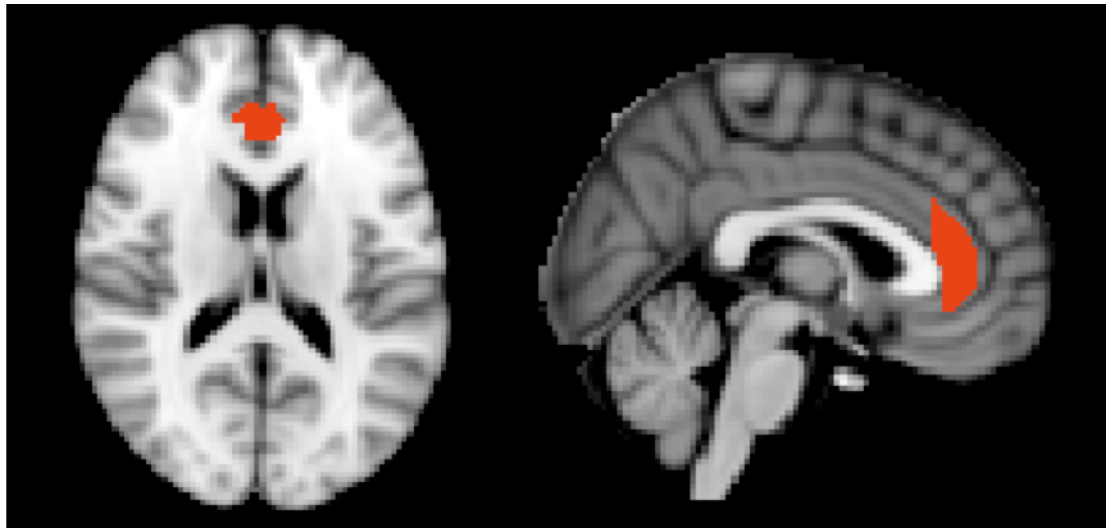
### *3.8.3.1.3 Stroop interference effect*

Neither group showed a significant Stroop interference effect for reaction time to respond to socially threatening words (bipolar phenotype:  $t(21)=0.392$ ,  $p=0.699$ ; controls:  $t(21)=0.875$ ,  $p=0.391$ ), physically threatening words (bipolar phenotype:  $t(21)=1.213$ ,  $p=0.238$ ; controls:  $t(21)=0.177$ ),  $p=0.861$ ), or positive words (bipolar phenotype:  $t(21)=0.956$ ,  $p=0.350$ ; controls:  $t(21)=0.530$ ,  $p=0.602$ ) compared to neutral words.

## **3.8.3.2 Functional MRI results: ROI**

### *3.8.3.2.1 rACC ROI*

Consistent with previous studies employing the emotional counting Stroop (Whalen, et al., 1998), participants showed significant deactivation of the rACC to neutral words compared to fixation ( $t(43)=2.837$ ,  $p=0.007$ ) (for image of structural ROI, see Figure 3.21). Furthermore, participants showed significant activation of the rACC to socially threatening ( $t(43)=2.622$ ,  $p=0.012$ ) and positive ( $t(43)=2.994$ ,  $p=0.005$ ) words compared to neutral words. However, activation of the rACC to physically threatening words did not differ significantly from activation to neutral words ( $t(43)=0.885$ ,  $p=0.381$ ).



**Figure 3.21** Axial and sagittal images depicting the rostral ACC region of interest.

For the negative vs. neutral contrast, percentage BOLD signal change was extracted from the rACC ROI for socially threatening, physically threatening, and neutral words. Mean reaction time was entered as a covariate in the repeated-measures ANOVA. There was no group x word type interaction ( $F(2,78)=1.429, p=0.246$ ), indicating that neural activity in the rACC was not differentially modulated by socially threatening, physically threatening, and neutral words across the two groups. There was no main effect of group ( $F(1,39)=0.796, p=0.378$ ), group x emotion x gender interaction ( $F(2,78)=0.583, p=0.561$ ), or main effect of word type ( $F(2,78)=1.806, p=0.171$ ).

For the positive vs. neutral contrast, extracted percentage BOLD signal change was compared for positive words and neutral words. Mean reaction time was entered as a covariate in the repeated-measures ANOVA. There was no group x word type interaction ( $F(1,39)=0.889, p=0.351$ ), indicating that neural activation of the rACC was not differentially modulated by positive and neutral words across the two groups. There was no main effect of group ( $F(1,39)=2.094, p=0.156$ ), group x emotion x

gender interaction ( $F(1,39)=0.440$ ,  $p=0.511$ ), or main effect of word type ( $F(1,39)=0.004$ ,  $p=0.949$ ).

### 3.8.3.3 Functional MRI results: Whole brain analysis

#### 3.8.3.3.1 Main effect of task (control participants)

Control participants showed increased activation in the frontal pole/frontal medial cortex for negative vs. neutral words. For the positive vs. neutral comparison, control participants showed increased activation in the anterior cingulate gyrus/frontal medial cortex and the precuneus cortex/posterior cingulate gyrus (Table 3.10).

**Table 3.10** Peak cluster activation in brain regions of significantly increased BOLD response during the emotional counting Stroop task.

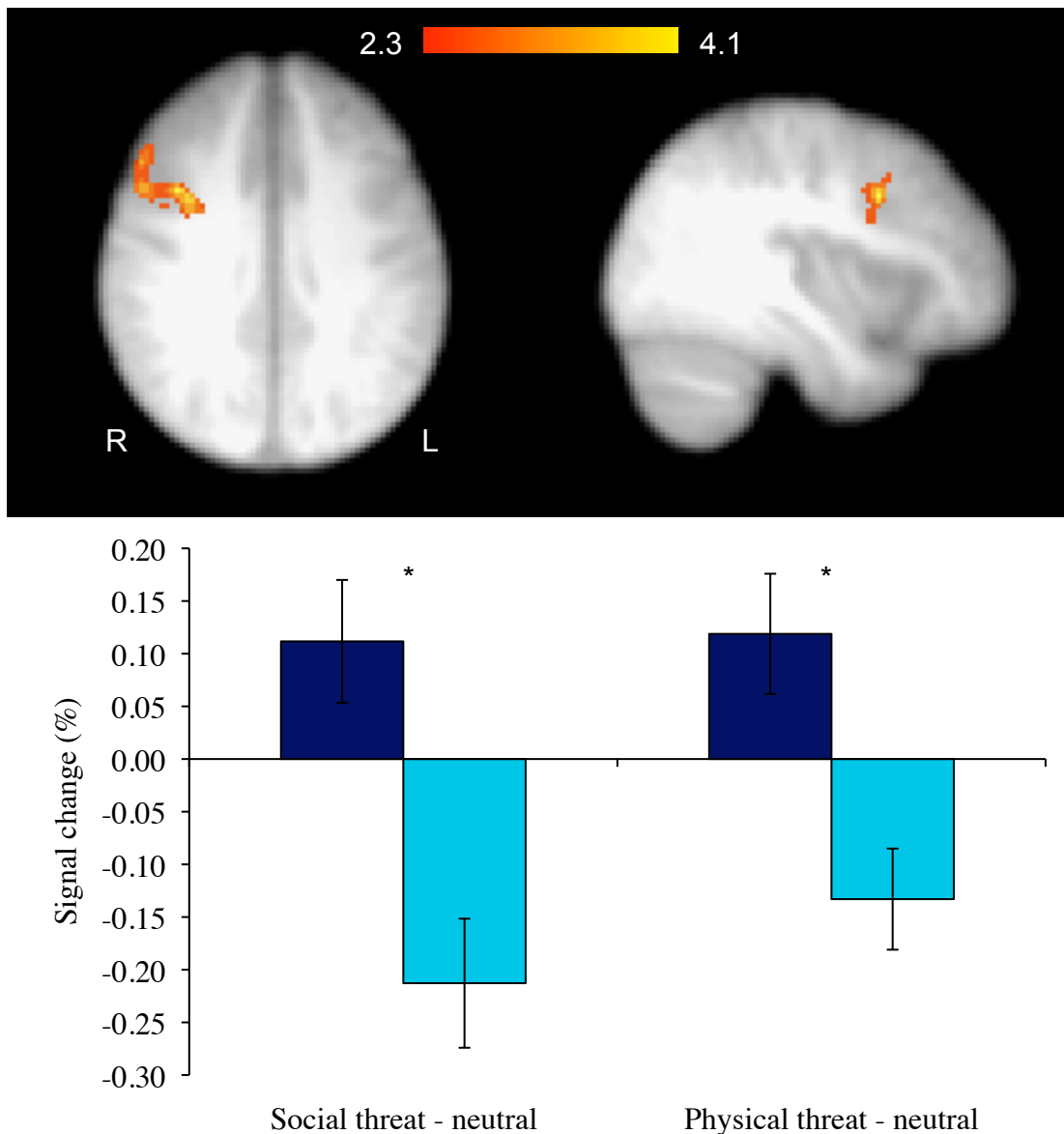
Brain region	Cluster size (voxels)	Z value	Coordinates <sup>a</sup>		
			x	y	Z
<b>Controls</b>					
Negative vs. neutral					
Frontal pole/frontal medial cortex	360	3.60	-2	62	-4
Positive vs. neutral					
Anterior cingulate gyrus/frontal medial cortex	1474	3.96	-2	26	12
Precuneus cortex/posterior cingulate gyrus	814	4.13	-4	-56	20
<b>Bipolar phenotype vs. controls</b>					
Negative vs. neutral					
Middle frontal gyrus	399	3.94	38	12	36

Brain region refers to peak voxel (other regions included in cluster). <sup>a</sup> Montreal Neurological Institute (MNI) coordinates (x, y, z) refer to peak activation within each cluster identified, thresholded at  $Z>2.3$  and  $p<0.05$  corrected.

#### 3.8.3.3.2 Group x word type interaction

For the negative vs. neutral comparison there was a significant group x emotion interaction. Bipolar phenotype participants vs. controls showed significantly greater activation in the right middle frontal gyrus (MNI coordinates:  $x=38$ ,  $y=12$ ,  $z=36$ ; Table 3.10) (cluster-based thresholding with height threshold of  $Z>2.3$  and whole-

brain corrected spatial extent threshold of  $p < 0.05$ ). Post-hoc analysis of percent BOLD signal change revealed a significant group difference both for the socially threatening vs. neutral word comparison ( $F(1,40)=15.626$ ,  $p < 0.001$ ) and for the physically threatening vs. neutral word comparison ( $F(1,40)=11.000$ ,  $p = 0.002$ ) (Figure 3.23).



**Figure 3.23** Top: Axial and sagittal images depicting significantly greater activation in the right dorsolateral prefrontal cortex in bipolar phenotype participants vs. controls for the threatening vs. neutral word contrast. Images were thresholded at  $Z > 2.3$ ,  $p < 0.05$ , whole-brain corrected. Bottom: Percent signal change extracted from the above significant cluster for bipolar phenotype group (dark bars) and control

group (light bars). Error bars represent SEM (\*  $p < 0.05$  for comparison between bipolar phenotype group and controls).  
There was no group x emotion x gender interaction ( $F(2,80)=1.131, p=0.328$ ).

There were no clusters for which there was a group x emotion interaction for the positive vs. neutral contrast (thresholded at  $Z > 2.0, p < 0.05$ , whole-brain corrected).

### **3.8.4 Exclusion of participants with a bipolar diagnosis**

To assess whether group differences may have been related to bipolar diagnosis, analyses were performed excluding two participants with a diagnosis of bipolar II and three participants with a diagnosis of bipolar NOS.

For the facial expression matching task, there was no longer a trend towards a group x emotion x gender interaction ( $F(1,35)=2.217, p=0.145$ ) for percentage BOLD signal change in the bilateral amygdalae. For female participants, there remained a trend towards a main effect of group ( $F(1,18)=3.575, p=0.075$ ). Furthermore, compared to controls, the trend towards reduced percentage BOLD signal change in the bipolar phenotype group in response to fearful faces in the bilateral amygdalae became significant ( $F(1,18)=4.150, p=0.048$ ).

For the emotional counting Stroop task, there remained a significant group x emotion interaction ( $F(2,70)=12.189, p < 0.001$ ) for percentage BOLD signal change in the right DLPFC cluster for the negative vs. neutral contrast. Furthermore, neural responses in the DLPFC for socially threatening vs. neutral words ( $F(1,70)=16.574, p < 0.001$ ) and physically threatening vs. neutral words ( $F(1,70)=13.410, p=0.001$ ) remained significantly different across the two groups. There remained no significant

group x emotion interaction for percentage BOLD signal change in the rACC ROI for the negative vs. neutral contrast ( $F(2,70)=0.807, p=0.450$ ) or the positive vs. neutral contrast ( $F(1,35)=0.122, p=0.729$ ).

### **3.9 Discussion and conclusion**

#### **3.9.1 Summary of findings**

Positive biases in emotional processing were recorded in students with the bipolar phenotype. Bipolar phenotype participants showed increased processing of positive vs. negative emotional stimuli across a number of measures, including enhanced recognition of surprised faces and impaired recognition of disgusted faces. Functional MRI analyses supported these results and revealed that bipolar phenotype participants showed a trend towards reduced neural activation of the bilateral amygdalae to fearful faces (female subjects only) and significantly increased functional activation of the regulatory region, the right DLPFC, in response to negative vs. neutral words.

#### **3.9.2 Use of an at-risk group**

The Mood Disorder Questionnaire (MDQ) (Hirschfeld, et al., 2000b) is a self-report screening tool that explores symptoms of mood elevation. High scores on the MDQ indicate considerable experience of mood-elevation, which is associated with subsequent depression and bipolar disorder (Lewinsohn, et al., 2003). The MDQ was used with a cut-off of seven symptoms of mood-elevation (without problems), which has been shown to give a moderately high positive predictive value (34%) for bipolar diagnosis in a student population (see **Chapter 2**) (Rock, Chandler, Harmer, Rogers, & Goodwin, 2010 *in preparation*). Indeed, at interview, twelve of the 32 bipolar phenotype participants (38%) completing behavioural tasks were found to be remitted from bipolar II, NOS, or major depressive disorder. However participants had neither sought help for their mood disorder nor been previously diagnosed or medicated. The high MDQ sample was accordingly drawn from a group at significant risk for the

bipolar phenotype. Therefore, these findings provide a step towards understanding the abnormalities associated with the bipolar phenotype independent of medication confounds.

### **3.9.3 Discussion of results**

#### ***3.9.3.1 Positive biases in emotional processing***

The positive biases recorded in this group are striking, particularly when contrasted with findings from studies of subjects at risk for affective disorder and euthymic bipolar patients. In the facial expression recognition task, the bipolar phenotype group showed facilitated recognition of surprised faces and impaired recognition of the negative emotion of disgust. These findings are in the opposite direction to observations of impaired recognition of happy faces associated with high neuroticism (N), a risk factor for depression (Chan, et al., 2007), and acute episodes of major depression (Surguladze, et al., 2004). These results are not consistent with previous findings of enhanced recognition of disgusted facial expressions (Harmer, et al., 2002) and impaired recognition of surprised facial expressions (Summers, et al., 2006) in euthymic bipolar patients. However, such differences may have been the result of confounds relating to residual depressive symptoms in the euthymic patients (Ferrier, Stanton, Kelly, & Scott, 1999), experience of repeated illness episodes, or current medication (Lawrence, et al., 2004).

In line with effects seen in the facial expression recognition task, the bipolar phenotype group showed faster recognition memory for positive vs. negative personality trait words, suggesting easier access to positive self-referent memories.

Although usually seen in accuracy rather than speed measures, these findings are opposite to the enhanced memory for negative vs. positive self-referent adjectives associated with depression (Bradley & Mathews, 1983) and high neuroticism (N) (Chan, et al., 2007). Therefore, these findings provide further support for the increased processing of positive emotional stimuli that may be involved in mood-elevation experience in the bipolar phenotype group.

The emotion-potentiated startle was used to give a physiological measure of emotional reactivity. Both groups showed the expected pattern of enhanced eye-blink magnitude during negative compared to neutral or positive picture presentation. However, the bipolar phenotype group showed a trend towards relatively smaller eye-blink magnitude across negative and neutral vs. positive conditions compared to the control group. Although this result does not reach traditional levels of significance, this pattern suggests a diminution of reactivity to threat stimuli and an increase in reactivity to positive stimuli, consistent with the enhanced discrimination of surprised faces, impaired discrimination of disgusted faces, and facilitated recognition memory for positive vs. negative words recorded in the bipolar phenotype group.

In line with behavioural effects of positive biases in emotional processing, the facial expression matching task revealed a trend towards reduced neural activity in the bilateral amygdalae in response to fearful faces, limited to female bipolar phenotype participants compared to controls. Since the amygdalae are part of the ventral emotional processing system and are involved in assessing the emotional salience of stimuli (Phillips, et al., 2003a), this finding may reflect reduced emotional significance of the negative fearful faces. Such effects provide evidence for the neural

bases of the positive emotional processing biases recorded in the behavioural tasks and may contribute to the mood-elevation symptoms experienced by bipolar phenotype participants. These results are interesting in the light of previous findings from functional imaging studies of healthy volunteers following seven-day antidepressant administration. Such studies suggested that antidepressants may redress the negative cognitive biases found in depression (Harmer, et al., 2004), i.e. by reducing processing of negative vs. positive information. For example, treatment with the SSRI citalopram has been found to reduce bilateral amygdalae responses to masked presentations of threatening stimuli (Harmer, Mackay, Reid, Cowen, & Goodwin, 2006). Furthermore, a study employing the facial expression matching task found that short-term antidepressant treatment was associated with increased amygdala activity to happy vs. fearful facial expressions, driven by an increase in response to happy faces (Norbury, Taylor, et al., 2009). In light of these findings in healthy volunteers, the positive biases revealed in bipolar phenotype participants suggest that exacerbation of biased emotional processing may play a role in switching or mood instability following antidepressant treatment in bipolar disorder (Sachs, et al., 2007).

The present finding of a trend towards reduced activation of the bilateral amygdalae to fearful faces contradicts previous reports of increased left amygdala responses to intensely fearful facial expressions in euthymic bipolar patients (Lawrence, et al., 2004). Such a difference may relate to experience of severe illness episodes, long duration of illness ( $15.4 \pm 13.4$  years), and high levels of residual depressive symptoms (BDI:  $15.3 \pm 9.2$ ) in the bipolar I patients included in the previous study (Lawrence, et al., 2004). Finally, this trend towards reduced neural activity in the

bilateral amygdalae was found only in female bipolar phenotype participants compared to controls, suggesting that alternative neural abnormalities may be involved in the positive biases present in male bipolar phenotype participants. Furthermore, since this effect was only a trend, replication is required in a larger sample of male and female participants.

Consistent with the positive emotional processing biases and the trend towards reduced neural responses to fearful faces in the amygdalae, the emotional counting Stroop revealed significantly increased activation of the right DLPFC in response to negative vs. neutral words. The right DLPFC is part of the dorsal emotional processing system and is involved in the integration of emotional and cognitive information and in effortful emotion regulation (Phillips, et al., 2003a; Phillips, Ladouceur, & Drevets, 2008). Therefore, these findings may imply that there is more regulation of threatening stimuli in bipolar phenotype subjects. Increased activation of this regulatory region in response to negative words may represent increased control of negatively-valenced stimuli, contributing to the positive biases and mood-elevation symptoms found in the bipolar phenotype group.

Altered activation of the DLPFC during emotional processing tasks has been recorded in previous studies of patients with bipolar disorder. These changes have been posited to reflect problems in the integration of emotional and cognitive information during emotion regulation (Phillips, et al., 2003a). Increased activation of the right DLPFC during emotional interference in bipolar phenotype participants is consistent with the proposal that dysfunction in this area may be involved in mediating vulnerability to the bipolar phenotype.

The rACC is part of the ventral emotional processing system and is involved in assessing the salience of emotional stimuli and in the encoding and automatic regulation of emotion (Phillips, et al., 2003a). Previous neuroimaging investigations have revealed altered activation within this area and increased functional connectivity with the hippocampus in bipolar disorder (Almeida, et al., 2009). However, results from this task suggest that changes in functional activation of the rACC are not seen in unmedicated students on a continuum of risk for the bipolar phenotype.

In line with an absence of attentional effects on the dot-probe task, neither group showed a Stroop response latency interference effect for emotional words, consistent with previous studies employing this version of the emotional counting Stroop in the scanner in healthy volunteers (Whalen, et al., 1998). However, bipolar phenotype participants showed a trend towards being slower to respond across all word types, which may represent greater task interference for both emotional and non-emotional stimuli. Mean reaction time was included as a covariate of no interest in all imaging analyses with the aim of controlling for this group difference.

Overall, these behavioural and functional MRI results provide evidence of positive biases in emotional processing and give rise to potential neural correlates that may contribute to the experience of mood-elevation symptoms in the bipolar phenotype group. These findings are in line with cognitive psychological theories, which posit a role for biased emotional processing in the maintenance of mood disorders (Beck, et al., 1979). Enhanced interpretation, memory, and reactivity to positive vs. negative stimuli may reinforce inflated thoughts about oneself and one's ability to control and

contribute to external events. Increased neural responses to negative stimuli in regulatory brain regions and reduced responses to negative stimuli in brain areas involved in assessing emotional salience may represent the neural correlates of such positive biases. Finally, positive emotional processing bias is one mechanism of action of antidepressants clearly seen in healthy volunteers (Harmer, et al., 2004). Therefore, the present findings may also offer a potential explanation for why antidepressants appear to be less effective or may lead to mood instability in some patients with bipolar disorder (Sachs, et al., 2007).

### ***3.9.3.2 Neuroticism***

The effects seen in the high MDQ bipolar phenotype group oppose the negative biases found to be associated with high neuroticism (N), a risk factor for major depression (Chan, et al., 2007). This is despite higher neuroticism (N) (1.6 times greater) and higher levels of negative mood and anxiety in the bipolar phenotype group. Therefore, cognitive psychological theories of depression (Beck, et al., 1979), which posit negative processing bias as the logical route to depression in the face of adverse life events, may not be tenable for high MDQ cases. Instead, alternative mechanisms may be related to how subjects process reward and make risky choices (Chandler, et al., 2009) (see **Chapter 4**).

### ***3.9.3.3 The bipolar phenotype does not involve biases in attention***

There was no evidence for effects of MDQ score on the attentional vigilance word dot-probe task, suggesting that marked attentional biases are not associated with experience of mood elevation and risk for the bipolar phenotype. This is unsurprising as attentional biases at relatively short exposure durations appear to be particularly

important in anxiety rather than mood disorders (MacLeod, Mathews, & Tata, 1986), but given the increased neuroticism (N) score and high prevalence of anxiety disorders in bipolar patients this discrepancy is still of interest. It suggests that anxiety in the bipolar phenotype may be different from anxiety more generally and further research is required to assess the mechanisms underlying anxiety in bipolar disorder.

### **3.9.4 Limitations**

There are a number of limitations to this study. Firstly, the use of a previously undiagnosed screened population generates a medication-naïve sample and minimises previous illness, but it is not known how many of the bipolar phenotype students will go on to develop clinically significant bipolar disorder except by extrapolation from other studies. However, as shown in **Chapter 2**, participants in the high MDQ bipolar phenotype group do have significant levels of co-morbidity, so this group of both diagnosed and undiagnosed students is still of interest.

Secondly, although all participants were euthymic during testing (HAM-D and YMRS scores  $\leq 8$ ), participants in the bipolar phenotype group had significantly higher levels of low mood and anxiety. Whilst one might argue that this could be addressed by carrying out analyses of covariance to covary out the effects of mood, the small differences in state and trait subjective mood are characteristic of the bipolar phenotype. Therefore, removing the effects of slight differences in mood may reduce the relevance of any findings and their ability to be applied to the bipolar phenotype.

Thirdly, first-degree relatives were not directly assessed so it is not known how accurately family history was captured as an independent risk factor for mood disorder.

Finally, this study did not exclude participants with a bipolar diagnosis, as these subjects form an important part of the bipolar phenotype. However, when analyses were repeated without subjects with a bipolar diagnosis, the main effects remained unchanged, indicating that the effects recorded were not attributable solely to diagnosed bipolar participants.

### **3.9.5 Conclusion**

Altered behavioural performance and neural activity were seen in response to emotional stimuli in a group of participants who were part of a continuum of risk for the bipolar phenotype. This study provided evidence of positive biases in emotional processing and revealed potential neural correlates of such changes.

Enhanced recognition of surprised facial expressions, impaired recognition of disgusted facial expressions, enhanced recognition memory for positive vs. negative personality trait words, and a trend towards increased emotion-potentiated startle response to positive vs. negative and neutral pictures were seen in bipolar phenotype students selected by virtue of high scores on the MDQ. These processing biases towards positive emotional information and away from negative emotional information may contribute to the mood-elevation symptoms experienced by the bipolar phenotype group. Therefore positive emotional processing bias may represent a vulnerability marker associated with the bipolar phenotype.

A trend towards reduced reactivity of the bilateral amygdalae to negative stimuli may contribute to the positive biases in emotion processing observed in female bipolar phenotype participants. However, other mechanisms may be at play in male subjects. Increased functional activation of the right DLPFC to threatening words was seen in the emotional Stroop task and may reflect increased regulation of negative stimuli. This functional abnormality may play a role in the positive biases recorded in both male and female bipolar phenotype participants.

In conclusion, results from these emotional processing tasks provide evidence that unmedicated bipolar phenotype subjects show altered behavioural performance and abnormal recruitment of brain regions previously implicated in bipolar disorder (Gruber, et al., 2004; Lawrence, et al., 2004; Phillips, et al., 2003a; Yurgelun-Todd, et al., 2000). Together, these abnormalities represent positive biases in emotional processing and may account for vulnerability to mood elevation associated with the bipolar phenotype. Furthermore, disruption of emotional processing and regulation and altered neural processing in these regions is consistent with emotion dysregulation and may be involved in the aetiology of the disorder (Phillips, 2006).

Longitudinal studies are required to understand the factors contributing to translation into more severe mood disorder and the role played by positive emotional processing biases.

## 4 Decision-making and the bipolar phenotype

### 4.1 Introduction

**Chapter 2** characterised a group of bipolar phenotype students who were selected by virtue of mood-elevation experience and high scores on the Mood Disorder Questionnaire (MDQ) (Hirschfeld, et al., 2000b). The bipolar phenotype was shown to be associated with a high degree of co-morbidity as well as increased prevalence of bipolar diagnosis. For example, students with the bipolar phenotype were found to be at increased risk for neuroticism and depressive symptoms in addition to the mood-elevation symptoms that resulted in their high scores on the MDQ. Furthermore, within the bipolar phenotype group, there were considerably elevated levels of gambling participation and alcohol and substance misuse, with over half of subjects endorsing the risk-taking behaviour item on the MDQ.

**Chapter 3** addressed the mood symptoms that are characteristic of the bipolar phenotype and revealed positive biases in emotional processing that may underlie the mood-elevation symptoms seen in this group. Meanwhile, the psychological and neural changes underlying risk-seeking behaviour, gambling, and impulsivity remain relatively unknown in individuals with the bipolar phenotype. Therefore, this chapter extends assessment of the bipolar phenotype with the use of two laboratory decision-making paradigms: the framed risky-choice task and the risky decision-making task.

In addition to increased risk-seeking behaviour, disrupted cognitive flexibility has also been recorded in patients with bipolar disorder (Bearden, Hoffman, & Cannon, 2001; Clark, Sarna, & Goodwin, 2005) and their first-degree relatives (Clark, et al.,

2005). Therefore, this chapter also included the intra-dimensional/extra-dimensional attentional set-shifting task to assess different components of attentional flexibility such as reversal discrimination learning, intra-dimensional set-shifting, and extra-dimensional set-shifting in bipolar phenotype participants.

## **4.2 Aim**

This chapter investigates cognitive flexibility and risky decision-making in a group of medication-naïve and previously undiagnosed students with the bipolar phenotype. Alterations in cognitive flexibility and decision-making and their neural substrates were assessed using the intra-dimensional/extra-dimensional attentional set-shifting task, the framed risky-choice task (Chandler, Wakeley, Goodwin, & Rogers, 2009), and the risky decision-making task (Rogers, et al., 2004; Rogers, et al., 2003; Rogers, Wakeley, Robson, Bhagwagar, & Makela, 2007), the latter of which was completed with concurrent fMRI. It was hypothesised that bipolar phenotype subjects would show disrupted extra-dimensional set shifting and altered risky decision-making. Furthermore, it was predicted that abnormal activation of brain regions involved in processing of reward and reinforcement cues, including the ventral striatum and orbitofrontal cortex (OFC), would be associated with the bipolar phenotype.

### **4.3 Methods 1: Participant characteristics**

Participants previously described in **Chapter 3** completed this study. All 62 participants from **Chapter 3** completed the intra-dimensional/extra-dimensional attentional set-shifting task. Of these, there were 32 bipolar phenotype participants (17 female, 15 male) and 30 controls (14 female, 16 male). A sub-sample of 46 participants completed the framed risky-choice task. Of these, there were 23 bipolar phenotype participants (14 female, 9 male) and 23 controls (14 female, 9 male). Finally, the 44 participants who completed the imaging section of **Chapter 3** also completed the risky decision-making task with concurrent fMRI. Of these, there were 22 bipolar phenotype participants (11 female, 11 male) and 22 control participants (11 female, 11 male).

## **4.4 Methods 2: Behavioural tasks**

### **4.4.1 Intra-dimensional/extra-dimensional attentional set-shifting task**

#### ***4.4.1.1 Stimuli and procedure***

The intra-dimensional/extra-dimensional set-shifting task was used to assess rule acquisition and cognitive flexibility as part of visual discrimination learning. It examined visual discrimination, attentional set formation, and maintenance, shifting and flexibility of attention. Two arbitrary dimensions were used in the test: colour-filled shapes and white lines. Simple stimuli were made up of just one of these dimensions, whereas compound stimuli were made up of both, i.e. white lines overlaying colour-filled shapes.

Two simple colour-filled shapes were presented on a computer screen and the participants had to learn which one was correct by touching it. Feedback allowed the participant to learn which stimulus was correct to a criterion of six correct consecutive responses, at which point the stimuli and/or rules were changed. These shifts were initially intra-dimensional, i.e. colour-filled shapes remained the only relevant dimension. Later, after an extra-dimensional shift, white lines then became the only relevant dimension. Participants progressed through the test by satisfying the same set criterion of six consecutive correct responses. If at any stage the participant failed to reach this criterion after 50 trials, the test terminated.

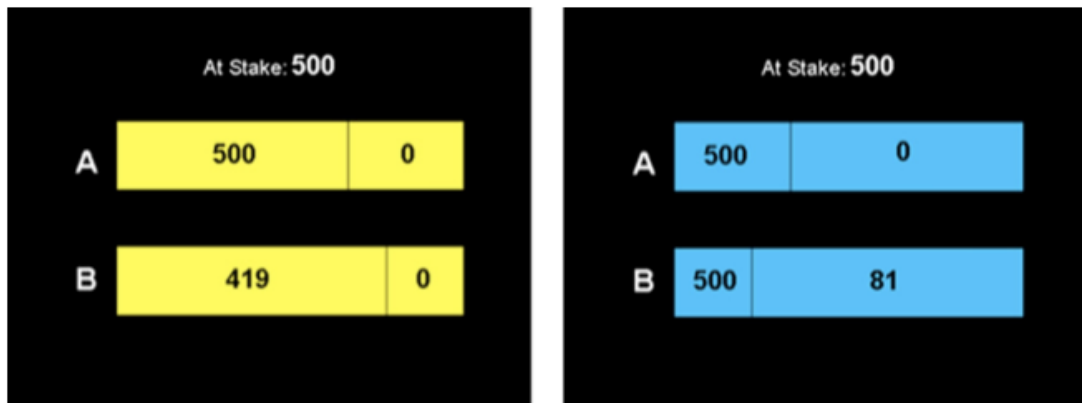
There were four reversal stages (simple discrimination reversal, compound discrimination reversal, intra-dimensional reversal, and extra-dimensional reversal),

an intra-dimensional set-shift, and an extra-dimensional set-shift. The outcome measures were the total number of errors to criterion for the reversal stages, the intra-dimensional set-shift stage, and the extra-dimensional set-shift stages, as well as reaction times for these three sections.

#### 4.4.2 Framed risky-choice task

##### 4.4.2.1 Stimuli and procedure

The framed risky-choice task consisted of a series of dilemmas involving two gambles to secure all or a proportion of a monetary reward or stake. This task has been described previously by Chandler and colleagues (2009) and assesses the framing effect, which is an example of non-normative decision-making described in **Chapter 1**.



**Figure 4.1** One positively-framed dilemma (coloured yellow) and one negatively-framed dilemma (coloured blue), each with a stake of 500 points. In the positively-framed dilemma, option A is the risky option with a 0.67 probability of winning 500 points and a 0.33 probability of winning nothing. Option B is the safe option, with a 0.80 probability of winning 419 points and a 0.20 probability of winning nothing. In the negatively-framed dilemma, option A is the risky option with a 0.67 probability of losing nothing and a 0.33 probability of losing 500 points. Option B is the safe option with a 0.80 probability of losing 81 points and a 0.20 probability of losing 500 points. (Chandler, Wakeley, Goodwin, & Rogers, 2009)

During the positively-framed dilemmas, participants made decisions to win all or some of the stake. During the negatively-framed dilemmas, participants made decisions to avoid losing all or some of the stake.

Figure 4.1 shows a positively-framed dilemma and a negatively-framed dilemma. In each case, the gambles were represented by coloured horizontal bars that were divided into two sections by a vertical line. The position of the vertical line signalled the relative probabilities of winning or losing rewards, the magnitude of which was indicated in black font within that section of the bar. Each dilemma contained a safe option and a risky option. The safe option had a high probability ( $p=1.00$  or  $p=0.80$ ) of winning or losing some of the stake. On the other hand, the risky option had a lower probability ( $p=0.33$  or  $p=0.67$ ) of winning or losing some of the stake.

Each participant made decisions about positively- and negatively-framed dilemmas that involved each combination of safe ( $p=1.00$  or  $p=0.80$ ) and risky ( $p=0.33$  or  $p=0.67$ ) options over four sizes of stake (200, 300, 400, and 500 points), resulting in 32 dilemmas. Importantly, the gambles of each dilemma had equal expected values, calculated as the sum of their two outcomes, each weighted by their probability of occurrence. Moreover, each positively-framed dilemma had an equivalent negatively-framed dilemma in which the expected values were identical. For the dilemmas shown in Figure 4.1, for the positively-framed dilemma shown, the expected value of both options A and B is to win 335 points, i.e. to lose 165 points of the 500 points stake. Equally, for the negatively-framed dilemma shown, the expected value of both options A and B is to lose 165 points, i.e. to conserve 335 points of the 500 points

stake. This meant that any variation in preference for risky or safe options in the positively-framed vs. negatively-framed dilemmas could not have been due to differences in the monetary values of the gambles.

Each dilemma remained displayed on the computer screen until the participant chose one of the two displayed gambles by pressing the appropriate key. Participants were told to take as long as they needed to make their decisions. Feedback about the outcome of the participant's choice was delivered for a duration of 4s. For positively-framed dilemmas, this feedback consisted of the word "WIN" followed by the proportion of the stake won, e.g. WIN 419/500. For negatively-framed dilemmas, feedback display consisted of the word "LOSE" followed by the proportion of the stake lost, e.g. LOSE 81/500. The inter-trial interval was set at 2s.

Participants made decisions over 16 positively-framed dilemmas and 16 negatively-framed dilemmas that were presented in a random order. The rewards won or lost over the course of the task were summed and given to the participants as part of their study remuneration.

Half of bipolar phenotype participants and half of controls completed a version of the task in which the positively-framed dilemmas were displayed in yellow and negatively-framed dilemmas were displayed in blue. The remaining bipolar phenotype and control participants completed a version of the task with reverse colour-to-frame mapping, i.e. with positively-framed dilemmas being displayed in blue and negatively-framed dilemmas being displayed in yellow.

Participants received structured training before completing the framed risky-choice task. This involved inspection of sample dilemmas and instruction on how to distinguish the probabilities of gamble outcomes and how to select between gambles. At the end of the experiment, participants completed a questionnaire about their experiences relating to completion of the framed risky-choice task.

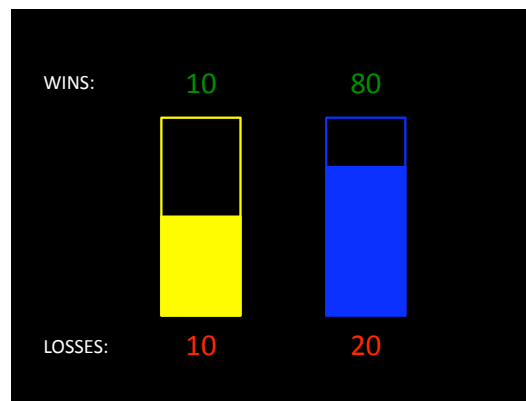
The outcome measures were the proportion of risky choices in response to the positively-framed and negatively-framed dilemmas and mean deliberation times for safe and risky decisions under each of these framing conditions.

## 4.5 Methods 3: Functional imaging task

### 4.5.1 Risky decision-making task

#### 4.5.1.1 Stimuli and procedure

The risky decision-making task required participants to choose between two simultaneously presented gambles. The version of this task suitable for fMRI scanning has been described previously by Rogers and colleagues (2004). Each gamble was represented visually by a histogram, the height of which indicated the probability of winning a given number of points. The possible gains were indicated in green ink above the histogram and the possible losses were indicated in red ink below the histogram (see Figure 4.2).



**Figure 4.2** An example trial from the risky decision-making task, consisting of an ‘experimental’ gamble with a 0.75 probability of winning 80 points and a 0.25 probability of losing 20 points versus a control gamble with a 0.5 chance of winning 10 points and a 0.5 chance of losing 10 points.

One gamble (coloured yellow) was the control gamble and always had a 0.5 probability of winning 10 points and a 0.5 probability of losing 10 points, and therefore an expected value of 0. The alternative ‘experimental’ gamble (coloured

blue) varied in the probability of winning (high 0.75 vs. low 0.25), the magnitude of possible gains (large 80 points vs. small 20 points), and the magnitude of possible losses (large 80 points vs. small 20 points). These variables were completely crossed to produce eight trial types with expected values that varied between -55 and +55 (see Table 4.1).

**Table 4.1** The eight types of ‘experimental’ gamble resulting from the combination, in a completely crossed design, of two levels of probability, possible gains, and possible losses.

Probability	Possible gains	Possible losses	Expected value <sup>A</sup>
High (0.75)	Large (80)	Large (80)	40
		Small (20)	55
	Small (20)	Large (80)	-5
		Small (20)	10
Low (0.25)	Large (80)	Large (80)	-40
		Small (20)	5
	Small (20)	Large (80)	-55
		Small (20)	-10

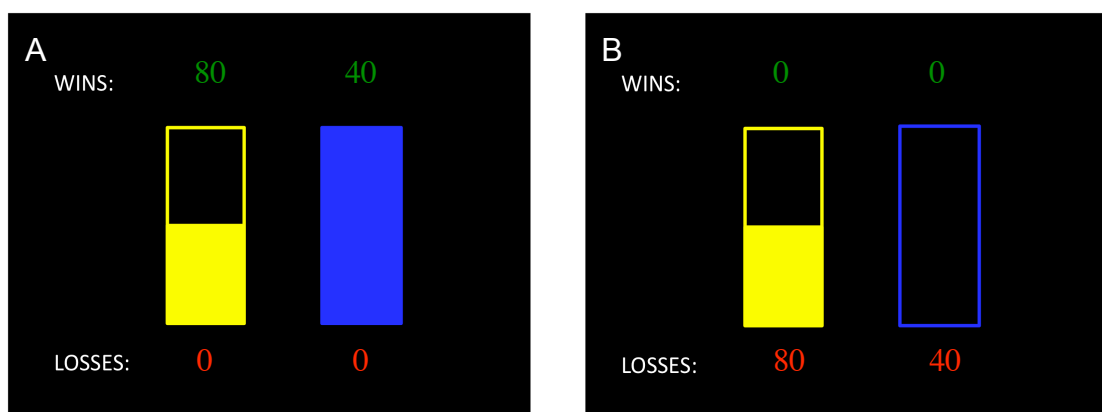
<sup>A</sup> The ‘expected value’ for each gamble equals the sum of its gains and losses, each weighted by their probability of occurrence. These values vary between -55 and +55 points, with a mean of 0.

The control and ‘experimental’ gamble appeared randomly on the left or right of the screen. Participants were required to press the left button or the right button of a button box to indicate whether they wanted to choose the left or right gamble respectively. The outcome measures were (i) the proportion of choices of the ‘experimental’ gamble over the control gamble as a function of probability of winning, magnitude of possible gains, and magnitudes of possible losses associated with the ‘experimental gamble’ and the mean deliberation time (ms) for these choices and (ii) the proportion of choices of the ‘experimental’ gamble over the control gamble as a function of the expected value of the ‘experimental gamble’ and the mean deliberation time (ms) for these choices.

The eight trial types described above were presented pseudo-randomly within three blocks of trials. Across the three blocks, there were six repetitions of each ‘experimental’ gamble. At the beginning of each block of trials, participants were given 100 experimenter-defined points and asked to make choices that would increase this amount by as much as possible. Visual and auditory feedback was given after each choice and revised points total was presented for 2s before the next trial. At the end of each block, participants were given a final score for that block. Participants were informed that the participant with the highest accumulated points score would win a £50 voucher.

#### 4.5.1.1.1 Models of non-normative risky choice: the ‘reflection effect’

The reflection effect, which is an example of non-normative decision-making, was also assessed in this task. To this end, two further trial types were included (with six repetitions each across the three blocks) and represented choices known to be subject to the non-normative biases of risk-averse and risk-seeking choices when confronted with certain wins or certain losses (Shafir & Tversky, 1995).



**Figure 4.4** Two trial types involved in assessing non-normative decision-making, i.e. the ‘reflection effect’: (A) ‘Gains only’ trial (B) ‘Losses only’ trial.

The first type was a ‘gains only’ trial in which participants were asked to choose between a guaranteed win of 40 points and a gamble with a 0.5 chance of winning 80 points and a 0.5 chance of losing 0 points; neither option involved losses (**Figure 4.4A**). By contrast, the second type was a ‘losses only’ trial in which participants were asked to choose between a guaranteed loss of 40 points and a gamble with a 0.5 chance of losing 80 points and a 0.5 chance of losing 0 points; neither option involved gains (**Figure 4.4B**).

Within each of the gains only and losses only trial types, the expected value of each gamble was equal. However, decision-makers usually exhibit marked risk aversion in the former case (i.e. they choose the guaranteed gain of 40 points), but marked risk-seeking behaviour in the latter case (i.e. they choose the gamble with a 0.5 chance of losing 80 points and a 0.5 chance of losing 0 points) (Shafir & Tversky, 1995). For both the gains only and losses only trials, the dependent measures were the proportion of trials in which the participants chose the guaranteed outcome and the associated mean deliberation time (ms) for making decisions in these trials.

#### **4.5.2 Image acquisition**

Imaging data for the risky decision-making task were collected in the same scanner and with the same scan parameters as described in **Chapter 3**.

#### **4.5.3 fMRI data analyses**

fMRI data were analysed using the same parameters as those described in **Chapter 3**, with the only alteration being that the risky decision-making task had an event-related

design. The following explanatory variables for the ‘decision-making’ period were modelled with a duration equal to the deliberation time for each trial: high probability of winning, low probability of winning, large possible gains, small possible gains, large possible losses, small possible losses, gains only trials, and losses only trials. Furthermore, for the ‘outcome’ period, explanatory variables for wins and for losses were modelled with a duration of 1s. Therefore, the following contrasts were considered along with their opposites: high-low probability of winning, large-small magnitude of possible gains, large-small magnitude of possible losses, losses only-gains only, and gains-losses.

As described in **Chapter 3**, significant activations were identified using cluster-based threshold of statistical images with a height threshold of  $Z > 2.3$  with a spatial extent threshold of  $p < 0.05$ , whole-brain corrected for multiple comparisons at the cluster level. For those regions for which a significant interaction was identified, percentage blood oxygenation level-dependent (BOLD) signal change for each explanatory variable was extracted in order to identify the profile of the group effect.

#### **4.5.4 Region-of-interest analyses**

Regions of interest (ROI) were defined based on a priori regions implicated in decision-making and found to be disrupted in bipolar disorder (see **Chapter 1**). ROI were defined for each participant for the ventral striatum (bilateral nucleus accumbens) was generated using a robust model-based segmentation/registration tool (Patenaude, et al., 2008) implemented within FSL. Furthermore, group structural ROI were defined within FSL based on the Harvard-Oxford cortical structural atlas for the bilateral orbitofrontal cortex (OFC) (<http://www.fmrib.ox.ac.uk/fsl/>). Mean parameter

estimates for each explanatory variable, for each participant, across the entire ROIs, were extracted and converted to percent signal change.

#### **4.6 Methods 4: Statistical analyses**

Baseline demographic and participant characteristics were analysed using univariate analyses of variance (ANOVA) with group and gender as between-subjects factors using the Statistical Package for Social Scientists (Version 16.0 for Mac, SPSS Inc.). A significance threshold of  $p < 0.05$  was used for all analyses.

For the intra-dimensional/extra-dimensional attentional set-shifting task, errors to criterion and reaction time for reversal learning, intra-dimensional shifts, and extra-dimensional shifts were analysed using one-way ANOVAs with group and gender as between-subjects factors.

For the framed risky-choice task, the proportionate choice data of the risky option over the safe option were arcsine-transformed as is appropriate whenever the variance of a measure is proportional to its mean (Howell, 1987). However, the data reported in text, figures, and tables show untransformed proportionate choice values. The transformed data were analysed with a repeated-measures ANOVA with group and gender as between-subjects factors and frame (positive vs. negative) as the within-subjects factor. The mean deliberation times were analysed with a repeated-measures ANOVA with group and gender as between-subjects factors and frame (positive vs. negative) and choice (risky vs. safe) as the within-subjects factors. Significant interactions were followed up with univariate ANOVAs with group and gender as between-subjects factors.

For the risky decision-making task, the proportionate choice data of the 'experimental' gamble over the control gamble were also arcsine-transformed

(Howell, 1987) and data reported in text, figures and tables show untransformed proportionate choice values. The transformed data and the mean deliberation times were analysed with repeated-measures ANOVAs with group and gender as between-subjects factors and probability of winning (high vs. low), magnitude of possible gains (large vs. small), and magnitude of possible losses (large vs. small) as within-subjects factors.

Additionally, the transformed proportionate choice data and the mean deliberation times were analysed using a repeated-measures ANOVA with group and gender as between-subjects factors and with expected value (-55, -40, -10, -5, +5, +10, +40, +55) as the within-subjects factor. Finally, non-normative decision-making, i.e. the reflection effect, was assessed using a repeated-measures ANOVA with group and gender as between-subjects factors and trial type (gains only vs. losses only) as the within-subjects factor. Significant interactions were followed up with univariate ANOVAs with group and gender as between-subjects factors. Extracted percent BOLD signal change was analysed using repeated-measures ANOVAs with group and gender as between-subjects factors and laterality (left/right where appropriate) and one of (i) probability of winning (high vs. low), (ii) magnitude of possible gains (large vs. small), (iii) magnitude of possible losses (large vs. small), (iv) outcome (win vs. loss), (v) trial type (gains only vs. losses only), or (vi) section of task (decision-making vs. outcome) as within-subjects factors.

#### 4.7 Results 1: Demographics and questionnaire responses

The 32 bipolar phenotype participants and 32 controls who completed the intra-dimensional/extra-dimensional attentional set-shifting task were described in the behavioural results section of **Chapter 3**. The two groups were well matched for age, gender, and IQ, although bipolar phenotype participants had significantly higher trait and state levels of depressive mood and anxiety, and lower levels of positive mood and energy (Table 3.1).

The 22 bipolar phenotype participants and 22 controls who completed the risky decision-making task with concurrent fMRI were described in **Chapter 3**'s functional imaging results section and were similarly well matched, but with higher levels of depressive mood and anxiety, and lower levels of positive mood and energy in the bipolar phenotype group (Table 3.3).

**Table 4.3** Subjective mood and personality characteristics of participants who completed the framed risky-choice task.

	Bipolar phenotype N=23	Control N=23	Significance <i>df</i> =1,42
Mood Disorder Questionnaire	8.9 (1.4)	0.7 (0.9)	-
EPQ neuroticism	8.8 (2.9)	5.7 (2.9)	$F=14.056, p=0.001$
Hamilton Depression Rating Scale	3.4 (2.4)	1.9 (1.9)	$F=5.116, p=0.029$
Young Mania Rating Scale	3.8 (2.8)	1.4 (1.5)	$F=11.067, p=0.002$
Befindlichkeit Scale	29.5 (21.2)	11.8 (9.1)	$F=16.223, p<0.001$
Beck Depression Inventory	8.1 (5.9)	2.7 (3.1)	$F=14.999, p<0.001$
State Anxiety Inventory	18.0 (5.7)	15.7 (4.0)	$F=3.072, p=0.087$
Trait Anxiety Inventory	22.3 (6.3)	16.6 (3.5)	$F=13.059, p=0.001$
State Positive Affect Schedule	31.4 (8.0)	33.3 (4.4)	$F=1.558, p=0.219$
State Negative Affect Schedule	13.7 (2.8)	12.8 (3.4)	$F=0.729, p=0.398$
Trait Positive Affect Schedule	32.7 (5.7)	34.3 (4.3)	$F=1.730, p=0.196$
Trait Negative Affect Schedule	15.7 (4.5)	13.7 (2.7)	$F=3.201, p=0.081$
Visual Analogue Scales:			
Happy	68.0 (17.5)	73.5 (14.4)	$F=2.980, p=0.092$
Sad	25.0 (20.8)	12.6 (12.8)	$F=5.975, p=0.019$
Irritable	30.4 (24.7)	15.3 (13.4)	$F=6.753, p=0.013$
Anxious	28.7 (24.7)	25.8 (19.8)	$F=0.081, p=0.777$
Interested in others	72.4 (19.4)	74.7 (16.8)	$F=0.221, p=0.641$
Content	66.0 (25.7)	78.2 (16.1)	$F=5.722, p=0.021$
Talkative	60.2 (19.8)	64.8 (18.4)	$F=1.361, p=0.250$

Values represent means (standard deviations).

The 23 bipolar phenotype participants and 23 controls who completed the framed risky-choice task were well matched for age (bipolar phenotype vs. controls:  $20.1 \pm 0.9$  vs.  $20.5 \pm 1.6$  years), gender, verbal IQ ( $128.7 \pm 6.0$  vs.  $128.4 \pm 5.4$ ) and full-scale IQ ( $117.2 \pm 5.7$  vs.  $118.5 \pm 3.7$ ), but again bipolar phenotype participants showed higher levels of neuroticism, depressive mood and anxiety, and lower levels of positive mood and energy (Table 4.3).

Of the 23 bipolar phenotype participants who completed the framed risky-choice task, the following DSM-IV-TR diagnoses were made: 4 bipolar II, 5 bipolar NOS, and 2 major depressive disorder. The following anxiety co-morbidities were present in the bipolar phenotype group: 2 cases of lifetime panic disorder and 2 cases of agoraphobia. There were 6 (3) cases of lifetime (current) alcohol dependence in the bipolar phenotype group and 2 (1) cases in the control group; clinical judgement was used to include these participants owing to lack of functional impairment. Family history data were missing for 6 of the 23 bipolar phenotype participants and for 7 of the 23 control participants. For bipolar phenotype participants for whom family history data were available, 29% (5 people) endorsed a family history of mood disorder of which 6% (1 person) endorsed a family history of bipolar disorder, 18% (3 people) endorsed a family history of major depressive disorder, and 6% (1 person) endorsed a family history of both depression and anxiety disorder. For control participants for whom family history data were available, 13% (2 people) endorsed a family history of major depressive disorder.

## 4.8 Results 2: Behavioural tasks

### 4.8.1 Intra-dimensional/extra-dimensional attentional set-shifting task

Results from the intra-dimensional/extra-dimensional attentional set-shifting task are shown in Table 4.4.

**Table 4.4** Errors to criterion and reaction times for reversal learning, intra-dimensional shifts, and extra-dimensional shifts.

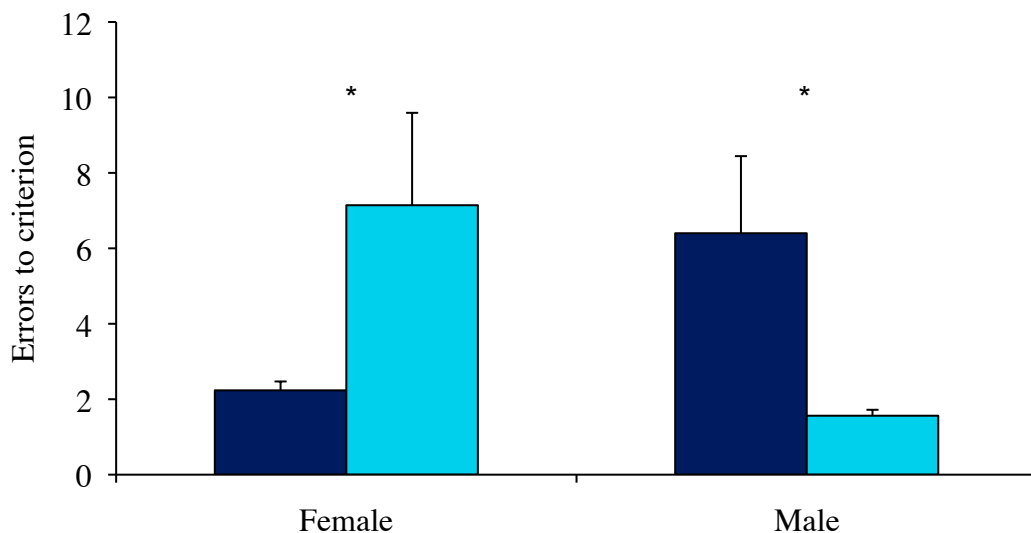
	Bipolar phenotype N=32	Controls N=30
Reversal learning		
Errors	6.4 (5.5)	5.4 (1.3)
Reaction time (ms)	1078 (244)	998 (211)
Intra-dimensional shift		
Errors	0.4 (0.9)	0.3 (0.5)
Reaction time (ms)	1543 (510)	1322 (405)
Extra-dimensional shift		
Errors	4.2 (5.8)	4.2 (6.8)
Reaction time (ms)	1358 (420)	1592 (1981)

Values represent means (standard deviations).

For reversal learning, there was no effect of group on errors to criterion (group:  $F(1,58)=0.890$ ,  $p=0.349$ ; group x gender:  $F(1,58)=0.082$ ,  $p=0.776$ ) or reaction time (group:  $F(1,58)=2.002$ ,  $p=0.162$ ; group x gender:  $F(1,58)=0.124$ ,  $p=0.726$ ).

For intra-dimensional shifts, there was no effect of group on errors to criterion (group:  $F(1,58)=0.205$ ,  $p=0.653$ ; group x gender:  $F(1,58)=0.510$ ,  $p=0.478$ ). However, there was a significant main effect of group on reaction time ( $F(1,58)=4.140$ ,  $p=0.046$ ), with bipolar phenotype participants ( $1543 \pm 510$  ms) having slower intra-dimensional shift reaction times than controls ( $1322 \pm 405$  ms). There was no group x gender interaction for reaction time ( $F(1,58)=0.157$ ,  $p=0.693$ ).

For extra-dimensional shifts, there was no main effect of group on errors to criterion ( $F(1,58)=0.001, p=0.981$ ), however, there was a significant group x gender interaction ( $F(1,58)=10.668, p=0.002$ ). Post-hoc analyses revealed that female bipolar phenotype participants made significantly fewer errors than female controls ( $F(1,29)=4.845, p=0.036$ ), whilst male bipolar phenotype participants made significantly more errors than male controls ( $F(1,29)=5.947, p=0.021$ ) (Figure 4.5). There was no group difference for reaction time (group:  $F(1,58)=0.309, p=0.580$ ; group x gender:  $F(1,58)=0.949, p=0.334$ ).



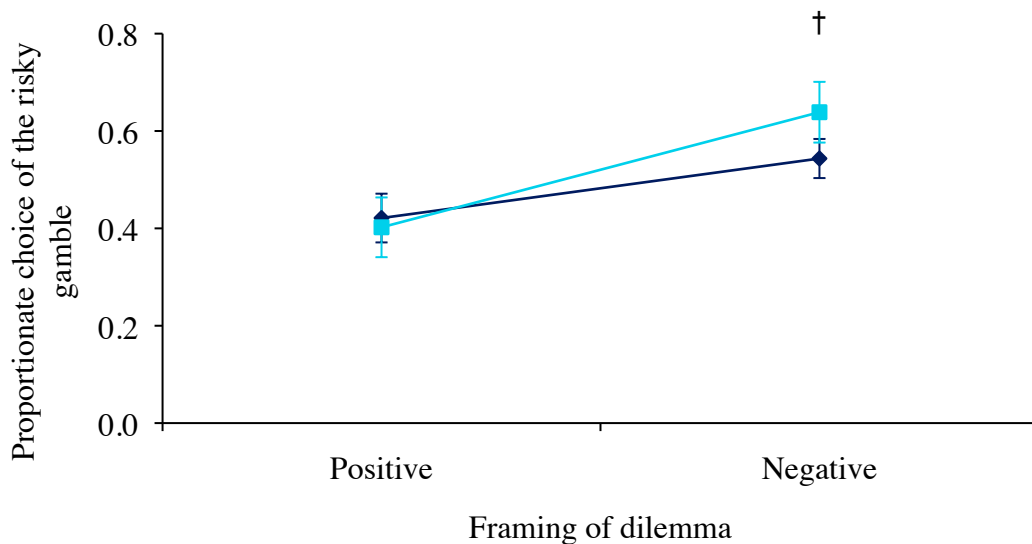
**Figure 4.5** Errors to criterion for extra-dimensional shift for female and male bipolar phenotype participants (dark bars) and control group (light bars). Error bars represent SEM (\*  $p<0.05$  for comparison between bipolar phenotype group and controls).

## 4.8.2 Framed risky-choice task

### 4.8.2.1 Proportionate choice

There was no main effect of group ( $F(1,38)=1.379, p=0.248$ ), indicating that bipolar phenotype participants ( $0.48 \pm 0.18$ ) did not differ in their proportionate choice of the risky gamble relative to controls ( $0.52 \pm 0.28$ ).

There was a main effect of frame (positively-framed vs. negatively-framed) ( $F(1,38)=27.077, p<0.001$ ), with participants choosing the risky gamble significantly more frequently for negatively-framed dilemmas ( $0.59 \pm 0.25$ ) than positively-framed dilemmas ( $0.41 \pm 0.27$ ). There was a trend towards a group x frame interaction ( $F(1,38)=3.377, p=0.074$ ), with bipolar phenotype participants choosing the risky gamble more frequently for positively-framed vs. negatively-framed dilemmas, i.e. a diminution of the framing effect described above (Figure 4.7). Post-hoc analyses revealed that bipolar phenotype participants showed a trend towards choosing the risky gamble less frequently for negatively-framed dilemmas ( $F(1,38)=3.925, p=0.055$ ), in the absence of a group difference in proportionate choice of the risky gamble for positively-framed dilemmas ( $F(1,38)=0.022, p=0.882$ ). There was no group x framing x gender interaction ( $F(1,38)=0.572, p=0.454$ ).



**Figure 4.7** Proportionate choice of the risky gamble over the safe gamble as a function of framing of dilemmas for bipolar phenotype group (dark diamonds) and control group (light squares). Error bars represent standard error of the mean (SEM) (†  $p<0.1$  for comparison between bipolar phenotype group and controls).

#### 4.8.2.2 Deliberation time

Mean deliberation times as a function of framing of dilemma and response type (risky vs. safe) are shown in Table 4.6. There was no main effect of group ( $F(1,33)=0.944$ ,  $p=0.338$ ), indicating that the average deliberation time of bipolar phenotype participants ( $3796 \pm 1457$  ms) did not differ significantly from that of control participants ( $4171 \pm 1642$  ms).

**Table 4.6** Mean deliberation time (ms) as a function of framing of dilemma and response type.

	Framing of dilemma		Response type	
	Positive	Negative	Risky	Safe
Bipolar phenotype	3391 (1376)	4201 (1684)	3759 (1595)	3843 (1491)
Controls	3615 (1464)	4726 (2073)	4381 (2036)	4083 (1992)

Values represent means (standard deviations).

There was a main effect of frame ( $F(1,33)=28.528$ ,  $p<0.001$ ), with significantly faster deliberation times for positively-framed ( $3503 \pm 1409$  ms) than negatively-framed ( $4464 \pm 1886$  ms) dilemmas. There was no group x frame interaction ( $F(1,33)=1.626$ ,  $p=0.211$ ), suggesting that the deliberation times of the two groups were not differentially affected by frame. There was no group x frame x gender interaction ( $F(1,33)=2.082$ ,  $p=0.158$ ).

There was no main effect of response type (risky vs. safe choice) ( $F(1,33)=2.404$ ,  $p=0.131$ ), indicating that deliberation time was not significantly affected by whether the participant chose the risky ( $4070 \pm 1836$  ms) or safe ( $3963 \pm 1744$  ms) option. Furthermore, there was no group x response type interaction ( $F(1,33)=0.122$ ,  $p=0.729$ ), suggesting that the deliberation times of the two groups were not differentially affected by response type. There was no group x response type x gender interaction ( $F(1,33)=1.867$ ,  $p=0.181$ ).

### **4.8.3 Exclusion of participants with a bipolar diagnosis**

To assess whether group differences may have been related to bipolar diagnosis, analyses were performed (i) excluding seven participants with a diagnosis of bipolar II and five participants with a diagnosis of bipolar NOS for the intra-dimensional/extra-dimensional attentional set-shifting task and (ii) excluding four participants with a diagnosis of bipolar II and five participants with a diagnosis of bipolar NOS the framed risky-choice task.

For the intra-dimensional/extra-dimensional attentional set-shifting task, there remained a significant group difference in reaction time for intra-dimensional shifts ( $F(1,46)=7.482, p=0.009$ ), with bipolar phenotype participants having slower reaction times than controls. There also remained a significant group x gender interaction for errors to criterion for intra-dimensional shifts ( $F(1,46)=5.771, p=0.020$ ). However, post-hoc analyses revealed only trends towards female bipolar phenotype participants making fewer errors than female controls ( $F(1,23)=3.178, p=0.088$ ) and towards male bipolar phenotype participants making more errors than male controls ( $F(1,23)=3.038, p=0.095$ ).

For the framed risky-choice task, there remained a trend towards a group x frame interaction ( $F(1,29)=3.210, p=0.084$ ), with bipolar phenotype participants choosing the risky gamble more frequently for positively-framed vs. negatively-framed dilemmas, i.e. a diminution of the framing effect. However, post-hoc analyses no longer showed a trend towards reduced proportionate choice of the risky gamble for negatively-framed dilemmas by bipolar phenotype participants ( $F(1,29)=1.832, p=0.186$ ).

## 4.9 Results 3: Functional imaging: Risky decision-making task

### 4.9.1 Behavioural results: Probability, gains, and losses

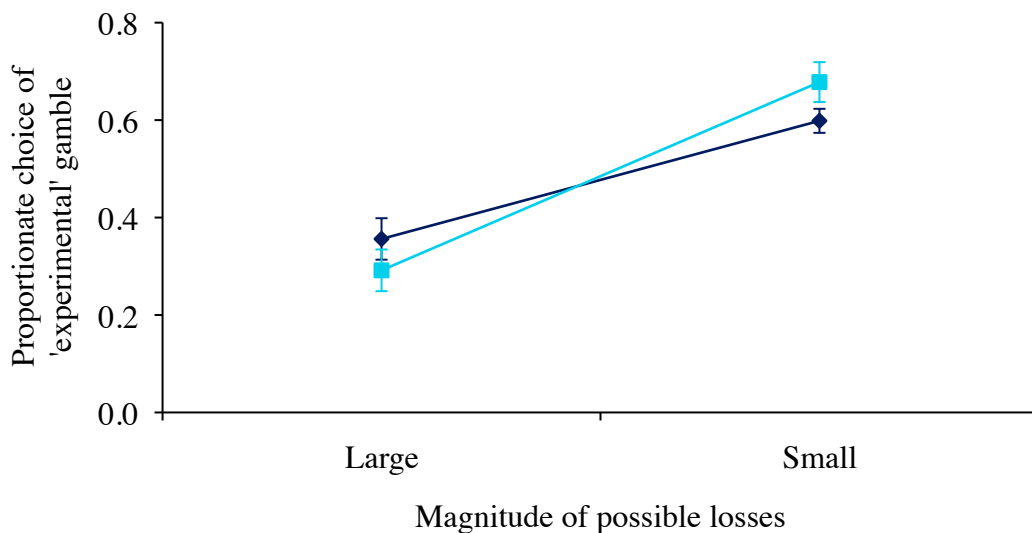
#### 4.9.1.1 Proportionate choice

Bipolar phenotype participants ( $0.49 \pm 0.10$ ) did not differ in their proportionate choice of the ‘experimental’ gamble compared to control participants ( $0.47 \pm 0.12$ ); there was no main effect of group ( $F(1,40)=0.192, p=0.663$ ).

There was a main effect of probability of winning ( $F(1,40)=84.599, p<0.001$ ), with participants choosing the ‘experimental’ gamble significantly more frequently when there was a high ( $0.73 \pm 0.22$ ) compared to low ( $0.22 \pm 0.20$ ) probability of winning. There was no group x probability of winning interaction ( $F(1,40)=0.793, p=0.378$ ), indicating that proportionate choice of the ‘experimental’ gamble was not differentially affected by probability of winning across the two groups. There was no group x probability of winning x gender interaction ( $F(1,40)=1.056, p=0.310$ ).

There was a main effect of magnitude of possible gains ( $F(1,40)=118.811, p<0.001$ ), with participants choosing the ‘experimental’ gamble significantly more frequently when possible gains were large ( $0.54 \pm 0.16$ ) compared to when possible gains were small ( $0.38 \pm 0.14$ ). There was no group x magnitude of possible gains interaction ( $F(1,40)=0.521, p=0.475$ ), indicating that proportionate choice of the ‘experimental’ gamble was not differentially affected by magnitude of possible gains across the two groups. There was no group x magnitude of possible gains x gender interaction ( $F(1,40)=2.617, p=0.114$ ).

There was a main effect of magnitude of possible losses ( $F(1,40)=174.662, p<0.001$ ), with participants choosing the 'experimental' gamble significantly more frequently when possible losses were small ( $0.64 \pm 0.13$ ) compared when possible losses were large ( $0.32 \pm 0.15$ ). There was no group x magnitude of possible losses interaction ( $F(1,40)=0.689, p=0.411$ ), indicating that proportionate choice of the 'experimental' gamble was not differentially affected by magnitude of possible losses across the two groups. However, there was a significant group x magnitude of possible losses x gender interaction ( $F(1,40)=4.254, p=0.046$ ). For female participants, there was no group x magnitude of possible losses interaction ( $F(1,20)=0.729, p=0.403$ ). For male participants, there was a significant group x magnitude of possible losses interaction ( $F(1,20)=4.364, p=0.050$ ), with male bipolar phenotype participants choosing the 'experimental' gamble more frequently when there were large vs. small possible losses compared to male control participants (Figure 4.9).



**Figure 4.9** Proportionate choice of the 'experimental' gamble over the control gamble as a function of magnitude of possible losses for male bipolar phenotype participants (dark diamonds) and male control participants (light squares). Error bars represent SEM.

However, post-hoc analyses revealed no significant group differences in proportionate choice of the ‘experimental’ gamble when there were large ( $F(1,20)=1.050, p=0.318$ ) or small ( $F(1,20)=2.853, p=0.107$ ) possible losses.

#### 4.9.1.2 Deliberation time

Mean deliberation times as a function of probability of winning, magnitude of possible gains, and magnitude of possible losses are shown in Table 4.8. There was no main effect of group on deliberation time ( $F(1,40)=0.303, p=0.585$ ), indicating that deliberation time did not differ significantly for bipolar phenotype participants ( $2710 \pm 708$  ms) and control participants ( $2856 \pm 1006$  ms).

**Table 4.8** Mean deliberation time (ms) as a function of probability of winning, magnitude of possible gains, and magnitude of possible losses.

	Probability of winning		Possible gains		Possible losses	
	High	Low	Large	Small	Large	Small
Bipolar phenotype	2523 (665)	2898 (818)	2728 (814)	2693 (657)	2817 (773)	2604 (689)
Controls	2722 (1021)	2990 (1080)	2802 (923)	2910 (1125)	3000 (1192)	2712 (878)

Values represent means (standard deviations).

There was a main effect of probability of winning ( $F(1,40)=15.228, p<0.001$ ), with participants responding with faster deliberation times when there was a high ( $2622 \pm 858$  ms) compared to low ( $2944 \pm 948$  ms) probability of winning. There was no group x probability of winning interaction ( $F(1,40)=0.423, p=0.519$ ), indicating that deliberation time was not differentially affected by probability of winning across the two groups. There was no group x probability of winning x gender interaction ( $F(1,40)=0.039, p=0.845$ ).

There was no main effect of magnitude of possible gains ( $F(1,40)=0.297, p=0.589$ ), indicating that deliberation time did not differ significantly for risky choices involving ‘experimental’ gambles with large or small possible gains. There was no group x magnitude of possible gains interaction ( $F(1,40)=1.162, p=0.287$ ), suggesting that deliberation time was not differentially affected by magnitude of possible gains across the two groups. There was no group x magnitude of possible gains x gender interaction ( $F(1,40)=0.294, p=0.590$ ).

There was a main effect of magnitude of possible losses ( $F(1,40)=11.346, p=0.002$ ), with participants responding with faster deliberation times when there was a small ( $2658 \pm 782$  ms) compared to large ( $2908 \pm 997$  ms) possible losses. There was no group x magnitude of possible losses interaction ( $F(1,40)=0.253, p=0.618$ ), suggesting that deliberation time was not differentially affected by magnitude of possible losses across the two groups. There was no group x magnitude of possible losses x gender interaction ( $F(1,40)=0.001, p=0.977$ ).

## **4.9.2 Behavioural results: Expected value**

### **4.9.2.1 Proportionate choice**

There was a main effect of expected value ( $F(7,280)=75.797, p<0.001$ ), with participants choosing the ‘experimental’ gamble more frequently as its expected value increased from a minimum of -55 to a maximum of +55 (Table 4.10). There was no group x expected value interaction ( $F(7,280)=0.687, p=0.683$ ), indicating that proportionate choice of the ‘experimental’ gamble was not differentially affected by

expected value across the two groups. There was no group x expected value x gender interaction ( $F(7,280)=1.225, p=0.289$ ).

**Table 4.10** Proportionate choice of the 'experimental' gamble as a function of its expected value.

Expected value <sup>^</sup>	Bipolar phenotype N=22	Controls N=22
55	0.95 (0.16)	0.95 (0.21)
40	0.82 (0.32)	0.77 (0.39)
10	0.90 (0.27)	0.86 (0.31)
5	0.53 (0.37)	0.54 (0.39)
-5	0.38 (0.31)	0.23 (0.29)
-10	0.14 (0.30)	0.20 (0.31)
-40	0.13 (0.24)	0.19 (0.25)
-55	0.04 (0.14)	0.02 (0.08)

Values represent means (standard deviations). <sup>^</sup> The 'expected value' for each gamble equals the sum of its gains and losses, each weighted by their probability of occurrence.

#### 4.9.2.2 *Deliberation time*

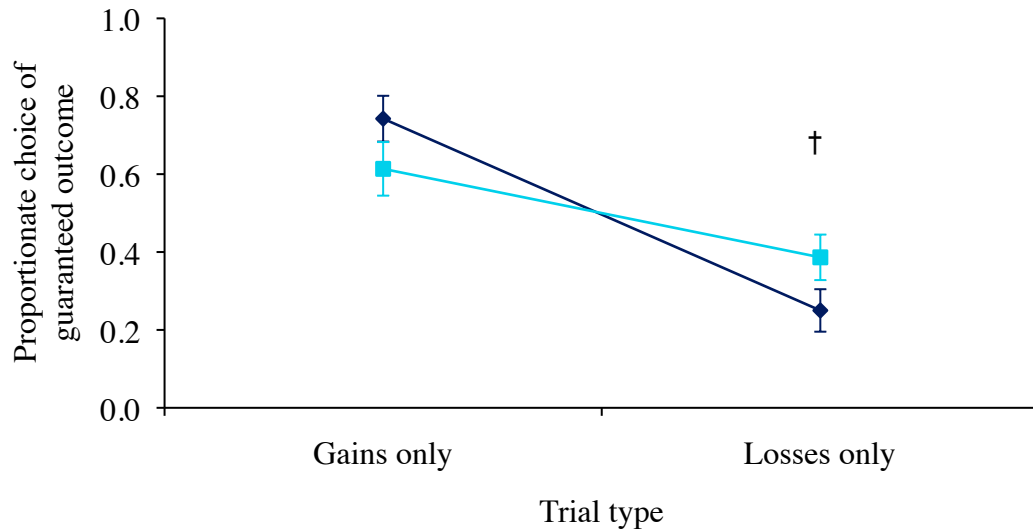
There was a main effect of expected value ( $F(7,280)=14.785, p<0.001$ ), with participants responding faster as expected value departed from 0 towards +55 or -55. There was no group x expected value interaction ( $F(7,280)=0.848, p=0.548$ ), indicating that deliberation time was not differentially affected by expected value across the two groups. There was no group x expected value x gender interaction ( $F(7,280)=0.273, p=0.964$ ).

### 4.9.3 Behavioural results: The reflection effect

#### 4.9.3.1 *Proportionate choice*

There was a main effect of trial type (gains only vs. losses only) ( $F(1,40)=43.375, p<0.001$ ), with greater preference for the guaranteed outcome for gains only ( $0.68 \pm 0.30$ ) compared to losses only ( $0.32 \pm 0.27$ ) trials, and therefore a significant reflection effect. There was a significant group x trial type interaction ( $F(1,40)=6.136,$

$p=0.018$ ), with bipolar phenotype participants choosing the gamble with the guaranteed outcome more frequently for gains only vs. losses only trial, i.e. an exaggeration of the reflection effect (Figure 4.11).



**Figure 4.11** Proportionate choice of the gamble with the guaranteed outcome for gains only and losses only trials for bipolar phenotype group (dark diamonds) and the control group (light squares). Error bars represent SEM (†  $p<0.1$  for comparison between bipolar phenotype group and placebo group).

Post-hoc analyses revealed that the bipolar phenotype group showed a trend towards reduced proportionate choice of the guaranteed outcome for losses only trials ( $F(1,40)=3.877$ ,  $p=0.056$ ), in the absence of a group difference for gains only trials ( $F(1,40)=1.907$ ,  $p=0.175$ ). There was no group x trial type x gender interaction ( $F(1,40)=0.787$ ,  $p=0.380$ ) or main effect of group ( $F(1,40)=0.024$ ,  $p=0.877$ ).

#### 4.9.3.2 Deliberation time

There was a main effect of trial type ( $F(1,40)=68.575$ ,  $p<0.001$ ), with significantly faster deliberation times for gains only ( $3236 \pm 1891$  ms) than losses only ( $4953 \pm 2270$  ms) trials. There was no group x trial type interaction ( $F(1,40)=0.266$ ,  $p=0.609$ ),

suggesting that deliberation times of bipolar phenotype and control participants were not differentially affected by trial type. There was no group x trial type x gender interaction ( $F(1,40)=0.014$ ,  $p=0.906$ ) or main effect of group ( $F(1,40)=2.366$ ,  $p=0.132$ ).

#### **4.9.4 Functional MRI results: ROI analyses**

##### **4.9.4.1 Excluded participants**

Functional imaging data from two bipolar phenotype participants were not available because of technical difficulties during data collection.

##### **4.9.4.2 Ventral striatum (bilateral nucleus accumbens)**

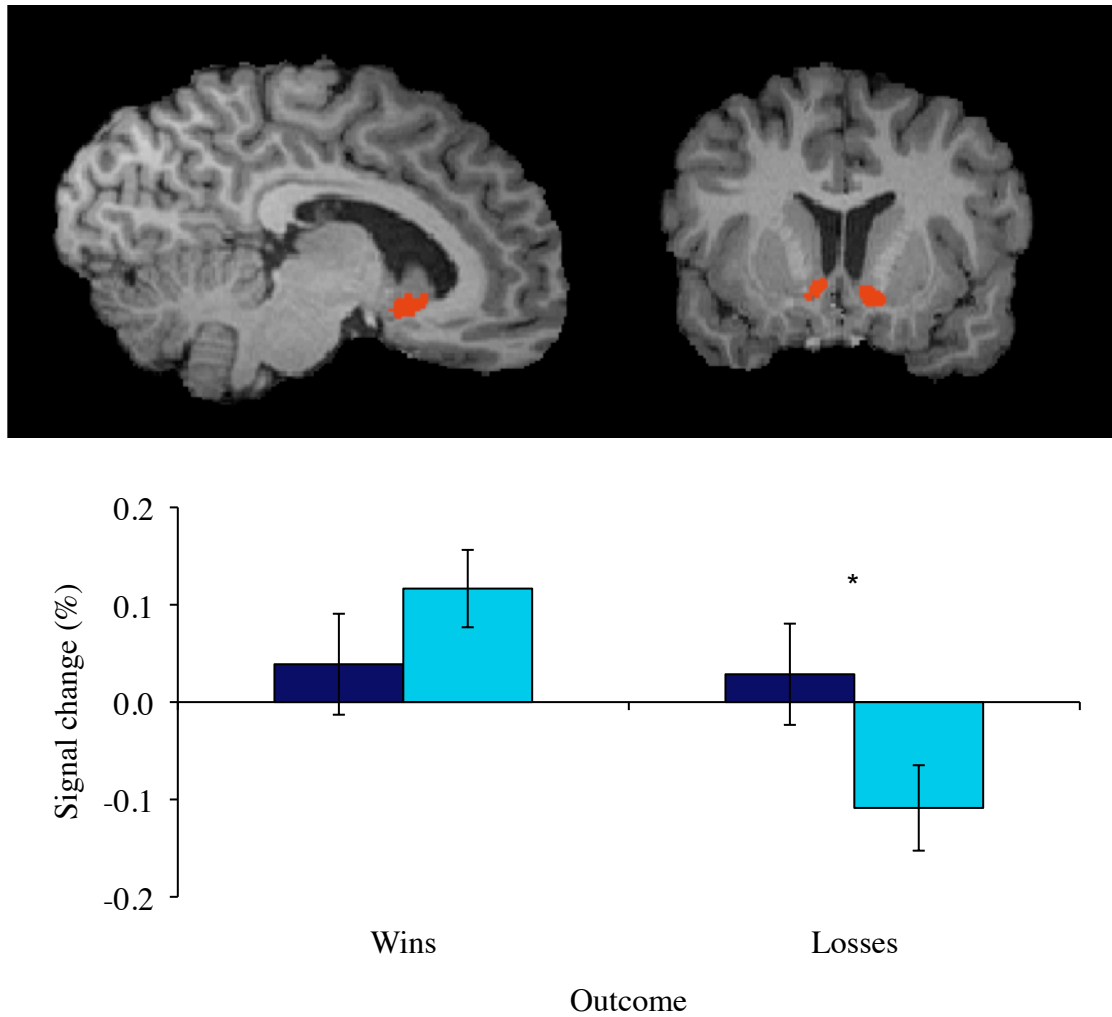
###### **4.9.4.2.1 Main effect of task**

There was significantly greater activation of the ventral striatum for high vs. low probabilities of winning ( $F(1,38)=8.578$ ,  $p=0.006$ ), large vs. small possible gains ( $F(1,38)=20.099$ ,  $p<0.001$ ), outcomes that were wins vs. losses ( $F(1,38)=8.466$ ,  $p=0.006$ ), and gains only vs. losses only trial types ( $F(1,38)=5.260$ ,  $p=0.027$ ). There was no main effect of magnitude of possible losses on activation of the ventral striatum ( $p > 0.1$ ).

###### **4.9.4.2.2 Group x task interaction**

There was a significant group x outcome (win/loss) interaction ( $F(1,38)=6.785$ ,  $p=0.013$ ), with bipolar phenotype participants showing significantly increased neural responses to losses vs. gains in the ventral striatum relative to controls. Post-hoc

analyses revealed that the bipolar phenotype group showed significantly increased activation of the ventral striatum for losses ( $F(1,38)=4.135, p=0.049$ ) in the absence of a group difference for wins ( $F(1,38)=1.253, p=0.270$ ) (Figure 4.13). There were no further significant interactions regarding activation of the ventral striatum.



**Figure 4.13 Top:** Sagittal and coronal images depicting segmented structural ROI for the ventral striatum (bilateral nucleus accumbens) from a representative subject. **Bottom:** Ventral striatum (bilateral nucleus accumbens) responses to wins and losses in bipolar phenotype participants (dark bars) and control participants (light bars). Error bars represent SEM (\*  $p<0.05$  for comparison between bipolar phenotype group and controls).

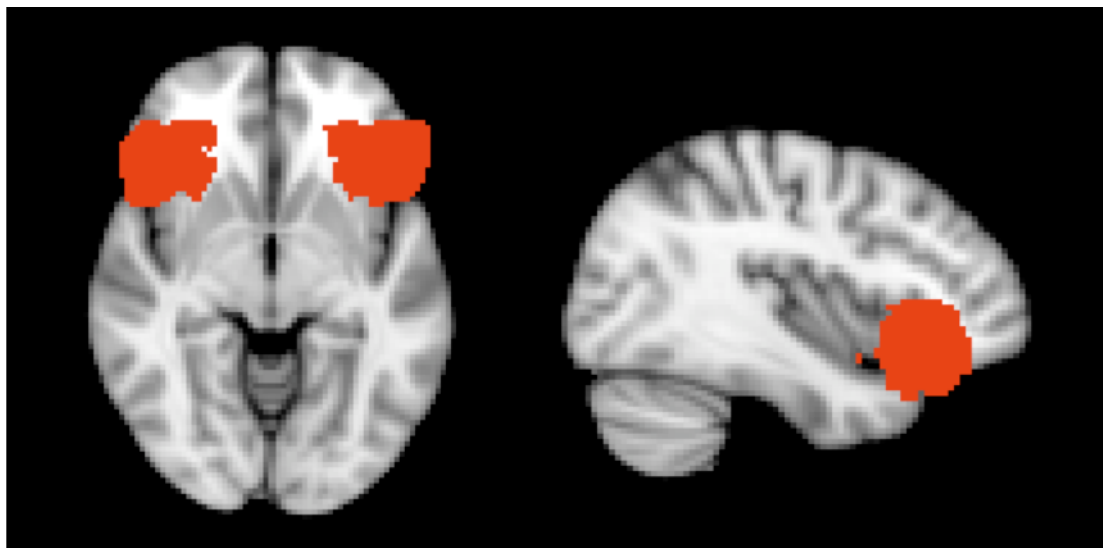
### **4.9.4.3 Bilateral orbitofrontal cortex (OFC)**

#### **4.9.4.3.1 Main effect of task**

There was significantly greater activation of the bilateral OFC for large vs. small possible gains ( $F(1,38)=4.569, p=0.039$ ) in the absence of a main effect of probability of winning, magnitude of possible gains, magnitude of possible losses, or outcome (win/loss) (all  $p$  values  $> 0.1$ ) (see Figure 4.15 for structural ROI).

#### **4.9.4.3.2 Group $\times$ task interaction**

There were no significant group  $\times$  task interactions for activation of the bilateral OFC.



**Figure 4.15** Axial and sagittal images depicting the structural ROI for the bilateral orbitofrontal cortex (OFC).

## 4.9.5 Functional MRI results: Whole brain analyses

### 4.9.5.1 Main effect of task (control participants)

#### 4.9.5.1.1 Decision-making: Probability of winning, magnitude of possible gains, and magnitude of possible losses

For control participants, neural signals associated with decision-making were modulated by probability of winning, with increased activation of bilateral frontal orbital cortex, subcallosal cortex, anterior cingulate gyrus, middle frontal gyrus, precentral gyrus, posterior cingulate gyrus, lingual gyrus, and cerebellum in response to high vs. low probabilities of winning (cluster-based thresholding with height threshold of  $Z > 2.3$  and whole-brain corrected spatial extent threshold of  $p < 0.05$ ) (Table 4.12). There were no significant clusters of activation for the opposite contrast (low vs. high probabilities of winning).

Furthermore, neural activation was modulated by magnitude of possible gains, with increased activation of the medial prefrontal cortex and anterior cingulate gyrus during decision-making involving large vs. small possible gains (cluster-based thresholding with height threshold of  $Z > 2.3$  and whole-brain corrected spatial extent threshold of  $p < 0.05$ ) (Table 4.12). There were no significant clusters of activation for the opposite contrast (low vs. high magnitudes of possible gains).

There were no significant clusters of activation for the large vs. small or small vs. large possible losses contrasts.

**Table 4.12** Peak cluster activation in brain regions of significantly increased BOLD response during the risky decision-making task.

Brain region	Cluster size (voxels)	Z value	Coordinates <sup>a</sup>		
			x	y	Z
<b>Controls</b>					
Decision-making					
High vs. low probability of winning					
Precentral gyrus/posterior cingulate gyrus	6596	4.15	50	-6	24
Middle frontal gyrus	2614	3.65	-32	-4	50
Anterior cingulate gyrus	712	3.51	-4	-12	42
Subcallosal cortex/frontal orbital cortex	658	3.92	8	12	-10
Cerebellum	566	3.47	38	-60	-30
Lingual gyrus/cerebellum	565	3.78	10	-58	-14
High vs. low magnitude of possible gains					
Frontal medial cortex/anterior cingulate gyrus	3748	3.73	0	44	-2
Gains only vs. losses only					
Occipital cortex/lateral occipital cortex	4296	4.24	12	-98	12
Occipital fusiform gyrus	935	3.64	-26	-76	-10
Frontal orbital cortex	744	3.78	14	8	-14
Postcentral gyrus/superior parietal lobule	421	3.44	-42	-36	58
Outcome					
Win vs. loss					
Occipital cortex/caudate/accumbens/ precuneous/superior frontal gyrus	34938	5.01	30	-94	-4
Occipital cortex/occipital fusiform gyrus	2646	4.4	-32	-94	6
Frontal medial cortex	566	3.92	-12	62	-4
Cerebellum	488	3.72	-2	-54	-8
Frontal medial cortex/paracingulate gyrus	434	3.49	0	42	-14
<b>Bipolar phenotype vs. controls</b>					
Outcome					
Loss vs. win					
Lateral occipital cortex	875	3.83	-46	-84	2
Precentral gyrus/postcentral gyrus	629	3.33	-54	-12	42
Lateral occipital cortex	481	3.54	48	-80	-2

Brain region refers to peak voxel (other regions included in cluster). <sup>a</sup> Montreal Neurological Institute (MNI) coordinates (x, y, z) refer to peak activation within each cluster identified, thresholded at  $Z > 2.3$  and  $p < 0.05$  corrected.

#### 4.9.5.1.2 Decision-making: The reflection effect

For the gains only vs. losses only contrast, there was increased activation of bilateral frontal orbital cortex, occipital fusiform cortex, lateral occipital cortex, postcentral gyrus, and superior parietal lobule (cluster-based thresholding with height threshold of  $Z > 2.3$  and whole-brain corrected spatial extent threshold of  $p < 0.05$ ) (Table 4.12).

There were no significant clusters of activation for the losses only vs. gains only contrast.

#### *4.9.5.1.3 Outcome*

For outcomes that were wins vs. losses, there was significant activation of a neural network including the frontal medial cortex, occipital cortex, occipital fusiform gyrus, superior frontal gyrus, caudate, accumbens, precuneus, paracingulate gyrus, and cerebellum winning (cluster-based thresholding with height threshold of  $Z > 2.3$  and whole-brain corrected spatial extent threshold of  $p < 0.05$ ) (Table 4.12). However, there were no significant clusters of activation for the losses vs. wins contrast.

#### **4.9.5.2 Group x task interaction**

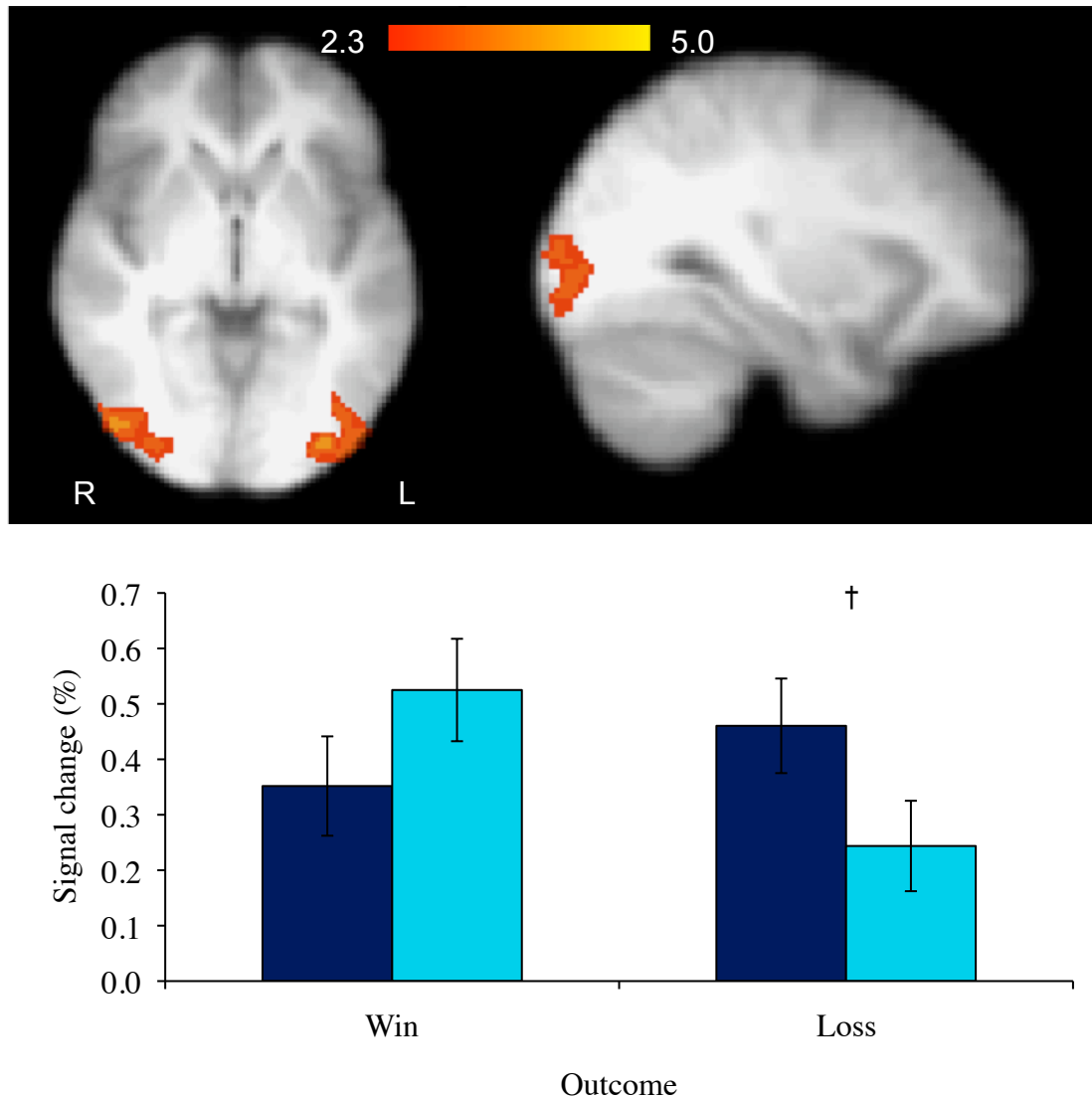
##### *4.9.5.2.1 Decision-making*

There were no significant clusters of activation for which there was a group x task interactions for probability of winning, magnitude of possible gains, magnitude of possible losses, or the reflection effect.

##### *4.9.5.2.2 Outcome*

There was a significant group x outcome interaction, with modulation of neural activation for the loss vs. win contrast across the two groups (cluster-based thresholding with height threshold of  $Z > 2.3$  and whole-brain corrected spatial extent threshold of  $p < 0.05$ ) (Table 4.12). Bipolar phenotype participants vs. controls showed significantly increased activation of the bilateral lateral occipital cortex for the loss vs. win contrast, reflecting reduced discrimination between wins and losses in this region by bipolar phenotype participants (Figure 4.17). Analysis of percent BOLD signal change revealed that the bipolar phenotype group showed a trend towards increased bilateral lateral occipital cortex activation for loss outcomes ( $F(1,38)=3.393, p=0.073$ )

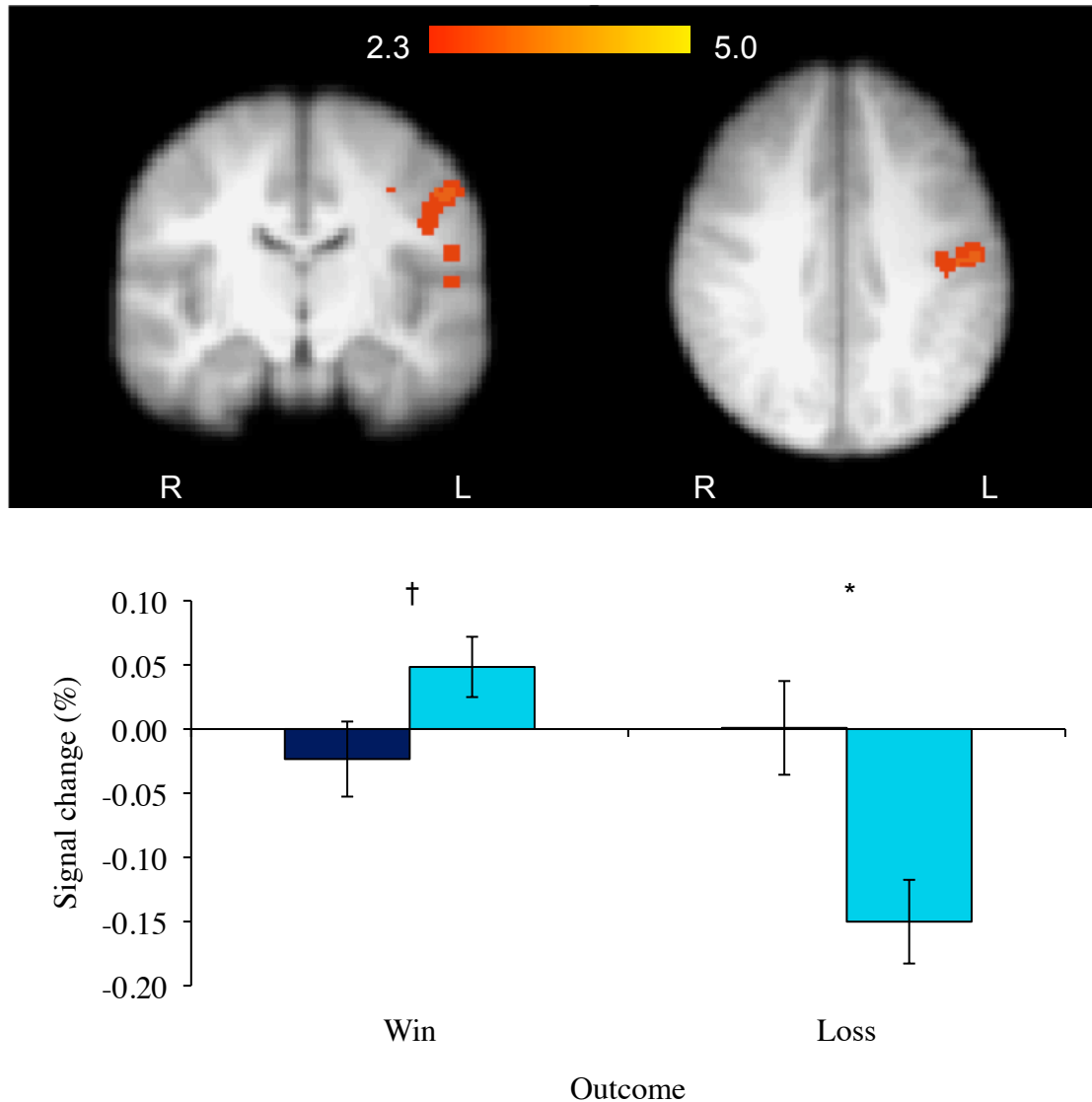
in the absence of a significant group difference for win outcomes ( $F(1,38)=1.842$ ,  $p=0.183$ ).



**Figure 4.17 Top:** Axial and sagittal images depicting significantly reduced activation in the bilateral lateral occipital cortex in bipolar phenotype participants vs. controls for win vs. loss outcomes contrast. Images were thresholded at  $Z>2.3$ ,  $p<0.05$ , whole-brain corrected. **Bottom:** Percent signal change extracted from the above significant cluster for bipolar phenotype group (dark bars) and control group (light bars). Error bars represent SEM (†  $p<0.1$  for comparison between bipolar phenotype group and controls).

Bipolar phenotype participants vs. controls also showed significantly increased activation of the left precentral and postcentral gyri for the loss vs. win contrast,

reflecting reduced discrimination between wins and losses in these regions in bipolar phenotype participants (Figure 4.19).



**Figure 4.19 Top:** Coronal and axial images depicting significantly reduced activation in the left precentral and postcentral gyri in bipolar phenotype participants vs. controls for win vs. loss outcome contrast. Images were thresholded at  $Z > 2.3$ ,  $p < 0.05$ , whole-brain corrected. **Bottom:** Percent signal change extracted from the above significant cluster for bipolar phenotype group (dark bars) and control group (light bars). Error bars represent SEM (\*  $p < 0.05$ , †  $p < 0.1$  for comparison between bipolar phenotype group and controls).

Analysis of percent BOLD signal change revealed that the bipolar phenotype group showed significantly increased activation (or reduced deactivation) of the left

precentral and postcentral gyri for outcomes that were losses ( $F(1,38)=9.401$ ,  $p=0.004$ ). The bipolar phenotype group also showed a trend towards reduced activation of this cluster for outcomes that were wins ( $F(1,38)=3.569$ ,  $p=0.067$ ).

### ***4.9.5.3 Exclusion of participants with a bipolar diagnosis***

#### *4.9.5.3.1 Behavioural results*

To assess whether group differences may have been related to bipolar diagnosis, analyses were performed excluding two participants with a diagnosis of bipolar II and three participants with a diagnosis of bipolar NOS.

For the risky decision-making task, the group x magnitude of possible losses x gender interaction was no longer significant, but there remained a trend ( $F(1,35)=3.737$ ,  $p=0.061$ ). For male participants, there remained a significant group x magnitude of possible losses interaction ( $F(1,17)=5.414$ ,  $p=0.033$ ), with male bipolar phenotype participants choosing the ‘experimental’ gamble more frequently when there were large vs. small possible losses compared to male control participants. There remained a significant group x trial type (gains only vs. losses only) interaction, with bipolar phenotype participants choosing the gamble with the guaranteed outcome more frequently for gains only vs. losses only trial, i.e. an exaggeration of the reflection effect. Post-hoc analyses revealed that the bipolar phenotype group showed significantly reduced proportionate choice of the guaranteed outcome for losses only trials ( $F(1,35)=4.876$ ,  $p=0.034$ ), whereas there was only a trend towards this result previously.

#### 4.9.5.3.2 *Functional MRI results*

For the ventral striatum ROI, there remained a significant group x outcome (win/loss) interaction ( $F(1,33)=5.549$ ,  $p=0.025$ ), with bipolar phenotype participants showing significantly greater activation to outcomes that were losses ( $F(1,33)=4.208$ ,  $p=0.048$ ) in the absence of a group difference to outcomes that were wins ( $F(1,33)=0.468$ ,  $p=0.499$ ) when participants with a bipolar diagnosis were excluded from analyses. There also remained a significant group x outcome interaction for the cluster that included the bilateral lateral occipital cortex ( $F(1,33)=23.522$ ,  $p<0.001$ ), with bipolar phenotype participants showing a trend towards greater activation to outcomes that were losses ( $F(1,33)=3.920$ ,  $p=0.056$ ) in the absence of a group difference to outcomes that were wins ( $F(1,33)=0.893$ ,  $p=0.351$ ). Finally, there remained a significant group x outcomes interaction for the cluster that included the left precentral and postcentral gyri ( $F(1,33)=28.663$ ,  $p<0.001$ ), with bipolar phenotype participants showing significantly greater activation to outcomes that were losses ( $F(1,33)=9.292$ ,  $p=0.005$ ) and a trend towards reduced activation to outcomes that were wins ( $F(1,33)=3.884$ ,  $p=0.057$ ), consistent with findings when all participants were included in analyses.

## **4.10 Discussion and conclusion**

### **4.10.1 Summary of findings**

Altered decision-making was recorded in students with the bipolar phenotype, with evidence that male subjects were particularly affected. During the risky decision-making task, male bipolar phenotype participants more frequently chose risky gambles associated with large vs. small losses relative to male control participants. Furthermore, compared to controls, male bipolar phenotype participants also made more errors before reaching criterion on the extra-dimensional block of the attentional set-shifting task, whilst female bipolar phenotype participants made fewer errors compared to controls. Bipolar phenotype participants of both genders showed a trend towards a diminution of the framing effect, i.e. reduced sensitivity to positive vs. negative framing. However, by contrast, these subjects also demonstrated enhanced non-normative decision-making by virtue of an exaggerated reflection effect. These changes in decision-making by bipolar phenotype participants were accompanied by altered patterns of neural activity in response to the outcome of their chosen gamble, including increased activation of the ventral striatum, bilateral lateral occipital cortex, and left precentral and postcentral gyri to outcomes that were losses vs. wins.

### **4.10.2 Discussion of results**

#### ***4.10.2.1 Reduced sensitivity to framing during positive and negative dilemmas***

The framed risky-choice task revealed that bipolar phenotype subjects showed a trend towards an attenuated non-normative framing effect and, therefore, were less sensitive to framing than controls. This finding is in line with previous reports of diminished

sensitivity to framing in medication-naïve and euthymic patients with bipolar disorder (Chandler, et al., 2009). Therefore, reduced sensitivity to framing reported in bipolar phenotype subjects here may represent a vulnerability marker associated with the bipolar phenotype. Further support for this suggestion comes from the findings that the trend towards an attenuated framing effect remained when analyses were repeated excluding participants with a diagnosis of bipolar disorder.

Reduced sensitivity to framing was proposed to relate to steeper psychometric functions that relate gains and losses to their subjective values (Chandler, et al., 2009). Steepening of the subjective value function in the bipolar phenotype may account for the diminished framing effect seen in this group. Typically, the subjective value of gains is expressed as a concave function of the nominal value, i.e. increasing gains relative to the same reference point produces diminishing increases in subjective value (Tversky & Kahneman, 1981). This translates to a preference for small certain gains rather than gambles for larger gains (i.e. risk aversion) under conditions of uncertainty. On the other hand, the subjective value of losses is expressed as a convex function of the nominal value (Tversky & Kahneman, 1981), which translates to a preference for gambling to avoid certain losses (i.e. risk-seeking behaviour) under conditions of uncertainty. For negatively-framed dilemmas, a steeper subjective value function (as was proposed for patients with bipolar disorder (Chandler, et al., 2009)) would produce a larger reduction in subjective value (i.e. become more aversive) for larger losses in bipolar phenotype participants than in controls, resulting in increased risk aversion as observed. Significant changes in risk aversion were limited to negatively-framed dilemmas in bipolar phenotype participants. Therefore, it is possible that bipolar phenotype participants had steeper psychometric functions

relating losses to their subjective values, but not relating gains to their subjective values.

#### ***4.10.2.2 Altered processing of punishment-related reinforcement cues***

Bipolar phenotype participants showed altered processing of punishment-related reinforcement cues in both the framed risky-choice task and the risky decision-making task. In addition to the trend towards reduced sensitivity to framing described above, findings from the framed risky-choice task have further implications for the bipolar phenotype. Post-hoc analyses of proportionate choice of the risky gamble during positively-framed and negatively-framed dilemmas indicated that responses during negatively-framed dilemmas were particularly disrupted in bipolar phenotype participants. Thus, the bipolar phenotype was associated with a trend towards reduced proportionate choice of the risky gamble during negatively-framed dilemmas compared to controls. The responses of bipolar phenotype subjects were less risk-seeking than those demonstrated by controls during negatively-framed dilemmas, indicating that bipolar phenotype participants were responding in a manner consistent with these dilemmas being intermediate between positively-framed and negatively-framed dilemmas. Therefore, whilst this finding is not consistent with previous reports of increased risk-seeking behaviour in bipolar disorder, it does however provide further support for the positive biases recorded in **Chapter 3**.

Further evidence of disrupted processing of punishment-related reinforcement cues comes from the risky decision-making task. Male bipolar phenotype participants showed significantly increased proportionate choice of 'experimental' gambles associated with large vs. small losses compared to controls. This finding suggests that

male bipolar phenotype subjects showed reduced discrimination between large and small losses, which may contribute to the disrupted decision-making that is characteristic of bipolar disorder, particularly during (hypo-) manic episodes. Furthermore, impaired discrimination between different magnitudes of losses may represent reduced processing of these punishment-related stimuli, consistent with positive biases recorded in this group in **Chapter 3**.

#### ***4.10.2.3 Disrupted non-normative decision-making***

Assessment of non-normative decision-making (the reflection effect) with gains only and losses only trials within the risky decision-making task provided further evidence of disrupted decision-making within the bipolar phenotype. Bipolar phenotype participants showed an enhanced reflection effect, with increased proportionate choice of the gamble with the guaranteed outcome for gains only vs. losses only trials. Further analyses revealed that responses during the losses only trials were particularly disrupted in the bipolar phenotype group. Thus, bipolar phenotype participants showed a trend towards reduced proportionate choice of the gamble with the guaranteed outcome (i.e. increased choice of the risky gamble) for losses only trials relative to controls. Contrary to findings of reduced proportionate choice of the risky choice during negatively-framed dilemmas in the framed risky-choice task discussed above, this result suggests that bipolar phenotype participants showed increased risk-seeking behaviour during conditions of uncertainty that involve losses only. Such a finding may be consistent with evidence of increased risk-taking behaviour recorded in bipolar disorder and experienced by bipolar phenotype subjects (see **Chapter 2**), but is not in line with findings from the framed risky-choice task. This discrepancy will be discussed under Limitations below.

#### ***4.10.2.4 Reduced neural discrimination between wins and losses***

Functional imaging analyses uncovered neural abnormalities that may be related to findings of altered processing of (punishment-related) reinforcement cues that were recorded in the framed risky-choice task and in the risky decision-making task and discussed previously. Whole-brain analyses of brain function during the risky decision-making task revealed increased activation of the bilateral lateral occipital cortices in response to outcomes that losses vs. wins and reduced deactivation of left precentral and postcentral gyri for the same contrast, consistent with reduced neural discrimination between losses and wins. The postcentral gyrus is part of the parietal cortex, which is sensitive to uncertainty of rewards during decision-making under risk (Platt & Glimcher, 1999), suggesting that bipolar phenotype participants may have altered responsivity to uncertainty of rewards, which may contribute to impaired risky decision-making in this group.

Furthermore, ROI analyses revealed significantly increased activation of the ventral striatum in response to outcomes that were losses vs. wins, which is consistent with bipolar phenotype participants showing diminished neural discrimination between losses and wins. The ventral striatum is involved in identification of the emotional significance of environmental stimuli and in the production of affective states (Phillips, et al., 2003a). Previous research revealed greater activation in the ventral striatum to emotional stimuli in euthymic patients with bipolar disorder (Phillips, et al., 2003b; Phillips, et al., 2008). Furthermore, it has been proposed that increased activity in such sub-cortical and limbic regions, including the ventral striatum, may contribute to mood instability in bipolar disorder (Phillips, 2006; Phillips, et al., 2003b). The present findings are therefore important as disrupted activation of the

ventral striatum may represent a neural correlate of the disrupted decision-making seen behaviourally in bipolar phenotype participants. However, contrary to this argument, the OFC did not show corresponding effects in response to outcomes that were losses vs. wins which may be predicted on account of the OFC being part of the ventral neural system described above (Phillips, et al., 2003a). Furthermore, the differences in activation were seen only during outcome (win/loss), but not during decision-making, which might have been expected.

These findings suggest that increased activation of cortical and sub-cortical regions, including the ventral striatum, in response to outcomes that were losses vs. wins may represent a vulnerability marker for the bipolar phenotype. Furthermore, these effects remained when participants with a diagnosis of bipolar disorder were excluded, indicating that these abnormalities were not related solely to experience of episodes of bipolar illness.

#### ***4.10.2.5 Reduced cognitive flexibility in male bipolar phenotype subjects***

Findings from the intra-dimensional/extra-dimensional attentional set-shifting task provided further evidence of disrupted cognitive processing in the bipolar phenotype. Firstly, slower response times were recorded in bipolar phenotype participants during intra-dimensional shifts. Furthermore, cognitive flexibility was particularly disrupted in male bipolar phenotype participants during extra-dimensional shifts, whilst female bipolar phenotype participants showed improved performance compared to controls. Therefore, difficulties in over-riding an acquired attentional set may amplify problems with decision-making, consistent with previously discussed disruption to risky decision-making in male bipolar phenotype participants.

### **4.10.3 Limitations**

This study has a number of limitations. Firstly, findings from the framed risky-choice task and results from the assessment of non-normative decision-making (i.e. the reflection effect) in the risky decision-making task appear to oppose one another. The framed risky-choice task revealed that the bipolar phenotype was associated with decreased sensitivity to framing and a trend towards reduced proportionate choice of risky gambles during negatively-framed dilemmas. On the other hand, in the risky decision-making task, bipolar phenotype participants demonstrated an exaggerated reflection effect, with a trend towards reduced choice of the guaranteed outcome (i.e. increased choice of the risky gamble) during losses only trials. However, the inconsistency in findings between the framed risky-choice task and the risky decision-making task can be accounted for by differences in task design. In the framed risky-choice task, the positively-framed and negatively-framed options were designed to have equal expected values. For example, a positively-framed win of 335/500 points had an equivalent negatively-framed loss of 165/500 points within the task. This was not the case for the gains only and losses only reflection effect trials in the risky decision-making task. Therefore, discrepancies between the two tasks may have resulted from differences in the monetary value of gambles between gains only and losses only trials (in the risky decision-making task) that did not exist for positively-framed and negatively-framed dilemmas (in the framed risky-choice task). Consequently, the findings from these two tasks suggest that the bipolar phenotype is associated with reduced sensitivity to framing and, additionally, increased sensitivity to the overall monetary value of gambles (positive outcomes for gains only trials and negative outcomes for losses only trials).

Secondly, a number of the effects recorded in bipolar phenotype participants in this study, including an attenuated framing effect, reduced proportionate choice of the risky gamble during negatively-framed dilemmas, reduced proportionate choice of the guaranteed outcome during losses only trials, and increased functional activation of the bilateral lateral occipital cortices to losses (in particular) were not demonstrated at conventional levels of statistical significance. Additionally, some effects, including diminished sensitivity to magnitude of possible losses and number of errors to criterion for the extra-dimensional set-shifting block, were found only in male bipolar phenotype subjects. Finally, when analyses were repeated excluding participants with a bipolar diagnosis, there was no longer a trend towards this reduced risk-seeking behaviour in negatively-framed dilemmas in bipolar phenotype participants. This may suggest that specific alterations in risk-taking behaviour may be driven by differences in diagnosed participants, or could have resulted from a reduction in statistical power associated with the smaller sample size. Therefore further investigation is required in larger samples of male and female participants.

#### **4.10.4 Conclusion**

Disrupted behavioural performance and neural processing of reinforcement cues were seen during tasks assessing risky decision-making, sensitivity to framing during risky choice, and cognitive flexibility in a group of participants who were part of a continuum of risk for the bipolar phenotype. This study showed that the bipolar phenotype was associated with increased choice of risky gambles associated with large losses (male subjects only) and reduced sensitivity to framing of risky choices. Furthermore, increased functional activation of the ventral striatum, bilateral lateral

occipital cortex, and left precentral and postcentral gyri to outcomes that were losses vs. wins was seen in bipolar phenotype participants. In addition to these alterations in risky decision-making, male bipolar phenotype participants also showed reduced cognitive flexibility. Overall, bipolar phenotype participants showed abnormal decision-making and altered neural processing of outcomes that were losses vs. wins, which may relate to increased risk-seeking behaviour, gambling, and impulsivity associated with the bipolar phenotype, particularly in male subjects.

## 5 Sleep and circadian rhythms and the bipolar phenotype

### 5.1 Introduction

**Chapter 2** investigated the levels of bipolar diagnosis and associated co-morbidity in bipolar phenotype participants who had experience of mood elevation by virtue of high scores on the Mood Disorder Questionnaire (MDQ) (Hirschfeld, et al., 2000b). The bipolar phenotype was found to be associated with mood abnormalities (e.g. increased neuroticism and depression), decision-making abnormalities (e.g. risk-taking behaviour), and disrupted sleep (e.g. reduced need for sleep). **Chapter 3** and **Chapter 4** investigated emotional processing and decision-making in previously undiagnosed students with the bipolar phenotype and found behavioural and neural abnormalities across these two domains. However, one area not previously considered is that of sleep and circadian rhythmicity, which is important because over two thirds of bipolar phenotype participants reported previous experience of a reduced need for sleep (e.g. feeling rested after only a few hours' sleep) and, furthermore, over four fifths endorsed experience of symptoms of abnormally elevated energy and activity levels.

Disruptions to sleep and circadian rhythms are common in mood disorders (Wulff, et al., 2010). Indeed, hypersomnia and insomnia are diagnostic features of a depressive episode and hyposomnia and a reduced need for sleep are characteristic of episodes of (hypo-) mania. In a recent study of young medication-naïve and euthymic bipolar patients, rest-wake actigraphy revealed increased activity levels during sleep, reduced relative amplitude, which reflects activity during the most active 10 hours compared to activity during least active five hours, and reduced inter-daily stability, which

reflects less consistent patterns of activity from day to day (Chandler, et al., 2008). It is therefore of interest to investigate whether similar disruptions to relative amplitude and inter-daily stability are found in bipolar phenotype participants.

## **5.2 Aim**

This chapter will investigate sleep and circadian rhythms in medication-naïve students with the bipolar phenotype using actigraphy. It was hypothesised that bipolar phenotype subjects may show signs of increased activity during sleep and a reduced relative amplitude as well as a reduced inter-daily stability.

### **5.3 Methods 1: Participants characteristics**

#### **5.3.1 Participants**

A sub-sample of 44 participants from **Chapter 3** completed this study. Twenty-three participants (12 female, 11 male) were in the high MDQ bipolar phenotype group by virtue of high scores on the MDQ (mean MDQ score  $\pm$  standard deviation =  $9.2 \pm 1.4$ , range = 7-12). Twenty-one participants (10 female, 11 male) were in the control group by virtue of low scores on the MDQ (mean MDQ score  $\pm$  standard deviation =  $0.3 \pm 0.6$ , range = 0-2). All participants were euthymic (HAM-D  $\leq$  8 and YMRS  $\leq$  8).

#### **5.3.2 Characterisation of chronotype**

Diurnal (day/night) preference, i.e. chronotype, was assessed with the Morningness-Eveningness questionnaire, which has been validated for young adults (Horne & Ostberg, 1976). Higher scores are associated with a greater degree of morningness, which is associated with earlier waking and bedtime, whilst eveningness is associated with later waking and bedtime. A score of 16-30 represents extreme evening type, 31-41 represents moderate evening type, 42-58 represents neither type, 59-69 represents moderate morning type, and 70-86 represents extreme morning type in student-aged subjects (Horne & Ostberg, 1976).

#### **5.4 Methods 2: Sleep**

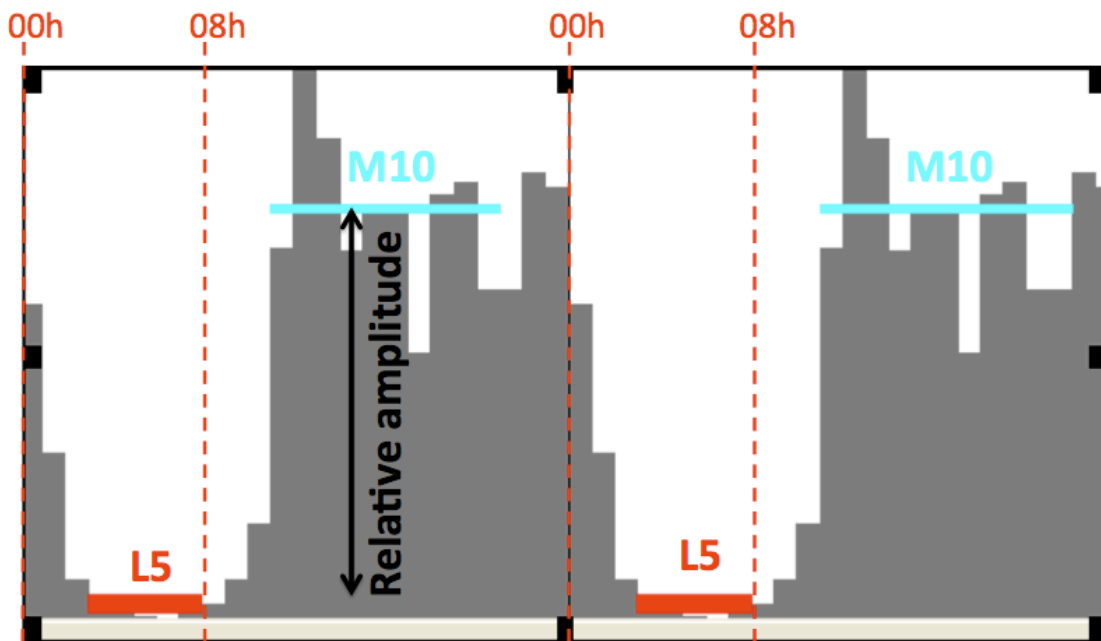
Participants wore an Actiwatch® on their non-dominant wrist for approximately two weeks (12-16 days) to monitor activity and light levels. The Actiwatch® relied upon piezoelectric sensors to measure acceleration, which was integrated over time to generate an activity score linked to the amplitude of movement. Equidistant one-minute sampling was used to give an activity score that represented the sum of the maximum activity counts for each of 60 one-second epochs within each minute. Participants wore the watch continuously, but removed it when it might get wet or damaged such as during showering or sport. Participants also completed a diary, in which they recorded bedtime, wake-up time, naps, sedentary activity, and any periods during which the watch was removed.

Actigraphy data were edited to replace periods longer than 30 minutes when the watch had been removed with a daily average of activity and light levels. Any days for which the watch was removed for more than three hours were excluded from circadian rhythm analysis, but were included in sleep timing analysis.

Sleep analysis was carried out using Actiwatch® Activity & Sleep Analysis software (Cambridge Neurotechnology Version 7.23) with the aid of the participant's diary. Bedtime was denoted as the time from which the participant was trying to sleep, i.e. lights were off and participant was lying still. Wake-up time was the earliest time at which there was significant and sustained movement in the morning.

Sleep parameters were calculated automatically by the Actiwatch® Activity & Sleep Analysis software and included sleep onset, final wake time, total sleep period (from

sleep onset to final wake time), total sleep time (total sleep period excluding times of activity above threshold of 40 activity counts, defined as ‘wake time’ by the software’s algorithm), sleep latency (from bedtime until sleep onset), sleep efficiency (total sleep time as a percentage of time in bed, which includes sleep latency), percentage immobility, fragmentation index (measure of restlessness; >50 is considered bad, <20 is considered very good), activity during least active five hours (L5 activity) and L5 onset, and activity during most active ten hours (M10 activity) and M10 onset (Figure 5.1).



**Figure 5.1** Graphic of L5, M10 and relative amplitude parameters over 48 hours.

### **5.5 Methods 3: Circadian rhythms**

Circadian rhythm analysis was also performed using Actiwatch® Activity & Sleep Analysis software 7 (Cambridge Neurotechnology Version 7.23). This analysis was carried out on actigraphy data for time periods of at least two consecutive days.

Circadian rhythm parameters were also calculated automatically by the Actiwatch® Activity & Sleep Analysis software and included relative amplitude, inter-daily stability, and intra-daily variability. Relative amplitude reflects the difference between M10 activity and L5 activity and is calculated as follows:  $(M10-L5)/(M10+L5)$  (Figure 5.1). In healthy people high circadian relative amplitude values result from greater daytime activity and reduced activity during sleep. Relative amplitude scores theoretically range from 0 to 1, with higher values indicating a circadian rhythm of higher amplitude. Inter-daily stability represents the degree of consistency of activity patterns from one day to the next. Inter-daily stability scores range from 0 to 1, and may typically be 0.6, with lower score representing poor consistency of activity patterns. Intra-daily variability quantifies the fragmentation of periods of activity from periods of rest within a 24-hour period. Intra-daily variability scores range from 0 to 2 and are typically below 1. Higher intra-daily variability values indicate a more fragmented rhythm and reflect shorter periods of rest and activity rather than one extended active period during the daytime and one extended rest period at night.

## **5.6 Methods 4: Statistical analyses**

Sleep and circadian rhythm statistics were analysed using univariate analyses of variance with group and gender as fixed factors. A chi-square test was used to analyse Morningness-Eveningness questionnaire responses for differences in chronotype distribution between groups. All statistical analyses were performed using SPSS (version 16.0 for Mac, SPSS Inc.). A significance threshold of  $p < 0.05$  was used for all analyses.

## 5.7 Results 1: Demographics and chronotype

Forty participants had at least nine days of useable actigraphy data and were included in the final analysis. There were 19 (10 female, 9 male) bipolar phenotype participants (mean MDQ score  $\pm$  standard deviation =  $9.0 \pm 1.5$ , range = 7-12) who had 9-15 days' worth of actigraphy data. There were 21 (10 female, 11 male) control participants (mean MDQ score  $\pm$  standard deviation =  $0.3 \pm 0.6$ , range = 0-2) who had 9-16 days' worth of actigraphy data. On average, the control group wore the Actiwatch® for one day longer than the bipolar phenotype group (mean  $\pm$  standard deviation: bipolar phenotype vs. controls:  $12.5 \pm 1.7$  days vs.  $13.4 \pm 1.8$  days).

Of the 19 bipolar phenotype participants, there were 4 cases of bipolar II, 3 cases of bipolar not otherwise specified (NOS), 2 cases of major depressive disorder, and 4 cases of anxiety co-morbidity.

Results from the Morningness-Eveningness questionnaire (Horne & Ostberg, 1976) are shown in Table 5.1. Responses from one bipolar phenotype participant are missing. The distributions of chronotype are largely similar across the two groups ( $\chi^2(4) = 1.450$ ,  $p = 0.835$ , but 8 cells had an expected count  $< 5$ ).

**Table 5.1** Morningness-Eveningness chronotype questionnaire results.

Chronotype (score range)	Bipolar phenotype N= 18	Controls N=21
Extreme evening (16-30)	3 (17)	3 (14)
Moderate evening (31-41)	4 (22)	4 (19)
Neither type (42-58)	7 (39)	10 (48)
Moderate morning (59-69)	3 (17)	4 (19)
Extreme morning (70-86)	1 (6)	0 (0)

Values represent N (%).

## 5.8 Results 2: Sleep

### 5.8.1 Actigraphy results

Sleep parameters for the two groups are shown in Table 5.3. Bipolar phenotype subjects and controls showed very similar values for sleep onset, final wake time, total sleep period, sleep latency, sleep efficiency, percentage immobility, fragmentation index, L5 onset, M10 activity, and M10 onset (all  $p$  values  $> 0.1$ ).

The bipolar phenotype group showed a trend towards reduced total sleep time (group:  $F(1,36)=3.321$ ,  $p=0.077$ ; group x gender:  $F(1,36)=0.008$ ,  $p=0.931$ ). This may have been driven by a strong trend towards increased activity during the least active five hours of sleep, i.e. L5 activity, in the bipolar phenotype group (group:  $F(1,36)=3.913$ ,  $p=0.056$ ). There was also a significant group x gender interaction for L5 activity ( $F(1,36)=5.975$ ,  $p=0.020$ ). For female participants, the bipolar phenotype group ( $2309 \pm 1274$ ) showed significantly greater L5 activity than controls ( $1195 \pm 425$ ) ( $F(1,18)=6.886$ ,  $p=0.017$ ). However, there was no such difference for male participants ( $F(1,18)=0.189$ ,  $p=0.669$ ).

**Table 5.3** Sleep parameters.

	Bipolar phenotype N=19	Controls N=21
Sleep onset	01:10 (00:31)	01:08 (00:55)
Final wake time	08:28 (01:13)	08:53 (00:51)
Total sleep period	07:19 (00:43)	07:43 (00:43)
Total sleep time	06:15 (00:39)	06:38 (00:40)
Sleep latency	00:05 (00:03)	00:06 (00:04)
Sleep efficiency (%)	84.0 (4.5)	84.6 (3.5)
Immobility (%)	85.2 (4.2)	86.6 (2.6)
Fragmentation index	30.6 (9.2)	27.4 (6.4)
L5 activity	1869 (1068)	1354 (583)
L5 onset	02:06 (00:19)	02:20 (00:46)
M10 activity	22590 (3281)	21680 (4463)
M10 onset	11:18 (01:39)	11:19 (01:44)

Values represent means (standard deviations).

### 5.8.2 Exclusion of participants with a bipolar diagnosis

To assess whether group differences may have been related to bipolar diagnosis, analyses were performed excluding four participants with a diagnosis of bipolar II and three participants with a diagnosis of bipolar NOS.

There remained a trend towards reduced total sleep time (group:  $F(1,29)=3.217$ ,  $p=0.083$ ; group x gender:  $F(1,29)=0.083$ ,  $p=0.775$ ) in the bipolar phenotype group. Furthermore, the trend towards increased L5 activity in the bipolar phenotype group became significant (group:  $F(1,29)=5.418$ ,  $p=0.027$ ). The group x gender interaction remained significant for L5 activity ( $F(1,29)=5.829$ ,  $p=0.022$ ), with female bipolar phenotype participants showing significantly greater L5 activity than female controls ( $F(1,14)=8.730$ ,  $p=0.010$ ) in the absence of a group difference for male participants ( $F(1,15)=0.005$ ,  $p=0.944$ ).

Finally, the bipolar phenotype group also showed significantly earlier final wake time (group:  $F(1,29)=4.300$ ,  $p=0.046$ ; group x gender:  $F(1,29)=1.397$ ,  $p=0.247$ ), significantly increased percentage immobility (group:  $F(1,29)=4.361$ ,  $p=0.046$ ; group x gender:  $F(1,29)=1.128$ ,  $p=0.297$ ), and a trend towards increased fragmentation index (group:  $F(1,29)=3.390$ ,  $p=0.076$ ; group x gender:  $F(1,29)=1.274$ ,  $p=0.268$ ), for which there had not been group differences previously.

## 5.9 Results 3: Circadian rhythms

### 5.9.1 Actigraphy results

Circadian rhythm parameters for the two groups are shown in Table 5.5. Bipolar phenotype participants and controls showed very similar intra-daily variability measures (all  $p$  values  $> 0.1$ ).

There was no group difference for the circadian measure of relative amplitude ( $F(1,36)=2.263, p=0.141$ ), however there was a significant group x gender interaction ( $F(1,36)=6.849, p=0.013$ ). For female participants, the bipolar phenotype group ( $0.81 \pm 0.10$ ) showed significantly reduced circadian relative amplitude compared to controls ( $0.89 \pm 0.03$ ) ( $F(1,18)=6.485, p=0.020$ ). However, there was no such difference for male participants ( $F(1,18)=0.901, p=0.355$ ).

There was no group difference in inter-daily stability ( $F(1,36)=0.068, p=0.795$ ), but there was a significant group x gender interaction ( $F(1,36)=5.121, p=0.030$ ). However, there was no significant group difference for female participants ( $F(1,18)=2.504, p=0.131$ ) or male participants ( $F(1,18)=2.763, p=0.114$ ).

**Table 5.5** Circadian rhythm parameters.

	Bipolar phenotype N=19	Controls N=21
Relative amplitude	0.85 (0.09)	0.88 (0.05)
Inter-daily stability	0.43 (0.11)	0.44 (0.09)
Intra-daily variability	0.98 (0.18)	0.99 (0.19)

Values represent means (standard deviations).

### **5.9.2 Exclusion of participants with a bipolar diagnosis**

When participants with a diagnosis of bipolar disorder (II or NOS) were excluded, there became a trend towards a reduction in relative amplitude in the bipolar phenotype group ( $F(1,29)=3.379, p=0.076$ ). Furthermore, the group x gender interaction remained significant for relative amplitude ( $F(1,29)=8.100, p=0.008$ ), with female bipolar phenotype participants showing significantly reduced relative amplitude compared to controls ( $F(1,14)=8.708, p=0.011$ ) in the absence of a group difference for male participants ( $F(1,15)=0.665, p=0.428$ ).

There remained a significant group x gender interaction for inter-daily stability (group:  $F(1,29)=0.198, p=0.659$ ; group x gender:  $F(1,29)=4.221, p=0.049$ ). However, consistent with previous findings, there was no group difference in inter-daily stability for female participants ( $F(1,14)=2.282, p=0.153$ ) or male participants ( $F(1,15)=1.946, p=0.183$ ).

## **5.10 Discussion and conclusion**

### **5.10.1 Summary of findings**

This study revealed a trend towards increased L5 activity in the bipolar phenotype group. Female bipolar phenotype participants in particular were found to have significantly elevated activity during their least active five hours (between 2am and 7am) and, consequently, showed significantly reduced relative amplitude of circadian rhythm. Both male and female bipolar phenotype participants showed a trend towards reduced total sleep time. Together, these findings suggest that disrupted sleep and circadian rhythms may be particularly prominent in female participants with the bipolar phenotype, whilst reduced total sleep time may be associated with the bipolar phenotype across both genders.

### **5.10.2 Discussion of results**

Sleep disruption and circadian instability are intrinsic features of bipolar disorder (Harvey, 2008; Wulff, et al., 2010; Wulff, et al., 2009), and previous studies have recorded abnormalities during mood episodes (Harvey, 2008) and euthymia (Harvey, et al., 2005; Jones, et al., 2005). This study used actigraphy to assess rest-activity patterns in previously undiagnosed and medication-naïve bipolar phenotype participants in order to overcome confounds related to experience of medications and repeated serious illness episodes potentially associated with research in euthymic bipolar participants.

Actigraphic analyses revealed a trend towards greater activity during sleep, including the least active five hours (L5 activity) between 2am and 7am, in bipolar phenotype

participants. Accordingly, the bipolar phenotype group showed a trend towards reduced total sleep time that was calculated by subtracting 'wake time' (i.e. when subjects were active) from the total sleep period (which did not differ significantly in duration between groups). Whilst the group difference in total sleep time affected male and female subjects to a similar extent and may therefore contribute to experience of mood-elevation symptoms across both genders, the increase in L5 activity was particularly prominent in female bipolar phenotype participants.

This pattern of findings was replicated when participants with a bipolar diagnosis were excluded. Analyses revealed that bipolar phenotype participants (without a bipolar diagnosis) showed significantly increased L5 activity and reduced circadian relative amplitude, driven by striking group differences within female participants. These results replicate findings of increased L5 activity and reduced circadian relative amplitude recorded in medication-naïve students with a bipolar diagnosis (Chandler, et al., 2008) and extend these observations to a sample including undiagnosed participants at-risk for bipolar disorder. Therefore, this study demonstrated that disruption to sleep and relative amplitude of the circadian rhythm is not limited to diagnosed patients, but is also seen in the bipolar phenotype and may be associated with vulnerability for bipolar disorder, especially in female subjects. Analyses excluding participants with a bipolar diagnosis also revealed that the bipolar phenotype was associated with earlier final wake time, increased percentage immobility, and a trend towards an increased fragmentation index. These changes may contribute to the elevated levels of activity during sleep and the reduction in total sleep time that represent vulnerability for bipolar disorder.

The present study did not replicate findings of reduced inter-daily stability as shown in medication-naïve students with a bipolar diagnosis (Chandler, et al., 2008). Disrupted stability of circadian rhythmicity from one day to the next (i.e. inter-daily stability) may be found specifically in diagnosed bipolar patients rather than in the bipolar phenotype and, therefore, may not represent a vulnerability marker for bipolar disorder.

This study identifies important gender differences in sleep and circadian rest-activity associated with the bipolar phenotype. These findings are not consistent with previous reports of largely similar profiles of bipolar disorder across the two genders (Akiskal, et al., 2006). The differences in L5 activity and relative amplitude reported here may not be applicable to male participants and may be limited in their ability to be interpreted for the bipolar phenotype in general.

### **5.10.3 Limitations**

This study had a number of limitations. Firstly, whilst actigraphy can be used over a number of days (or weeks) to investigate circadian rhythms, this technique is not able to provide information about sleep staging and spectral composition. Future studies employing electroencephalography (EEG) are necessary to determine whether increased L5 activity is associated with changes in sleep architecture and the temporal dynamics of sleep in bipolar phenotype subjects. Secondly, the study did not include a physiological measure of circadian phase such as an assessment of melatonin or cortisol levels, so it is not possible to make conclusions about differences in circadian rhythms associated with the bipolar phenotype.

#### **5.10.4 Conclusion**

Increased activity during sleep and, correspondingly, reduced relative amplitude of circadian rhythm were recorded in medication-naïve female bipolar phenotype participants. Findings of increased L5 activity and reduced relative amplitude suggest that sleep (and potentially circadian rhythm) disruption therefore may be associated with the bipolar phenotype, particularly in female subjects. These results provide useful insight into the potential role of circadian rhythm instability in the development of bipolar disorder, and may be important in understanding the efficacy of pharmacological treatments whose effects may be mediated through the improvement of sleep (Kasper, et al., 2010).

Future longitudinal actigraphy studies are required to assess whether these differences in L5 activity and circadian rhythms are stable over time and if those participants with particularly disrupted sleep and circadian rhythms are especially likely to go on to develop serious mood episodes. Furthermore, these studies may provide information about changes in sleep and circadian rhythms prior to mood episode onset and, therefore, actigraphy may have a potential role as an early warning system in patients with bipolar disorder.

## **6 The effects of quetiapine on emotional processing, decision-making, and sleep and circadian rhythms in healthy volunteers**

### **6.1 Introduction**

**Chapter 3**, **Chapter 4**, and **Chapter 5** recorded positive emotional processing biases, disrupted decision-making, and disturbed sleep and circadian rhythms in students with the bipolar phenotype. However it remains unknown whether pharmacological treatments for bipolar disorder target these neuropsychological and physiological markers and, consequently, whether resolution of these changes may be involved in the mechanism of action of drug treatments. This may be investigated by studying the effects of a drug that is used in the treatment of bipolar disorder. Such an approach has been applied to antidepressants used in the treatment of unipolar depression. For example, studies employing short-term antidepressant administration in healthy volunteers have recorded positive biases in emotional processing. On the basis of these findings it has been postulated that the therapeutic effects of antidepressants may be mediated by a reversal of the negative biases found in depression (Harmer, et al., 2003). To date, psychopharmacological investigation of treatments for bipolar disorder has been limited.

One drug used in the treatment of bipolar disorder is quetiapine, which has recently been shown to be an effective monotherapy for bipolar depression (Calabrese, et al., 2005) in addition to its role as an antipsychotic treatment for schizophrenia and bipolar mania (Bowden, et al., 2005). Like other atypical antipsychotics, quetiapine

shows dual antagonism of dopamine D<sub>2</sub> and serotonin 5-HT<sub>2A</sub> receptors (Kapur & Remington, 2001). Furthermore, quetiapine's active metabolite, norquetiapine, antagonises dopamine D<sub>2</sub> and serotonin 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors, acts as a partial agonist at 5-HT<sub>1A</sub> receptors, and inhibits noradrenaline reuptake via the noradrenaline transporter (Goldstein, et al., 2008), effects which may contribute to quetiapine's efficacy in the treatment of bipolar depression.

## **6.2 Aim**

This chapter will investigate emotional processing, decision-making, and sleep and circadian rhythms in healthy volunteers following one-week quetiapine administration. Since quetiapine is effective in the treatment of bipolar mania as well as bipolar depression, it is unclear whether quetiapine administration in healthy volunteers will be associated with biased emotional processing, as seen following antidepressant treatment, or whether the effects will be linked instead to mood stabilisation. In general, lower doses of quetiapine (up to 300mg per day) are effective in the treatment of bipolar depression (Calabrese, et al., 2005) whereas higher doses (400mg - 800mg per day) may be necessary in the treatment of bipolar mania (Bowden, et al., 2005). Therefore, at the low doses used in this study (150mg per day titrated over three days), it is hypothesised that mainly antidepressant effects will be recorded.

## **6.3 Methods 1: Participant characteristics**

### **6.3.1 Participants**

Forty participants (20 female, 20 male) were recruited through advertisements posted online and in University departments. All participants gave their written informed consent to participate in the study, which was approved by Oxfordshire Research Ethics Committee (REC 09/H0605/46).

### **6.3.2 Psychiatric and medical screening**

Volunteers were screened to exclude those with a current or previous history of psychiatric disorder, alcohol or substance abuse/dependence (assessed using the Mini International Neuropsychiatric Interview-Plus (Mini-Plus) (Sheehan, et al., 1998)), pregnancy or lactation, history of significant medical disorder, or current usage of any medication other than contraception. Two of the participants from the quetiapine group were occasional smokers, defined as five or fewer cigarettes per day.

Participants were screened with the 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young, et al., 1978) and were included only if  $\text{HAM-D} \leq 8$  and  $\text{YMRS} \leq 8$  to ensure that they were euthymic.

### **6.3.3 Demographic information**

Verbal IQ was assessed using the National Adult Reading Test (NART) (Nelson, 1982). Details of family history of mood disorders were sought. Participants with a family history of bipolar disorder or schizophrenia were not included.

### **6.3.4 Characterisation of subjective mood and personality characteristics**

To assess mood and personality characteristics and chronotype (diurnal preference), participants completed the following questionnaires at baseline before drug intervention: Mood Disorder Questionnaire (MDQ) (Hirschfeld, et al., 2000b), Eysenck Personality Questionnaire (EPQ) (Eysenck & Eysenck, 1975), and Morningness-Eveningness questionnaire (Horne & Ostberg, 1976). Subjective mood was recorded at baseline and at 1pm on day 8 using the following questionnaires: Befindlichkeit Scale of Mood and Energy (BfS) (von Zerssen, et al., 1974), Positive and Negative Affect Schedule (PANAS) (Watson, et al., 1988), State-Trait Anxiety Inventory (STAI) (Spielberger, et al., 1970), and 100m Visual Analogue Scales (VAS) for the following variables: happy, sad, irritable, anxious, interested in others, feel good, and talkative. The following questionnaires were also completed at 9pm on each of the seven days of drug intervention: Befindlichkeit Scale of Mood and Energy (BfS) (von Zerssen, et al., 1974), Positive and Negative Affect Schedule (PANAS) (Watson, et al., 1988), State-Trait Anxiety Inventory (STAI) (Spielberger, et al., 1970), 100m Visual Analogue Scales (VAS) for the following variables: happy, sad, irritable, anxious, interested in others, feel good, and talkative, and a side effects questionnaire.

### **6.3.5 Drug randomisation**

Healthy volunteers were randomly allocated to double-blind seven-day quetiapine or placebo administration. Twenty participants (9 female, 11 male) received 150mg doses of quetiapine XL (titrated over three nights in 50mg steps) at 9pm for seven nights (day 1 to day 7). Twenty participants (11 female, 9 male) received a placebo substance with sham titration. Participants were asked to refrain from drinking

alcohol, cycling, driving, and partaking in strenuous exercise during the study week in case of possible side effects of quetiapine. Female participants were given a pregnancy test at screening and instructed of the importance of using effective contraception for the entire duration of the study. Sub-chronic (i.e. 7-day) treatment with quetiapine was carried out in preference to a single dose study to allow for titration from 50mg to 150mg over three days. This minimised possible side effects such as sedation, which might otherwise have affected participants' performance during testing and furthermore allowed for stabilisation of blood serum concentrations.

## **6.4 Methods 2: Emotional processing tasks**

### **6.4.1 Emotional test battery**

Facial expression recognition, emotional categorisation, emotional memory, emotion-potentiated startle, and attentional word dot-probe tasks were completed (see **Chapter 3**).

### **6.4.2 Attentional vigilance faces dot-probe**

#### ***6.4.2.1 Stimuli***

Pairs of photographs of 20 individuals were taken from the JACFEE/JACNeuF sets of facial expressions (Matsumoto & Eckman, 1988). Each face pair was comprised of one emotional and one neutral expression of the same individual or two neutral expressions of the same individual. Half of the emotional faces were fearful and half were happy. Therefore, there were three types of face pair: fearful-neutral, happy-neutral, and neutral-neutral.

#### ***6.4.2.2 Procedure***

On each trial, a pair of faces (fearful-neutral, happy-neutral, or neutral-neutral) was presented on the screen with one face at the top and the other face at the bottom. The emotional faces appeared in the top and bottom position with equal frequency. In the unmasked condition the face pair was presented for 100ms and was immediately followed by a probe, whereas in the masked condition the face pair appeared for 16ms followed by the display (84ms) of a mask (constructed from a jumbled face). After that, a probe (two dots presented either vertically : or horizontally ..) was presented in

the location of one of the preceding faces. Participants were required to indicate the orientation of the dots by pressing a labelled key on the keyboard. For fearful-neutral and happy-neutral face pairs, if the probe was presented behind the emotional face it was the congruent condition, whereas if the probe was presented behind the neutral face it was the incongruent condition. The dots remained on the screen until the participants had made their response.

There were eight blocks of unmasked trials (12 trials per block) and eight blocks of masked trials (12 trials per block), presented in an alternating order. There were 192 trials in total, with 32 fearful-neutral, 32 happy-neutral, and 32 neutral-neutral pairs for the unmasked and masked conditions.

Attentional vigilance reaction times were calculated for both types of emotional face for each participant by subtracting mean reaction time for congruent trials (probe and emotional face appeared in same position) from the mean reaction time for incongruent trials (probe appeared in position opposite to the emotional face) (for correct responses only). Positive attentional vigilance scores reflected attention towards the emotional face (vigilance), whereas negative values reflected attention away from the emotional face (avoidance).

### 6.5 Methods 3: Risky decision-making task

A behavioural version of the risky decision-making task (see **Chapter 4**) was completed without concurrent fMRI. This version of the task differed in the probabilities of winning (high 0.6 vs. low 0.4), possible gains (large 70 points vs. small 30 points), and possible losses (large 70 points vs. small 30 points) (see Table 6.1). For gains only trials, participants were asked to choose between a guaranteed win of 30 points and a gamble with a 0.5 chance of winning 60 points and a 0.5 chance of winning 0 points; neither option involved losses. For losses only trials, participants were asked to choose between a guaranteed loss of 30 points and a risky gamble with a 0.5 chance of losing 60 points and a 0.5 chance of losing 0 points; neither option involved gains. The points had no monetary value to participants.

**Table 6.1** The eight types of ‘experimental’ gamble resulting from the combination, in a completely crossed design, of two levels of probability, possible gains, and possible losses.

Probability	Possible gains	Possible losses	Expected value <sup>A</sup>
High (0.6)	Large (70)	Large (70)	14
		Small (30)	30
	Small (30)	Large (70)	-10
		Small (30)	6
Low (0.4)	Large (70)	Large (70)	-14
		Small (30)	10
	Small (30)	Large (70)	-30
		Small (30)	-6

<sup>A</sup> The ‘expected value’ for each gamble equals the sum of its gains and losses, each weighted by their probability of occurrence. These values vary between -30 and +30 points, with a mean of 0.

## **6.6 Methods 4: Sleep and circadian rhythms**

Actigraphy (see **Chapter 5**) was used to assess sleep and circadian rhythms for one week pre-drug and one week during drug administration. The two weeks were analysed independently and compared to investigate the effects of quetiapine administration.

## **6.7 Methods 5: Statistical analyses**

### **6.7.1 Statistical analyses**

Baseline demographic and participant characteristics were analysed using univariate analyses of variance (ANOVA) with group (quetiapine vs. placebo) and gender as between-subjects factors. Subjective effects were analysed with repeated-measures ANOVAs with group and gender as between-subjects factors and time (baseline vs. post treatment) as the within-subjects factor.

Emotional processing measures were analysed using repeated-measures ANOVAs with group and gender as between-subjects factors and emotion as the within-subjects factor.

Decision-making measures were analysed using repeated-measures ANOVAs with group and gender as between-subjects factors and (a) probability of winning, magnitude of gains, and magnitude of losses, (b) expected value, or (c) trial type (gains only vs. losses only; to assess the reflection effect) as within-subjects factors.

Sleep and circadian rhythm parameters were analysed using repeated-measures ANOVAs with group and gender as between-subjects factors and time point (baseline week vs. during drug administration) as the within-subjects factor.

One-sample *t* tests were used for comparisons with a test value. Significant interactions were followed up with univariate ANOVAs with group and gender as

fixed factors. All statistical analyses were performed using SPSS (version 16.0 for Mac, SPSS Inc.). A significance threshold of  $p < 0.05$  was used for all analyses.

### **6.7.2 Signal detection analyses**

Target sensitivity ( $d'$ ) and response bias ( $\beta$ ) were calculated using the facial expression recognition and emotional recognition data according to equations described by Grier (1971) and described in **Chapter 3**. Target sensitivity ( $d'$ ) takes values between 0 and 1, and higher  $d'$  values are associated with better target sensitivity. Response bias ( $\beta$ ) takes values between -1 and +1, and higher  $\beta$  values are associated with a conservative response style, i.e. few false alarms.

### **6.7.3 Decision-making analyses**

Proportionate choice data were arcsine transformed as is appropriate when the variance of a measure is proportional to its mean (Howell, 1987) and as described in **Chapter 4**. However, the text and figures show untransformed data.

## **6.8 Results 1: Participant characteristics**

### **6.8.1 Demographics**

The two groups were well matched in terms of age (quetiapine vs. placebo:  $25.4 \pm 6.3$  years vs.  $23.6 \pm 3.2$  years;  $F(1,36)=1.367$ ,  $p=0.250$ ), gender, body mass index ( $23.6 \pm 3.2$  vs.  $22.8 \pm 2.9$ ;  $F(1,36)=0.746$ ,  $p=0.393$ ), and verbal IQ ( $112.0 \pm 5.2$  vs.  $113.0 \pm 5.3$ ;  $F(1,36)=0.361$ ,  $p=0.552$ ) assessed with the National Adult Reading Test (NART) (Nelson, 1982).

### **6.8.2 Subjective mood and personality characteristics**

The two groups were well matched for mood and personality characteristics assessed with the HAM-D (Hamilton, 1960), YMRS (Young, et al., 1978), EPQ neuroticism, liar and extraversion dimensions (Eysenck & Eysenck, 1975), and MDQ symptoms scores (Hirschfeld, et al., 2000a), and all participants had low scores on the HAM-D and YMRS (and were euthymic;  $\text{HAM-D} \leq 8$  and  $\text{YMRS} \leq 8$ ) during testing (Table 6.3). However, the quetiapine group showed a trend towards a lower psychoticism score on the EPQ (Eysenck & Eysenck, 1975), despite both groups having very low scores ( $2.5 \pm 1.5$  vs.  $3.6 \pm 2.8$ ).

The two groups were also well matched for baseline subjective affect and anxiety, including measures assessed by visual analogue scales (all  $p$  values  $> 0.1$ ). Furthermore, there were no differences in the modulation of subjective affect following treatment with quetiapine compared to placebo (Table 6.3), except a trend for differential modulation of talkativeness. Importantly, there were no significant

group differences in subjective affect at the end of the seven-day period (all  $p$  values  $> 0.1$ ).

**Table 6.3** Subjective mood and personality characteristics.

	Quetiapine N=20	Placebo N=20	Significance $df=1,36$
HAM-D	0.9 (1.6)	0.7 (1.0)	$F=0.132, p=0.719$
YMRS	1.2 (1.4)	0.6 (1.0)	$F=2.058, p=0.160$
EPQ neuroticism	4.5 (4.5)	4.0 (2.8)	$F=0.189, p=0.666$
EPQ psychoticism	2.5 (1.5)	3.6 (2.8)	$F=3.345, p=0.076$
EPQ liar	9.3 (4.6)	9.3 (4.0)	$F=0.007, p=0.935$
EPQ extraversion	16.7 (4.3)	16.5 (3.6)	$F=0.002, p=0.967$
MDQ	1.8 (2.3)	2.3 (3.2)	$F=0.551, p=0.463$
BFS			
Baseline	14.3 (15.2)	14.3 (14.3)	
Day 8	15.1 (17.6)	8.8 (8.1)	$F=1.232, p=0.274$
State positive affect			
Baseline	34.2 (6.7)	32.6 (7.4)	
Day 8	31.3 (8.2)	32.1 (7.3)	$F=1.184, p=0.284$
State negative affect			
Baseline	13.0 (5.9)	12.1 (2.8)	
Day 8	11.6 (2.5)	10.7 (1.3)	$F=0.000, p=1.000$
State anxiety			
Baseline	15.0 (3.8)	14.3 (3.2)	
Day 8	15.1 (4.0)	13.4 (3.1)	$F=0.640, p=0.429$
Visual analogue scales			
Happy			
Baseline	69.4 (15.1)	70.8 (14.5)	
Day 8	73.8 (15.1)	77.0 (14.2)	$F=0.211, p=0.649$
Sad			
Baseline	20.4 (24.2)	16.1 (13.1)	
Day 8	12.2 (16.7)	10.5 (13.5)	$F=0.228, p=0.636$
Irritable			
Baseline	26.2 (21.9)	23.2 (21.7)	
Day 8	18.5 (19.2)	13.4 (15.4)	$F=0.152, p=0.699$
Anxious			
Baseline	25.0 (21.7)	23.9 (20.3)	
Day 8	20.8 (24.2)	13.4 (13.2)	$F=1.161, p=0.289$
Interested in others			
Baseline	72.5 (16.3)	73.6 (16.4)	
Day 8	75.0 (13.1)	76.4 (17.0)	$F=0.021, p=0.884$
Feel good			
Baseline	70.5 (13.8)	73.8 (18.4)	
Day 8	73.5 (16.5)	73.3 (21.4)	$F=0.235, p=0.631$
Talkative			
Baseline	66.7 (24.4)	65.4 (21.2)	
Day 8	62.4 (22.1)	72.7 (16.6)	$F=4.076, p=0.051$

Values represent means (standard deviations).

### **6.8.3 Family history of mood disorder**

One participant in the quetiapine group had a family history of depression and no participants in the placebo group had a family history of mood disorder.

## **6.9 Results 2: Emotional processing tasks**

### **6.9.1 Facial expression recognition**

#### ***6.9.1.1 Accuracy***

There was a main effect of emotion ( $F(6,216)=24.722$ ,  $p<0.001$ ), indicating that percentage accuracy was significantly affected by the emotion of the facial expression being recognised. There was no group x emotion interaction ( $F(6,216)=0.589$ ,  $p=0.739$ ), indicating that accuracy of recognition was not differentially affected by emotion across the two groups. There was no main effect of group ( $F(1,36)=0.509$ ,  $p=0.480$ ) or group x emotion x gender interaction ( $F(1,36)=0.153$ ,  $p=0.988$ ).

#### ***6.9.1.2 Reaction time***

There was a main effect of emotion ( $F(6,216)=9.760$ ,  $p<0.001$ ), indicating that reaction time for recognition was significantly affected by the emotion of the face. There was no group x emotion interaction ( $F(6,216)=0.221$ ,  $p=0.970$ ), group x emotion x gender interaction ( $F(6,216)=0.490$ ,  $p=0.816$ ), or main effect of group ( $F(1,36)=0.002$ ,  $p=0.966$ ).

#### ***6.9.1.3 Misclassifications***

There was a significant main effect of emotion ( $F(6,216)=190.754$ ,  $p<0.001$ ), indicating that the number of misclassifications was significantly affected by facial expression. Out of a total of 250 trials, only ten facial expressions were neutral. Since lower intensities of emotional faces (e.g. 10% anger or 20% disgust) are hard to discriminate as showing an emotion, both groups showed very high rates of

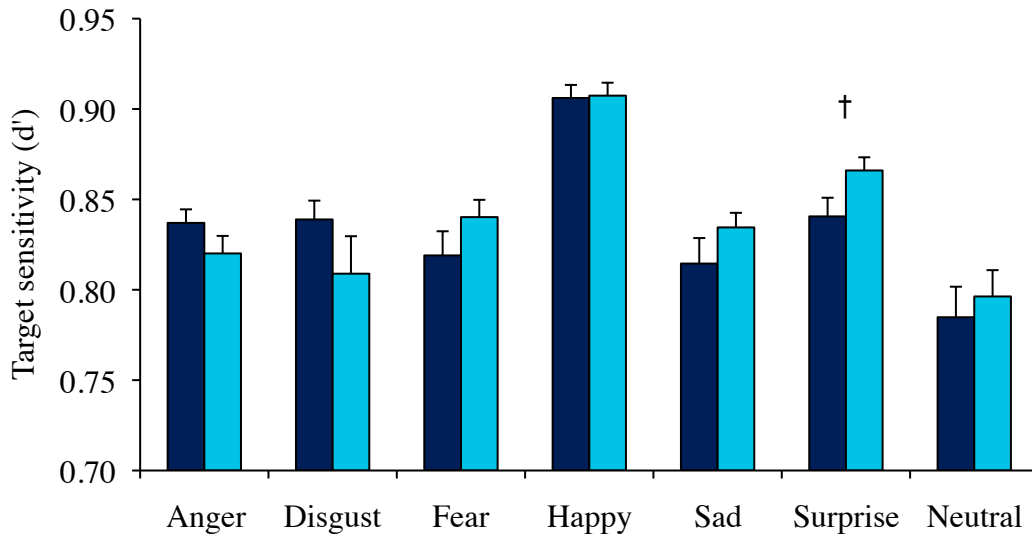
misclassification as neutral, i.e. indicating that the face was neutral when it was in fact a different facial expression. Participants in the quetiapine group made an average of  $66.5 \pm 19.6$  misclassifications as neutral and participants in the placebo group made an average of  $70.6 \pm 24.0$  misclassifications as neutral out of the 250 trials.

There was no group x emotion interaction ( $F(6,216)=1.013, p=0.418$ ), no group x emotion x gender interaction ( $F(6,216)=0.450, p=0.844$ ), and no main effect of group ( $F(1,36)=0.128, p=0.723$ ). However, exploratory analyses revealed that the quetiapine group showed a trend towards a reduced rate of misclassification as angry ( $F(1,36)=4.043, p=0.052$ ) in the absence of differences in misclassification rate for other emotions (all  $p$  values  $> 0.1$ ).

#### **6.9.1.4 Signal detection**

##### *6.9.1.4.1 Target sensitivity ( $d'$ )*

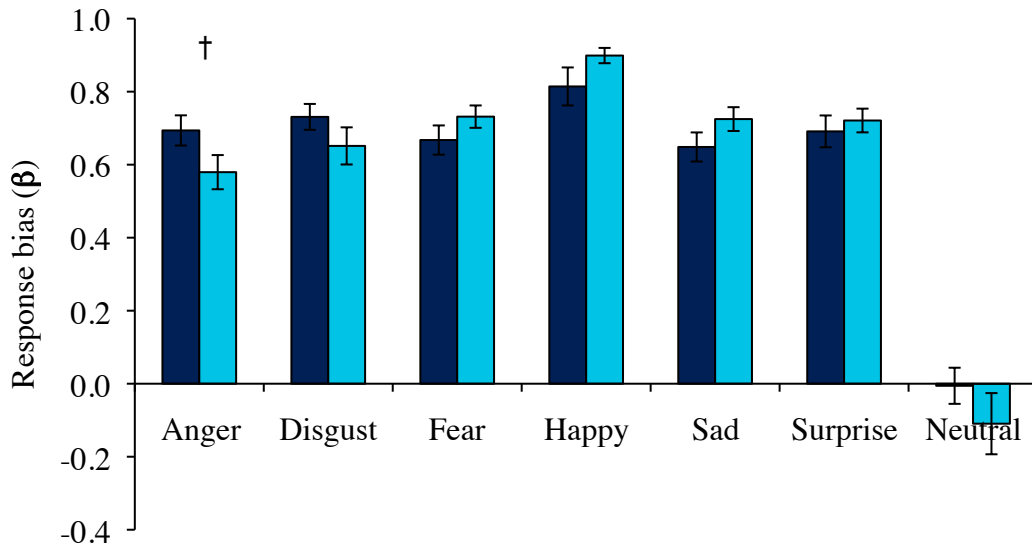
There was a main effect of emotion ( $F(6,216)=23.548, p<0.001$ ), indicating that target sensitivity ( $d'$ ) was significantly affected by the emotion of the facial expression being recognised. There was a trend towards a group x emotion interaction ( $F(6,216)=1.967, p=0.072$ ), reflecting differential effects of emotion on target sensitivity ( $d'$ ) across the two groups (Figure 6.1). The quetiapine group showed a trend towards reduced target sensitivity ( $d'$ ) for surprised faces ( $F(1,36)=3.875, p=0.057$ ), in the absence of differences in target sensitivity ( $d'$ ) for faces of other emotions (all  $p$  values  $> 0.1$ ). There was no group x emotion x gender interaction ( $F(6,216)=0.523, p=0.791$ ) or main effect of group ( $F(6,216)=0.145, p=0.705$ ).



**Figure 6.1** Target sensitivity ( $d'$ ) across emotions for quetiapine group (dark bars) and placebo group (light bars). Error bars represent SEM (†  $p < 0.1$  for comparison between quetiapine group and placebo group).

#### 6.9.1.4.2 Response bias ( $\beta$ )

There was a main effect of emotion ( $F(6,216)=92.325, p < 0.001$ ), indicating that response bias ( $\beta$ ) was significantly affected by the emotion of the facial expression being recognised. There was a trend towards a group x emotion interaction ( $F(6,216)=1.851, p=0.091$ ), reflecting differential effects of emotion on response bias ( $\beta$ ) across the two groups (Figure 6.3). Post-hoc analyses revealed that the quetiapine group showed a trend towards increased  $\beta$  for angry facial expressions ( $F(1,36)=3.434, p=0.072$ ) indicating a conservative response style (few false alarms) with respect to anger, in the absence of differences in response bias ( $\beta$ ) to faces of other emotions. There was no group x emotion x gender interaction ( $F(6,216)=0.377, p=0.893$ ) or main effect of group ( $F(1,36)=0.057, p=0.812$ ).



**Figure 6.3** Response bias (*beta*) across emotions for quetiapine group (dark bars) and placebo group (light bars). Error bars represent SEM (†  $p < 0.1$  for comparison between quetiapine group and placebo group).

## 6.9.2 Emotional categorisation

### 6.9.2.1 Accuracy

There was a main effect of word valence ( $F(1,36)=5.433, p=0.025$ ), with enhanced accuracy of categorisation for positive ‘likeable’ personality characteristics ( $96.5 \pm 3.9\%$ ) compared to negative ‘dislikeable’ personality characteristics ( $93.3 \pm 7.6\%$ ). There was no group x word valence interaction for accuracy of emotional categorisation ( $F(1,36)=0.053, p=0.819$ ), group x word valence x gender interaction ( $F(1,36)=0.476, p=0.495$ ), or main effect of group ( $F(1,36)=0.157, p=0.694$ ).

### 6.9.2.2 Reaction time

There was a main effect of word valence ( $F(1,36)=8.669, p=0.006$ ), with participants showing faster categorisation of positive personality characteristics ( $1039 \pm 173$  ms) compared to negative personality characteristics ( $1118 \pm 208$  ms). There was no group x word valence interaction ( $F(1,36)=0.005, p=0.942$ ), group x word valence x

gender interaction ( $F(1,36)=0.652, p=0.425$ ), or main effect of group ( $F(1,36)=0.425, p=0.519$ ).

### **6.9.3 Incidental emotional recall memory**

#### **6.9.3.1 True recall**

Participants from both groups performed well on this task and there was no main effect of group on the mean number of words correctly recalled ( $F(1,36)=0.000, p=1.000$ ). Quetiapine participants correctly recalled on average  $11.5 \pm 4.3$  personality characteristics and placebo participants correctly recalled on average  $11.3 \pm 3.8$  personality characteristics. More correctly recalled words were positive than negative for both quetiapine participants ( $t(19)=2.734, p=0.013$ ) and placebo participants ( $t(19)=2.169, p=0.043$ ). Percentage of positive words correctly recalled was not significantly affected by group ( $F(1,36)=0.010, p=0.920$ ) and there was no group x gender interaction ( $F(1,36)=0.002, p=0.966$ ).

#### **6.9.3.2 False intrusions**

False intrusions were recorded for only 26 participants (16 quetiapine participants and 12 placebo participants) and there were very few false intrusions. There was a trend towards a main effect of group on the number of false intrusions ( $F(1,36)=3.767, p=0.060$ ), with more false intrusions in the quetiapine group. The quetiapine group recorded on average  $1.8 \pm 1.2$  false intrusions and the placebo group recorded on average  $1.1 \pm 1.1$  false intrusions. More false intrusions were positive than negative for both the quetiapine group ( $t(15)=6.398, p<0.001$ ) and the placebo group ( $t(11)=2.548, p=0.027$ ). Percentage of positive false intrusions was not significantly

affected by group ( $F(1,24)=0.023$ ,  $p=0.880$ ) and there was no group x gender interaction ( $F(1,24)=0.045$ ,  $p=0.833$ ).

## **6.9.4 Emotional recognition memory**

### **6.9.4.1 Excluded participant**

One participant was excluded because they responded ‘familiar’ on 59 out of 60 trials.

### **6.9.4.2 Accuracy**

There was a main effect of word valence on emotional recognition accuracy ( $F(1,35)=26.272$ ,  $p<0.001$ ), with better recognition of positive ‘likeable’ personality characteristics ( $85.2 \pm 11.5$  %) than negative ‘dislikeable’ personality characteristics ( $76.2 \pm 12.5$  %). There was no group x word valence interaction ( $F(1,35)=1.772$ ,  $p=0.192$ ), group x word valence x gender interaction ( $F(1,35)=0.025$ ,  $p=0.875$ ), or main effect of group ( $F(1,35)=0.869$ ,  $p=0.350$ ).

### **6.9.4.3 Reaction time**

There was a main effect of word valence ( $F(1,35)=19.017$ ,  $p<0.001$ ), with faster recognition of positive ‘likeable’ personality characteristics ( $1317 \pm 254$  ms) than negative ‘dislikeable’ personality characteristics ( $1463 \pm 291$  ms). There was no group x word valence interaction ( $F(1,35)=1.586$ ,  $p=0.216$ ), group x word valence x gender interaction ( $F(1,35)=0.301$ ,  $p=0.587$ ), or main effect of group ( $F(1,35)=1.005$ ,  $p=0.323$ ).

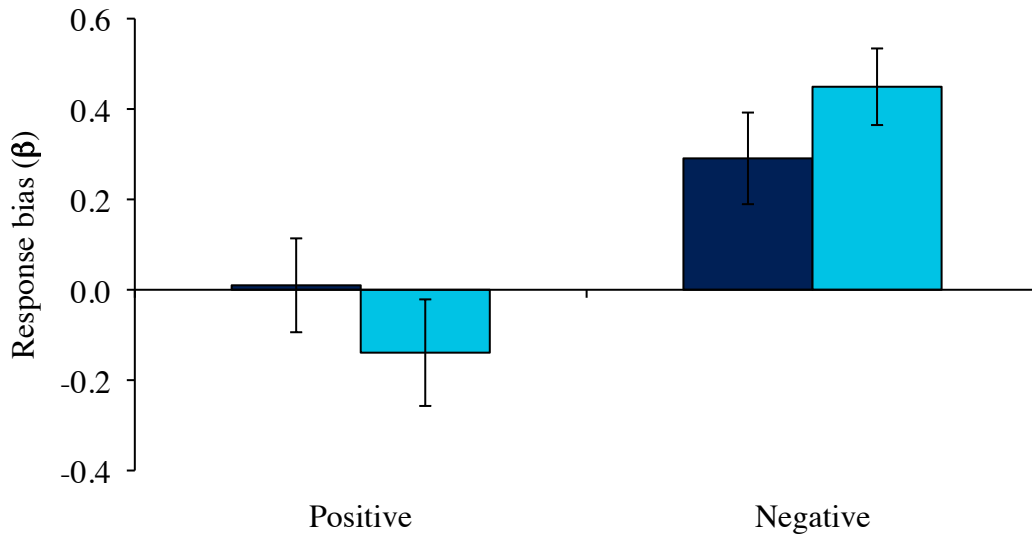
#### **6.9.4.4 Signal detection**

##### *6.9.4.4.1 Target sensitivity ( $d'$ )*

There was no main effect of word valence ( $F(1,35)=0.004, p=0.952$ ), indicating that target sensitivity did not differ for positive ‘likeable’ and negative ‘dislikeable’ personality characteristics. There was no group x emotion interaction ( $F(1,35)=0.213, p=0.647$ ), group x word valence x gender interaction ( $F(1,35)=0.063, p=0.803$ ), or main effect of group ( $F(1,35)=1.958, p=0.171$ ).

##### *6.9.4.4.2 Response bias ( $\beta$ )*

There was a main effect of word valence ( $F(1,35)=36.886, p<0.001$ ), indicating that response bias significantly differed for positive ‘likeable’ and negative ‘dislikeable’ personality characteristics. There was a significant group x word valence interaction ( $F(1,35)=4.983, p=0.032$ ), with quetiapine participants showing increased  $\beta$  for positive vs. negative personality characteristics, i.e. more conservative response style (fewer false alarms) for positive compared to negative words (Figure 6.5). However, post-hoc analyses revealed no group differences for  $\beta$  for positive ( $F(1,35)=0.967, p=0.332$ ) or negative ( $F(1,35)=1.400, p=0.245$ ) personality characteristics. There was no group x word valence x gender interaction ( $F(1,35)=0.480, p=0.493$ ) or main effect of group ( $F(1,35)=0.000, p=0.996$ ).



**Figure 6.5** Response bias (*beta*) towards positive and negative personality characteristics for quetiapine group (dark bars) and placebo group (light bars). Error bars represent SEM.

## 6.9.5 Emotion-potentiated startle

### 6.9.5.1 Excluded participants

Of the 20 participants who received quetiapine, seven were excluded from analyses because of equipment/signal failure or because they displayed a startle response on fewer than 25% of trials. Of the 20 participants who received placebo, three were excluded.

### 6.9.5.2 Raw startle amplitudes

Raw startle eye-blink amplitudes were significantly affected by emotion condition (positive, neutral, negative) ( $F(2,52)=14.450, p<0.001$ ), with potentiation of eye-blink responses being shown during negative picture presentation compared with both positive ( $t(29)=4.239, p<0.001$ ) and neutral ( $t(29)=5.154, p<0.001$ ) picture presentation. There was no group x emotion condition interaction ( $F(2,52)=0.200,$

$p=0.820$ ), group x emotion condition x gender interaction ( $F(2,52)=0.095$ ,  $p=0.910$ ), or main effect of group ( $F(1,26)=0.034$ ,  $p=0.856$ ).

### **6.9.5.3 Z-transformed startle data**

Z-transformed startle responses were also affected by emotion condition ( $F(2,52)=14.868$ ,  $p<0.001$ ), with potentiation of eye-blink responses being shown during negative picture presentation relative to positive and neutral picture presentation ( $t(29)=5.624$ ,  $p<0.001$ ). There was no group x emotion condition interaction ( $F(2,52)=0.210$ ,  $p=0.811$ ), group x emotion condition x gender interaction ( $F(2,52)=0.021$ ,  $p=0.979$ ), or main effect of group ( $F(1,26)=2.258$ ,  $p=0.145$ ).

## **6.9.6 Attentional vigilance word dot-probe**

### **6.9.6.1 Attentional vigilance reaction time**

There was no group x word valence x masking interaction ( $F(1,36)=0.126$ ,  $p=0.725$ ) or group x word valence x masking x gender interaction ( $F(1,36)=0.016$ ,  $p=0.901$ ). However, exploratory analyses will for the unmasked and masked conditions will be described below.

#### **6.9.6.1.1 Unmasked condition**

For the unmasked condition, there was no effect of word valence ( $F(1,36)=0.030$ ,  $p=0.864$ ), indicating that attentional vigilance reaction time did not differ between positive-neutral and negative-neutral word pairs in the unmasked condition. There was no group x word valence interaction ( $F(1,36)=0.400$ ,  $p=0.531$ ), group x word

valence x gender interaction ( $F(1,36)=0.301, p=0.587$ ), or main effect of group ( $F(1,36)=0.135, p=0.716$ ).

#### *6.9.6.1.2 Masked condition*

For the masked condition, there was no effect of word valence ( $F(1,36)=0.153, p=0.698$ ), indicating that attentional vigilance reaction time did not differ between positive-neutral and negative-neutral word pairs in the masked condition. There was no group x word valence interaction ( $F(1,36)=0.008, p=0.931$ ), group x word valence x gender interaction ( $F(1,36)=0.505, p=0.482$ ), or main effect of group ( $F(1,36)=0.059, p=0.809$ ).

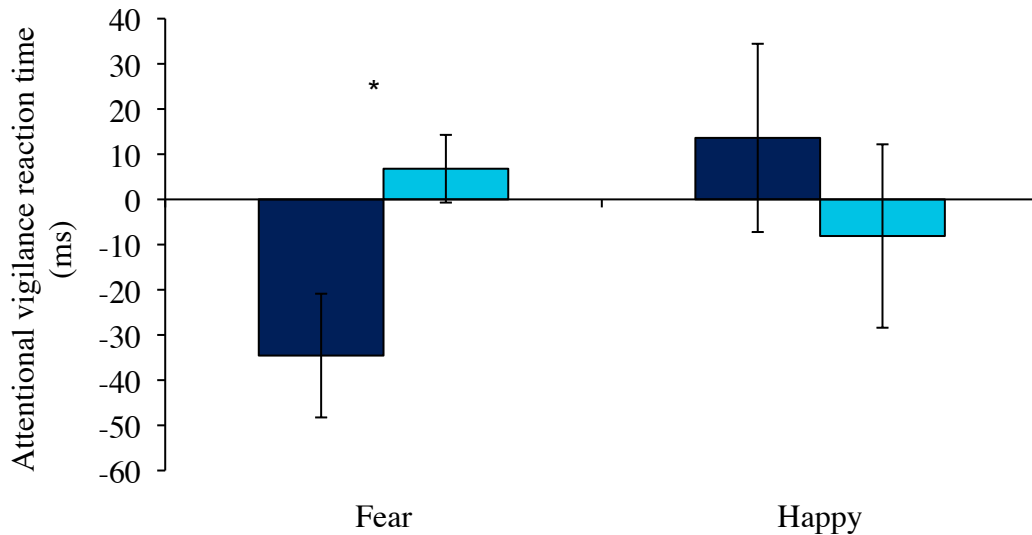
### **6.9.7 Attentional vigilance faces dot-probe**

#### *6.9.7.1 Attentional vigilance reaction time*

There was no group x emotion x masking interaction for attentional vigilance reaction time ( $F(1,36)=0.181, p=0.673$ ). There was a group x emotion x masking x gender interaction ( $F(1,36)=4.247, p=0.047$ ), suggesting that group x emotion x masking interactions were different across female and male participants. Post-hoc analyses revealed that there was no group x emotion x masking interaction for female participants ( $F(1,18)=2.123, p=0.162$ ) or male participants ( $F(1,18)=2.456, p=0.134$ ), however exploratory analyses for the unmasked and masked conditions will be described below.

#### 6.9.7.1.1 Unmasked condition

For the unmasked condition, there was a main effect of emotion ( $F(1,36)=4.125$ ,  $p=0.050$ ), with greater vigilance reaction time scores for happy faces ( $12 \pm 53$  ms) than for fearful faces ( $-6 \pm 44$  ms) in the unmasked condition. There was no group x emotion interaction ( $F(1,36)=0.340$ ,  $p=0.563$ ) or main effect of group ( $F(1,36)=0.034$ ,  $p=0.855$ ). There was a significant group x emotion x gender interaction ( $F(1,36)=6.611$ ,  $p=0.014$ ), suggesting that female and male participants showed differential vigilance to fearful and happy faces across the two groups. For female participants, there was a trend towards a group x emotion interaction ( $F(1,18)=3.748$ ,  $p=0.069$ ), and quetiapine participants showed reduced vigilance towards fearful vs. happy faces compared to controls (Figure 6.7). Post-hoc analyses revealed that quetiapine participants showed significantly reduced vigilance towards fearful faces compared to placebo participants ( $F(1,18)=7.747$ ,  $p=0.012$ ), in the absence of a group difference in vigilance towards happy faces ( $F(1,18)=0.549$ ,  $p=0.468$ ). For male participants, there was a weak trend towards a group x emotion interaction ( $F(1,18)=2.937$ ,  $p=0.104$ ). However, post-hoc analyses revealed no group differences for vigilance towards fearful faces ( $F(1,18)=1.358$ ,  $p=0.259$ ) or happy faces ( $F(1,18)=0.718$ ,  $p=0.408$ ).



**Figure 6.7** Attentional vigilance reaction times for female quetiapine participants (dark bars) and female placebo participants (light bars). Error bars represent SEM (\*  $p < 0.05$  for comparison between quetiapine group and placebo group).

#### 6.9.7.1.2 Masked condition

For the masked condition, there was no main effect of group ( $F(1,36)=0.045$ ,  $p=0.834$ ), indicating that vigilance towards fearful faces did not differ significantly from vigilance towards happy faces in the masked condition. There was no group x emotion interaction ( $F(1,36)=0.004$ ,  $p=0.950$ ) or main effect of group ( $F(1,36)=0.416$ ,  $p=0.523$ ).

## 6.10 Results 3: Risky decision-making task

### 6.10.1 Probability, gains, and losses

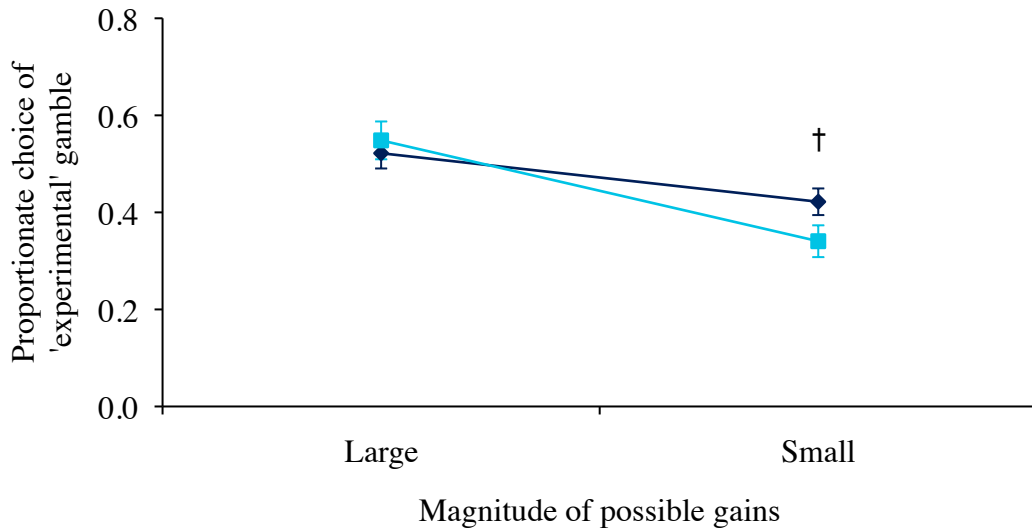
#### 6.10.1.1 Proportionate choice

There was no main effect of group ( $F(1,36)=0.742, p=0.395$ ) and quetiapine participants ( $0.47 \pm 0.11$ ) did not differ in their proportionate choice of the ‘experimental’ gamble compared to placebo participants ( $0.44 \pm 0.14$ ).

There was a main effect of probability of winning ( $F(1,36)=69.975, p<0.001$ ), with participants choosing the ‘experimental’ gamble significantly more frequently when there was a high ( $0.67 \pm 0.19$ ) compared to low ( $0.25 \pm 0.22$ ) probability of winning. There was no group x probability interaction ( $F(1,36)=0.859, p=0.360$ ), indicating that proportionate choice of the ‘experimental’ gamble was not differentially affected by probability of winning across the two groups. There was no group x probability of winning x gender interaction ( $F(1,36)=0.228, p=0.636$ ).

There was a main effect of magnitude of gains ( $F(1,36)=42.541, p<0.001$ ), with participants choosing the ‘experimental’ gamble significantly more frequently when possible gains were large ( $0.54 \pm 0.16$ ) compared when possible gains were small ( $0.38 \pm 0.14$ ). There was a group x magnitude of gains interaction ( $F(1,36)=5.773, p=0.022$ ), with quetiapine participants choosing the ‘experimental’ gamble significantly more frequently when there were small vs. large possible gains compared to placebo participants (Figure 6.9). Post-hoc analyses revealed that quetiapine participants showed a trend towards choosing the ‘experimental’ gamble

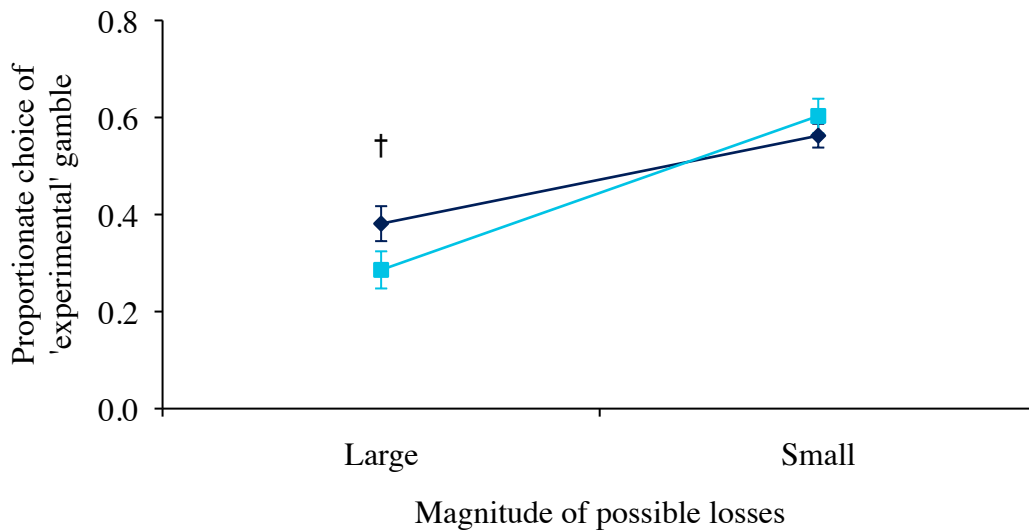
more frequently when there were small possible gains ( $F(1,36)=3.613, p=0.065$ ) in the absence of a group difference when there were large possible gains ( $F(1,36)=0.336, p=0.556$ ). There was no group x magnitude of gains x gender interaction ( $F(1,36)=0.112, p=0.739$ ).



**Figure 6.9** Proportionate choice of the ‘experimental’ gamble over the control gamble as a function of magnitude of possible gains for the quetiapine group (dark diamonds) and the placebo group (light squares). Error bars represent SEM (†  $p<0.1$  for comparison between quetiapine group and placebo group).

There was a main effect of magnitude of losses ( $F(1,36)=82.617, p<0.001$ ), with participants choosing the ‘experimental’ gamble significantly more frequently when there were small possible losses ( $0.58 \pm 0.14$ ) compared to large possible losses ( $0.33 \pm 0.17$ ). There was a group x magnitude of losses interaction ( $F(1,36)=5.806, p=0.021$ ), with quetiapine participants choosing the ‘experimental’ gamble significantly more frequently when there were large vs. small possible losses (Figure 6.11). Post-hoc analyses revealed that quetiapine participants showed a trend towards choosing the ‘experimental’ gamble more frequently when there were large possible losses ( $F(1,36)=3.278, p=0.079$ ), in the absence of a group difference when there

were small possible losses ( $F(1,36)=1.035, p=0.316$ ). There was no group x magnitude of losses x gender interaction ( $F(1,36)=1.169, p=0.287$ ).



**Figure 6.11** Proportionate choice of the ‘experimental’ gamble over the control gamble as a function of magnitude of possible losses for the quetiapine group (dark diamonds) and the placebo group (light squares). Error bars represent SEM (†  $p<0.1$  for comparison between quetiapine group and placebo group).

### 6.10.1.2 Deliberation time

Mean deliberation times as a function of probability of winning, magnitude of possible gains, and magnitude of possible losses are shown in Table 6.5. There was no main effect of group on deliberation time ( $F(1,36)=0.031, p=0.862$ ). Quetiapine participants responded with an average deliberation time of  $2255 \pm 805$  ms and placebo participants responded with an average deliberation time of  $2230 \pm 748$  ms.

**Table 6.5** Mean deliberation time (ms) as a function of probability of winning, magnitude of possible gains, and magnitude of possible losses.

	Probability of winning		Possible gains		Possible losses	
	High	Low	Large	Small	Large	Small
Quetiapine	2269 ± 801	2241 ± 873	2258 ± 864	2253 ± 794	2240 ± 770	2270 ± 862
Placebo	2241 ± 767	2218 ± 780	2225 ± 810	2234 ± 745	2201 ± 753	2258 ± 776

Values represent means ± standard deviations.

There was no main effect of probability ( $F(1,36)=0.280, p=0.600$ ), indicating that there was no significant difference in deliberation time for risky choices involving ‘experimental’ gambles with high or low probabilities of winning. Furthermore, there was no group x probability interaction ( $F(1,36)=0.000, p=0.983$ ), suggesting that deliberation time was not differentially affected by probability of winning across the two groups. There was no group x probability x gender interaction ( $F(1,36)=2.219, p=0.145$ ).

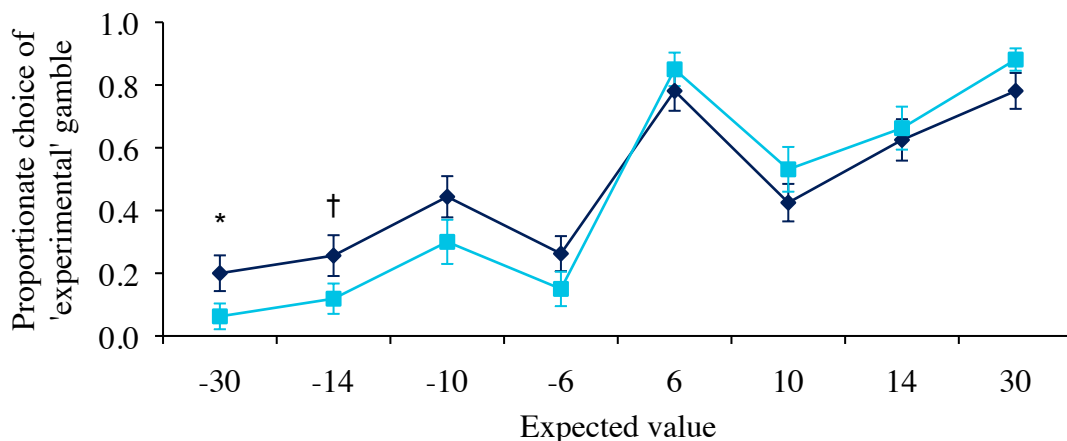
There was no main effect of magnitude of gains ( $F(1,36)=0.001, p=0.982$ ), indicating that deliberation time did not differ significantly for risky choices involving ‘experimental’ gambles with large or small possible gains. Furthermore, there was no group x magnitude of gains interaction ( $F(1,36)=0.002, p=0.966$ ), suggesting that deliberation time was not differentially affected by magnitude of possible gains across the two groups. There was no group x magnitude of gains x gender interaction ( $F(1,36)=0.346, p=0.560$ ).

There was no main effect of magnitude of losses ( $F(1,36)=0.677, p=0.416$ ), indicating that deliberation time did not differ significantly for risky choices involving ‘experimental’ gambles with large or small possible losses. Furthermore, there was no group x magnitude of losses interaction ( $F(1,36)=0.013, p=0.910$ ), suggesting that deliberation time was not differentially affected by magnitude of possible losses across the two groups. There was no group x magnitude of losses x gender interaction ( $F(1,36)=1.223, p=0.276$ ).

## 6.10.2 Expected value

### 6.10.2.1 Proportionate choice

There was a main effect of expected value ( $F(7,252)=54.427$ ,  $p<0.001$ ), with participants choosing the 'experimental' gamble more frequently as its expected value increased from a minimum of -30 to a maximum of +30 (Figure 6.13). There was a significant group x expected value interaction ( $F(7,252)=2.238$ ,  $p=0.032$ ), with quetiapine participants choosing the 'experimental' gamble more frequently for lower expected values and less frequently at higher expected values compared to placebo participants. Quetiapine participants selected the 'experimental' gamble significantly more frequently than placebo participants when the expected value was -30 ( $F(1,36)=5.446$ ,  $p=0.025$ ), with a trend towards this pattern when the expected value was -14 ( $F(1,36)=2.887$ ,  $p=0.098$ ). There was no group x expected value x gender interaction ( $F(7,252)=0.914$ ,  $p=0.496$ ).



**Figure 6.13** Proportionate choice of the 'experimental' gamble across different expected values for the quetiapine group (dark diamonds) and the placebo group (light squares). Error bars represent SEM (\*  $p<0.05$ , †  $p<0.1$  for comparison between quetiapine group and placebo group).

### **6.10.2.2 Deliberation time**

There was a main effect of expected value ( $F(7,252)=2.687, p=0.011$ ), suggesting that deliberation time was significantly affected by the expected value of the ‘experimental’ gamble. There was no group x expected value interaction ( $F(7,252)=1.063, p=0.388$ ), indicating that deliberation time was not differentially affected by expected value across the two groups. There was no group x expected value x gender interaction ( $F(7,252)=0.864, p=0.535$ ).

### **6.10.3 The reflection effect**

#### **6.10.3.1 Proportionate choice**

There was a main effect of trial type (gains only vs. losses only) ( $F(1,36)=54.769, p<0.001$ ), with a preference for the guaranteed outcome for gains only ( $0.78 \pm 0.28$ ) compared to losses only ( $0.29 \pm 0.28$ ) trials, and therefore a significant reflection effect. There was no group x trial type interaction ( $F(1,36)=1.162, p=0.288$ ), indicating that the reflection effect was not modulated by group. There was no group x trial type x gender interaction ( $F(1,36)=0.288, p=0.595$ ) or main effect of group ( $F(1,36)=1.108, p=0.300$ ).

#### **6.10.3.2 Deliberation time**

There was a main effect of trial type ( $F(1,36)=39.480, p<0.001$ ), with significantly faster deliberation times for gains only ( $1811 \pm 945$  ms) compared to losses only ( $3117 \pm 1456$  ms) trials. There was no group x trial type interaction ( $F(1,36)=0.894, p=0.351$ ), suggesting that deliberation times of quetiapine participants and placebo participants were not differentially affected by trial type. There was no group x trial

type x gender interaction ( $F(1,36)=0.008, p=0.928$ ) or main effect of group ( $F(1,36)=1.574, p=0.218$ ).

## 6.11 Results 4: Sleep and circadian rhythms

### 6.11.1 Participant characteristics and chronotype

#### 6.11.1.1 Participant characteristics

Thirty-three participants had at least three days' worth of actigraphy data both at baseline and during drug administration and were included in the final analysis. There were 16 (9 female, 7 male) quetiapine participants who had 3-9 days' worth of baseline actigraphy data and 3-6 days' worth of actigraphy data during quetiapine administration. There were 17 (11 female, 6 male) placebo participants who had 5-15 days' worth of baseline actigraphy data and 6 days' worth of actigraphy data during placebo administration.

#### 6.11.1.2 Chronotype

Results from the Morningness-Eveningness questionnaire (Horne & Ostberg, 1976) are shown in Table 6.7. Questionnaire responses from two quetiapine participants and one placebo participant were missing. The distributions of chronotype did not differ significantly between the two groups ( $\chi^2(3)= 4.736, p=0.192$ , but 6 cells had an expected count < 5).

**Table 6.7** Morningness-Eveningness chronotype questionnaire results.

Chronotype (score range)	Quetiapine N= 14	Placebo N=16
Extreme evening (16-30)	0 (0)	1 (6)
Moderate evening (31-41)	1 (7)	5 (31)
Neither type (42-58)	12 (86)	10 (63)
Moderate morning (59-69)	1 (7)	0 (0)
Extreme morning (70-86)	0 (0)	0 (0)

Values represent N (%).

### 6.11.2 Sleep

Baseline sleep parameters did not differ significantly between groups (all  $p$  values > 0.1), except for a marginal delay in M10 onset in the quetiapine group ( $F(1,29)=3.149, p=0.086$ ).

Sleep parameters during drug administration for the two groups are shown in Table 6.9. The effects of quetiapine did not differ significantly from the effects of placebo for sleep onset, fragmentation index, L5 activity, L5 onset, M10 activity, and M10 onset (all  $p$  values > 0.1).

**Table 6.9** Sleep parameters during drug administration.

	Quetiapine N=16	Placebo N=17
Sleep onset	01:12 (01:16)	01:10 (01:04)
Final wake time	09:38 (01:17)	08:57 (00:57)
Total sleep period	08:26 (00:51)	07:46 (00:39)
Total sleep time	07:27 (00:43)	06:38 (00:34)
Sleep latency	00:02 (00:01)	00:03 (00:02)
Sleep efficiency (%)	87.6 (3.6)	84.7 (4.7)
Immobility (%)	87.7 (3.4)	85.4 (4.1)
Fragmentation index	26.8 (7.0)	30.8 (9.8)
L5 activity	1004 (495)	1512 (935)
L5 onset	02:15 (01:26)	02:28 (00:57)
M10 activity	24907 (6090)	20939 (5538)
M10 onset	11:37 (01:49)	11:00 (02:14)

Values represent means (standard deviations).

Quetiapine administration significantly delayed final wake time (group x time:  $F(1,29)=12.241, p=0.002$ ; group x time x gender:  $F(1,29)=0.206, p=0.654$ ), significantly increased the total sleep period (group x time:  $F(1,29)=12.669, p=0.001$ ; group x time x gender:  $F(1,29)=0.850, p=0.364$ ), and significantly increased total sleep time (group x time:  $F(1,29)=18.528, p<0.001$ ; group x time x gender:  $F(1,29)=1.093, p=0.304$ ) compared to placebo.

Quetiapine administration did not significantly affect sleep latency compared to placebo (group x time:  $F(1,29)=1.032, p=0.318$ ), but there was a significant group x time x gender interaction ( $F(1,29)=4.350, p=0.046$ ). However, there were no significant group differences for female (group x time:  $F(1,18)=0.874, p=0.362$ ) or male ( $F(1,11)=3.106, p=0.106$ ) participants.

Quetiapine administration significantly increased sleep efficiency compared to placebo (group x time:  $F(1,29)=5.577, p=0.025$ ; group x time x gender:  $F(1,29)=0.024, p=0.877$ ).

Quetiapine administration significantly increased percentage immobility compared to placebo (group x time:  $F(1,29)=4.211, p=0.049$ ; group x time x gender:  $F(1,29)=0.120, p=0.732$ ).

### 6.11.3 Circadian rhythms

Baseline circadian rhythm parameters did not differ between group (all  $p$  values > 0.1).

Circadian rhythm parameters during drug administration for the two groups are shown in Table 6.11. The effects of quetiapine did not differ significantly from the effects of placebo for relative amplitude and inter-daily stability (all  $p$  values > 0.1).

**Table 6.11** Circadian rhythm parameters during drug administration.

	Quetiapine N=16	Placebo N=17
Relative amplitude	0.92 (0.04)	0.87 (0.06)
Inter-daily stability	0.49 (0.11)	0.43 (0.09)
Intra-daily variability	0.85 (0.26)	0.91 (0.23)

Values represent means (standard deviations).

There was a trend for participants who received quetiapine to have reduced intra-daily variability (group x time:  $F(1,29)=3.109, p=0.088$ ; group x time x gender:  $F(1,29)=2.227, p=0.146$ ).

## **6.12 Discussion and conclusion**

### **6.12.1 Summary of findings**

Seven-day quetiapine administration was associated with emotional processing biases away from both positive and negative stimuli, altered decision-making with reduced discrimination between different magnitudes of gains and losses, and increased total sleep time and improved circadian rhythmicity. Treatment with quetiapine was found to reduce discriminability of surprised faces, bias information processing away from negative angry faces during the facial expression recognition task, and to reduce attentional vigilance towards fearful faces in female participants during the unmasked dot-probe condition (with all effects at trend significance levels). On the other hand, at the recognition memory stage, a significant bias away from positive and towards negative information was recorded in participants who received quetiapine. These emotional processing changes took place in the absence of alterations to physiological reactivity assessed by the emotion-potentiated startle. Quetiapine altered processing of reinforcement cues during risky decision-making by reducing sensitivity to different magnitudes of gains and losses. In turn, this resulted in increased choice of gambles associated with negative vs. positive expected values by participants who received quetiapine. These changes took place in the absence of a modulation of non-normative decision-making, i.e. the reflection effect. Finally, actigraphic assessment revealed that quetiapine administration was associated with increased sleep duration, improved sleep efficiency, increased percentage immobility, and a trend towards improved intra-daily variability, i.e. less fragmented periods of wake and rest through the day.

### 6.12.2 Discussion of emotional processing results

Biases away from both positive and negative emotional stimuli were recorded at trend significance levels in the emotional processing tasks following quetiapine administration.

Firstly, although there were no group differences in accuracy or reaction time, signal detection analyses revealed subtle changes in facial expression recognition. Quetiapine administration was associated with a trend towards worse target sensitivity for surprised faces, which opposes findings of better target sensitivity in participants with the bipolar phenotype that were described in **Chapter 3**. Furthermore, in the emotional recognition memory task, biases away from positive and towards negative self-referent personality characteristic words were seen following one-week treatment with quetiapine. Therefore, quetiapine's effects of reduced processing of positive stimuli relative to negative stimuli may play a role in redressing positive emotional processing biases and, in turn, account for its ability to stabilise mood from (hypo-) manic episodes in bipolar disorder.

On the other hand, quetiapine administration was associated additionally with a trend towards a response bias away from angry faces in the facial expression recognition task, and, in female participants, there was a trend towards reduced attentional vigilance towards fearful faces in the unmasked condition of the dot-probe task. This bias away from negative emotional stimuli provides evidence in support of an antidepressant effect, consistent with changes reported following seven-day treatment with reboxetine in healthy volunteers (Harmer, et al., 2004). Quetiapine's shared pharmacological activity with reboxetine via noradrenaline reuptake inhibition may

account for this bias away from negative information and its ability to stabilise mood from depressive episodes in bipolar disorder.

In combination, the findings from the emotional processing tasks suggest that quetiapine administration was associated with biases away from both positive and negative emotional information. These changes may underlie quetiapine's ability to stabilise mood from both depressive and manic episodes in bipolar disorder and, therefore, its mood stabilising effect. However, these changes were small and so continued investigation of quetiapine's psychopharmacological effects is required to further elucidate its mechanisms of action.

Quetiapine administration had no significant effect on physiological reactivity assessed by the emotion-potentiated startle. This is consistent with findings following seven-day reboxetine administration (Harmer, et al., 2004), but does not align with the attenuated startle responses recorded during the negative condition following treatment one-week treatment with the selective serotonin reuptake inhibitor citalopram (Harmer, et al., 2004). This suggests that alterations in physiological reactivity to threat may be mediated by changes in serotonergic processing, for example following serotonin reuptake inhibition, rather than via changes in noradrenergic processing. Furthermore, since quetiapine has pharmacological effects at serotonin 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, and 5-HT<sub>1A</sub> receptors (Kapur & Remington, 2001), such changes in physiological reactivity to threat may be related to serotonin reuptake inhibition in particular.

### 6.12.3 Discussion of decision-making results

Quetiapine administration was associated with impaired discrimination between large and small gains and large and small losses during risky decision-making. In particular, participants who received quetiapine more frequently selected 'experimental' gambles with small gains and showed a trend towards more frequently selecting 'experimental' gambles associated with large losses compared to participants who received placebo. These changes in the processing of reinforcement signals may have resulted from increased salience of small reward-related cues and reduced salience of large punishment related cues. In turn, such altered risky decision-making led to quetiapine administration being associated with increased proportionate choice of 'experimental' gambles with negative vs. positive expected values compared to controls. Previous studies have found that reducing central serotonin activity by acute tryptophan depletion (Nishizawa, et al., 1997) impaired discrimination between different magnitudes of possible gains (Rogers, et al., 2003), whereas reducing dopamine function by tyrosine depletion (McTavish, Cowen, & Sharp, 1999) impaired discrimination between large and small losses (Scarna, et al., 2005). Together, therefore, evidence for disrupted processing of both reward and punishment cues presented here is in line with quetiapine and norquetiapine's combined pharmacological effects, including antagonism at dopaminergic  $D_2$ , serotonergic  $5-HT_{2A}$  and  $5-HT_{2C}$  receptors and partial agonism at serotonergic  $5-HT_{1A}$  receptors. It is possible that increased attention towards small possible gains and reduced attention towards large possible losses may mediate quetiapine's therapeutic effects as an antidepressant, particularly at the doses used in this study (Calabrese, et al., 2005).

#### **6.12.4 Discussion of sleep and circadian rhythms results**

Sleep and circadian rhythms were assessed using actigraphy for one baseline week (pre-treatment) and for one week during drug administration. Participants who received quetiapine had a longer total sleep period and increased total sleep time, with later waking, increased sleep efficiency and reduced percentage immobility, and also showed a trend towards improved intra-daily variability.

This study revealed that quetiapine administration was associated with increased total sleep time, which suggests that quetiapine may target insomnia in depression and target reduced sleep, which may precipitate (hypo-) manic episodes or be experienced during (hypo-) mania. Furthermore, although both groups of participants demonstrated typical intra-daily variability scores (mean scores below 1), those participants who received quetiapine showed a trend towards reduced intra-daily variability scores. This indicated that they had a less fragmented rhythm with periods of extended rest alternating with periods of extended activity. In combination with increased sleep duration, this finding of improved regularity of circadian rhythmicity may underpin quetiapine's therapeutic effects in the treatment of bipolar depression and mania, for which sleep disruptions are key symptoms (Wulff, et al., 2010).

#### **6.12.5 Limitations**

There are a number of limitations to this study. Firstly, quetiapine has a complicated pharmacological profile with effects on serotonergic, dopaminergic, and noradrenergic neurotransmitter systems. Therefore, it is not possible to determine the exact pharmacological bases of the effects recorded in this study. However, quetiapine is effective in the treatment of bipolar depression and mania, and this study

has taken a first step towards exploring its actions at a psychological level. Secondly, there was no physiological measure of compliance with the drug treatment. However, the significant effects of quetiapine on emotional processing, decision-making, and sleep and circadian rhythm measures make it likely that there was good compliance in at least the majority of participants. Thirdly, although the use of healthy volunteers allowed this study to assess the effects of quetiapine in the absence of confounds related to experience of repeated illness episodes and current medication or current mood state, further studies are required to investigate how quetiapine administration may affect emotional processing, decision-making, and sleep and circadian rhythmicity in patients with bipolar disorder during an episode of depression or mania.

#### **6.12.6 Conclusion**

In conclusion, seven-day administration with quetiapine had mood-stabilising effects on emotional processing (i.e. trends towards biases away from both positive and negative information), resulted in reduced sensitivity to magnitude of both reward and punishment cues during risky decision-making, and improved sleep and circadian rhythms. These effects are consistent with a mood-stabilising effect and may account for quetiapine's ability to stabilise mood from both (hypo-) manic and depressive episodes in bipolar disorder.

## 7 General discussion

### 7.1 Summary of findings

The series of studies reported here investigated bipolar phenotype subjects, selected on the basis of high scores on the Mood Disorder Questionnaire (MDQ) (Hirschfeld, et al., 2000b), by assessing experience of mood-elevation symptoms and associated co-morbidities. Psychological, neural, and physiological vulnerability markers associated with the bipolar phenotype were measured. Finally, the neuropsychological effects of one-week administration with the atypical antipsychotic quetiapine were studied.

**Chapter 2** assessed the utility of the MDQ as a screening tool for bipolar disorder when used with full validated screening criteria (seven or more mood-elevation symptom items plus problems) and threshold bipolar criteria (seven items alone). This chapter revealed that the MDQ could be used to easily identify a bipolar phenotype with either full or threshold bipolar criteria, and reported that the phenotype was relatively common and on a continuum of severity. Support for this came from the MDQ showing a high positive predictive value for DSM-IV-TR bipolar diagnosis when used with full screening criteria in the probable bipolar group (62%) and a moderate positive predictive value when used with threshold bipolar criteria (34%). Further evidence came from gradients of risk for associated co-morbidities, including neuroticism, experience of a depressive episode, substance misuse, gambling, and poor physical health across probable bipolar, threshold bipolar, and zero symptoms groups. Finally, probable bipolar subjects also differed from threshold bipolar subjects in terms of their particularly frequent experience of a cluster of behavioural

mood-elevation symptoms, including hyper behaviour, risk-taking, irritability, and irresponsible spending, relative to the threshold bipolar group.

**Chapter 3** and **Chapter 4** employed behavioural and functional magnetic resonance imaging (fMRI) techniques to investigate the psychological and neural vulnerability markers associated with the bipolar phenotype.

**Chapter 3** revealed that bipolar phenotype subjects showed positive biases in emotional processing, including enhanced recognition of surprised faces and impaired recognition of disgusted faces, faster recognition memory for positive vs. negative words, and increased emotional reactivity during positive vs. negative and neutral conditions. Bipolar phenotype participants demonstrated reduced neural processing of fearful faces (female subjects only) in the bilateral amygdalae, providing support for reduced salience of negative stimuli, and increased functional activation of the right dorsolateral prefrontal cortex (right DLPFC) to negative vs. neutral words, suggesting increased regulation of negative stimuli.

**Chapter 4** revealed that bipolar phenotype participants also showed disrupted decision-making. The bipolar phenotype was associated with a diminution of the framing effect, i.e. reduced sensitivity to positive vs. negative framing, and an exaggeration of the reflection effect, i.e. increased sensitivity to gains only vs. losses only trial types. Furthermore, male bipolar phenotype participants in particular made more frequent choices of risky gambles that were associated with large vs. small losses and made more errors before reaching criterion on the extra-dimensional block of the set-shifting task. Bipolar phenotype participants showed increased functional

activation of the ventral striatum (bilateral nucleus accumbens), bilateral amygdalae, bilateral lateral occipital cortices, and left precentral and post-central gyri to outcomes that were losses vs. wins.

**Chapter 5** used actigraphy to investigate alterations in sleep and circadian rhythmicity associated with the bipolar phenotype. This chapter revealed that bipolar phenotype participants (particularly female subjects) showed elevated activity during their least active five hours of sleep (between 2am and 7am) and consequently showed reduced sleep duration and reduced (i.e. poorer) relative amplitude.

**Chapter 6** investigated the effects of seven-day quetiapine administration on emotional processing, decision-making, and sleep and circadian rhythmicity in healthy volunteers. This chapter revealed that treatment with quetiapine biased information processing away from both positive and negative emotional stimuli, including impaired discrimination of surprised faces, bias away from angry faces, reduced attentional vigilance towards unmasked fearful faces (female subjects only), and bias away from positive and towards negative words during recognition memory. Participants who received quetiapine also showed reduced discrimination between large and small gains and between large and small losses, resulting in more frequent choices of gambles associated with negative expected values relative to participants who received placebo. Actigraphic measures revealed that quetiapine administration was associated with increased sleep duration and improved intra-daily variability, i.e. less fragmented periods of wake and rest.

## 7.2 Implications of findings

### 7.2.1 The MDQ as a screening tool for the bipolar phenotype

The Mood Disorder Questionnaire (MDQ) was designed to screen for mood-elevation symptoms and has been validated with full screening criteria ( $\geq 7$  mood-elevation symptoms and endorsement of the co-occurrence and problematic nature of symptoms) (Hirschfeld, et al., 2000b). The MDQ was found to have a high sensitivity for detecting bipolar disorder (0.73) when used with these validated screening criteria (Hirschfeld, et al., 2000b), hence subjects satisfying these criteria were described as ‘probable bipolar’ participants. The present research extended investigation of the MDQ by using (i) probable bipolar criteria and (ii) threshold bipolar criteria ( $\geq 7$  mood-elevation symptoms *without* co-occurring and problematic symptoms) to detect a bipolar phenotype in a student population. **Chapter 2** revealed that one third (34%) of individuals identified using the new and more liberal threshold bipolar criteria had a diagnosis of bipolar II or bipolar NOS at interview. This finding is of importance because conventional probable bipolar screening criteria would not have identified these subjects as being vulnerable for bipolar disorder. The MDQ is a quick pencil-and-paper self-report screening tool and, as such, may provide a viable means of mass screening for symptoms of mood elevation in patients presenting with major depression. The current findings of a moderate prevalence of bipolar diagnosis and relatively high levels of associated vulnerability in threshold bipolar subjects suggest that the MDQ, when used with less stringent criteria, remains a clinically-relevant screening tool. Effective screening for bipolar disorder is important because patients frequently receive an incorrect initial diagnosis of major depression (Ghaemi, et al., 1999) owing to symptoms of mood-elevation not being reported, particularly when

they are expressed as hypomania rather than mania (Cassano, et al., 1999). Assessment of patients presenting with major depression using a screening tool such as the MDQ may increase identification of bipolar disorder and reduce the frequency of incorrect treatment with antidepressants without concurrent mood stabilisation (Perlis, 2005) that may otherwise contribute to switching to mania and worsen clinical outcome (Ghaemi, et al., 2000).

### **7.2.2 The bipolar phenotype and a continuum approach**

Growing interest in a continuum approach to bipolar disorder has placed increasing significance on symptoms of mood elevation in the definition of bipolar spectrum disorder (Akiskal, et al., 2000; Angst, et al., 2003). As described above, the MDQ is a suitable screening tool for mood-elevation symptoms. This research implemented the MDQ with probable bipolar criteria and threshold bipolar criteria to identify subjects at increased risk of bipolar disorder and who were therefore described as ‘bipolar phenotype’ subjects. **Chapter 2** showed that one fifth (21.8%) of respondents to the online Student Stress Survey satisfied threshold bipolar criteria on the MDQ and were bipolar phenotype subjects. This finding is consistent with the idea that there is a relatively common adolescent bipolar phenotype (Tijssen, et al., 2010). Furthermore, of the 92 bipolar phenotype subjects who were interviewed with the Mini International Neuropsychiatric Interview – Plus (MINI-Plus) (Sheehan, et al., 1998) (in collaboration with Rebecca A Chandler), two fifths (39.8%) had a DSM-IV-TR bipolar diagnosis. These findings demonstrate that when the MDQ was used with threshold bipolar criteria in a student population it was able to identify a relatively common adolescent bipolar phenotype that included a sub-group of subjects with a bipolar diagnosis. Therefore, this research revealed that the MDQ detected a group at

significant risk for bipolar disorder; a sample of these bipolar phenotype subjects was investigated further in **Chapter 3**, **Chapter 4**, and **Chapter 5**.

The sample used in the present research included medication-naïve and previously undiagnosed bipolar phenotype subjects. This is an example of an investigation employing the continuum approach, which has become increasingly popular and involves assessment of subclinical or spectrum psychiatric disorders in order to uncover potential risk markers associated with these disorders. For example, a previous study used neuroticism (N) as a risk marker for depression and found that negative biases in emotional processing were present in never-depressed subjects with high neuroticism (N), consistent with the hypothesis that negative biases may precede depression and represent a vulnerability marker for depression (Chan, et al., 2007). Such studies have the advantage of addressing some of the potential confounds seen in purely patient samples, including those related to experience of repeated illness episodes or current medication (Lawrence, et al., 2004). The current research is therefore of clinical relevance because the differences recorded in bipolar phenotype subjects remained significant even when those subjects with a diagnosis of bipolar disorder were excluded from analyses. This suggests that the effects recorded (and discussed below) were present in subjects both with and without a bipolar diagnosis, implying that these differences may precede the disorder and be important risk factors. However, it remains of importance to refine the measurements used in this research and to apply them to a patient group.

### **7.2.3 Biased emotional processing in the bipolar phenotype**

Overall, the results from **Chapter 3** revealed that the bipolar phenotype was associated with positive biases in emotional processing. Psychological, physiological, and neural assessments provided converging evidence that positive vs. negative stimuli had greater significance to bipolar phenotype subjects than controls. In line with cognitive psychological theories (Beck, et al., 1979), the positive biases in emotional processing recorded in this investigation may account for experience of mood-elevation symptoms and may represent vulnerability markers associated with bipolar disorder. The consistency of the directionality of these findings across a number of measures is important given the lack of clarity yielded by studies of emotional processing in patients with bipolar disorder to date (Harmer, et al., 2002; Lyon, et al., 1999; F. C. Murphy, et al., 1999; Rubinow & Post, 1992; Summers, et al., 2006; Yurgelun-Todd, et al., 2000).

Positive biases in emotional processing have also been recorded following administration with antidepressants in healthy volunteers (Harmer, et al., 2004; Harmer, et al., 2003). For this reason, the therapeutic effects of antidepressants have been postulated to be mediated by a reversal of the negative biases found in depression (Harmer, et al., 2003). Therefore, exacerbation of positive biases (associated with the bipolar phenotype) may represent a cognitive psychological explanation for the mood instability that results from antidepressant treatment in some patients with bipolar disorder (Sachs, et al., 2007).

#### 7.2.4 Disrupted decision-making in the bipolar phenotype

A further study was carried out to assess the extent to which decision-making was disrupted in the bipolar phenotype. Understanding the possible factors underlying risky behaviour in bipolar phenotype participants was of clinical importance because experience of risk-taking behaviour was recorded in almost two thirds (62.5%) of the bipolar phenotype participants investigated in **Chapter 2**. The results from **Chapter 4** demonstrated that risky decision-making and cognitive flexibility were disrupted in participants with the bipolar phenotype, especially in male subjects. However, in contrast to the strikingly consistent findings across a range of emotional processing tasks in **Chapter 3**, the risky decision-making, framed risky-choice, and intra-dimensional/extra-dimensional set-shifting tasks described in **Chapter 4** (and which will be discussed below) yielded less clear-cut results.

Increased risk-taking behaviour for gambles with disadvantageous large vs. small losses and impaired cognitive flexibility during extra-dimensional set shifting were recorded in male bipolar phenotype participants. Specific disruption in male bipolar phenotype subjects indicated a potential gender difference in risky decision-making that might be expected to be reflected by frequency of experience of mood-elevation symptoms involving risky behaviour. Accordingly, there were significantly higher levels of endorsement of the risky behaviour item on the MDQ by male (68.3%) than female (57.1%) participants ( $X^2(1)=7.538, p=0.006$ ) in spite of a non-significant difference in overall number of mood-elevation symptoms experienced by male ( $8.8 \pm 1.7$  items) and female ( $8.6 \pm 1.6$  items) bipolar phenotype participants ( $F(1,564)=2.718, p=0.100$ ). These findings suggest that altered cognitive flexibility and processing of punishment-related reinforcement cues may contribute to risk-

seeking behaviour in male bipolar phenotype subjects. However, since these effects were recorded solely in male subjects, further explanations were required to account for risky behaviour across both male and female bipolar phenotype subjects. Altered performance in the framed risky-choice task was seen in bipolar phenotype participants of both genders, and the implications of these results will be described next.

### **7.2.5 Steeper subjective value function in the bipolar phenotype**

The previous sections have discussed findings of abnormal emotional processing and risky decision-making in bipolar phenotype participants. Therefore, it is unsurprising that this research also recorded altered performance during the framed risky-choice task, which combines information about emotional context with risky decision-making.

The framed risky-choice task assessed risky decision-making under conditions of uncertainty that were described in terms of gains (positively-framed) or in terms of losses (negatively-framed). Typically, decision-makers make risk-averse choices during positively-framed dilemmas and risk-seeking choices during negatively-framed dilemmas (Tversky & Kahneman, 1981). However, compared to controls, bipolar phenotype participants showed a trend towards making more risky choices to obtain increased gains in positively-framed dilemmas and fewer risky choices to avoid certain (or highly probable) losses in negatively-framed dilemmas. This suggests that bipolar phenotype participants were less sensitive to the changes in the emotional context of the dilemma that normally modulates riskiness of behaviour under conditions of uncertainty (Kahneman & Tversky, 2000).

Reduced sensitivity to framing has been reported previously in patients with bipolar disorder and was proposed to relate to steeper psychometric functions that relate gains and losses to their subjective values (Chandler, et al., 2009). Therefore, the present research is of clinical significance because changes in sensitivity to framing and, potentially, alteration of the subjective value function are present in the bipolar phenotype and may represent vulnerability markers for bipolar disorder. Since bipolar phenotype participants showed changes in risk aversion during negatively-framed but not positively-framed dilemmas, bipolar phenotype participants may only have had steeper psychometric functions relating losses to their subjective values. This finding is important because it suggests that changes in steepness of the gains part of the subjective value function may be related to disease progression rather than representing a potential vulnerability marker for bipolar disorder.

Meanwhile, results from the risky decision-making task revealed that bipolar phenotype participants showed increased loss aversion for gains only trials and increased risk-seeking behaviour for losses only trials relative to controls, i.e. an exaggeration of the reflection effect. Alteration of non-normative decision-making in this manner cannot be accounted for by steeper subjective value functions, and differences in findings between the risky decision-making task and the framed risky-choice task may be attributed to differences in task design relating to actual monetary values of the outcomes. Changes in non-normative decision-making have been recorded in previous studies that have involved modulation of serotonin activity. For example, tryptophan supplementation has been found to attenuate the reflection effect (Murphy, Longhitano, et al., 2009), whilst tryptophan depletion increased the reflection effect (as in the present study) in healthy volunteers (Campbell-Meiklejohn

et al., unpublished data). Therefore, the current findings could imply that serotonin activity may be decreased in the bipolar phenotype in both male and female participants. This is of clinical relevance because correction of changes in non-normative decision-making may represent one psychological mechanism through which the (particularly serotonergic) pharmacological effects of medications may be mediated in the treatment of bipolar disorder. This suggestion is supported by the changes in functional activation of brain structures involved in processing reward and in emotion regulation, which will be described in the next section. However, further confirmation is required using manipulation studies, for example by employing tryptophan depletion, in bipolar phenotype participants.

#### **7.2.6 The neural correlates of disrupted emotional processing and decision-making in the bipolar phenotype**

The neural correlates of emotional processing and decision-making in participants with the bipolar phenotype were assessed in two neuroimaging studies that were described in **Chapter 3** and **Chapter 4**. Overall, bipolar phenotype participants demonstrated altered activation of a number of cortical and sub-cortical regions involved in assessing emotional salience, emotion regulation, and cognitive control. These changes were consistent with positive biases in emotional processing and altered processing of punishment-related reinforcement cues, and may therefore unpin the behavioural effects described previously.

**Chapter 3** employed emotional processing tasks that assessed the salience of happy and fearful faces (in the facial expression matching task) and assessed the extent to which positive and negative emotional stimuli interfered with the cognitive task at

hand (emotional counting Stroop). For example, the facial expression matching task required participants to match an emotional face with a face showing the corresponding emotion, without extended deliberation. A similar set-up existed for the emotional counting Stroop, which involved covert presentation of emotional words and required participants only to count the number of words present. In both tasks, participants did not spend much time selecting their response and, furthermore, there was no feedback or emotional outcome. Results from the emotional-processing tasks revealed reduced activation of the bilateral amygdalae, which are involved in assessing emotional salience (Phillips, et al., 2003a), to fearful faces (female subjects only) and increased activation of a regulatory region, the right DLPFC (Phillips, et al., 2003a), in response to negative vs. neutral words during the emotional counting Stroop. Together, these findings indicated that there was increased regulatory control of negatively-valenced stimuli and, therefore, reduced salience in bipolar phenotype participants. This may be of clinical significance because disrupted activation of these regions has been proposed to underlie emotion dysregulation and emotional lability in bipolar disorder (Phillips, 2006; Phillips, et al., 2003b). Furthermore, since these effects remained when participants with a bipolar diagnosis were excluded from analysis, these differences may precede illness onset and may represent vulnerability markers for bipolar disorder.

Meanwhile, **Chapter 4** described a risky decision-making task that required participants to deliberate between two gambles. This enabled assessment of neural activation (i) during deliberation between risky choices and (ii) when participants were presented with an emotionally-salient outcome (e.g. win or loss). Whilst bipolar phenotype participants did not show differences in neural responses during

deliberation between the two gambles, increased activation of the ventral striatum and cortical regions (including bilateral lateral occipital cortex and left precentral and postcentral gyri) was recorded for outcomes that were losses vs. wins. Therefore, altered functional activation of these regions may represent potential neural correlates of the disrupted decision-making seen behaviourally in bipolar phenotype participants.

### **7.2.7 Disrupted sleep and circadian rhythms in the bipolar phenotype**

Altered sleep and circadian rhythms are a common feature of many psychiatric disorders, including bipolar disorder (Wulff, et al., 2010). Indeed sleep disruption is found in all phases of bipolar disorder, with patients experiencing insomnia or hypersomnia during depressive episodes and reduced need for sleep during (hypo-) manic episodes. Investigation of sleep and circadian rhythms is of clinical importance because previous experience of reduced need for sleep was recorded in over two thirds (68.8%) of the bipolar phenotype participants investigated in **Chapter 2**. Therefore, a further study was carried out employing actigraphy to assess sleep and circadian rhythmicity in participants with the bipolar phenotype.

**Chapter 5** revealed that bipolar phenotype participants had greater activity during sleep, particularly during their least active five hours of sleep (L5 activity). This led to reduced total sleep time, which could potentially account for the experience of mood-elevation symptoms in this group, consistent with findings from sleep deprivation studies (Wu & Bunney, 1990). Sleep disruption was particularly prominent in female bipolar phenotype participants who also showed reduced (i.e. poorer) relative amplitude of circadian rhythm, reflecting reduced difference in activity between their

most active and least active periods. These results are consistent with findings of increased L5 activity in a recent study of unmedicated and euthymic bipolar patients (Chandler, et al., 2008). However, the current study did not replicate the finding of reduced inter-daily stability that was also recorded in the unmedicated and euthymic bipolar patients (Chandler, et al., 2008). Therefore, the present research highlights particular sleep and circadian rhythm disturbances in the bipolar phenotype. Furthermore, these findings are of clinical interest as they suggest that increased activity during sleep and, correspondingly, reduced sleep duration may represent potential vulnerability markers for bipolar disorder in female subjects.

#### **7.2.8 Gender differences in vulnerability markers for bipolar disorder**

The present research has identified a number of potential vulnerability markers for bipolar disorder that were recorded in participants of only one gender. For example, reduced neural responses in the amygdalae in response to fearful facial expressions and increased activity during sleep were found only in female participants. This is consistent with modulation of emotional processing more frequently being seen in female participants than male participants (Murphy, Longhitano, Ayres, Cowen, & Harmer, 2006). On the other hand, increased proportionate choice of risky gambles associated with large vs. small losses and more errors to criterion for extra-dimensional set-shifts were seen only in male participants. The latter result is not in line with findings of poorer spatial working memory, but not cognitive flexibility assessed by the intra-dimensional/extra-dimensional set-shifting task, in male vs. female bipolar patients (Barrett, Kelly, Bell, & King, 2008). However, this inconsistency may have resulted from grouping together of reversal, intra-dimensional shifting, and extra-dimensional shifting trials in the previous study.

These findings suggest that different mechanisms may be involved in mediating risk for bipolar disorder across the two genders. This implies that some treatments may be more effective in patients of one gender. For example, a psychosocial therapy such as social rhythm therapy, which focuses on maintaining a regular daily routine and consistent sleep-wake patterns (Frank, et al., 2000), may be a more effective adjunct to pharmacological treatments in female than male bipolar patients. The current research therefore provides specific hypotheses that can be tested in future patient studies.

### **7.2.9 Quetiapine**

In the previous sections, disruptions to emotional processing, decision-making, and sleep and circadian rhythmicity in bipolar phenotype participants have been discussed. The final study presented in this research investigated the effects of seven-day quetiapine administration on these measures in healthy volunteers with the aim of uncovering the potential mechanisms of action of this pharmacological treatment. As described in **Chapter 1**, quetiapine has a complex pharmacological profile that is contributed to by its active metabolite, norquetiapine. In combination, quetiapine and norquetiapine show antagonism at dopaminergic D<sub>2</sub> receptors and serotonergic 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors, partial antagonism at serotonergic 5-HT<sub>1A</sub> receptors, and blockade of the noradrenaline transporter.

Quetiapine is an effective mood stabiliser from episodes of mania (Bowden, et al., 2005; Langosch, et al., 2008; Sajatovic, et al., 2008) and bipolar depression (Calabrese, et al., 2005; Endicott, et al., 2008; Endicott, et al., 2007; Goldstein, et al., 2008). Indeed, **Chapter 6** revealed that one-week administration with quetiapine in

healthy volunteers resulted in a number of effects that may be involved in mediating the mood-stabilising effects of quetiapine.

Firstly, quetiapine administration was associated with biases away from both positive (surprised) and negative (angry and fearful) emotional faces and away from positive and towards negative information during recognition memory. These findings are of clinical significance because they suggest that quetiapine may reduce processing of emotional information. Therefore, biases away from emotional information may represent a psychological mechanism through which the pharmacological effects of quetiapine are mediated in order to achieve mood stabilisation. Furthermore, the observation of worse target sensitivity for surprised faces in participants who had received quetiapine opposed the finding of better target sensitivity in bipolar phenotype participants described in **Chapter 3**. This suggests that the effects of quetiapine may oppose those abnormalities recorded in the bipolar phenotype in order to redress the positive emotional processing biases, thereby stabilising mood from (hypo-) manic episodes. However, biases away from angry and, in female participants, fearful faces could not play a role in correcting the positive emotional processing biases associated with the bipolar phenotype as described in **Chapter 3** and, indeed, would exaggerate such positive biases. On the other hand, a combination of biases away from both positive and negative emotional stimuli may account for the mood-stabilisation effects of quetiapine. Meanwhile, these findings of impaired discrimination (poorer discrimination or bias away) of surprised and angry faces directly opposes the effects recorded following quetiapine administration in patients with schizophrenia (Cabral-Calderin, et al., 2010). This inconsistency may be accounted for by differences in the study populations used in these two studies.

Quetiapine administration did not affect physiological responses during the emotion-potentiated startle, suggesting that quetiapine would not redress the increased responsivity to positive vs. negative and neutral conditions found in bipolar phenotype participants. This is of clinical significance because it suggests that alternative treatments may be required to alter physiological reactivity, for example those modulating serotonin reuptake inhibition (as discussed in **Chapter 3**), which is not affected by quetiapine.

The effects of quetiapine were not limited to emotional processing biases and were also detected during the risky decision-making task. Specifically, quetiapine administration was associated with increased proportionate choice of gambles with large losses and small gains and, therefore, greater choice of gambles with negative expected values. Previous studies revealed that modulation of serotonin and dopamine activity affected attention towards gains (Rogers, et al., 2003) and losses (Scarna, et al., 2005) respectively. This suggests that the present findings were consistent with quetiapine's combined pharmacological activity at serotonergic and dopaminergic receptors. These findings are of clinical relevance because they represent reduced attention to information about losses and increased attention to information about gains, consistent with an antidepressant effect.

Finally, actigraphy revealed that quetiapine increased total sleep time and improved intra-daily variability, resulting in a less fragmented pattern of rest and activity. Whilst these changes did not correspond exactly with the abnormalities recorded in bipolar phenotype participants, they are still of clinical significance because

improvements in sleep quality could benefit patients during either manic or depressive episodes. As described above, **Chapter 5** revealed a trend towards reduced total sleep time in bipolar phenotype participants. Since quetiapine administration was associated with increased total sleep time, quetiapine may act to redress the reduction in sleep found in the bipolar phenotype group, which may precipitate (hypo-) manic episodes (Wu & Bunney, 1990) or be experienced during (hypo-) mania. **Chapter 5** also revealed that participants with the bipolar phenotype had higher activity levels during sleep, in particular higher mobility during the least active 5 hours of sleep (L5 activity). However, quetiapine administration was not associated with any changes in activity during sleep, suggesting that correction of this abnormality may not be accounted for solely by pharmacological treatments such as quetiapine. Alternatively, actigraphic assessment in healthy volunteers may not have been sensitive to changes in activity during sleep because it is unlikely that drug treatment could have further reduced sleep activity in this non-clinical group.

## **7.3 Limitations**

### **7.3.1 Sample**

The first limitation of this research relates to how bipolar phenotype participants were selected. Scoring at least seven mood-elevation symptoms on the MDQ is associated with higher probability of bipolar diagnosis (Hirschfeld, et al., 2000b) and associated vulnerability (see **Chapter 2**). However, the transition from the common adolescent bipolar phenotype to more severe bipolar disorder remains poorly understood and is an important target for future study.

The second limitation of this research relates to the use of healthy volunteers in the investigation of the effects of quetiapine administration. Whilst this allowed for assessment of changes in the absence of confounds related to current mood, medication, or previous illness episodes, such research cannot increase understanding of how quetiapine may affect emotional processing, decision-making, and sleep and circadian rhythmicity specifically in the bipolar phenotype.

### **7.3.2 Positive biases in emotional processing**

The third limitation of this research relates to the positive biases found in bipolar phenotype participants. As described above, bipolar phenotype participants were identified based on experience of mood-elevation symptoms that were screened for using the MDQ. Therefore, it is possible that the positive biases recorded in the present research were a result of the screening method used to identify the bipolar phenotype subjects. Perhaps, had selection of bipolar phenotype participants been based on experience of symptoms of depression in addition to symptoms of mood

elevation, biases towards both positive and negative stimuli may have been recorded, i.e. increased sensitivity to emotional stimuli. However, the impetus for the current research arose from interest (i) in mood elevation and the bipolar spectrum, (ii) in the utility of the MDQ as a relatively simple screening tool for mood-elevation symptoms that are frequently unreported in bipolar disorder, and (iii) in characterising a bipolar phenotype.

### **7.3.3 Sleep architecture**

The fourth limitation of the current research relates to actigraphic measurements not being able to provide information about sleep staging and spectral composition. This is important in order to determine if changes in activity during sleep and total sleep time do indeed affect the relative compositions of REM and non-REM sleep. The present research also did not include a physiological measure of circadian phase, which should be addressed by future work.

### **7.3.4 Neural correlates of the effects of quetiapine**

The final limitation relates to the lack of functional neuroimaging data that could be used to gain understanding of the neural changes accompanying the emotional processing biases and changes in decision-making recorded following one-week quetiapine administration.

#### **7.4 Further work**

In order to address some of the limitations described above, possible avenues for further work will be outlined in this section. Firstly, future studies could investigate emotional processing, decision-making, and sleep and circadian rhythmicity in at-risk subjects identified using alternative methods of screening. Examples of these methods include screening for experience of subthreshold mood-elevation and depressive symptoms or selecting undiagnosed subjects with a first-degree family member who suffers from bipolar disorder.

Secondly, further investigation should include electroencephalography (EEG) to investigate sleep architecture in bipolar phenotype participants and the changes in sleep architecture during quetiapine administration. Furthermore, a physiological measure of circadian phase (e.g. melatonin or cortisol levels) should also be included.

Thirdly, future research should assess the effects of quetiapine administration in bipolar phenotype participants. However, such a study would have to be carefully monitored in case of adverse effects following quetiapine administration in a vulnerable group.

Finally, future work should include a functional imaging investigation of the effects of quetiapine in order to uncover potential neural correlates of the mood stabilisation effects and alterations in decision-making described in **Chapter 6**.

## **7.5 Conclusions**

The present research showed that the MDQ is a useful screening tool for bipolar disorder, even when used with more liberal threshold bipolar criteria. This research revealed that the bipolar phenotype is associated with a relatively high prevalence of bipolar disorder and associated vulnerability (such as substance misuse, health problems and gambling behaviour). Furthermore, this research presented a number of studies that demonstrated positive biases in emotional processing, altered decision-making, and disrupted sleep in bipolar phenotype participants. Functional neuroimaging data revealed potential neural correlates of these changes that related to altered neural responses in cortical (regulatory) regions, including the right DLPFC, and sub-cortical regions involved in assessing emotional salience, such as the amygdalae and ventral striatum. A preliminary investigation of quetiapine administration in healthy volunteers revealed effects potentially related to quetiapine's ability to stabilise mood from manic and depressive episodes in bipolar disorder. This provided a first step towards uncovering the psychological mechanisms through which quetiapine's clinical effects may be mediated.

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