Characterising the neural mechanisms of reward processing in bipolar disorder using EEG and fMRI

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Medical and Human Sciences

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CONTENTS

List of figures.................................................................................................................. 9
List of tables ...................................................................................................................... 11
List of abbreviations ......................................................................................................... 12
Abstract ............................................................................................................................ 13
Declaration ......................................................................................................................... 14
Copyright statement .......................................................................................................... 15
Acknowledgements ........................................................................................................... 16
The author ......................................................................................................................... 17
Rationale for submitting the thesis in an alternative format ............................................. 17
Publications and conferences ........................................................................................... 18

CHAPTER 1: General Introduction ................................................................................... 23

Review of reward dysregulation in bipolar disorder: What can cognitive neuroscience tell
us? ........................................................................................................................................ 24

Abstract ............................................................................................................................ 25

Introduction ......................................................................................................................... 26

Neural correlates of BAS hypersensitivity in Bipolar Disorder ........................................... 33

Neurobiological models of motivation in Bipolar Disorder ................................................. 42

Integration with psychological accounts ........................................................................... 47

Conclusion ........................................................................................................................... 51

Supplementary Material .................................................................................................... 52

Thesis Aims, Hypotheses and Predictions ......................................................................... 57

Hypothesis 1: Impulsivity and risk-taking in bipolar disorder arise from increased
sensitivity to reward .......................................................................................................... 57

Hypothesis 2: Reward processing abnormalities represent an endophenotype that
precedes the onset of bipolar disorder ............................................................................. 59
Hypothesis 3: In bipolar disorder there is misrepresentation of the probability and value associated with actions and behaviours ................................................................. 60

Hypothesis 4: Impaired reinforcement learning underlies persistent engagement in maladaptive behaviours in bipolar disorder ........................................................................ 61

CHAPTER 2: General Methodology ................................................................. 62

Definition of at-risk population based on Hypomanic Personality .................. 63
Cognitive neuroscience tools for characterising motivational processing ........ 65
Delay Discounting as a Tool for Measuring Impulsivity .................................. 65
Event-related potentials: An overview ................................................................. 68
Functional neuroimaging: An overview ............................................................. 75
Simultaneous EEG-FMRI .................................................................................. 76
Paradigm Development: in search of a risk-taking task .................................... 95
The Balloon Analogue Risk-Taking Task & Influence of Mood Induction ....... 95
Wheel of Fortune Task with EEG ...................................................................... 100

CHAPTER 3: Better than I thought: positive evaluation bias in hypomania ......... 105

Abstract .................................................................................................................. 106
Introduction ............................................................................................................. 107
Materials and Methods ....................................................................................... 111
Results ..................................................................................................................... 117
Personality and symptom questionnaires ............................................................ 117
Reward learning task .............................................................................................. 117
ERP-domain Analysis .......................................................................................... 119
Time-Frequency-domain Analysis ....................................................................... 122
Discussion ............................................................................................................... 123
Supplementary Material ....................................................................................... 128
CHAPTER 4: I want it now! Neural correlates of hypersensitivity to immediate reward in hypomania .......................................................... 130

Abstract ............................................................................................................. 131
Introduction ............................................................................................................. 132
Methods .................................................................................................................. 136
  Two Choice Impulsivity Paradigm (TCIP) ......................................................... 136
  Fixed Delays Task .............................................................................................. 137
Results .................................................................................................................... 141
  Experiment 1: Two-Choice Impulsivity Paradigm ........................................... 141
  Experiment 2: Fixed Delays Task ....................................................................... 141
Discussion ............................................................................................................. 148

Prelude to Chapters 5 and 6 .............................................................................. 152

CHAPTER 5: Top-down control during anticipation regulates sensitivity to reward in bipolar disorder ................................................................. 153

Abstract ............................................................................................................. 154
Introduction .......................................................................................................... 155
Methods .................................................................................................................. 159
Results .................................................................................................................... 167
Discussion ............................................................................................................. 178
Supplementary Material ....................................................................................... 183

CHAPTER 6: Evolution of reward network abnormalities over time: EEG-fMRI integration in bipolar disorder ...................................................... 201

Abstract ............................................................................................................. 202
Introduction .......................................................................................................... 203
Methods .................................................................................................................. 207
  Participants, self-report measures and Task ...................................................... 207
  Joint EEG-fMRI Recording ................................................................................ 207
Removal of fMRI artifacts .......................................................................................... 208
ERP Analysis ............................................................................................................. 209
Source Analysis ......................................................................................................... 210
Results ....................................................................................................................... 212
ERP Domain .............................................................................................................. 212
Crossmodal (FRN-BOLD) Correlations ................................................................. 215
Source Domain ......................................................................................................... 216
Discussion ................................................................................................................ 222
ERP and source-domain analyses ......................................................................... 222
Integration of EEG and fMRI findings .................................................................... 225

CHAPTER 7: GENERAL DISCUSSION ....................................................................... 230
Abstract ................................................................................................................... 230
Summary of experimental work ............................................................................... 231
Synthesis and relationship to hypotheses ............................................................... 234
Hypothesis 1: Impulsivity and risk-taking in bipolar disorder arise from increased sensitivity to reward ................................................................. 234
Hypothesis 2: Reward processing abnormalities represent an endophenotype of bipolar disorder that precedes onset of the disorder ............................................. 244
Hypothesis 4: Impaired reinforcement learning underlies persistent engagement in maladaptive behaviours in bipolar disorder ................................................... 250
Neurobiological model of reward dysregulation in BD: Revisited .......................... 254
Limitations of this thesis ......................................................................................... 257
Future Research ....................................................................................................... 259
Conclusion ............................................................................................................... 261

References ............................................................................................................... 262
Appendix A: Self-report measures ......................................................................... 285

Total word count: 54,700
LIST OF FIGURES

Figure 1.1. The limbic system, including striatum, develops quicker than the prefrontal cortex .........................................................................................................................................................43

Figure 1.2. Tripartite model of reward dysregulation in bipolar disorder ........................................45

Figure 1.3. Psychological and pharmacological interventions may accomplish the same end- goal via distinct biopsychological mechanisms .................................................................................................................46

Figure 2.1. Prevalence of hypomanic personality traits, as measured by the Hypomanic Personality Scale, is normally distributed in the general population .................................................................64

Figure 2.2. Example of event-related potentials of the EEG ........................................................................69

Figure 2.3. Processes measured by electrophysiological (EEG), haemodynamic (fMRI) and behavioural indices ....................................................................................................................................................78

Figure 2.4. First 32 channels of ongoing electroencephalography (EEG) .............................................81

Figure 2.5. Ongoing electroencephalograph (EEG) contaminated by gradient artefact (GA). 83

Figure 2.6. Sampling of the gradient artefact with asynchronous onset between MR slice acquisition ..................................................................................................................................................85

Figure 2.7. The electrocardiogram (ECG) inside and outside the scanner ...........................................87

Figure 2.8. Photodiagram of EEG-fMRI set up inside the scanner used ..............................................89

Figure 2.9. Schematic of a single trial .......................................................................................................97

Figure 2.10. Example of choices on two separate trials ........................................................................101

Figure 2.11. Schematic of a single trial .....................................................................................................103

Figure 3.1. Schematic diagram of the experimental design ........................................................................113

Figure 3.2. Average waveforms for all conditions by group ..................................................................119

Figure 3.3. Topographical plot of the 50/50 difference wave ................................................................120

Figure 3.4. Time-frequency spectra of the difference in total power (current density; μV2) between outcomes ........................................................................................................................................122

Supplementary Figure 3.1. Mean bet size shown by block and group ..................................................129

Supplementary Figure 3.2. Frequency spectra showing total power for 50% condition by outcome and group ........................................................................................................................................129

Figure 4.1. Schematic showing stimuli and time course of a trial ..........................................................139
Figure 4.2. N1 indexes temporal discounting ................................................................. 144
Figure 4.3. The delay associated with motivational feedback is encoded in the human electroencephalograph ................................................................. 145
Figure 4.4. Steeper temporal discounting in individuals prone to hypomania .......... 146
Figure 5.1. Participants made bets on which colour would win in a Roulette gamble .... 162
Figure 5.2. Evolution of the reward network over time .............................................. 170
Figure 5.3. Between-groups comparison of activity in nucleus accumbens ............. 172
Figure 5.4. Modulation of reward outcomes in NAcc of BDR participants by residual mania and depression .......................................................... 173
Figure 5.5. Right dorsolateral prefrontal cortex (dLPFC) function in bipolar disorder group 175
Supplementary Figure 5.1. Patients with bipolar disorder show increased reward response when evaluating gain outcome compared to healthy controls .... 189
Figure 6.1. N1 at occipital electrodes ........................................................................... 213
Figure 6.2. FRN at electrode FCz. Healthy controls (HC), bipolar disorder in remission (BD) .................................................................................. 214
Figure 6.3. P300 at centroparietal electrode Pz. Healthy controls (HC), bipolar disorder in remission (BD) ................................................................. 214
Figure 6.4. Activity in nucleus accumbens (NAcc), as measured by fMRI, correlates with the feedback-related negativity brain potential (FRN, measured by EEG) ................. 215
Figure 6.5. Generators of the N1 ................................................................................... 217
Figure 6.6. Sources during early FRN window .............................................................. 218
Figure 6.7. Sources during late FRN window ............................................................... 220
Figure 6.8. Sources during P300 window .................................................................... 221
Figure 6.9. Reward>Loss contrast (p<.0001, 100 voxel extent threshold) from the fMRI analysis ...................................................................................... 228
Figure 6.10. Reduced dACC-FRN in patients may arise from a relative dominance of affective (ventral) portion of ACC ......................................................................... 229
Figure 7.1. Psychological and pharmacological interventions may accomplish the same end-goal via distinct biopsychological mechanisms .......................................................... 242
Figure 7.2. Schematic of rose-tinted evaluation bias in hypomania ........................... 251
Figure 7.3. Dorsal and ventral pathways in the reward network in healthy individuals (top) and BD (bottom) .............................................................................. 256
LIST OF TABLES

Supplementary Table 1.1. Summary of neuroimaging studies in relation to the Behavioural Approach System (BAS) and its likely neural correlates ................................................................. 52

Table 4.1. Demographics and self-report measures. Significantly greater psychometric risk for hypomania .................................................................................................................. 138

Table 4.2. The hypomania-prone group made significantly more immediate choices overall, as well as more consecutive immediate.................................................................................. 141

Table 4.3. Across groups, reaction times faster for reward trials than penalty trials (p<.01), and for immediate outcomes relative to delayed outcomes (p<.05) ........................................ 142

Table 5.1. Demographics and behavioural data. BD patients did not differ from the controls in their response time or proportions ...................................................................................... 168

Supplementary Table 5.1. Activated foci for main whole-brain analysis. EV, expected value; PE, prediction error ........................................................................................................................... 190

Supplementary Table 5.2. Activated foci for supplementary analyses at whole-brain level 197
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>Anterior Cingulate Cortex</td>
</tr>
<tr>
<td>BAS</td>
<td>Behavioural Approach System</td>
</tr>
<tr>
<td>BIS</td>
<td>Behavioural Inhibition System</td>
</tr>
<tr>
<td>BD</td>
<td>Bipolar Disorder</td>
</tr>
<tr>
<td>DA</td>
<td>Dopamine</td>
</tr>
<tr>
<td>[dl]PFC</td>
<td>[dorsolateral] Prefrontal Cortex</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>ERP</td>
<td>Event-Related Potential</td>
</tr>
<tr>
<td>FRN</td>
<td>Feedback-Related Negativity</td>
</tr>
<tr>
<td>FFFS</td>
<td>Fight/Flight/Fright System</td>
</tr>
<tr>
<td>HPS</td>
<td>Hypomanic Personality Scale</td>
</tr>
<tr>
<td>MCL</td>
<td>Mesocorticolimbic</td>
</tr>
<tr>
<td>NAcc</td>
<td>Nucleus accumbens</td>
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<tr>
<td>OFC</td>
<td>Orbitofrontal Cortex</td>
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ABSTRACT

Characterising the neural mechanisms of reward processing in bipolar disorder using EEG and fMRI

Liam Mason, The University of Manchester

For the degree of Doctor Philosophy (PhD) 10th September 2012

One of the key features of bipolar disorder (BD) is risky and impulsive decision-making, behaviours theorised to arise from dysregulation in a biobehavioural system governing approach of rewards. However, the neural mechanisms of this conceptual model have not been well specified, and there remains a gap between this model and key clinical phenomena such as mixed episodes. This thesis takes a neuroeconomics and reinforcement learning approach to characterise the neural mechanisms of motivational decision-making in BD. A review of the neurobiological evidence for reward dysregulation in BD (Chapter 1) arrives at a model in which striatal hypersensitivity is exacerbated by reduced dorsolateral prefrontal cortical (dLPFC) control. This model is tested by four studies using electrophysiology, source analysis and functional neuroimaging.

Chapters 3 and 4 employ EEG to explore how hypomanic traits modulate motivational processing in contexts requiring learning and trade-offs between risk and between immediate and delayed reward. In Chapter 3, high trait hypomania was associated with impaired loss learning and a neural evaluation of rewards and losses more favourably, relative to low hypomania. This “rose-tinted” bias may reinforce risky behaviours that pay off and reduce learning from aversive repercussions. Chapter 4 reports an attentional bias towards immediate reward which may drive a steeper delay discounting trajectory and an inability to delay gratification.

In Chapters 5 and 6 simultaneous electrophysiological and functional neuroimaging was utilised to characterise spatial and temporal perturbations to the mesocorticolimbic reward network in a clinical sample of BD. Patients showed a poorer ventromedial prefrontal cortical representation of the objective value of outcomes as well as a heightened striatal reward response. The latter finding was related to decreased dLPFC activation, which also interacted with residual manic symptoms. This is interpreted in terms of reduced top-down executive control that is exacerbated by residual manic symptoms, suggesting a potential mechanism underlying relapse and extremely high levels of reward-seeking seen during mania. EEG source imaging localised differences during reward outcome evaluation to early sensory-attentional (N1), reward evaluation (FRN) and cognitive (P300) stages of processing. For rewards, patients exhibited greater activity in precuneus, frontal eye fields (N1) and ventral anterior cingulate (FRN), consistent with an attentional bias to reward that drives hyperactivity in reward circuitry.

Collectively the results provide evidence of reward dysfunction from behavioural measures and two neuroimaging modalities. The results support a model in which a core hypersensitivity to reward and a “rose-tinted” evaluation bias act to 1) potentiate the impact of rewarding outcomes and 2) attenuate aversive ones maintains a distorted representation of objective likelihood and value associated with actions. This is exacerbated by reduced prefrontal control – which may be particularly associated with mania – highlighting a potential target for novel pharmacological and psychological interventions.
DECLARATION

No portion of work referred to in this thesis has been submitted in support of an application for another degree of qualification of this or any other institute of learning.
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Thank you also to my other supervisors and collaborators, Sara Tai, Daniela Montaldi and Noreen O’Sullivan, who provided invaluable expertise, discussion and critical thought that helped to develop my ideas. This project would not have been possible without you.

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THE AUTHOR

Liam Mason completed an undergraduate degree in Cognitive Neuroscience and Psychology at the University of Manchester. He subsequently completed a postgraduate diploma in Advanced Practice Mental Health Interventions whilst working in the NHS delivering psychological therapy in primary care. His PhD research was supported by an interdisciplinary studentship awarded jointly by the Medical Research Council and Economic and Social Research Council. He is due to commence doctoral training in clinical psychology at the Institute of Psychiatry, London.

RATIONALE FOR SUBMITTING THE THESIS IN AN ALTERNATIVE FORMAT

This work in this thesis formed the basis of five articles that were prepared for publication and are at various stages of publication (see below). This process has provided the author with invaluable feedback on the content of these articles.
PUBLICATIONS AND CONFERENCES

Parts of this thesis form the basis of articles that are published or under peer review, either directly or indirectly. The results were also presented at oral and poster presentations.

**Based on Chapter 1:**

Mason, L., Tai, S., El-Deredy, W., & Bentall, R. BAS and the brain: what can cognitive neuroscience tells us about reward dysregulation in bipolar disorder? *Currently under review for publication in Psychological Medicine.*


**Based on Chapter 3:**


Prediction Errors: Implications for Psychopathology. *International Conference on Cognitive Neuroscience* (ICON; Mallorca, 26th September 2011).
Based on Chapter 4:


Reward Differences in Mania: Risk and Impulsivity in Individuals Vulnerable to Bipolar Disorder. *International Review of Bipolar Disorders* (IRBD; Rome, 10th June 2011)

Based on Chapter 5:

Mason, L., O'Sullivan, N., Montaldi, D., Bentall, R., & El-Deredy, W. Top-down control during anticipation regulates sensitivity to reward in bipolar disorder. *Currently under review for publication in Archives of General Psychiatry.*

Other projects:


Preface

One of the most notable features of bipolar disorder (BD) is an extreme fluctuation in motivation and emotion that can culminate in episodes of mania and depression. In addition, BD is associated with impulsive and risky decisions that frequently have highly damaging consequences and are later greatly regretted by the individual. Elevated rates of spending sprees, unprotected sex, alcohol and substance abuse, and suicide have been linked to a core impulsivity in BD that pervades all phases of the disorder (Strakowski et al., 2010). Lamentably, clinical outcome is generally poor and nearly three-quarters of patients relapse in five years despite treatment (Gitlin et al., 1995). Estimates of symptom heritability for BD are as high as 80% in offspring (McGuffin et al., 2003), with a ten-fold risk of receiving a BD diagnosis (Jordan & Christine, 2003).

Affective and motivational dysregulation have been theorised to arise from fluctuations in a conceptual biobehavioural system governing approach and experience of reward, leading to unstable levels of positive affect, energy, drive, and confidence. However, the neurobiological mechanisms of this psychological framework have not been well characterised. This lack of communication between the disciplines of clinical psychology and neuroscience misses the opportunity to learn more about the biological processes that underpin and maintain BD – particularly the specific stages of processing and the exact parameters that go awry. A better understanding of the psychobiological mechanisms of motivation dysregulation in BD may improve diagnosis and lead to more effective psychological and pharmacological interventions. In addition there has been growing interest in identifying endophenotypes in the DSM-V conceptualisation of BD (Phillips & Vieta, 2007) – that is, biological characteristics that are tied to fewer genes and bridge the gap between genotype and psychophysiological expression. One established endophenotype in BD is abnormal facial emotion labelling, which has been linked to hyperactivity in ventral frontolimbic circuits (Rosen & Rich, 2010). Given the involvement of this network in motivation and reward-seeking
(e.g. Rolls, 1999; see section 1.1 of this thesis) it is plausible that these abnormalities also underpin impulsive and risky choice in BD.

With this in mind, the present thesis aimed to better understand motivation and decision-making in BD through the application of cognitive neuroscience principles. This approach offers complementary models of the neural systems involved in motivation *per se*, as well as tools and established paradigms for probing disordered processing. In particular, we sought to establish a relationship between impulsivity and risk-taking and functionality of networks underpinning reward, attention and cognitive control. This was accomplished by applying theory from economic decision-making and reinforcement learning theory, which have advanced understanding of irrational and suboptimal decision-making both in the general population and in other psychiatric disorders. Ultimately this thesis aimed to provide a bridge between clinical psychology and cognitive neuroscience accounts of motivation dysregulation in BD.

This thesis adheres to the following structure. In Chapter 1 a review of the neurobiological evidence for reward dysregulation in BD is presented, and this arrives at a model in which dominant mesocorticolimbic processing of reward is exacerbated by reduced prefrontal control. Based on this a number of hypotheses and predictions are proposed to then be tested by the experimental chapters. An overview of the methods and paradigm development is provided in Chapter 2. Chapter 3 examines risk-taking and reward learning in a non-clinical at-risk sample and uses event-related potentials (ERPs) and time-frequency analysis to uncover a prediction error deficit. In the same population, Chapter 4 focuses on impulsivity and, using ERPs, establishes that steeper discounting of delayed reward is driven by an attentional bias towards immediate reward. Chapters 5 and 6 utilise simultaneous EEG-fMRI in a clinical sample of BD. In Chapter 5, fMRI is used to test and ultimately demonstrate a striatal hypersensitivity to reward in striatum that is related to a misrepresentation of expected value in ventromedial prefrontal cortex and reduced top-down control in dorsolateral prefrontal cortex. Chapter 6 avails of EEG source imaging to examine the chronometry of reward dysfunction, and uncovers both early attentional and evaluatory deficits, along with delayed
information processing. Cross-modality correlation demonstrates a positive relationship between reward hypersensitivity in the mesocorticolimbic pathway and the FRN attenuation observed in patients. A general discussion chapter integrates the experimental work with the wider literature, and revisits the model proposed at the outset. Put together, the thesis concludes that BD is underpinned by abnormalities in the mesocorticolimbic reward network, potentiated by an attentional bias to reward and reduced reappraisal from higher prefrontal cortical regions. A consequence is that decisions may be more guided by reflexive impulses than by longer-term goals, leading to impulsive and risky behaviours. We hope that the work of this thesis will ultimately lead to interventions that strengthen the integrity of top-down systems and sustaining pursuit of longer-term goals and aspirations.
CHAPTER 1: GENERAL INTRODUCTION

Preface

This chapter begins with a review of the literature implicating dysregulation of the reward system in the pathogenesis of bipolar disorder (section 1.1). It takes an established conceptual model as a start-point and considers whether it can be supported and enriched by the extant cognitive neuroscience literature. The review and model lead to a number of hypotheses and predictions (section 1.2) to be tested by the experimental work (Chapters 3 - 6).
1.1. Review of reward dysregulation in bipolar disorder: What can cognitive neuroscience tell us?

* A version of this chapter is currently under review for publication in Psychological Medicine
Abstract

Bipolar disorder is associated with dysregulated affect and motivation, as well as impulsive and risky decision-making. These features have been explained by changes in the sensitivity of a conceptual system governing approach and experience of reward, but there remains a gap between this account and contemporary cognitive neuroscience understanding of these systems. We review findings in clinical and at-risk populations and arrive at a biopsychological model in which dysregulated and reflexive processing of reward, threat and risk cues are exacerbated by a reduction in reflective cognitive control. In addition, the neural mechanisms underlying biases towards expectancy of positive outcomes and rose-tinted evaluation are discussed in relation to risk-taking. The parallels of this model with existing cognitive psychological models are considered, along with its potential to explain the therapeutic mechanisms of psychological interventions. Additionally the potential for vulnerability markers in at-risk individuals and prospects for novel interventions that integrate recent cognitive neuroscience findings are considered.
1.1.1. INTRODUCTION

1.1.1.1. Overview of bipolar disorder

Bipolar Disorder (BD) is a debilitating psychological disorder characterised by periods of mania or hypomania and periods of depression interspersed with relatively normal functioning. BD has been ranked as the sixth leading cause of disability in the developed world (Pini et al., 2005) and is associated with loss of economic productivity, reduced life expectancy and considerable burden to the individual, carers and society (Das Gupta & Guest, 2002). Cognitively, BD is associated with extreme appraisals that overemphasise the importance of achievement and goal-striving (Johnson & Carver, 2006; Lam et al., 2004), and relapse into mania/hypomania and depression is often triggered by life events involving goal attainment or goal failure, respectively (Johnson, 2005b; Johnson et al., 2008). Clinically, BD is associated with impulsivity and risk-taking, especially in the manic/hypomantic phase, that can be damaging to the individual and others (APA, 2000). These characteristics distinguish the clinical profile of BD from major depressive disorder (MDD), and impulsivity may partly account for the five-fold increase in completed suicide in BD compared with MDD (Tondo et al., 2007). Greater impulsivity is also associated with earlier onset and a worse course, with increased relapse and co-morbid alcohol or substance use (Swann et al., 2004).

An influential psychological framework contends that these features of BD can be explained in terms of dysregulation in neural systems governing motivation and affect (Urosevic et al., 2008) and hyperactivity in this system has been proposed as an endophenotype for BD (Hasler et al., 2006). However, there exists a gap between this model and empirical findings in clinical neuroscience and as such the neural mechanisms of this system remain poorly specified. In this review we aim to bridge this gap and integrate empirical findings and paradigms from cognitive neuroscience with psychological frameworks of motivation and emotion in BD. This
approach allows more detailed characterisation of the psychological processes involved in motivation and may facilitate the identification of transdiagnostic endophenotypes for bipolar spectrum and other impulsivity disorders.

1.1.1.2. BAS dysregulation theory of bipolar disorder

People vary substantially in their subjective experience of mood and motivation, with the extremes of these experiences typically associated with psychological disorder. Gray’s reinforcement sensitivity theory (revised; Gray & McNaughton, 2000) is an influential biopsychological framework that explains these phenomena in terms of activity in a few distinct systems in the brain. Briefly, a behavioural approach system (BAS) generates optimism, drive, confidence, joy and euphoria (i.e. positive affect). A complementary behavioural inhibition system (BIS) serves to interrupt or modulate approach behaviour and is conceptualised as an executive or conflict resolution system in the most recent model (1991), mediating between reward-approach and threat-inhibit impulses, and in this way sitting atop a hierarchical network above two subordinate systems. The BAS has several notable motivational and emotional outputs, chiefly invoking positive affect—that is, feelings of optimism, energy, confidence, joy and euphoria. Conversely, activity in the BIS and Fight/Flight/Fright (FFFS; described in greater detail in 1.1.1.3) systems produce increased vigilance and negative affect, respectively; heightening attention and arousal (Amodio et al., 2008). Positive and negative affect refer to pleasant and aversive emotional states and, have been argued to lie on independent axes (Watson et al., 1988), paralleling similar arguments for the orthogonality of manic and depression symptoms (Johnson et al., 2011).

Individual variation in BIS and BAS sensitivity has been proposed to be related to personality (Smillie et al., 2006) and, by extension, psychological dysfunction (Amodio et al., 2008; Depue & Collins, 1999). In particular, BAS sensitivity is proposed to account for trait sensation-seeking and tolerance for taking risks, and
is cited in the pathophysiology of impulsivity disorders (Johnson et al., 2003). It has been proposed that mania and depression can be explained by extremes of BAS function (see Urosevic et al., 2008). On the one hand, the profile of mania is consistent with high BAS output and is typified by activated mood (either elevated or irritable), reduced need for sleep, increased activity, racing thoughts, surges of confidence and pursuit of enjoyable and often risky pursuits. Conversely, low BAS output may explain symptoms of depression such as anhedonia, pessimism and reduced goal-directed activity (APA, 2000). People with a BD diagnosis score higher on self-report measures of BAS that tap approach traits such as drive, reward responsiveness, and fun (or sensation) seeking (Alloy et al., 2008; Carver & White, 1994). Rewards elicit gross surges in confidence and self-efficacy (Johnson, 2005b) and increases in manic symptoms over time (Meyer et al., 2001). Indeed the involvement of life events involving goal attainment (reward) and failure (loss) in triggering affective episodes further suggests BAS dysregulation (Urosevic et al., 2008).

The BAS dysregulation theory can account for much of the clinical features of BD. However, the BAS dysregulation theory does not adequately explain inter-individual differences observed for vulnerability to bipolar disorders. In addition, BAS reactivity does not fully account for the mechanisms responsible for the transition from a manic to a depressive phase (and vice versa), or for mixed episodes, in which patients experience high levels of both negative and positive affect (Meyer & Hofmann, 2005). There is also equivocal evidence that the self-report measures of BAS are stable over time. One study found BAS to be stable and predict subsequent symptom levels (e.g. Carver & Johnson, 2009), consistent with being a trait feature, which does not sit well with the view of an alternating hyper- and hypo-active BAS in different phases of BD. However, another study found that BAS scores were only elevated in the manic phase (Van der Gucht et al., 2009), suggesting that BAS may be a state marker (and may be elevated in euthymia because of its sensitivity to subclinical manic symptoms). Finally, a key feature of the BAS dysregulation theory is the importance of life events involving goal-
attainment in triggering episodes. However, this association weakens over the course of BD, and a ‘kindling hypothesis’ (Post, 1992) proposes that stressors have a greater impact and lead to more frequent relapse over time, pointing to the involvement of other biopsychosocial mechanisms (see 1.1.3.1).

1.1.3. What can cognitive neuroscience tell us about BAS?

The BAS model is a conceptualisation that was developed before the availability of neuroimaging. This section considers the empirical evidence and how this might inform and extend the BAS framework whilst preserving its useful insights. This provides a bridge between BAS and the advances made by the neuroimaging field in characterising the psychological processes involved in motivation and emotion.

Neurally, BAS sensitivity would be expected to correspond to networks implicated in motivation, goal-directed action and gratification. Dopamine (DA) is a neurotransmitter that is expressed in the midbrain, particularly the ventral tegmental area (VTA) which projects to targets in the striatum, limbic system and frontal cortex (Koob, 1992; Van den Heuvel & Pasterkamp, 2008). The DA system was initially identified as playing a role in these phenomena in the 1950s, when it was demonstrated that rodents would compulsively self-administer electrostimulation to this system by issuing lever presses thousands of times per day (Olds & Milner, 1954). In humans, money is selected to index reward, because it is deemed to be something that is universally desirable (people prefer to gain money than lose it) (Rolls, 1999). However, clearly people vary in the value they ascribe to money over other rewards such as goal-attainment, socialising, and building a good reputation. Nevertheless a seminal study by Elliott et al. (Elliott et al., 2000) demonstrated that VTA and ventral striatum are activated by monetary reinforcement task, and more recently social rewards have activated the same circuitry (Izuma et al., 2008). There is individual difference in this reward response, which positively correlates with trait BAS (Hahn et al., 2009; Simon et al., 2009)
and sensation-seeking is also associated with reduced inhibitory control within the DA system (Zald et al., 2008). Further, when receiving unexpectedly rewarding feedback, both self-reported BAS and trait positive affect correlate with the size of an electrical brain potential that represents how motivationally salient outcomes are (Nijs et al., 2007; Van den Berg et al., 2011). Similarly, impulsivity has been linked to BAS fun-seeking and reward-reactivity by factor analysis (Smillie et al., 2006) and is associated with greater amplitude of another brain potential reflecting DA system activity (P2a; Martin & Potts, 2004; Potts et al., 2006b). This suggests that in people valuing reward there is greater reactivity of the DA system, particularly when rewards are unexpected or novel. We review findings of brain potentials elicited by reward and punishment in hypomania-prone individuals in (section 1.1.2.5).

The feedback-related negativity (FRN) signals when behaviour-generated outcomes are aversive or worse-than-expected (e.g. Holroyd et al., 2008), and is attenuated in impulsive individuals (Onoda et al., 2010). Linking to Gray’s model (revised; Gray & McNaughton, 2000), this finding fits with a blunted punishment sensitivity, or reduced sensitivity in a FFFS system. In this vein, the amygdala has been proposed as a substrate of the FFFS, given its central role in the processing of aversive and punishing stimuli as well as a “behavioural brake” on potentially harmful behaviours (Zald, 2003). Like the FFFS, the amygdala is consistently implicated in anxiety disorders (Etkin & Wager, 2007). However, research is increasingly supporting a more general role for the amygdala in processing both appetitive (BAS) and aversive (FFFS) stimuli, making dichotomous distinctions between Gray’s (e.g. Gray & McNaughton, 2000) systems less tenable. Alternatively, the insular cortex and habenula are regions that both play a role in processing punishment, risk (Campbell-Meiklejohn et al., 2008) and avoidance learning (Samanez-Larkin et al., 2008; Shumake et al., 2010). Importantly, these regions are outside of the dopamine system, broadening the scope beyond just one neurotransmitter that have been the focus of accounts in the past (Berk et al., 2007).
Finally, plausible neural substrates for the BIS include parts of the prefrontal cortex (PFC) that are linked to behavioural inhibition (Amodio et al., 2008), metacognition (Schmitz et al., 2004), reappraisal (Wager et al., 2008), cognitive control (Carver et al., 2008) and coordination of higher-level goals (Koechlin et al., 1999). Evidence of reduced PFC activity in BD is reviewed in section 1.1.2.

In summary, the BAS theory offers an intuitive framework for affect and motivation, but has been criticised as being too broad a concept. Recently there has been interest in extracting more specific components of BAS sensitivity in BD (Johnson et al., 2012). For example, dissociating mechanisms involved in goal-directed approach and valuation (“wanting”) versus the hedonic response to the reward (“liking”) respect (Berridge et al., 2009). Another aspect is extending the conceptualisation of BAS beyond a purely hedonic system to also consider its other outputs, such as energy and psychomotor activity which help to accomplish goals (Depue & Collins, 1999). For example, in the “wanting” of reward or goals we may reconsider based on how much risk we are willing to take, and the effort we are prepared to expend. Both phenomena are well studied from a cognitive neuroscience perspective and have been linked to different aspects of DA system functionality; phasic surges in activity versus tonic or baseline levels. For example increased surges in striatal activity predict impulsive choices (McClure et al., 2004), whereas people’s baseline levels of DA predict willingness to expend effort to obtain reward (Wardle et al., 2011). This gives insight into the impulsivity and risk-taking, (APA, 2000), intense goal-striving (Johnson, 2005b) and greater mobilisation (“pushing”) in response to rewards and goal progress (Fulford et al., 2010) in people with BD.

DA is also implicated in learning to associate goal-directed actions outcomes by generating prediction error signals that result from the mismatch between expected and actual outcomes (Schultz, 1998). Disorders characterised by perturbations to tonic (baseline) DA levels have been linked to learning impairment and risk-taking (e.g. Olvet & Hajcak, 2008; Tripp & Wickens, 2009).
Finally, DA has been theorised to signal *agency*; when goal-directed behaviour results in an outcome or goal, DA cells fire to let the organism know that it was caused by them and their recent set of actions (Redgrave *et al.*, 2008). During mania, aberrant signalling of agency might cause superstitious inference that external events were due to their own goal-striving behaviours (Corlett *et al.*, 2010). This exemplifies how integrating BAS theory with extant cognitive neuroscience approaches to motivational processing can enrich our understanding of clinical phenomena.
1.1.2 NEURAL CORRELATES OF BAS HYPERSENSITIVITY IN BIPOLAR DISORDER

This section provides an overview of the structural (volumetric, diffusion tensor imaging), functional (task, resting state), electrophysiological and neurochemical (pharmacological, genetic, PET) evidence for BAS dysregulation in BD. A literature search in PubMed was restricted to the terms “bipolar” or “mania” and “reward” or “motivation” or “decision-making” or “dopamine” from the last decade (2002 to 2012), and only cognitive neuroscience studies were included. We additionally searched for systematic reviews and meta-analyses of structural and functional neuroimaging in BD, to summarise (functional) neuroanatomical differences. Research from cognitive and emotional processing tasks has been extensively reviewed elsewhere (Phillips et al., 2008; Strakowski et al., 2012) and so this section devotes more attention to the details of the relatively few studies of motivation and decision-making. The characteristics of clinical samples and key findings are summarised in Supplementary Table 1.1. The findings generally support a BAS dysregulation view, but lead to a biopsychological model incorporating a hierarchical structure that also allows cognitive influences to be specified (section 1.1.3). A limitation of the literature is that almost without exception patients were in receipt of medication, although studies of unmedicated at-risk individuals are also included and discussed in (section 1.1.2.5). There was also considerable variability with regards to the diagnosis (type 1, type 2, cyclothymia) as well as affective state of patients, both within and between study samples, limiting interpretation of trait versus state effects.
1.1.2.1. Structural and Neuropsychological Differences and Lesion Studies

A number of reviews of structural differences in BD exist (see e.g. Arnone et al., 2009; Hallahan et al., 2011; Kempton et al., 2008; Strakowski et al., 2004). Of relevance to the current review, these note increased striatal volume (caudate and putamen), and frontal cortical differences in anterior cingulate and orbitofrontal cortices and dorsolateral PFC (dIPFC). An important dissociation was provided by a volumetric study of the habenula, a structure involved in suppressing dopaminergic activity, particularly when expected rewards are absent. Volume reduction in this structure showed specificity to BD (Savitz et al., 2011). One meta-analysis found reduced brain volume, particularly in the prefrontal lobe, and increased striatal volume (globus pallidus) (Arnone et al., 2009). Another meta-regression reported increased dorsal striatum (right putamen) as well as ventricular and temporal lobe increases (Hallahan et al., 2011). In contrast, a meta-analysis by Kempton, et al. (2008) found changes in cortical grey matter and ventricular size but failed to show any regionally specific differences in BD.

Diffusion tensor imaging (DTI) provides a more detailed index of the white matter connectivity between structures. A systematic review of DTI studies in affective disorders found reductions in a measure of structural connectivity, with a particularly large effect size for superior frontal tracts that comprise dIPFC and anterior cingulate cortex (ACC) circuits (Sexton et al., 2009). However, there exist two studies with conflicting findings of increased white matter connectivity from the ventral ACC (Houenou et al., 2007) and orbitofrontal cortex (OFC) (Versace et al., 2008), a region implicated in representing reward value (Elliott et al., 2003) and inhibiting prepotent behaviours that have become suboptimal due to environment changes (see Elliott & Deakin, 2005 for a review). Neuropsychological tests of executive function additionally point towards reduced prefrontal function in BD (see Robinson & Nicol Ferrier, 2006 for a systematic review). The majority of these studies report selective deficits to sustained attention and inhibitory control,
without disruptions to memory (verbal, visual or procedural), visuospatial ability, or language, that are evident during euthymia but correlated with residual symptoms and are more pronounced during mania (Dixon et al., 2004). In addition, worse deficits are associated with more episodes of mania (Robinson & Nicol Ferrier, 2006).

Whereas the above imaging studies provide important insights into the mapping between reward-related structures, lesion studies have more potential in identifying causality to be inferred. Several case have been documented where focal lesions to the striatum and OFC have evoked mania (e.g. Okun et al., 2003; Robinson et al., 1988), Similarly lesions to ventral PFC precipitate uncharacteristically impulsive behaviour (Bechara et al., 2000).

1.1.2.2. Functional Neuroimaging Differences

A recent meta-analysis found increased activity in ventral limbic regions (Houenou et al., 2011) and this was replicated by another larger meta-analysis (Chen et al., 2011), again reporting hyperactivity in limbic and basal ganglia structures (including striatum and amygdala). This latter study was able to explore relationships with mood state, and this finding was concluded to be state-independent, providing support for BAS hypersensitivity as an endophenotype (Hasler et al., 2006) rather than an epiphenomenon of affective episodes. A second finding was that the manic state was marked by hypoactivity in ventral PFC, particularly inferior frontal gyrus (IFG), a region that provides effortful inhibition of prepotent or impulsive responses (Aron et al., 2004). Reduced metabolism in dIPFC was also concluded by a review also including PET studies (Savitz & Drevets, 2009).

There exist very few studies of reward processing in BD. Reduced IFG in mania has also been reported during a decision-making task through PET (Rubinsztein et al., 2001) and in a response inhibition study through fMRI (Townsend et al., 2012).
Notably the latter study also found reduced limbic activity (including striatum and OFC). Abler et al. (2007c) compared anticipation and evaluation of reward in patients experiencing mania to standard healthy and clinical (schizophrenia patients) control groups. Although the pure reward response was not measured, manic patients demonstrated a reduced difference between reward system activity for rewarding and non-rewarding outcomes during anticipation. This effect was driven by an elevated response for the small and non-rewarding outcomes (rather than a blunted reward response), consistent with an expectancy bias towards positive outcomes (O’Sullivan et al., 2011). After conceptually dissociating BAS processes, the evidence reviewed by Johnson, Carver & Edge (Johnson et al., 2012) suggests that BD is characterised more by increases in “wanting” (drive to obtain rewards) than by extreme “liking” (hyperhedonia after obtaining the reward; see section 1.1.1.3). This is supported by the above finding, and a recent study of euthymic BD. Nusslock et al. (2012) reported increased reward anticipatory activity in striatum and OFC, compared to controls, with no group difference for anticipation of loss.

Borrowing from economic theory, appraisal and anticipation of reward and punishment can be further dissociated into assessment of the valence, likelihood and magnitude of these prospects. So-called “neuroeconomic” research has shown that people encode the objective multiplication of these variables (‘expected value’) and use this to guide their decisions (Glimcher & Rustichini, 2004). One study probed this index in BD by comparing neural activity during anticipation with what would be expected based on objective expected value (Bermpohl et al., 2010). Patients experiencing mania misrepresented expected value in OFC, further indicating unrealistically optimistic expectations about goal-directed actions in BD. OFC lesions have been demonstrated to impair recognition of negative facial expressions (e.g. Elliott & Deakin, 2005). Hence, state impairment of OFC during mania may explain individuals’ reduced ability to read cues of concern (Lembke & Ketter, 2002). Bermpohl et al. (2010) failed to find a difference in striatal activity during anticipation, but did not examine outcome-locked activity.

The study by Abler et al. (2007c) is the only one to detect differences in outcome processing, again finding a reduced differential signal between rewards and losses,
which was interpreted as signifying impaired striatal learning (prediction error signalling) in mania. This interpretation contrasts with the picture that emerges from existing BAS findings which generally do not support differences in the “liking” of outcomes or in reinforcement learning (see Johnson et al., 2012; section 1.1.1.3). However, impaired learning has been reported a behavioural study in euthymic BD (Pizzagalli et al., 2008b) and by two other cognitive neuroscience studies in non-clinical populations exhibiting high levels of hypomanic personality traits (O'Sullivan et al., 2011; see section 1.1.2.5). These findings are consistent with clinical characteristics such as repeated engagement in risky behaviours despite having experienced negative ramifications and experiencing regret (APA, 2000).

A limitation of the extant studies of reward processing in clinical populations discussed above is that patients were in receipt of antipsychotics. Although broad reviews have concluded that medication in BD generally ameliorates rather than exacerbates group differences (Hafeman et al., 2012; Hallahan et al., 2011; Savitz & Drevets, 2009), antipsychotics have been demonstrated to markedly disrupt reward-related activity, even at single doses and in healthy controls (Abler et al., 2007a; Pizzagalli et al., 2008a). Findings in unmedicated individuals vulnerable to BD are particularly important for this reason and are reviewed in section 1.1.2.5. Very recently, we found a greater striatal response to rewards in euthymic patients not receiving antipsychotic medication (Mason et al., under review), suggesting that medication may mask true differences in hedonic response. Top-down dLIFC control was negatively correlated with striatal reward hypersensitivity, providing further evidence for prefrontal control mechanisms.

During resting state, mania is associated with elevated resting activity in the caudate and dorsal ACC (Blumberg et al., 2000). Connectivity during rest gives an indication of the functional coupling between brain regions and has been investigated in BD by two studies. One found reduced connectivity between amygdala and lateral PFC, and increased inter-hemispheric connectivity of ventral striatum (Chepenik et al., 2010). These findings suggest that there is increased activity in the limbic system that is modulated less strongly by PFC, conceivably
giving rise to a dominance of BAS output. Another study demonstrated decreased connectivity between pregenual ACC and 1) amygdala 2) thalamus, and 3) striatum, structures that comprise major motivation and mood-regulating circuits (Anand et al., 2009). However limitations of this study are the small sample size of episodic patients and that half were experiencing mania whilst the other half were experiencing depression.

1.1.2.3. Frontal Cortical Asymmetry

A frontal cortical asymmetry theory postulates that a prefrontal system underpinning approach or appetitive behaviour (i.e. BAS) is left-lateralised, whilst BIS is right-lateralised (Amodio et al., 2008; Davidson, 1998). In line with this account, some studies have found left frontal decreases in depression (see Davidson, 1998), and there is preliminary evidence that focal transcranial magnetic stimulation (TMS) to left sites provides benefit for depressive symptoms (George et al., 1997), whereas right hemispheric stimulation may reduce manic symptoms (Grisaru et al., 1998). Further, relative increases in left PFC (i.e BAS-related) activity have been reported in individuals prone to hypomania (Harmon-Jones et al., 2002) and undergraduates meeting the criteria for cyclothymia or BD-II (Harmon-Jones et al., 2008). Of more relevance to the BAS theory are the findings that whilst virtual lesions to right PFC (induced through transcranial magnetic stimulation) increase risk preference (Knoch et al., 2006), sensitising this same structure (using direct current stimulation) suppresses risk-taking (Fecteau et al., 2007). Frontal cortical asymmetry is not well supported by functional neuroimaging, however, and how the proposed laterality effects map onto wider networks implicated in reward and motivation is not clear (but see Harmon-Jones et al., 2010). One possibility comes from rodent anatomical evidence that mesocortical projections may be relatively more left-lateralised (Berridge et al., 2003).
1.1.2.4. Neurochemical Differences

The direct evidence for DA in the pathogenesis of BD has been reviewed in-depth elsewhere (see Berk et al., 2007; Cousins et al., 2009) and as such is only briefly described here. Pharmacotherapy for BD frequently targets DA either by direct antagonism as with antipsychotics (Cookson, 2001) or indirectly as with mood stabilisers (Friedman & Gershon, 1973). More recently, deep brain stimulation of dopaminergic neurons in striatum has been reported to precipitate a (hypo)mania in patients being treated for alcoholism (Heldmann et al., 2012) and obsessive compulsive disorder (Haq et al., 2010). Also, abnormalities in the availability of a DA transporter protein (DAT) that regulates DA levels have been found in BD, but with equivocal results. In the striatum, both increases (Chang et al., 2010) and decreases in DAT availability (Anand et al., 2011) have been reported. Lastly, a polymorphism of a DAT-encoding gene is associated with BD (Pinsonneault et al., 2011), and increased rates of relapse into mania have been linked to genetic polymorphism that is associated with increased DA turnover (Benedetti et al., 2011).

1.1.2.5. Can neural signatures of reward dysregulation help predict who is at risk of BD?

Neuroimaging research focussing on clinical populations was reviewed in above sections. Given the heterogeneity of clinical populations with respect to medication and comorbidity (within and across samples), and that controls can rarely be matched on important variables (e.g. mood, medication, alcohol and substance use, life stressors, number of hospitalisations), complementary approaches are warranted. Studies of individuals at elevated familial or psychometric risk avoid these confounds and facilitate the identification of
potential vulnerability markers, which could expedite intervention and improve clinical outcome.

Through fMRI, O’Sullivan et al (2011) probed reward learning in individuals exhibiting high levels of hypomanic traits (hypomania-prone sample; HP). Reward-predicting cues elicited greater activity in dorsal striatum, a region representing the value of goal-directed actions. This group also demonstrated enhanced tracking of rewards in dorsal striatum and, when rewards were not obtained, greater activity in the insula cortex, a region linked to frustration and disgust (Abler et al., 2005). This provides initial neuroimaging evidence that vulnerability to BD is associated with both an increased drive to obtain reward and focus on goal progress. Differences in outcome evaluation was also found by two electrophysiology studies of the FRN, a brain potential that is larger for worse-than-expected outcomes than rewarding ones and varies along a good-bad continuum (see Holroyd et al., 2008). The FRN was blunted FRN in HP individuals both for gains and losses, which was accompanied by impaired reinforcement learning behaviourally (Mason et al., in press). Hence a positive outcome (“rose-tinted”) evaluation bias in BD may prevent the correction of unrealistically optimistic expectations about reward and risk (c.f. disrupted expected value seen in mania; Bermpohl et al., 2010). A separate study examined impulsivity in HP individuals by measuring the rate of delay discounting. This measures the subjective value of immediate rewards, relative to larger but delayed options (Rachlin & Green, 1972), which is inflated in clinical populations of BD during all phases (Adida et al., 2008; Strakowski et al., 2010). Mason et al. (2012) found that HP individuals recruit more attention to immediate rewards and show a greater FRN response (i.e. more aversive evaluation) to delayed ones.

Cortical asymmetry, as probed by EEG, has also been used to detect differences in BAS sensitivity in HP individuals. One study demonstrated increased left (relative to right) cortical activity when generating anger, indicating increased BAS activity in challenging or frustrating contexts (Harmon-Jones et al., 2002), corroborating the increased insula finding in the study by O’Sullivan et al. (2011).
Siblings of patients with BD show elevated ACC and OFC reactivity to a sad mood induction (Kempton et al., 2009) but susceptibility to the mood induction compared to patients. This may have been due to greater recruitment of medial PFC, which is implicated in the reappraisal of feelings (Ochsner et al., 2002). These results highlight the potential utility of this approach in also identifying resilience factors and emphasises the overlap between motivation and emotion networks.

Collectively the cognitive neuroscience studies reviewed in this section support the BAS sensitivity hypothesis but extend it in several ways. Firstly, emphasis is placed on considering different time scales of motivational behaviour and considering economic and learning parameters such as expected value and prediction error. Neuroscientific tools such as EEG also afford rapid measurements and demonstrated differences in early attentional processes which may be most amenable to mindfulness approaches, thereby informing choice of intervention. Finally, studies in at-risk populations highlight reward sensitivity differences as vulnerability markers for BD.
1.1.3. NEUROBIOLOGICAL MODELS OF MOTIVATION IN BIPOLAR DISORDER

Given that the cognitive neuroscience of reward processing in BD is still in its infancy, specific models have not been proposed. However, there exist informative frameworks from other populations characterised by risk-taking, and from related perspectives of BD such as emotion regulation. These are discussed in this section and lead to a model of reward dysregulation in BD.

1.1.3.1. Existing models of risk-taking and emotion regulation

Risk-taking in healthy adolescence has been proposed to arise from a dominance of reward-seeking impulses arises, due to a relative imbalance between striatum and supervisory control provided by PFC (Ernst et al., 2006). This is supported by a neurodevelopmental account of adolescent risk-taking which cites the sharper developmental trajectory of the striatum, relative to the PFC, as a reason for this imbalance (Casey et al., 2008; Figure 1.1). Tolerance of risky behaviours in adolescence may be further compounded by reduced amygdala reactivity to punishment cues (Ernst et al., 2006). This neurodevelopmental trajectory may offer some insight into the peak onset of BD, which is typically in late adolescence (Bebbington & Ramana, 1995).
Figure 1.1. The limbic system, including striatum, develops quicker than the prefrontal cortex, potentially giving rise to dominance of reflexive (e.g. reward-approach) impulses over modulatory inputs during adolescence. A similar imbalance, either structurally or functionally, may underlie risk-taking and impulsivity in bipolar disorder. Reproduced with permission from Casey, Getz, & Galvan (2008).

Emotion regulation models of BD have benefitted greatly from integrating empirical neuroimaging data, of which there is substantially more than for motivational processing in BD. These models are therefore well placed to inform reward dysregulation and risk-taking accounts, particularly given the high overlap between emotion and motivation. Mood swings in BD are generally conceptualised as arising from abnormalities in anterior limbic systems, particularly the amygdala, compounded by diminished corticolimbic connectivity and consequently reduced prefrontal modulation. This dysregulation of limbic drives causes a loss of “affective homeostasis” (Phillips et al., 2008; Strakowski et al., 2012; Strakowski et al., 2004). Whereas limbic overactivity seems to be omnipresent in the course of BD, mood episodes may result from periodic compromises to prefrontal control, corroborated by decreased ventral PFC representing a state marker of mania (Chen et al., 2011). Chang et al. (2004) speculated that progressive hypofrontality might increase relapse frequency over time, providing a neural mechanism for the kindling hypothesis (Post, 1992; see section 1.1.1.2). Longitudinal studies will be needed to assess whether this represents an accurate mechanism of disorder progression.
1.1.3.2. Synthesis of a neurobiological model of reward dysregulation in BD

A tripartite model (see Figure 1.2) encapsulates the literature reviewed in this article, which suggests that there is in BD:

1) Trait hypersensitivity to reward cues and goal-attainment, arising from structural and functional differences in striatum and other midbrain structures, and modulated by mood symptoms.

2) Dysregulated processing of punishment and risk cues, mediated by the amygdala, insula and ACC. This may be differentially related to state insomuch as amygdala has been reported to be hyperactive in bipolar depression (Almeida et al., 2009), and blunted during mania (Strakowski et al., 2011). Insula and ACC deficiencies may promote risk-taking (‘not knowing when to stop’; Campbell-Meiklejohn et al., 2008).

3) Unstable and inefficacious effortful (‘top-down’) control mediated by PFC. Relapse into mania is associated with reduced PFC (Chen et al., 2011) and progressive weakening of PFC control may explain increased relapse frequency (Chang et al., 2004), in line with the kindling hypothesis. This faculty is likely intact in at-risk and preclinical groups (who exhibit hypomanic personality traits and reward hypersensitivity but who are high functioning) and may be a potential target for interventions (see below).
Figure 1.2. Tripartite model of reward dysregulation in bipolar disorder

a) In Euthymia, prefrontal cortex is able to ‘override’ hypo- and hyper-reactivity of subcortical structures that reflexively process cues of reward (e.g. ‘This feels great, but maybe I should slow down because last time I felt like this I got myself in trouble’) or threat (e.g. ‘I’d feel so much safer staying in bed again today, but last time this led to a downward spiral, so maybe it’s better to get myself ready and see how I feel then’). Adapted with permission from Ernst, Pine, & Hardin (2006).

b) Predictions of symptom increases and decreases made from the tripartite model.

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↑Increased activity; ↓Decreased activity; R, Remission; D, Depressive symptoms; M, Manic symptoms; HM, hypomanic symptoms
In summary, it is proposed that PFC modulates the two reflexive systems in a hierarchical manner, in line with other neurobiological models of risk-taking (Ernst et al., 2006; Somerville et al., 2010), self-regulation (Carver et al., 2008) and emotion dysregulation in MDD (DeRubeis et al., 2008) and BD (Strakowski et al., 2012). Disturbances to any of these three systems (approach, avoid, override) could disrupt homeostasis and give rise to increases in manic or depressive (and also anxiety) symptoms. Competing intra-limbic activity between striatal-approach and amygdalar-threat impulses may produce distinct states depending on which dominates; predominantly euphoric and goal-directed mania in the first case, anhedonic, avolitional and anxious depression in the latter case, and mixed states when the two dysregulated impulses oscillate simultaneously (Strakowski et al., 2012). Dysregulation of amygdalar-threat impulses, linked to anxiety disorders (Etkin & Wager, 2007) may also explain high comorbidity in BD.

Compromised PFC-mediated supervisory control and metacognition worsens affective and motivational symptoms, by 1) increasing the impact of the extreme and reflexive limbic responses to reward/punishment cues, and 2) preventing their subsequent contextual (re)appraisal, especially with respect to long-term goals. A final point is that this model fits well with other accounts highlighting the role of reduced serotonergic PFC functioning in impulsivity and diminished self-regulation (Carver et al., 2008), broadening the scope beyond purely dopaminergic dysregulation (Berk et al., 2007).
1.1.4. INTEGRATION WITH PSYCHOLOGICAL ACCOUNTS

1.1.4.1. Comparison with BAS dysregulation theory and other psychological models

The empirical cognitive neuroscience findings and resulting model (see 1.1.3.2) are broadly consistent with the BAS dysregulation theory but paint a more informative picture, particularly with respect to rapid symptom fluctuation and mixed episodes. The model presented is more consistent with Gray (Gray & McNaughton, 2000)'s revised theory in which the activity of reflexive systems, BAS and FFFS, is mediated by a top-down control system (BIS), but the underlying brain systems extend beyond the septohippocampal structures originally proposed from rodent models. The empirical findings paint a more detailed picture of the networks involved and provide a richer conceptualisation of motivated behaviour and decision-making as dynamic and across separate time-courses. In mania for example, increased activity in dopaminergic systems (striatum and ventral tegmental area) may bring about increased “wanting”, leading to overpowering reward-seeking and goal-directed behaviour. Selection of suboptimal or damaging behaviours such as substance abuse and spending sprees may arise from distorted representation of expected value (OFC) and risk (insula, amygdala), as well as myopic overvaluation of immediate gratification at the expense of delayed but superior options and long-term goals (c.f. FRN brain potential findings). Once obtained, excessive “liking” of rewards (striatum) and disrupted error signalling (FRN, striatum), weakened “behavioural brakes” (amygdala) and inability to resist additional reward-seeking (ACC, insula) may prevent devaluation of future expectations (OFC), allowing maladaptive behaviours to persevere.

The model presented in 1.1.3.2 is also consistent with a cognitive account of mood swings in which there is 1) conflict between appraisal of internal states and 2)
inconsistent and inefficacious attempts to regulate these states (Mansell et al., 2007). In this model, cognitions arising from extreme appraisals can initiate further changes at the neurobiological level through attention, arousal, psychomotor activity and sleep cycle changes. Whereas dopaminergic activity is linked to these features, dIPFC function is associated with control of longer-term and higher order (Carver et al., 2008). Conflicts in this goal system may therefore play a role in escalation of the physiological differences, although the precise interaction between these biopsychological mechanisms remains to be fully elucidated. How the present model fits in with sleep and circadian rhythm disruption in BD is likely to be complex and is beyond the scope of this review. However, there is very recent evidence that the DA system modulates the pineal gland, inhibiting synthesis of the sleep hormone melatonin (González et al., 2012). Furthermore, a recent review implicated prefrontal dysfunction in circadian disruption in BD (McKenna & Eyler, 2012). The interplay between these neurobiological systems and the cognitive, affective and motivational deficits will be an important research area for development.

1.1.4.2. Implications for interventions and future directions

This framework can explain how both pharmacological and psychological interventions exert their therapeutic effects on motivation and emotion. Whereas pharmacological agents may act to reduce limbic hyperactivity directly, cognitive therapy promotes efficacious prefrontal function (DeRubeis et al., 2008), encouraging empirical top-down control over of reflexive drives, challenging automatic thoughts, and structuring and resolving conflicting goals. Over time, both mechanisms converge to the same therapeutic endpoint, by bringing the prefrontal-limbic network back into homeostatic balance (see Figure 1.3). An influential cognitive behavioural model for the treatment of mood swings
advocates fostering a reflective mind set and balancing conflict, rather than allowing behaviour to be governed purely by internal states (Mansell et al., 2007) which can be seen as analogous to the reflexive systems discussed in this article. This highlights how cognitive control is more flexible than simply “inhibiting” or “overriding” the reflexive drives and appraisals, and instead incorporates conflict resolution between different life goals.

Figure 1.3. Psychological and pharmacological interventions may accomplish the same end-goal via distinct biopsychological mechanisms. Adapted from DeRubeis et al. (2008).

Cognitive neuroscience findings may be used to inform interventions in BD, in particular the upward spiral of reward-seeking and risk-taking in prodromal mania. Research indicates that this may be driven by the greater susceptibility shown by people with a BD diagnosis to surges in confidence and self-efficacy following success (Johnson, 2005b), and that reduced recruitment of PFC may play a role
Experimentally, healthy controls asked to use cognitive reappraisal strategies recruit additional prefrontal resources (Wager et al., 2008) and this is effective in negating the risk-promoting effects of positive mood induction (Heilman et al., 2010). Distancing, a form of cognitive reappraisal, has been shown to modulate both the anticipation (Staudinger et al., 2011) and experience (Staudinger et al., 2009) of rewards via recruitment of dIPFC. The model can also explain the efficacy of behavioural interventions that either increase activity and engagement with sources of reward in depression (behavioural activation; Cuijpers et al., 2007) or limit access to sources of gratification in prodromal mania (avoiding ascent behaviours; Lam & Wong, 1997). Approaches such as neurofeedback training of prefrontal control may be a useful adjunctive or alternative treatment option to cognitive therapies in the future.

As a final comment, BAS dysregulation is implicated in numerous impulsivity and externalising disorders including alcoholism, substance use disorder, and attention-deficit hyperactivity disorder (ADHD) (e.g. Hundt et al., 2008). The extensive overlap in terms of symptoms, comorbidity, cross-heritability (Alloy et al., 2009; McElroy et al., 1996) and implication of the reward system, implies the existence of an endophenotype that cuts across diagnostic categories (Gottesman & Gould, 2003). Research will be needed to clarify the similarities and differences in reward function across these disorders.
1.1.5. CONCLUSION

In summary, we present cognitive neuroscience findings and use them to test the predictions and extend the scope of the BAS dysregulation model of bipolar disorder. The pervasive dysregulation of motivation, including impulsivity, risk-taking and extremes in goal-striving, may be explained by dysregulation of limbic systems that reflexively processing cues of reward, threat and risk. Reduced prefrontal cortical function results in compromised higher cognitive prefrontal control over these impulses, in line with cognitive models of BD in which extreme and ineffectual control of internal states cause “see-sawing” of mood. Emerging neuroimaging studies of at-risk individuals also demonstrate potential biological vulnerability markers for BD, and may ultimately lead to earlier provision of psychological intervention.
### Supplementary Table 1.1

Summary of neuroimaging studies in relation to the Behavioural Approach System (BAS) and its likely neural correlates. Table is ordered by date and with meta-analyses and systematic reviews at the top, followed by specific motivation and decision-making tasks most relevant to the present review (bold) and then individual studies examining cognition and emotion in bipolar disorder (BD). Technique used is bracketed in design; structural (sMRI) and functional (fMRI) magnetic resonance imaging, electroencephalography (EEG), diffusion tensor imaging (DTI), positron emission tomography (PET), transcranial magnetic stimulation (TMS). [Dorsolateral] prefrontal cortex ([dl]PFC), anterior cingulate cortex (ACC); orbitofrontal cortex (OFC), inferior frontal gyrus (IFG).

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Mood State</th>
<th>Main findings in patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Houenou et al., 2011</td>
<td>Meta-analysis (fMRI)</td>
<td>Various, effects not assessed</td>
<td>Increased activity in ventral limbic regions</td>
</tr>
<tr>
<td>Chen et al., 2011</td>
<td>Meta-analysis (fMRI)</td>
<td>Various, effects not assessed</td>
<td>Underactivation of IFG in mania but not euthymia, and of amygdala in euthymia but not mania. Overactivation of medial temporal structures (parahippocampal gyrus, hippocampus, and amygdala) and basal ganglia / limbic system across mood states.</td>
</tr>
<tr>
<td>Hallahan</td>
<td>Meta-analysis</td>
<td>Various,</td>
<td>Increased right lateral ventricle, left</td>
</tr>
<tr>
<td>Study/Review</td>
<td>Methodology</td>
<td>State Effect Assessed</td>
<td>Effects Not Assessed</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
<td>-----------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>et al., 2011;</td>
<td>sMRI</td>
<td>temporal lobe, and right putamen volumes.</td>
<td>Increased hippocampal and amygdala volume compared with patients not treated with lithium and healthy comparison subjects</td>
</tr>
<tr>
<td>Savitz &amp; Review, 2009</td>
<td>fMRI, PET</td>
<td>Various, Elevated activity in the hippocampus, OFC and ventral PFC. Hypometabolism of dorsal PFC. Ventriculomegaly and white matter hyperintensities in elderly populations of depression. Medication noted as an important confound of studies</td>
<td></td>
</tr>
<tr>
<td>Sexton et Review, 2009</td>
<td>DTI</td>
<td>Various, Reduced white matter tract connectivity (anisotropy) in dIPFC and ACC circuits</td>
<td></td>
</tr>
<tr>
<td>Arnone et Review, 2009;</td>
<td>sMRI</td>
<td>Various, Whole brain and prefrontal lobe volume reductions, and also by increases in the volume of the globus pallidus and lateral ventricles</td>
<td></td>
</tr>
<tr>
<td>Kempton Meta-analysis, 2008;</td>
<td>sMRI</td>
<td>Various, Lateral ventricle enlargement, increased rates of deep white matter hyperintensities, gray matter volume increased related to lithium</td>
<td></td>
</tr>
<tr>
<td>Strakowski Review, 2004</td>
<td>sMRI, fMRI</td>
<td>Various, Subgenual ACC, striatum and amygdala differences present from early stages of disorder. Aberrant activity, metabolism and bioenergetics in striatum and prefrontal cortex</td>
<td></td>
</tr>
<tr>
<td>Study ID</td>
<td>Type</td>
<td>Group/State</td>
<td>Main Findings</td>
</tr>
<tr>
<td>------------------</td>
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<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ibanez et al., 2012</td>
<td>EEG</td>
<td>BD-II, euthymia</td>
<td>Enhanced responses to reward magnitude regardless of valence.</td>
</tr>
<tr>
<td>Nusslock et al., 2012</td>
<td>fMRI</td>
<td>BD-I, euthymia</td>
<td>Reward task (card-guessing). Greater ventral striatal and OFC activity during anticipation, but not outcome</td>
</tr>
<tr>
<td>Mason et al., 2012</td>
<td>EEG</td>
<td>Non-clinical hypomania</td>
<td>Delay discounting impulsivity task. Steeper devaluation of delayed rewards according to behavior and ERP amplitude (N1, FRN)</td>
</tr>
<tr>
<td>O'Sullivan et al., 2011</td>
<td>fMRI</td>
<td>Non-clinical hypomania</td>
<td>Reinforcement learning task. Increased coupling between dorsal striatal activity and 1) objective expected value metric during anticipation, and 2) prediction error during outcome</td>
</tr>
<tr>
<td>Jogia et al., 2011</td>
<td>fMRI</td>
<td>BD-I, euthymia</td>
<td>Reduced frontopolar prefrontal cortex, increased ACC during Iowa Gambling Task</td>
</tr>
<tr>
<td>Bermpohl et al., 2010</td>
<td>fMRI</td>
<td>BD-I, mania</td>
<td>Impaired representation of expected value in left IOFC; increased response during expectation of increasing gain and decreased responses during expectation of increasing loss. OFC response normalised in 7 patients re-tested in remission</td>
</tr>
<tr>
<td>Abler et al. (2007b)</td>
<td>fMRI</td>
<td>BD-I, mania</td>
<td>Reward task (speeded response time). Reduced difference between gains and losses in VTA during anticipation, and in striatum during outcome</td>
</tr>
<tr>
<td>Townsend et al., 2012</td>
<td>BD-I</td>
<td>Go/NoGo response inhibition task.</td>
<td>Euthymia</td>
</tr>
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</tr>
<tr>
<td>Heldmann et al., 2012</td>
<td>Case</td>
<td>Alcoholism</td>
<td>Hypomania elicited by electrostimulation of striatum</td>
</tr>
<tr>
<td>Anand et al., 2011</td>
<td>Study</td>
<td>BD type not specified, euthymia &amp; depression</td>
<td>Lower availability of dopamine transporter in striatum</td>
</tr>
<tr>
<td>Pinsonneau et al., 2011</td>
<td>Study</td>
<td>BD type not specified, mood state irrelevant</td>
<td>Higher rates of rs27072 polymorphism of dopamine transporter gene</td>
</tr>
<tr>
<td>Benedetti et al., 2011</td>
<td>Study</td>
<td>BD-I, mood state irrelevant</td>
<td>Increased rates of mania relapse in Val/Met polymorphism of COMT gene (involved in breakdown of dopamine)</td>
</tr>
<tr>
<td>Chang et al., 2010</td>
<td>Study</td>
<td>BD-I and BD-II, euthymia</td>
<td>Higher availability of striatal dopamine transporter</td>
</tr>
<tr>
<td>Chepenik et al., 2010</td>
<td>Study</td>
<td>BD type not specified, all states</td>
<td>Reduction in the negative correlation between ventral PFC and amygdala activity</td>
</tr>
<tr>
<td>Haq et al., 2010</td>
<td>Case</td>
<td>OCD case</td>
<td>Mania triggered by electrostimulation of striatum</td>
</tr>
<tr>
<td>Anand et al., 2009</td>
<td>Study</td>
<td>Mania, depression</td>
<td>Resting state. Decreased connectivity between pregenual ACC and 1) bilateral</td>
</tr>
</tbody>
</table>
dorsomedial thalamus 2) bilateral amygdala 3) left striatum. No difference by mood state, but small subgroups ($n=6$)

<table>
<thead>
<tr>
<th>Study</th>
<th>BD-II, cyclothymia; euthymia</th>
<th>Anagram solving task. Greater relative left frontal cortical activation in preparation for the hard trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>okun et al., 2003</td>
<td>Two healthy cases</td>
<td>Transient hypomania following pallidotomy</td>
</tr>
<tr>
<td>Harmon-Jones et al., 2002</td>
<td>Non-clinical hypomania</td>
<td>Anger-evoking task. Increased relative left frontal cortical activity</td>
</tr>
<tr>
<td>Rubinszttein et al., 2001</td>
<td>BD-I, Mania</td>
<td>Decision-making task. Decreased IFG and right frontal polar region and increased left dorsal ACC that correlated with manic symptoms.</td>
</tr>
<tr>
<td>Blumberg et al., 2000</td>
<td>BD-I; Mania, euthymia</td>
<td>Resting state task. Increased left ACC and caudate activity during mania</td>
</tr>
<tr>
<td>Anand et al., 2000</td>
<td>BD-I and II; Euthymia</td>
<td>Amphetamine challenge. Transient hypomania induced in patients but no difference in striatal binding from controls</td>
</tr>
<tr>
<td>Robinson et al., 1988</td>
<td>17 healthy cases</td>
<td>Secondary mania following brain injury associated with damage limbic efferents in right hemisphere</td>
</tr>
<tr>
<td>Grisaru et al., 1998</td>
<td>BD-I; mania</td>
<td>Greater reduction in Mania Scale scores following TMS to right compared to left hemisphere</td>
</tr>
</tbody>
</table>
1.2. Thesis Aims, Hypotheses and Predictions

This thesis sought to extend the BAS sensitivity account of BD (Johnson et al., 2012; Urosevic et al., 2008) and better characterise risky and impulsive decision-making in BD. In particular, we sought to apply neuroimaging tools (EEG and fMRI) and existing frameworks from cognitive neuroscience (particularly neuroeconomics and reinforcement learning theory) to examine motivational processing. A secondary aim was to examine whether vulnerability to hypomania is related to trait differences in motivational processing.

A number of hypotheses and predictions lead from the literature reviewed in section 1.1 and these are outlined below.

1.2.1. HYPOTHESIS 1: IMPULSIVITY AND RISK-TAKING IN BIPOLAR DISORDER ARISE FROM INCREASED SENSITIVITY TO REWARD

This is based on numerous avenues of non-physiological research from clinical, theoretical and behavioural evidence reviewed in section 1.1.1 as well as physiological evidence reviewed in 1.1.2.

1.2.1.1. Prediction 1a: Reward hypersensitivity will manifest in early, reflexive processing

Rewarding outcomes generally exert their hedonic “feel-good” impact at a sub-cognitive (i.e. early) level: it is easy to say that we like something, but harder to articulate why we like it. For this reason, rewards occupy a strong position to influence emotion and cognition, including decision-making, particularly in BD.
where events have been theorised to impact strongly on the individual (Urosevic et al., 2008). The feedback-related negativity (FRN) represents a somewhat automatic and “non-volitional” evaluation of events (Gehring & Willoughby, 2002) that is modulated by trait impulsivity (Onoda et al., 2010; section 1.1.1.3) and by psychiatric disorders conceptualised by reward dysfunction (e.g. Hewig et al., 2010; Morris et al., 2011; Santesso et al., 2008; van Meel et al., 2011). Given that the FRN amplitude is negatively correlated with the subjective hedonic impact of outcomes (e.g. Holroyd et al., 2004a), reward hypersensitivity would be manifest as a greater FRN reduction for gains in BD and related samples, compared to controls. This was tested in Chapters 3, 4 and 6 of this thesis.

1.2.1.2. Prediction 1b: Reward hypersensitivity has its pathophysiological roots in the mesocorticolimbic network

This follows from abundant evidence implicating the mesocorticolimbic pathway as the major neural substrate of reward processing and is modulated by individual difference in sensation-seeking and reward sensitivity traits (see section 1.1.1.3). In addition, structural and functional neuroanatomy implicates this network in BD (section 1.1.2).

1.2.1.3. Prediction 1c: There is an imbalance between reflective prefrontal and reflexive limbic impulses

The model synthesised in section 1.1.3 proposes dysregulation between higher- and lower- order systems in BD, in line with theoretical models of self-regulation and emotion regulation (Carver et al., 2008; Strakowski et al., 2012). Specifically, structural and functional neuroanatomy highlights reduced dIPFC function and dominance of limbic drives (see 1.1.3).
1.2.2. HYPOTHESIS 2: REWARD PROCESSING ABNORMALITIES REPRESENT AN ENDOPHENOTYPE THAT PRECEDES THE ONSET OF BIPOLAR DISORDER

This is based on the high genetic heritability of BD (section 1.1.1) and its cross-heritability with impulsivity disorders in which reward system abnormalities have already been established (section 1.1.4.2). This is further suggested by the finding that vulnerability to BD lies on a continuum that correlates with BAS sensitivity and sensation-seeking (see section 2.1). The following predictions follow on from this standpoint:

1.2.2.1. Prediction 2a: Individuals vulnerable to bipolar disorder show increased impulsivity and risk-taking

1.2.2.2. Prediction 2b: Reward hypersensitivity will be present in individuals vulnerable to mania

1.2.2.3. Prediction 2c: The degree of reward hypersensitivity is positively correlated with vulnerability to mania

These predictions are tested in Chapters 3 and 4 by assessing modulation of ERPs elicited during risk-taking and impulsivity tasks.
1.2.3. HYPOTHESIS 3: IN BIPOLAR DISORDER THERE IS MISREPRESENTATION OF THE PROBABILITY AND VALUE ASSOCIATED WITH ACTIONS AND BEHAVIOURS

Leading on from previous studies that implicate disrupted representation of expected value in acute mania (reviewed in section 1.1.2.2), this characteristic may explain suboptimal decision-making in other stages of the disorder, including remission.

1.2.3.1. Prediction 3a: There is an appraisal bias towards expecting rewarding outcomes that fails to be moderated by objective probability

This is tested by tasks that aimed to isolate the contributions of probability (Chapter 3) and expected value (Chapter 5) during learning and motivational decision-making.
1.2.4. HYPOTHESIS 4: IMPAIRED REINFORCEMENT LEARNING UNDERLIES PERSISTENT ENGAGEMENT IN MALADAPTIVE BEHAVIOURS IN BIPOLAR DISORDER

A reinforcement learning deficit in BD is indicated by 1) repeated engagement in risky activities despite previously having experienced negative consequences (APA, 2000; section 1.1.1 of this thesis) and 2) perturbations to dopamine and the reward system (section 1.1.2). Two predictions follow from this.

1.2.4.1. Prediction 4a: Prediction errors are incorrectly calculated

1.2.4.2. Prediction 4b: Prediction errors are not utilised to guide future behaviour and expectations

These possibilities are assessed by comparing neural representation of prediction error with objective metrics based on neuroeconomic models and contrasting BD and BD-related samples with controls (Chapters 3 and 5). The relationship to future expectations and action are also explored in these chapters, using behavioural and neural measures.
CHAPTER 2: GENERAL METHODOLOGY

Preface

This chapter details the methods used in the experimental thesis and begins with a rationale and justification for the analogue approach to studying psychiatric disorders. A description of the cognitive neuroscience tools utilised in this thesis follows: an overview of measuring reward impulsivity is followed by a brief outline of electrophysiology (EEG), neuroimaging (fMRI) and a discussion of simultaneous EEG-fMRI acquisitions and off-line fusion. Finally, the development and testing of two experimental paradigms is documented.
2.1. Definition of at-risk population based on Hypomanic Personality

The healthy participants that comprised the samples for Chapters 3 and 4, and the paradigm development work documented in section 2.3, were recruited based on their scores on an online form of the Hypomantic Personality Scale (HPS; Eckblad & Chapman, 1986; Appendix A1). This approach is based on the assumption that (hypo)manic symptoms lie on a continuum that extends into the general population (Figure 2.1). The HPS identifies members of the general public holding attenuated hypomanic symptoms and beliefs, with 78% of “high” HPS individuals (defined as two or more standard deviations above the mean) meeting the criteria for BD (Eckblad & Chapman, 1986). The scale has good internal consistency and re-test reliability (Eckblad & Chapman, 1986; Meads & Bentall, 2008). In addition to this cross-section and factor analytic evidence, the scale has also been demonstrated to reliably identify those at risk of becoming unwell in the future, predicting clinical episodes in three-quarters of high scoring college students followed up thirteen years later (Kwapil et al., 2000). Research has shown that high scorers show similar traits to clinical populations on measures such as the BIS/BAS scales (Carver & White, 1994). Indeed, HPS score positively correlates with all of the BAS subscales (drive, reward responsiveness and fun seeking; Johnson & Carver, 2006). In this way, at-risk or preclinical groups can be studied to uncover vulnerability markers and endophenotypes that confer higher risk to BD. In addition, this approach has the advantage of avoiding confounding variables typically limiting comparison of controls to clinical populations, such as current mood state, comorbidity, medication, past hospitalisations, and socioeconomic status. Previous studies have referred to this population as “hypomania-prone”, “at-risk”, or “vulnerable” to BD, or as an “analogue” sample of BD (Bentall et al., in press; Harmon-Jones et al., 2002; Johnson & Carver, 2006; Meyer & Hofmann, 2005). In this thesis the first two terms will be generally used to refer to this population, and their use is intended to emphasise different characteristics of the sample.
Figure 2.1. Prevalence of hypomanic personality traits, as measured by the Hypomanic Personality Scale, is normally distributed in the general population. Participants scoring 2 standard deviations above the mean show elevated risk for developing BD.
2.2. Cognitive neuroscience tools for characterising motivational processing

2.2.1. DELAY DISCOUNTING AS A TOOL FOR MEASURING IMPULSIVITY

Impulsivity has been defined as \textit{action without foresight}, but is recognised to be a multi-faceted construct (Barratt \textit{et al.}, 1997; Winstanley \textit{et al.}, 2006). There is considerable variation in the literature as to the individual facets (see Evenden, 1999, for a review), but a representative distillation includes: inability to delay gratification, inattention, rapid response and decreased inhibitory control (Evenden, 1999; Strakowski \textit{et al.}, 2010). There is some evidence that these facets are independent and may even be underpinned by partially separate neurobiological systems (Evenden, 1999). Hence, they may be differentially related to disorders characterised by impulsivity, such as BD. However, previous investigations have failed to find facet-specific dissociations in BD (e.g. Christodoulou \textit{et al.}, 2006; Strakowski \textit{et al.}, 2010). Given the direct relevance to the BAS dysregulation theory of BD (Urosevic \textit{et al.}, 2008) and evidence for reward system abnormalities (see section 1.1), this thesis focuses on impulsivity in the context of reward.

‘Delay discounting’ refers to the subjective devaluation of motivational outcomes \textit{(i.e. rewards or penalties)} as a function of the time lapse before these outcomes are to be experienced (Ainslie, 1975; Rachlin & Green, 1972). It is well established that immediate rewards are valued more highly than those that are delayed and there are a number of real-word examples of this phenomena in financial, health and psychiatric domains. For instance, we struggle to save money for the future or pay into our pension scheme; instead that money burns a hole in our pocket and goes towards dining out again, or on the latest smart phone. Similarly, keeping to our goal of healthy eating can often give way to splurging on a muffin with our
coffEE. Economic models assert that humans calculate the net utility (or value) of a reward according to the following equation:

\[ V = kD \cdot U \]

where \( V \) is the net (discounted) value, \( D \) is the delay-dependent discount factor, \( k \) is the individual’s discount rate parameter and \( U \) is the undiscounted utility (i.e. if there were no delay before its receipt).

There exist individual differences in how steeply delayed outcomes are discounted (McKerchar et al., 2009). Experimentally, people will generally accept an offer of £5 immediately over receiving £6 tomorrow, but might reject the immediate offer if the delayed offer is increased to £20 tomorrow. People differ in the exact amount needed to tip the balance in favour of the delayed option (some people require a lesser value, others more) and steeper discounting correlates with personality traits of impulsivity (Kirby et al., 1999), extraversion (Richards et al., 1999) and sensation-seeking (Mitchell, 1999; Richards et al., 1999).

Studies have demonstrated dissociable neural systems responding to immediate and delayed outcomes by regressing parameters from economic models of delay discounting. Whereas ventral limbic regions such as ventral striatum have been linked to selection of immediate rewards, parietal and dorsal prefrontal regions bring about selection of distal outcomes (Ballard & Knutson, 2009; Ernst et al., 2005; Tanaka et al., 2004). Crucially, individual differences in temporal discounting are also manifested neurally, with preference for immediate rewards predicted by 1) increased striatal reactivity to these choices (Hariri et al., 2006) and 2) reduced activity in parietal and dorsolateral prefrontal cortices to delayed options (Ballard & Knutson, 2009).

Clinically, abnormalities in the neural substrates of immediate and delayed choice have also been reported. In ADHD, one study found a reduced ventral striatal response to immediate rewards, but increased amygdala activation to
delayed rewards (Plichta et al., 2009), consistent with delay aversion. Whilst behavioural evidence demonstrates an immediacy bias in BD patients (Strakowski et al., 2010), the neural mechanisms have not been demonstrated. Chapter 4 aimed to address this using electrophysiological measures of attention and outcome evaluation. Delay discounting was used as a tool for quantifying impulsivity in a non-clinical at-risk sample to establish that, as per clinical populations, trait impulsivity is elevated. Whilst clinical populations score highly on several facets of impulsivity (Strakowski et al., 2010), this thesis focused on reward impulsivity because of its hypothesised relevance to risky decision-making in BD.
2.2.2. EVENT-RELATED POTENTIALS: AN OVERVIEW

2.2.2.1. Principles and origins of event-related potentials

Electroencephalography (EEG) is a technique used to measure the electrical activity of the brain through electrodes placed on the scalp. Change in scalp potential (voltage) is primarily produced by excitatory post-synaptic potentials (EPSPs) in surface brain tissue. EPSPs are generated when a number of inputs arrive at a cell body and possess two properties that render them detectable by EEG. Because the EPSP represents 1) the net gain of all input signals and 2) is a sustained signal, it allows a build-up or summation of signals. If an entire ensemble of neurons fire at the same time, this gives rise to many hundreds of thousands of EPSPs (a “summation of summations”) that ultimately contributes to a measurable change in scalp potential. The cytoarchitecture of cortical regions lends itself to this situation because neurons tend to be arranged in columns that run perpendicular to the electrodes on the scalp, causing a “stacking” of electrical potentials (Luck, 2005).

However, the raw EEG signal comprises a mix of miscellaneous neuronal activity across the brain – only a subset of which is involved in conscious processes or the current task at hand – along with noise. Noise has a number of physiological causes, including muscular artifacts (chiefly due to activity of ocular, neck and craniofacial muscles). Crucially, these confounding contributions to the ongoing EEG are mostly asynchronous with the onset of task stimuli and so ERPs can be extracted by averaging the same fixed stretch of EEG data that immediately follows each instance of stimulus presentation. With repeated stimulus presentation the random, asynchronous noise cancels out, leaving an augmented average signal of the stimulus-locked response.
Figure 2.2. Example of event-related potentials of the EEG. Voltages displayed classically, with negativity up (above baseline) and positively down (below grey line).

Averaged ERPs, depicted in Figure 2.2, are analysed by measuring the amplitude of the ERP peak between subjects and entering this into statistical analysis. Typically the grand averaged ERP (mean across all subjects in a group) is used to select a latency window that covers the build, peak and decline of the ERP of interest. Most commonly the average voltage over this window is taken as the measurement of the ERP, but some researchers measure the ERP as the absolute peak value, or by measuring the magnitude of the difference between the peak of interest and the peak that preceded it. This latter measurement takes into consideration the fact that the absolute voltage of the ERP of interest is somewhat dependent on how big or small the preceding component was (if the earlier peak was highly positive, then the current component would need to be more highly negative to offset this and yield a negative peak). There is often individual variability in 1) ERP onset and 2) the maximal topography or manifestation of the ERP on the scalp and so a broad window is selected around the mean, and often a number of adjacent electrodes are averaged or “clustered” together. In this thesis we have generally utilised mean amplitude measurement of ERPs of interest. One exception is in Chapter 3, where the component preceding our ERP of interest was also modulated by task parameters. In this case the mean amplitude approach
would have led to inaccurate measurement and so the peak-to-peak approach was adopted (see Chapter 3 for a further discussion of this issue).

Because voltage changes can be measured at an extremely high rate – down to the sub-millisecond level – EEG is a powerful tool for tracking the precise time course of a cognitive process and disentangling it from other stages of processing. For example, a visual stimulus elicits a series of ERPs (see Figure 2.1) ranging from early sensory-attentional representations (P1, N1) to more elaborative processing such as perceptual matching and whether the stimulus is expected or not (P2, N2), followed by a more cognitive appraisal such as the motivational significance of the stimulus (P3, also termed P300). However, EEG is limited by its inability to reliably infer the source of neural activity. Because the electrodes are situated on the scalp, they lie over a centimetre away from the source activity and have to traverse cerebrospinal fluid, skull and skin tissue before being recorded. The poor conductance of these substrates results in substantial blurring of the signals (Luck, 2005). For this reason EEG possesses significantly poorer spatial resolution than other imaging modalities such as functional magnetic resonance imaging (fMRI; see section 2.3).

2.2.2.2. ERPs involved in performance-monitoring and outcome evaluation

Several ERPs have been identified as having relevance to reward processing. This section will focus on the error-related negativity (ERN), feedback-related negativity (FRN) and P300. The ERN occurs shortly after the commission of behavioural errors - particularly mistakes occurring in speeded response tasks. The ERN manifests as a negative deflection at frontocentral electrodes and occurs around 80-100ms after motoric commission of error (Boksem et al., 2006; Luu et al., 2003; Overbeek et al., 2005). Because errors generally carry aversive (sometimes life-threatening)
consequences, error detection is likely to be highly linked to motivational systems (Luu et al., 2000). Indeed, ERN shows enhancement if errors result in monetary loss or omission of monetary gain, suggesting that this early error detection system is linked to reward systems (Chiu & Deldin, 2007). A closely related component, the FRN, is elicited by feedback stimulus (typically visual) rather than the endogenous motoric trigger of the ERN. In reward tasks, feedback of monetary reinforcement or punishment (loss of money) elicits a negative deflection 260-320 ms post-feedback. This deflection is larger for losses (and reward omission) as compared to rewards, and has been argued to evaluate outcomes along a continuum with highly advantageous and highly disadvantageous outcomes at opposing poles (Holroyd et al., 2004a). In addition to valence, the FRN has also been demonstrated to encode the magnitude of reward or loss (e.g. Wu & Zhou, 2009), particularly in relation to the alternative outcomes that would have been available (c.f. context dependence of the FRN; Holroyd et al., 2004a). Accordingly the FRN has been ascribed a functional role of evaluating the subjective motivational significance of outcomes that is relatively automatic or pre-conscious in nature (Gehring & Willoughby, 2002). More recently, FRN has been demonstrated to be modulated by the expectancy of outcomes (e.g. Hajcak et al., 2005), collectively leading to a theory that this component represents a prediction error (Holroyd & Coles, 2002; Holroyd et al., 2008; see below).

Both the ERN and FRN have been repeatedly localised to dorsal anterior cingulate cortex (dACC) by several EEG studies utilising a number of techniques (e.g. Bellebaum & Daum, 2008; Christie & Tata, 2009; Santesso et al., 2011). The dACC has been implicated in guiding action selection and performance monitoring using fMRI (Botvinick et al., 2004; Holroyd et al., 2004c) and is also a major component of the reward network, receiving dense projections from mesencephalic dopamine neurons (e.g. Rolls, 1999). This has led to a theory that the FRN is a corollary of the midbrain prediction error, and the proposal of a mechanism by which this phasic dopamine input arrives in and causes inhibition of ACC neurons. By this view, rewards lead to high inhibition of ACC whereas losses or reward omission, which suppress midbrain dopamine firing, result in disinhibition.
of the ACC (Holroyd et al., 2008). In support of this, studies have shown that the ERN is increased by a drug promoting phasic dopamine increases (amphetamine) (de Bruijn et al., 2004), whereas a dopamine blocker (haloperidol) produced the opposite effect (de Bruijn et al., 2006; Olvet & Hajcak, 2008). Increasing tonic (baseline) dopamine levels through chronic administration of L-DOPA have been shown to also reduce the ERN, and this may be due to narrowing the range of phasic changes in the dopamine signal (Olvet & Hajcak, 2008). This has relevance for clinical disorders characterised by dopamine reductions (e.g. Parkinson’s disease; Frank, 2005) and increases (e.g. mania and schizophrenia; Berk et al., 2007). In both cases, reduced prediction errors may arise from a restricted range of phasic dopamine firing (too little dopamine to generate a sizeable signal in the first case, and too much dopamine to generate a detectable difference from baseline in the latter case).

An alternative perspective for the morphology of the FRN is based on an expectancy bias. Oliveira et al. (2007) reason that negative feedback elicits a larger FRN than positive feedback because of an optimism bias that people show when judging their own performance. Accordingly, people are “more surprised” when they receive a negative outcome, eliciting large prediction error, and “less surprised” when they obtain a favourable outcome consistent with their expectancy bias. This tallies with the “gamblers’ fallacy” in which the person focuses on favourable outcomes, explaining them within their own ability or superior strategy, whilst unfavourable outcomes are largely ignored. This may explain the finding that amphetamine, which fosters unrealistically high confidence, enlarges the FRN.

However, ERN and FRN is also found to be enlarged in depression (Bruder et al., 2009; Foti & Hajcak, 2009) which does not fit with the view that this disorder is characterised by a negative outcome-expectancy bias (Eisner et al., 2008). One explanation for this discrepancy is that these electrophysiological measures carry both the error signal and the subjective aversive value individuals attach to the experience and are therefore more pronounced in punishment-averse, or high-BIS, individuals. In this vein, differences in ERN have commonly been reported in
externalising/impulsivity disorders, including self-reported trait externalising (Hall et al., 2007), alcoholism (Olvet & Hajcak, 2008). This has been linked to a key clinical feature of these disorders, “punishment insensitivity”. This has parallels for mania which is also characterised by repeated engagement in risky behaviours, despite experience of negative consequences in the past. Perhaps a blunted FRN to these aversive outcomes represents a failure to recruit the ACC and consequently lesser performance optimisation and reduced impact of this type of feedback, allowing maladaptive behaviour to persevere. In relation to reward outcomes, FRN has been found to be reduced in pathological gamblers (Hewig et al., 2010; Oberg et al., 2011). Similar reductions are observed in adolescence (Santesso et al., 2011; Segalowitz et al., 2011), which is a period particularly associated with increased reward sensitivity and risk-taking (Casey et al., 2008). Because smaller FRN is elicited by highly favourable outcomes, this effect has been interpreted as a hyperpositive evaluation of rewards, or a “reward hypersensitivity”.

The P300 is a later component that occurs after the FRN and is thought to represent more conscious cognitive processes (Polich, 2007). P300 is highly sensitive to expectancy violation and, like FRN, has been demonstrated to show modulation in tasks tapping motivation and reward processing (e.g. Nieuwenhuis et al., 2004; Sato et al., 2005; Yeung & Sanfey, 2004). One view is that the P300 represents a more elaborative evaluation of predictions than the FRN, incorporating higher-order aspects of the feedback stimulus and signalling retrieval of information from working memory (Wu & Zhou, 2009). Whereas P300 activity has been speculated to also relate to activity in the mesocorticolimbic pathway, a recent framework argues that this component is generated by multiple and widespread sources and is most sensitive to phasic enhancement of stimulus salience by norepinephrine pathways from locus coeruleus to prefrontal cortex (Nieuwenhuis et al., 2005). In auditory and visual target detection tasks abnormalities in the P300 have been demonstrated in a range of psychiatric disorders, including schizophrenia, addiction, depression and BD (Bruder et al., 2009; Iacono et al., 2003). However, very few studies have examined the reward-
P300 in clinical populations, and none in relation to BD. This thesis utilises the FRN and P300 to infer the subjective motivational significance of outcomes (Chapters 3, 4 and 6), and to probe prediction error signalling in reinforcement learning contexts (Chapter 3). Whilst to date the N1 component has not been linked to reward processing, this ERP plays a role in very early sensory-attentional processing (that precedes FRN and P300; see Figure 2.2). In this way the N1 is a useful tool for characterising attentional bias to reward in Chapters 4 and 6.
This section will focus on a single functional neuroimaging technique, functional magnetic resonance imaging (fMRI), as this was employed in the current thesis (Chapter 5). Functional MRI is the most commonly used technique for inferring brain activity due to the availability of MRI scanners and the relatively low cost per scan. Unlike some other modalities, there are no directly hazardous consequences of undergoing a scan (such as radiation exposure in the case of positron emission tomography; PET). In fMRI studies, images of the brain’s activity are acquired at regular time points while the participant is at rest or performing a task, allowing inference of the brain regions and networks involved. Images are equally divided into voxels, three-dimensional cubes (typically around 2 mm$^3$ in size) and the brightness intensity of each voxel is used to infer its level of activity. The brightness is a measure of the blood-oxygen-level-dependent (BOLD) signal thereby assuming that when neuronal structures increase their activity, they require concomitant increases in oxygen and glucose from the blood. In this way the BOLD signal uses deoxyhaemoglobin (deoxygenated red blood cells) as an endogenous contrast agent that determines the image intensity (Toronov et al., 2003).

Functional MRI possesses excellent spatial accuracy in localising brain activity because measurement accuracy of the BOLD signal is not reduced by distance of the scanner equipment from the neuronal source, or distorted by travelling through tissue. This is in contrast to EEG which possesses poor spatial resolution due to volume conduction, making it impractical for measuring deep brain activity. This accuracy is increased by scanners with higher magnetic field strength, but 1.5 Tesla scanners can resolve brain activity to within approximately 4 mm of its source (Toronov et al., 2003). However, because the vascular response that provides blood-oxygen to active structures is relatively slow, in the order of seconds, fMRI is not powerful in detecting rapid changes in activity (i.e. less than 2-3 seconds). Given that neuronal activity occurs in the order of milliseconds, this limits the applicability of this technique to differentiating stages of processing.
within a given brain region. Inferring brain activity with fMRI can be likened to trying to navigate the world with eyes that only update the image on the retina once every few seconds. In fact, the BOLD signal represents an accumulation of activity over this time period that filters out high frequencies (Liu & He, 2008) and is therefore more similar to taking a photograph with an exposure time of several seconds. This will produce a higher quality picture if the scene does not change, but result any activity or movement in the scene will be blurred across the image. In this way EEG and fMRI show complementary advantages and disadvantages that make them well suited to being combined when imaging the brain.

2.2.4. SIMULTANEOUS EEG-FMRI

2.2.4.1. Rationale for concurrent EEG-fMRI

Chapters 5 and 6 examine motivational decision-making in patients with a diagnosis of bipolar disorder using simultaneous EEG-fMRI. A number of factors led to this design.

First, anticipating challenges in recruitment of our specific subpopulation (see below), the study was designed to maximise the amount of data obtained from the sample. A high proportion of this population are in receipt of antipsychotic medication, posing a potential methodological confound. Because these agents exert their therapeutic effect through antagonism of dopamine (D₂) receptors within the mesocorticolimbic network (Kapur et al., 2000) – i.e. the same network that instantiates motivational processing – this class of medication itself alters prediction error signalling (Abler et al., 2007a; Pessiglione et al., 2006). However, no existing studies have examined decision-making in BD patients not in receipt of DA blockers and this may be a source of inconsistency between existing studies, resulting in either artifactual findings (i.e. medication effect) or non-findings (where the medication has ameliorated an underlying DA abnormality) (see
Hallahan et al., 2011, for a meta-analysis of medication effects in neuroimaging studies of BD). For these reasons, antipsychotic medication was an exclusion criterion for the study. Imposing this additional constraint on participant eligibility approximately doubled the recruitment effort needed to reach the necessary sample size; not only did patients need to be found, volunteer to take part, be currently euthymic and meet the health and safety EEG-fMRI criteria, but they also needed to be off DA medication. Because of the ethical issues around requiring participants to discontinue their treatment days or weeks before the study, we opted to recruit only patients not in receipt of this class of medication.

Second, simultaneous EEG-fMRI acquisition removes several methodological confounds arising from separate-session acquisition. These include practice and repetition effects, differences in task engagement, and effects of different presentation orders. A further criticism of comparing separately acquired multimodal data streams has been made specifically for studies of motivation. This argument (Harmon-Jones et al., 2010) stems from an embodied cognition perspective: whereas EEG is typically recorded in a seated position, fMRI requires a supine body position. An EEG study has demonstrated that the neural correlates of motivation differ between these two body positions (Harmon-Jones & Peterson, 2009).

2.2.4.2. Methodological issues in combined EEG-fMRI

Whilst simultaneous EEG-fMRI recordings of a solution to the above issues, this approach poses additional methodological challenges, as well as safety considerations (see 2.2.4.3). A major distinction between EEG and fMRI pertains to differences in their spatial (“where”) and temporal (“when”, “how”) resolution. Whereas EEG makes measurements at the millisecond level, fMRI is only able to resolve activity to within a few seconds (Toronov et al., 2003). Conversely, fMRI offers considerably more accurate identification of the specific brain regions
involved, particularly subcortical sources which are generally considered to contribute very little to the EEG recording because of their distance from scalp electrodes (section 2.2; but see Rektor, 2002). Consequently the fusion of the two modalities has gathered considerable interest in the past decade. However, in the majority of the analysis frameworks proposed the fusion is “asymmetric”; it involves using the findings from the first modality to inform the second, rather than deriving a third “modality-free” model that considers both contributions equally. Data-driven approaches such as joint ICA treatment are a notable exception (e.g. Moosmann et al., 2008) but also possess disadvantages. Unlike model-based strategies, the data-driven approach complicates and limits inferences about which aspects of stimuli (or time stages of trials) the neural activity pertains to. Furthermore, both data- and model-driven approaches assume that EEG and fMRI are measuring the same neuronal processes i.e. that the information from one modality is actually useful in explaining the variance in the other (Figure 2.3, Case 4). However, the evidence for this is equivocal (see below) and where there are discrepancies between the two modalities, fusion can produce estimation bias and erroneous results (Laufs et al., 2008).

Figure 2.3. Processes measured by electrophysiological (EEG), haemodynamic (fMRI) and behavioural indices. Some (A, B, C), but not all (D) of the brain’s activity manifests in these three modalities. Whereas some neural processes will manifest selectively in only one of the three (1-3), a smaller number of processes will manifest in multiple modalities (shaded overlap). Only for this latter case (4) is an EEG-fMRI fusion justified. Adapted from Laufs et al. (2008).
Whereas EEG records the electrical field potential induced by synchronous populations of neurones (Luck, 2005), fMRI utilises changes in the blood-oxygen consumption of neuronal tissues and hence indirectly infers their level of activity (Ogawa et al., 1990; see also section 2.2 of this thesis). Accordingly, EEG and fMRI may be sensitive to somewhat different biopsychological phenomena, and this might account for discrepant findings between the two modalities. Simultaneous fMRI and intracranial electrodes recordings in primates have indicated that, as with EEG, fMRI primarily measures local field potentials (Logothetis et al., 2001), but the differences in temporal resolution means that the two modalities could still be capturing different phenomena. Indeed, whereas fMRI captures activity occurring slower than 1Hz, EEG comprises functionally distinct frequency bands ranging from delta (up to 4Hz), theta, alpha, beta and through to gamma (as high as 30-100Hz) bands. It has been proposed that the slower neurovascular coupling underpinning fMRI measurements acts as a “low-pass filter” of the fast electrical activity indexed by EEG (Logothetis et al., 2001) resulting in a signal that is “smoothed” or “average accumulated” over time (Liu & He, 2008). This can result in “fMRI invisible sources”, which are too transient to accumulate into a substantial haemodynamic response but are nonetheless visible to EEG recording. On the other hand, as mentioned previously, deeper brain sources are typically “EEG invisible”. Hence, a combination of both modalities can elucidate a more detailed picture of the neural mechanisms underlying motivation and decision-making phenomena.

Given the novelty of the application, particularly with respect to BD, a conceptual fusion which considers each data stream in its entirety (and does not constrain consideration to only the signal common to both) would be the most thorough. For this reason data from the two modalities are first reported separately: whereas Chapter 5 deals with conventional fMRI analysis that identifies the spatial elements of the reward network, in Chapter 6 the high temporal resolution of EEG was used to characterise how activity in this network evolves over time, as well as to identify transient electrocortical sources that are invisible to slower fMRI measurement. A theoretical integration or “conceptual fusion” of the two data streams is provided at the end of Chapter 6.
2.2.4.3. Critical Safety Hazards of in-scanner EEG recordings

Recording EEG within the scanner produces numerous additional safety and methodological issues that must be strictly adhered to for the sake of participant safety and obtaining useable data. The remainder of this chapter will detail the hazards to the participant, the origin of the artifacts caused by recording in this environment and efforts to optimise data quality. A detailed discussion of the physics underlying these issues is beyond the scope of this section and can be found elsewhere (Lemieux et al., 1997).

Ordinarily participants are asked to remove all metallic implements from their person before undergoing MRI. Magnetic and paramagnetic objects pose several risks; they can become projectiles, attracted by the high magnetic field strength of the scanner; or they can heat dramatically due to electromotive forces (EMFs; see below). Accordingly, this protocol is critical to prevent impaling and burn injuries to participants. EEG acquisition contradicts these guidelines, requiring that electrical potentials are recording from the scalp and conducted to amplifiers using individual metallic electrodes and wires. Acquisition of fMRI slices relies on excitatory radiofrequency pulses and rapidly varying gradient fields, which induce EMFs in the EEG leads and result in two potential hazards (e.g. Lemieux et al., 1997). The first is that the participant may conduct substantial electrical currents from these leads, resulting in risk of skin electrolysis and electric shock. Accordingly, leads are specially manufactured to limit high current by using resistors, but high current can cause these resistors to heat up substantially, resulting in a second serious hazard. The main risk factor is looping or coiling of the EEG leads, which produces a low impedance pathway for induced EMFs. Given that there are usually 64 electrode leads, looping or coiling is would be very highly likely to occur if caution is not taken when routing these leads. Particular care must be taken to remove excess wire length from coiling underneath the participant’s head when resting on the scanner bed. Similarly, the additional ECG lead that is routinely placed on the back below the scapula (see below), is substantially longer than the scalp leads and is therefore more susceptible to EMF induction – this must be carefully routed in a straight line.
Differences in fMRI acquisition techniques influence the amount of RF energy delivered to the subject and EEG leads, and so can also play a role in the above EMF hazards. Non-standard sequences, such as spin and dual echo, are becoming increasingly common and are both associated with more heating than standard single shot techniques. Sequences must be approved by the manufacturer for the specific scanner model and EEG cap, and otherwise full tests on electrode temperatures must be performed (and on phantoms, not human participants).

2.2.4.4. The Gradient Artifact: its origin and principles for its correction

As mentioned above, image acquisition relies on rapid switching of scanner gradients that is typically continuous throughout a task. This produces a very large artifact that can be 10-50 times the typical EEG signal, and up to 1000 times that of its constituent neural activity (Mullinger et al., 2011; see Figure 2.4 of this thesis).

![Figure 2.4](image)

**Figure 2.4.** First 32 channels of ongoing electroencephalography (EEG) a) contaminated by the continuous gradient artefact (GA) during an fMRI sequence and b) after GA correction by average artifact subtraction method. In b) the characteristic scalp potentials are retrieved, along with the electrocardiogram trace toward the bottom.
However, because the gradient artifact (GA) is time locked to slice and volume acquisition, its exact periodicity is known. Further, because reliable image acquisition requires that the repeated gradient activity be extremely stable and repeatable, the artifact profile is invariant at any given location (see Figure 2.5a). Indeed although the GA manifests differently between electrodes, the profile at each electrode stays constant if the entire apparatus (electrodes, connecting leads, amplifiers, etc) remain immobile. Correction techniques capitalise on the assumption that each artefact is identical, by calculating a mean artifact template for each EEG channel and subtracting this at each GA occurrence (average artifact subtraction, AAS; Allen et al., 2000). The onset of each GA occurrence can be obtained by writing a marker to the EEG dataset each time the scanner acquires a new volume (‘TR markers’) for volume-based AAS. These are typically every 50-100 ms and their periodicity should be invariant. However, diagnostic tests on our Phillips Intera MRI system revealed that this is not always the case and there are slight perturbations to the actual onset of each slice acquisition. This was assessed by comparing the TR markers sent by the MRI system with the actual onset of the artefact on the EEG recording. We relied on an artefact detection algorithm for this diagnostic and used this to re-write the TR markers.
Figure 2.5. Ongoing electroencephalograph (EEG) contaminated by gradient artefact (GA). The scale for panes A-B is 5000 µV, roughly 1000 times greater than neural activity contained in the EEG (a subset of pane c). a) 500 millisecond epoch at 5000Hz sampling rate for two scalp channels. The shaded window shows the artefact for a single slice acquisition. Note that the gradient artefact profile differs greatly between the two channels but is identical within each channel for each
subsequent slice acquisition. **b) Two GA at 250 Hz sampling rate (typically used for standard EEG outside of scanner).** Note that the less precise measurement results in unstable GA shape between slices, which would corrupt the average artefact template and result in legitimate EEG being subtracted out during GA correction. **c) Corrected EEG at same scale as artifact panes A and B (top) and magnified (bottom).**

Another challenge is the extremely fast voltage acceleration that is induced by the GA (how steeply the voltage increases). The main issue is in accurately characterising the slope of this increase (the “shape” of the GA). Despite the high temporal resolution of EEG, standard sampling rates are insufficient, a typical sampling rate of 250 Hz would acquire a data point approximately every 4 milliseconds whereas in 1 millisecond the GA voltage typically changes by over 1000 µV. This would lead to the shape of each GA instance being very different and so the average would not closely represent any single artefact instance (Figure 2.5b), resulting in over- and under- correction of the data after AAS. This issue necessitates equipment that is capable of recording at 10-20 times typical rates (i.e. 5000Hz or one datapoint every 0.2 ms). However, even at higher sampling rates there is no guarantee that the datapoints are sampled at exactly the same time with respect to GA onset. For example, if the EEG system is acquiring datapoints every 0.2 ms, the first datapoint collected during slice 1 might be 0.05 ms later than slice onset, whereas the first datapoint for slice 2 might be 0.1 ms late. Given the extremely fast acceleration of the GA, the profile of the GA will look different between the two slices (see Figure 2.6). The solution is to synchronise the EEG datapoint acquisition with the scanner clock, which also ensures that the volume (TR) markers are correctly aligned with the beginning of the fMRI volume. This is accomplished with a specialised piece of hardware that is plugged directly into the scanner mainframe in the cooled “plant” room (rather than the scanner console in the observation room).
Figure 2.6. Sampling of the gradient artefact with asynchronous onset between MR slice acquisition a) Even at high sampling rate, the latency of the datapoints acquired with respect to slice onset can differ. For Slice 1 (blue), the first datapoint is collected at exact slice onset whereas for Slice 2 (red) each datapoint is stagger by approx 0.05 ms after slice onset. b) Despite the gradient artefact being identical in reality, the shape of the artefact recorded differs dramatically between the two. c) When computing the average artefact template (green, which is then subtracted from each individual artefact) the result will be intermediate between the two samples (blue and red). Accordingly, when average (green) is subtracted from the individual slices, there is mismatch between the two ('Error', shown against red sample). This results in under- or over- correction (i.e. too much or too little being subtracted, compromising the underlying neural activity). Note that in volume-based AAS, each sample is one volume of X slices (concatenated).
2.2.4.5. The Ballistocardiogram Artifact: its origin and principles for its correction

A second artifact that is also unique to simultaneous EEG-fMRI is the ballistocardiogram (BCG) artifact. This is caused by the cardiac cycle and has three sources. First, the pulsatility caused by blood flow in veins causes physical movement of the cap and housed electrodes overlaying them, once per heart beat. This induces a local change in 1) the effect of the static magnetic field ($B_0$) and 2) the gradient artifact profile. Second, the movement of blood induces a local change in magnetic field because the paramagnetic properties of the iron contained in haemoglobin. Unlike the gradient artifact, the BCG is dynamic and highly variant over time. Aside from natural fluctuations in the ECG, it is affected by pulse rate which will change throughout the task (and possibly in relation to task stimuli). This property makes it similar to a blink or eye movement, which are commonly corrected for using independent component analysis (ICA) which relies on many samples of the blink occurring in the same electrodes (i.e. frontal electrodes, which are nearest to the eyes) over the course of the experiment. However, unlike ocular artifacts the BCG topography is not fixed and it manifests at multiple sources and at different times. Briefly, as blood enters the head it may cause a pulse at the carotid artery under the left temple, then manifest later at the back of the head (particular as the participant is putting pressure here by lying on it) before causing another pulse at the temple while exiting via the jugular vein. Its unstable and rotating sources properties make it unsuited to ICA but, as with GA correction, AAS is well suited to removing this artefact (Allen et al., 1998).

In the AAS approach, an ECG recording is made from near the heart and this is used to indicate on the latency of heart beat instances on the scalp EEG data recording. Subsequently an algorithm is used to detect the resulting manifestation in the scalp channels, as well as the lag ('time delay') between the two events (i.e. the time taken for the blood to be pumped from the heart to the head). The most
prominent part of the ECG cycle is the ‘R’ component (see Figure 2.7a). An average template is built from many BCG instances but, because of the variability in the cardiac cycle (e.g. heart rate or cardiac output may increase or decrease during the scan), a dynamic ‘sliding’ template is used. Typically 21 samples are used which means that the average template completely adjusts to a change in the cardiac cycle after 21 heart beats (about 20 seconds). Subtracting this ‘local average’ ensures that what is removed matches most closely to each true artifact instance in amplitude and shape (analogous to the gradient artefact subtraction).

Figure 2.7. The electrocardiogram (ECG) inside and outside the scanner a) Diagram of the ECG as recorded outside the scanner. The most prominent and consistent component is the ‘R’ wave b) ECG channel recorded inside the scanner (note the inverted polarity and slightly different shape due to magnetic field $B_0$). c) An
algorithm is used to detect onset of each ‘R’ wave to then know which exact onset of the artefact in the scalp EEG recording so that it can be subtracted. After gradient artefact correction the signal is degraded, resulting in individual peaks being split into several sub-peaks (stitching). This can be problematic for the algorithm used to place ‘R’ markers (bottom) and result in them being omitted (“??”) or misplaced (red).

2.2.4.6. Initial data collection approach and limitations

Five initial datasets were collected, cleaned and analysed using the following standard procedure. Participants were positioned in the scanner using standard approach for MRI, which involves centring of the nasion into the isocentre of the scanner bore by the radiographer. The left and right exit sockets for amplifier one and two, respectively, were routed symmetrically along the edges of the scanner bore (see Figure 2.8a). Short (20 cm) ribbon cables were used to connect the subject to the amplifiers because the reduced length reduces the amount of artifact they collect. Amplifiers were positioned inside the scanner bore, at the rear, with the ribbon cables fully extended.
Figure 2.8. a) Standard setup used for initial participants. Flat cables routed symmetrically along opposite sides of the scanner bore with short cables (to reduce artefact saturation) and amplifiers sat in scanner bore (cushioning was added to dampen scanner vibrations). b) Optimised setup for remaining sample. Flat cables clipped together to ensure equivalent artefact profiles on each cable. To reduce vibration and cable movement, cables were sandwiched between sandbags and amplifiers were stationed outside of the scanner on a tower/plinth. This set up more than offset the disadvantage of using the longer cables.

These initial datasets were cleaned using volume-based AAS method (i.e. each sample in the template was one whole volume of 30 slices). Gradient and BCG artifacts were substantially reduced but there remained residual artifact in the same order of voltage as the ongoing EEG. Because of this, the quality of “landmark” event-related potentials (ERPs) obtained after averaging was poor, even after EEG pre-processing (filtering, ocular/blink correction, excluding bad trials, etc). The visually evoked potential (VEP) was absent or drastically reduced in
amplitude in the majority of datasets (<0.5 µV, compared to 5-10 µV typically observed outside of the scanner). Exploration of the data suggested that the residual artefact was due to an unstable gradient artifact profile in the data, causing the mean artifact template to poorly represent the data and leading to suboptimal correction (c.f. Figure 2.6). Listed below are the theoretical assumptions of EEG cleaning approaches and how they were violated in practice when using the standard approach. We conclude with the improved approach that was used to collect the final datasets (Figure 2.8b).

Assumption 1: Invariant Gradient Artifact within EEG leads

The AAS technique assumes that the GA shows minimal variation over time. However this assumption is valid only while the electrodes and leads remain stationary and is violated whenever there is movement, of which there are three main sources in the scanner. Firstly, pulsatility due to cardiac cycle results in unavoidable movement of the electrodes by the blood vessels underneath them. Secondly, participant movements result in translation and rotation of the electrodes in space. Thirdly, vibrations from the scanner can propagate along the leads and ribbon cables. The following modifications to data collection strategy were made to combat these causes: 1) further padding the head to reduce head movement 2) padding the leads using sandbags and seating amplifiers on cushions (while in the scanner) to absorb vibration.

Off-line, a modified AAS was implemented. We used a sliding average template with a window of 21 samples of the entire volume artefact (30 slices). The template therefore consisted of the mean of the current sample and the 10 samples before and after. This allowed greater sensitivity to changes in the GA profile, with full adaptation occurring by after 21 volumes or 51.45 seconds (i.e 21*TR; TR = 2.45 seconds).
**Assumption 2: In-scanner recordings contain the true EEG plus artifact**

An assumption of simultaneous in-scanner EEG is that the end recording comprises the true electrophysiological recording – in its complete form, and as would be obtained outside of the scanner – plus superimposed artifact(s). However, because the recording equipment has a limited bandwidth that can be reached (and exceeded) by the large dynamic range of voltages, some of the true neuronal signal can be lost due to saturation. Saturation is less of an issue for scalp channels but common in the ECG lead because it is considerably longer and picks up more artifact than the scalp channels. In these instances, the gradient AAS is less effective because part of the artifact is missing (wherever there is saturation) resulting in more mismatch or ‘Error’ (as per gradient artifact AAS; Figure 2.6c) between the average template and the individual BCG artifacts. Crucially, this results in degradation of the ECG recording after correction (‘stitching’; Figure 2.7c) which reduces the accuracy by which the algorithm can detect pulse onsets. If individual pulse onset markers are missed entirely, these instances of the BCG artifact remain untouched in the EEG. A worse situation is if the markers are misplaced (either on an ‘R’-like peak that is either before or after the true ‘R’; Figure 2.7c), resulting in the average being subtracted from the wrong portion of the EEG (earlier or later than the true BCG onset). The consequence of this is that substantial removal of neural activity occurs.

Whilst stitching is largely uncontrollable, we reduced its effect on peak detection both with on- and off-line techniques. First, we optimised the magnitude of the cardiac cycle recording by locating an optimal site for the ECG lead that was closest to the heart and in receipt of the least conductance impedance from the ribcage. This was determined to be off-centre, below the left scapula and in an intercostal gap between vertebrae. Off-line, the ECG recording was band-pass filtered (9 – 14 Hz) to include only meaningful cardiac frequencies and reduce low and high frequency noise.
Assumption 3: Equivalent gradient profile between amplifiers

For a 64-electrode system there are typically two amplifiers, each receiving from 32 electrodes. The AAS algorithm selects an initial GA template based on a representative lead (typically an electrode with maximal gradient artifact is selected). This lead will belong to one amplifier, and the process assumes that the channels in the other amplifier possess similar GA profiles. Whilst the amplifiers are positioned close in space (they are typically stacked and some distance from the maximal magnetic field) and so receive highly similar artifact, the signal to each amplifier is conducted via separate ribbon cables that are routed from the cap. These ribbon cables acquire considerable artifact because of their length and also because they span portions of the scanner bore where the gradient artifact is greatest.

Short ribbon cables were used for the initial scans to off-set the above issue. However, because the ribbon cables are separate (one per amplifier) and therefore occupy distinct locations in space, they acquire a different artifact profile. This was worsened by routing them separately along either side of the scanner bore (Figure 2.8a) and led to the initial GA template estimates calculated from one amplifier being suboptimal for the other. To reduce this issue for future recordings the flat cables were routed together (by clipping/taping them), thus improving the similarity of the GA profile in each amplifier.

Unstable Gradient Profile in Final Datasets

The dramatically attenuated ERPs obtained after artefact correction, rejection and averaging indicated over- or under- correction of the dataset due to mismatch between local average and individual volumes. Accordingly stretches of data around substantial changes in the artefact profile were most poorly corrected.
These stretches were identified by cross-referencing the movement parameters from SPM’s motion correction algorithm (used to realign the fMRI images after participant movement) and examining these periods of the EEG recording. To address this issue of sluggish updating of the average template, slice-based AAS was attempted as an alternative to volume-based AAS. This involved detecting 30 individual slices per volume and using each of these as a sample for the average template. The advantage of this is that the template updates quicker – 30 times quicker than volume-based AAS – following a movement or other perturbation to the GA profile. However, this also revealed a design problem of the fMRI sequence which posed no problem to fMRI analysis but reduced its compatibility with concurrently recorded EEG. Whilst the scanner clock was synchronised with the EEG equipment (as outlined in section 2.2.4), and hence drove EEG datapoint acquisition, phase-locked to volume onsets, this did not translate to synchrony with individual slice onsets. This was because of the TR selected for the fMRI sequence: the 30-slice volume TR of 2.45 seconds resulted in an individual slice latency (of 81.6 [recurring] ms) that was not an integer multiplication of the sampling rate. At 5000Hz sampling rate, data points are acquired every 0.2 ms, and this resulted in data points being sampled imprecisely around the actual slice onset (i.e. immediately before the current slice, 81.6 ms, or shortly after, 81.8 ms) and resulting in a latency jitter. This meant that the profile of the slice artefact also jittered between two configurations, resulting in suboptimal matching to either one and resulting in systematic over- or under-correction (see Figure 2.6).

To correct the above problem, samples were defined as three-slice ‘micro-volumes’, which had a total latency that was an integer multiplication of the sampling rate. These micro-volumes had a consistent latency of 245 ms and still resulted in an improvement in the issue of sluggish template update. The three-slice micro-volumes resulted in a ten-fold acceleration in adaptation to perturbations in the GA profile (5.145 secs or less than half a trial) compared to standard volume-based AAS (approximately 51 secs).
2.2.4.7. Final procedure and improvements for future work

The above optimised procedure was used for the remainder of the datasets. Despite the issue identified about suboptimal TR, we did not alter this parameter in the fMRI sequence for future scans. The reason for this was that we were limited to an agreed number of scans (because of the financial cost of each fMRI scan) and wanted to be able to compare the fMRI scans of the initial ‘pilot’ EEG recordings with those of the subsequent scans. Indeed, fMRI images were not affected by the EEG procedure. However, future studies would benefit from ensuring that the fMRI sequence is modified to use a volume TR that is divisible by the sampling rate. In addition, securing the amplifiers outside of the scanner bore on top of a plinth would reduce the micro-vibrations propagated throughout the scanner. Finally, there is preliminary evidence to suggest that GA amplitude can be reduced by up to 30% by unconventionally positioning subjects further out of the scanner (a shift of 3 cm in the axial plane was found to be optimal; Mullinger et al., 2011). This may arise from the positioning of the electrodes in the isocentre of the scanner bore where the field homogeneity is highest, and may offset saturation and residual artefact.
2.3. Paradigm Development: in search of a risk-taking task

Following on from limitations of the first risk-taking task (Chapter 3), two additional tasks were piloted with a view to using one of them in the combined EEG-fMRI study with a clinical sample. In particular, a task with a minimal learning component was desirable. In both studies hypomania vulnerability was used as a non-clinical surrogate model of BD, in order to assess whether the tasks would be likely to detect risk-taking in the clinical population. This section provides a brief report of these tasks and their strengths and weaknesses. Ultimately both tasks proved to be suboptimal for our purposes and were abandoned in favour of a third task.

2.3.1. THE BALLOON ANALOGUE RISK-TAKING TASK & INFLUENCE OF MOOD INDUCTION

2.3.1.1. Purpose and objectives

The pilot aimed to validate a task primarily established in substance-dependent individuals, and determine whether it would be sensitive to risk-taking in an analogue (hypomania-prone) sample. A relatively low number of participants were recruited (n=23) and there were no physiological measures.

Poor emotion regulation has been linked to risky behaviours, including smoking and alcohol addiction (Magar et al., 2008). A dual motivational pathway account posits that risk-taking may be driven either by a ‘hedonic’ pathway (associated with positive affect and extraversion) or a ‘coping’ pathway (associated with negative emotionality and driven by escaping aversive emotional states) (Cooper et al., 2000). Both positive and negative affect characterise BD (including
mania; Meyer & Hofmann, 2005) and the BAS dysregulation theory (Urosevic et al., 2008; section 1.1) predicts greater reactivity to appetitive and aversive cues in this population. However, their relative contributions to risk-taking have not been examined experimentally.

The Balloon Analogue Risk Task (BART) predicts real-life risk taking behaviours (Lejuez et al., 2002) and distinguishes clinical risk-taking populations (substance-dependent and conduct disordered patients) from controls (Crowley et al., 2009). In BD, elevated BART risk-taking was reported only in subgroup with prior substance-dependence (Holmes et al., 2009), but this study included patients in all phases of the disorder and did not examine the effect of affective symptoms. Positive and negative mood induction in controls increase and decrease BART risk-taking respectively (Heilman et al., 2010). We examined the relationship between risk-taking and hypomaniac traits whilst experimentally manipulating mood and predicted a positive correlation between these traits and 1) risk-taking and 2) susceptibility to mood induction.

2.3.1.2. Methods and Materials

We used a within-subjects design to reduce the sample size for this pilot, examining linear relationships between hypomaniac traits and task variables. To this end, we ensured a spread of scores on the HPS (which is otherwise normally distributed; see Figure 2.1), by recruiting equal numbers of low (0-15), medium (15-25) and high (30-48). Participants were recruited from an online pool (see section 1.1) and remunerated in cash. Depressive symptoms were assessed with the Depression, Anxiety and Stress Scale (DASS; Henry & Crawford, 2005).

Participants attended two sessions roughly one week apart. In each session participants completed the brief Positive and Negative Affect Scale (PANAS) (Watson et al., 1988) before and after being played one of two sets of musical excerpts, which were selected for their evocative features. For the sad mood
condition, the musical excerpts were: *Alexander Nevsky: Russia under the Mongolian yoke* (at three-quarter speed), *the theme from Schindler’s List* (at three-quarter speed). For the happy mood condition the excerpts were: *A-Ha - Take on me* and *Delibes – Coppelia*. The two sets of music clips were intended to induce either positive or negative mood and their presentation was counter-balanced with respect to session. In the BART, participants made incremental decisions on whether or not to inflate a balloon for more monetary reward whilst considering the risk of losing the reward accrued so far (if the balloon pops) (Lejuez et al., 2002; see Figure 2.9). Participants completed six blocks of 20 trials and heard the musical clips again before beginning every other block (baseline, after block 2, after block 4). Participants completed the PANAS again at the end of both sessions and we ensured that participants did not report feeling distressed when leaving either session.

**Figure 2.9.** Schematic of a single trial. On each trial, participants are given two options: to press the right button to continue inflating the balloon or to press the left button to withdraw. The participants’ choice to inflate the balloon leads to two possible outcomes that are immediately fed back to them: a no-explosion in which they accrued the amount gambled, or a loss event in which the cumulative winnings were lost.
2.3.1.3. Results

The difference between baseline and post-induction PANAS was significant for positive [difference greater than zero; \( t(22)= 36.6, p<.001 \)] and negative [difference less than zero; \( t(22)= 11.4, p=.003 \)] confirming that the induction succeeded. The negative mood induction showed similar efficacy for decreasing positive affect [\( t(22)= 4.13, p=.05 \)] and increasing negative affect [\( t(22)= 12.9, p=.002 \)]. There were no effects of HPS score as a covariate (\( p\geq .13 \)). However, when controlling for total DASS score, HPS increased the change in positive affect following mood induction [\( F(1,20)= 3.96, p=.06 \)]. Paired sample \( t \)-tests revealed significant differences in baseline mood of participants in the sad and happy sessions: PANAS-P [\( t(22)= 2.52, p=.019 \)] and a similar trend for PANAS-N [\( t(22)= -1.58, p=.1 \)]. In both cases there were main effects of HPS score when this was entered as a covariate (\( p<.05 \)), which were due to higher PANAS scores in high HPS participants.

Average number of balloon inflations was entered into an ANOVA with mood condition as (happy, sad) a factor and HPS and DASS scores as covariates. Contrary to our hypotheses there was no effect of mood condition (\( p=.79 \)). However, this effect was present when controlling for the above differences in baseline positive and negative affect [\( F(1, 21)=5.98, p=.023 \)].

2.3.1.4. Discussion

Overall, positive mood increased risk-taking in line with BAS theory (Gray, 1991) and susceptibility to mood induction positively correlated with hypomanic traits. In spite of this we were unable to detect a direct relationship between hypomania and risk-taking, and several methodological factors can be considered. First, the study may have been underpowered and although previously we employed between-group designs (Chapters 3 and 4) and in one case excluded moderate or
high depressive symptoms (Chapter 3), the current design was within-subjects and did not exclude depressive symptoms. Whilst this ensured a representative sample, depressive symptoms may have obscured a relationship between hypomania and risk-taking by decreasing sensitivity to reward (Pizzagalli et al., 2009) or fostering a negative-outcome expectancy bias (Eisner et al., 2008). Our attempts to control for depressive symptoms may have further weakened the study’s power. Another possibility is that both the positive and negative mood inductions increased risk-taking in the hypomania-prone individuals, via distinct mechanisms (i.e. ‘hedonic’ and ‘coping’ routes respectively; Cooper et al., 2000; see 2.3.1.1). This is in accordance with the higher levels of both positive and negative emotionality in this population found here and elsewhere (Meyer & Hofmann, 2005). A third “neutral” mood session could shed light on this possibility.

Finally, the BART may be sensitive to facets of risk-taking uniquely associated with addiction rather than BD, as indicated by a previous study finding greater BART in a previously substance-dependent subgroup of BD (Holmes et al., 2009). However, this subgroup also showed higher impulsivity, and this trait may augment risk-taking through both positive and negative affective pathways (Cooper et al., 2000).

In conclusion, we provide further support for positive mood fostering risk-taking and for a relationship between hypomania vulnerability and susceptibility to mood manipulation. The BART may however be relatively sensitive to risk-taking in BD-related samples, or risk-taking in this population may be driven by both positive and negative mood states.
2.3.2. WHEEL OF FORTUNE TASK WITH EEG

2.3.2.1. Purpose and objectives

This study looked to localise the neuroeconomic parameters conferring increased risk-taking and reward sensitivity in a previous EEG study of at-risk individuals (Mason et al., in press; Chapter 3 of this thesis). In this prior study, free-choice on bet size conflated the effects of expectancy and magnitude on group differences (see Chapter 3). A variant of the Wheel of Fortune (WoF) game allows these parameters to be orthogonalised (Smith et al., 2009; see Figure 2.10) and simplified versions not separating these parameters have detected gross behavioural differences in paediatric BD (Ernst et al., 2004) and functional neuroanatomical differences in depression (Smoski et al., 2009). We sought to adapt this paradigm for EEG and characterise these parameters in hypomania-prone individuals, a surrogate model for the clinical sample of BD to be recruited for Chapter 5.
Figure 2.10. Example of choices on two separate trials. In Trial X, the participant has a simple “no-brainer” choice with a clearly superior choice (note that the alternative outcome is zero gain, not loss). In Trial Y participants choose between a “safe” but small amount (shown in blue) and a “risky” alternative with higher payoff. Crucially the “safe” and risky” gambles are matched for expected value (probability x magnitude) allowing their contrast to yield variance associated with risk. Other comparisons shown the neural representation of value/magnitude and probability to be isolated.

Our primary outcome measures were the feedback-related negativity (FRN) and P300, which are thought to preferentially represent valence, probability and value to different extents (e.g. Yeung & Sanfey, 2004). We hypothesised that these components would be modulated by the contrasts in Figure 2.10 and sought to the variability due to hypomanic traits. In particular, does risky choice in hypomania-prone individuals result from hyperoptimistic predictions (i.e. blunted effect of probability), from magnification of the available payoff (differences in magnitude contrast) or insensitivity to risk (reduction in risk contrast).
2.3.2.2. Methods and Materials

17 participants were recruited via the same procedure as for another pilot study, described in section 2.4.1. We recorded EEG using a 64-electrode BioSemi® system, which is described in detail in Chapters 3 and 4.

The WoF task (Smith et al., 2009) is a computerised two-choice decision-making task involving probabilistic monetary outcomes. On each trial, participants were presented with a single wheel divided into two slices (choices). In the main variant, the two slices represented 25% or 75% probability of reward (see Figure 2.10). Note that the alternative outcome is no-reward, rather than loss of the money at stake. Two types of wheels are used: in the “safe/risky” wheel (Figure 2.10, Trial ‘Y’) participants chose between a likely but small (“safe”) option and a less likely but large reward (“risky”) option. In the “no-brainer” wheel (Figure 2.10, Trial ‘X’), the choice is between a likely and high payoff and a clearly inferior unlikely and small payoff. For variety, the exact values were varied between two smaller amounts (2 pence and 6 pence) or two higher amounts (5p and 15p) which were presented equally frequently and were intended to be collapsed together for final analysis. In a second variant, the two slices represented 50% probability of reward each and losses were the alternative eventuality of the gamble (signified by a red ring around the pie chart), rather than non-reward. This allowed us to explore neural activity associated with rewards, non-rewards and losses.

The colour of each option was counterbalanced and presented in a random order. The choice selected by the participant was underlined on the screen for 1000 ms with outcome displayed immediately afterwards (see Figure 2.11a). In total there were 360 trials over five blocks of 72 trials (6.2 minutes each), yielding 240 “safe/risky” wheels, 40 “no brainer” wheels, and 80 “50-50” wheels (see Figure 2.11b).
Figure 2.11. a) Schematic of a single trial. The design allowed both anticipatory and evaluatory brain activity to be probed. b) Diagram to illustrate number (n) of final outcome trials. Initially there are 240 trials (half of which are £1/£3 stake; shown, and the other half £5/£15). Assuming participants choose the safe and risky options equally, a minimum of 20 trials in each condition. However, participants biased toward one or the other result in insufficient trials per condition.

2.3.2.3. Summary and Recommendation

A number of methodological issues arose while conducting this pilot study, which will now be briefly summarised. First, due to time constraints and challenges in recruiting the extreme low and high thirds of the hypomania spectrum, the study
concluded with 17 participants in total. Second, free-choice on “safe” versus “risky” gambles led to insufficient trials in four participants showing marked risk-seeking or risk-averse biases. Third, the EEG data for two participants was extremely noisy and had to be discarded, and two further participants showed insufficient EEG trial numbers (n<20; Marco-Pallares et al., 2011) following rejection of muscular and ocular artefacts. This led to a final sample of nine datasets that were not analysed due to insufficient statistical power and precision.

During completion of this pilot study, a number of issues were identified that led to selection of a different paradigm for the simultaneous EEG-fMRI clinical study (Chapter 5), and so no more datasets were collected. The participants showing strong risk biases were extreme scorers on the HPS (±2 SD from the mean). Given that we expect highest risk-taking in clinical populations of BD, this methodological confound itself precluded using the WoF task for the patient study (Chapter 5). In a previous fMRI application of the WoF task in depressed sample (Smoski et al., 2009), multiple participants were excluded due to insufficient trials (Smoski et al., 2009, personal communication). This was further tempered by limited scanning hours awarded, as well as considerations around volunteers’ time commitment and the extra discomfort associated with the EEG cap. In this way it would have been unethical to commence the study knowing that a large number of patients would be excluded post-hoc, nullifying their sacrifice for the research study.
CHAPTER 3: BETTER THAN I THOUGHT: POSITIVE EVALUATION BIAS IN HYPOMANIA*

* This chapter has been accepted for publication in PLoS ONE and is currently in press.


The results were also presented at *Organisation for Human Brain Mapping* (OHBM; Barcelona, 7th June, 2010) and *International Review of Bipolar Disorders* (IRBD; Rome, 10th June 2011) conferences.
Abstract

Background:
Mania is characterised by increased impulsivity and risk-taking, and psychological accounts argue that these features may be due to hypersensitivity to reward. The neurobiological mechanisms remain poorly understood. Here we examine reinforcement learning and sensitivity to both reward and punishment outcomes in hypomania-prone individuals not receiving pharmacotherapy.

Method:
We recorded EEG from 45 healthy individuals split into three groups by low, intermediate and high self-reported hypomanic traits. Participants played a computerised card game in which they learned the reward contingencies of three cues. Neural responses to monetary gain and loss were measured using the feedback-related negativity (FRN), a component implicated in motivational outcome evaluation and reinforcement learning.

Results:
As predicted, rewards elicited a smaller FRN in the hypomania-prone group relative to the low hypomania group, indicative of greater reward responsiveness. The hypomania-prone group also showed smaller FRN to losses, indicating diminished response to negative feedback.

Conclusion:
Our findings indicate that proneness to hypomania is associated with both reward hypersensitivity and discounting of punishment. This positive evaluation bias may be driven by aberrant reinforcement learning signals, which fail to update future expectations. This provides a possible neural mechanism explaining risk-taking and impaired reinforcement learning in BD. Further research will be needed to explore the potential value of the FRN as a biological vulnerability marker for mania and pathological risk-taking.
3.1. Introduction

Bipolar Disorder (BD) is characterised by episodes of mania and depression, interspersed with periods of relatively normal functioning. Pervasive impairments in decision-making are present in all phases of the disorder (Swann et al., 2001; 2003; 2008), marked by increased goal-pursuit, impulsivity and risk-taking activities with high potential for damaging consequences in manic episodes (including substance use, unprotected sex, gambling and spending sprees; DSM-IV-TR, 2000). Psychological models are consistent with these features being due to increased sensitivity to rewarding events, and argue that increased activity in a Behavioural Approach System (BAS; Gray, 1991) produces concomitant increases in manic symptoms (Johnson, 2005a; Urosevic et al., 2008). Conversely, reduced BAS activation is linked to depressive symptoms such as apathy, anhedonia and amotivation (see Urosevic et al., 2008 for discussion of the BAS dysregulation theory). In this way BD may be associated with dysregulation in the processing of rewarding outcomes. Factor analytic (Cassidy et al., 1998), cross-sectional (Bauer et al., 2005; Carver & Johnson, 2008) and longitudinal (Johnson et al., 2011) designs indicate that mania and depression are relatively independent phenomena in BD. This allows the underlying cognitive basis for mania to be explored separately from vulnerability to depression.

Clinical populations of mania are typically in receipt of psychotropic medication, and frequently experience hospitalisation and high rates of comorbidity, all of which present a challenge to studying psychological processes associated with BD. Manic symptoms are known to lie on a spectrum that extends into the general population (Akiskal et al., 2000; Angst & Gamma, 2002), making it possible to identify individuals in the general population experiencing attenuated symptoms. The Hypomanic Personality Scale (HPS) identifies people meeting criteria for bipolar spectrum disorder but not yet in treatment (Eckblad & Chapman, 1986), and predicts clinical episodes after thirteen-year follow-up (Kwapil et al., 2000). HPS also correlates with trait measures of reward sensitivity (the BIS/BAS scales;
Carver & White, 1994; Johnson & Carver, 2006). Hence it is possible to study reward processing in populations exhibiting similar cognitive biases whilst avoiding confounds from psychotropic medication, hospitalisation and comorbidity.

Reward processing has been linked to mesocorticolimbic pathways projecting from midbrain structures to orbitofrontal and anterior cingulate cortices (Depue & Zald, 1993), with dopamine (DA) encoding both anticipation and experience of reward stimuli (Schultz, 2002). Abnormal DA neurotransmission is a hallmark feature of BD (Berk et al., 2007; Jacobs & Silverstone, 1986), with DA-antagonists ameliorating manic episodes (Cookson, 2001) and evidence that antidepressants may ultimately exert their therapeutic effect via the DA system (e.g. Willner et al., 2005). Experimentally, mania has been associated with aberrant reward-related activity in DA-rich midbrain structures (Abler et al., 2007c), although confounds from medication cannot be completely ruled out. This is especially problematic given that pharmacological agents act on the neural circuitry that mediates reward processing, as illustrated, for example, in the finding of disrupted reward-related activity following single doses of an antipsychotic in healthy controls (Pessiglione et al., 2006). We have previously found that functional activity in striatum in response to rewarding outcomes was more strongly modulated by reward value in a hypomania sample (O'Sullivan et al., 2011). Similar patterns of activity have been reported in clinical populations exhibiting impulse-control disorders (Voon et al., 2010) and in healthy individuals receiving L-DOPA, a dopamine precursor (Pessiglione et al., 2006). Event-related potentials (ERPs) offer greater temporal resolution to investigate reinforcement learning processes in (hypo)mania.

The feedback-related negativity (FRN) is an event-related component that occurs as a negative deflection (260-320 ms) and is implicated in motivational processing, appearing larger (i.e. more negative) for worse-than-expected outcomes and attenuated (more positive) or absent for better-than-expected outcomes (see Holroyd et al., 2008). In this way the FRN may represent a system subjectively
evaluating outcomes along a good-bad continuum (Holroyd et al., 2004b), which therefore makes it a useful tool for probing individual differences in sensitivity to reward and punishment outcomes. The FRN is also linked to learning of motivational outcomes, with an influential theory stating that its amplitude reflects a reversal of the prediction error signal (the difference between the predicted and actual outcome) generated in the midbrain (Holroyd & Coles, 2002; Holroyd et al., 2008). Experimental evidence generally demonstrates that the FRN conforms to associative learning theory assumptions (HajiHosseini et al., 2012; Luque et al., 2011). Therefore this component is also a useful tool for probing reward learning deficits, which have been previously implicated in clinical populations of BD (Pizzagalli et al., 2008b).

While the FRN has not been investigated in relation to mania, depressive symptoms are associated with larger FRN (i.e. a greater negative deflection), most notably for losses and negative feedback (Holmes & Pizzagalli, 2008; Mies et al., 2011; Yasuda et al., 2004). This is consistent with a hypersensitivity to adverse events and a bias towards negative (self)evaluation. Further, there is evidence that the FRN elicited by positive feedback (e.g. monetary reward) is also larger in individuals exhibiting depressive symptoms (i.e. the FRN appears more loss-like; Foti & Hajcak, 2009). In this way depression is also characterised by blunted reward sensitivity, consistent with neuroimaging studies showing reduced reward-related activity in midbrain regions (Elliott et al., 1998; Pizzagalli et al., 2009). Conversely, impulsivity is associated with a tendency to overvalue rewards (Pine et al., 2010) and a failure to learn from the negative consequences of behaviour (i.e. reduced punishment sensitivity; Patterson & Newman, 1993). Consequently impulsive individuals exhibit the opposite pattern to that described in depression, showing reduced FRN for motivational outcome information (Onoda et al., 2010) and dampened error processing (Hall et al., 2007; Potts et al., 2006a). Further, self-reported reward sensitivity, BAS and sensation-seeking are linked to reduced FRN for both reward and punishment (Santesso et al., 2011; Segalowitz et al., 2011). Finally, reduced FRN has also been reported in psychiatric disorders characterised by impulsivity and risk-taking, including alcohol dependence (Kamarajan et al.,
2010), substance abuse (Franken et al., 2007), attention-deficit hyperactivity disorder (van Meel et al., 2011) and pathological gambling (Hewig et al., 2010). We have also demonstrated in a delay-discounting paradigm that immediate rewards elicit smaller FRN than delayed rewards, and that this effect is steeper in individuals prone to hypomanic symptoms (Mason et al., 2012), consistent with elevated impulsivity in clinical samples of BD (Swann et al., 2001; 2003; 2008). Collectively, evidence suggests that manic symptoms would be associated with a similar FRN attenuation for both reward and punishment.

Here we sought to characterise motivational processing in well-functioning individuals with psychometric vulnerability to BD (but no psychiatric diagnosis), allowing us to exclude confounds from psychotropic medication and hospitalisation, and to potentially uncover vulnerability markers for the disorder. Because manic and depressive symptoms frequently co-occur in BD (e.g. Goldberg et al., 2009) and these features are associated with opposing perturbations of FRN and other markers of motivational processes (see above), we excluded depressive vulnerability so as to isolate electrophysiological markers uniquely associated with susceptibility to hypomania. We hypothesised that these individuals would show a bias towards positive evaluation of motivational outcomes and impaired learning of reward contingencies. Given that the FRN codes subjectively advantageous outcomes with reduced amplitude, relative to disadvantageous ones, we predicted 1) reduced FRN amplitude for gain relative to losses, and 2) that the hypomania-prone individuals would show a smaller FRN for gains (relative to the other groups), indicative of a greater hedonic impact of rewards in this group. A second prediction was that FRN deflection elicited by punishment outcomes would also be reduced in the hypomania-prone group (relative to the other groups), consistent with findings that aversive outcome processing is dampened by trait impulsivity. We also made between-group comparisons of outcomes in the time-frequency domain. We focussed on the theta band as this is thought to reflect the activity of a wider action regulation network than FRN (Luu et al., 2003), permitting a more detailed characterisation of the neural functioning associated with hypomania susceptibility.
3.2. Materials and Methods

3.2.1 PARTICIPANTS

49 right-handed individuals (24 male, 25 female, \(M_{\text{age}} = 21.4, \ SD = 2.41\)) were sampled from a larger pool (N=652) of students at the University of Manchester that had completed an online battery of questionnaires (see below). An online screening questionnaire was used to exclude participants reporting current or past history of psychiatric or neurological illness and receiving psychotropic medication.

3.2.2 SELF-REPORT MEASURES

All participants from the larger pool had completed the 48-item Hypomanic Personality Scale (Eckblad & Chapman, 1986), 21-item BIS/BAS scales (Carver & White, 1994), and 24-item Dysfunctional Attitudes Scale; (Lam et al., 2004). Both the HPS (Eckblad & Chapman, 1986; Kwapi et al., 2000) and BIS/BAS scales (Meyer et al., 1999) have been robustly demonstrated to predict BD, whereas the DAS has been shown to measure depressive cognitive style (Power et al., 1994; Weissman & Beck, 1978). Hypomanic and depressive symptoms often co-occur in clinical (Goodwin & Jamison, 1990) and non-clinical (Bentall et al., in press) samples of BD. Hence, in order to isolate differences specifically associated with hypomanic symptoms, participants with depressive cognitive styles were excluded using a DAS cut-off of one standard deviation above the mean (\(M = 98.5, \ SD = 17.8\)). Three groups were then selected on the basis of their online HPS scores and contacted to take part in the study. Using established HPS cut-offs (e.g. Hofmann & Meyer, 2006; Meyer & Maier, 2006) we defined high hypomania (Hi-hyp; \(n = 17\)) by the upper decile of the larger pool (N=652). A medium hypomania (Mid-hyp; \(n = 15\)) was defined by scores around the mean (\(M \pm SD\)), and a low hypomania group (Lo-
hyp; n = 17) comprised individuals with HPS scores in the lower two deciles. All groups were selected to have near-equal distribution of male and female participants and did not differ significantly in age \( F(2,42) = 3.39, p = .715 \).

### 3.2.3 STIMULI AND TASK

Participants played a computerised card game, in which they learned the reward contingencies of three cues (circle, square, and triangle) associated with 20%, 50% and 80% chance of reward (which are referred to as ‘punishment’, ‘50-50’ and ‘reward’ conditions, respectively). The contingencies carried by each shape were counterbalanced across participants. Participants used this information to guide their choices of how much to bet in pence (23p, 14p, 8p, 3p). These values are in accordance with those routinely reported in the literature (Foti & Hajcak, 2009; Gehring & Willoughby, 2002; Goldstein \textit{et al.}, 2006; Kamarajan \textit{et al.}, 2009) and were piloted, along with the contingencies, to confirm that they elicit reward in the present setting. After placing a bet, feedback was delivered indicating whether the sum of money was won or lost (indicated by an upward or downward arrow respectively). Participants were instructed to maximise their winnings whilst minimising their losses, and that they would be paid their actual winnings at the end of the experiment. See Figure 3.1a for a schematic diagram of the trials. The experiment consisted of four blocks of 90 trials, with a five minute break after each. Of the 360 total trials, these were equally distributed into the three categories \( i.e. \) 120 reward, 120 punishment, 120 50-50 trials) and hence yielded six outcomes with the following frequencies. Reward condition: 96 x gain (‘expected gain’), 24 x loss (‘unexpected loss’); Punishment condition: 24 x gain (‘unexpected gain’), 96 x loss (‘expected loss’); 50-50 condition: 60 x gain, 60 x loss (‘50-50 gain’ and ‘50-50 loss’, respectively).

Unbeknownst to participants, everyone was reimbursed £10 regardless of performance (the average profit made when the paradigm was piloted).
Figure 3.1  

**a)** Schematic diagram of the experimental design. Participants learned the reward contingencies associated with the three cues (circle, square, triangle) and decide how much to bet (23, 14, 8, or 3 pence). One second later they received feedback indicating gain (up arrow) or loss (down arrow).  

**b)** Percentage of optimal choices by group, cue and block. Optimal choices were defined as either of the lower bet sizes (for the 20% reward condition) and either of the larger bet sizes (80% reward condition).
3.2.4 EEG ACQUISITION, PROCESSING AND ANALYSIS

Continuous EEG recording was obtained from 64 scalp electrodes using ActiveTwo system (BioSemi, Amsterdam, Netherlands) and Actiview® software (BioSemi, Netherlands). Pre-processing was performed off-line using Brain Electrical Source Analysis 5.2 (BESA; Gräfelfing, Germany). Data was re-referenced to the average of all channels and only trials from the second block onwards were analysed, to ensure that participants had learned the reward contingencies. Ocular artefact correction was performed on the entire file using a cut-off of ±150 μV using an established approach (Gratton et al., 1983). Any outstanding portions of the EEG file with excessive absolute amplitude (> 120 μV), voltage gradient between two neighbouring data points (> 75 μV) or low signal (< .01 μV). Epochs were defined as -500 ms to 1000 ms relative to the outcome feedback (vertical arrow indicating gain or loss), with baseline defined as the 100 ms prior to feedback. The data were then averaged using a high-pass filter of 0.1 Hz (forward phase shift). MATLAB® 6.5 (MathWorks, USA) was used to pick peaks for our ERPs of interest on averages (see below) filtered with a low-pass filter of 30 Hz. Participants with fewer than 18 trials in each condition were excluded.

The feedback-related negativity (FRN) was identified as a negative deflection in frontal electrodes occurring 250-300 ms post feedback. We measured the FRN as the peak-to-peak difference between the P2 (maximum in the window 150-230 ms) and N2 (minimum in the window 180-320 ms) using an algorithm similar to Holroyd et al (2003). Hence FRN voltage is always a positive value when there is an N2 deflection, and equals zero if there is no negative deflection (Holroyd et al., 2003; Wu & Zhou, 2009). This approach controls for the effect of the preceding P2 component on FRN measurement. Analyses were conducted on a frontocentral electrode cluster (F1, Fz, F2, FC1, FC2, and FCz). All participants had at least 16 trials per averaged condition and the mean number of trials for final analysis did not differ between hypomania groups (p=.788). Finally, we performed time-frequency (TF) analysis on the 50% condition because the outcomes under this
condition did not differ in monetary value (bet size). An epoch window of −400 to +1200 ms (relative to outcome stimulus) was selected to ensure that edge effects did not contaminate our windows of interest (confirmed by visual inspection; see Figure 3.4 and Supplementary Figure 3.3). TF analysis was performed using a complex Morlet wavelet transformation following Tallon-Baudry, Bertrand, Delpuech, & Peronnet (1999). Frequency bins were extracted to cover 1–49 Hz with spectral resolution of 1 Hz. Change in signal power, a measure of the magnitude (absolute value, in μV²) of the wavelet coefficients, was calculated for individual trials relative to a 200 ms pre-stimulus baseline.

3.2.5 STATISTICAL ANALYSIS

Task performance was quantified as the percentage of ‘optimal bets’ each participant made (i.e. one of the two larger bet sizes for reward trials, or one of the two smaller bet sizes for punishment trials). Participants that did not make these selections on at least 75% of trials in blocks 2, 3 and 4 were presumed to have not learned the reward contingencies and were excluded from further analyses. Proportions of choices were normalised through square-root transformation (Hoyle, 1973) before using parametric tests. Group differences in task performance and amplitudes on the electrophysiological measures were tested using repeated measures analysis of variance (ANOVA). To dissociate whether the processing of reward and punishment showed a specific relationship with hypomania, we adopted an established approach (Santesso et al., 2011) in which neural responses to reward and punishment were entered into the same step of a regression analysis with HPS score as the outcome variable. For the TF analysis, a repeated measures ANOVA was performed with factors valence (50% gain, 50% loss) and hypomania group. Into this ANOVA, average power (200 to 600 ms post-feedback in the theta band; 3 to 8 Hz) at the peak electrode (Fz) was entered for each condition.
3.2.6 ETHICAL STATEMENT

The study was approved by the University of Manchester research ethics committee. Informed written consent was obtained from all participants and the study was conducted in accordance with the Declaration of Helsinki.
3.3. Results

3.3.1 PERSONALITY AND SYMPTOM QUESTIONNAIRES

In the screening sample \((n=652; \ M = 19.9, \ SD = 8.01)\), HPS score positively correlated with the BAS subscales: drive \((r = 0.268, \ p< .001)\), reward responsiveness \((r = 0.21, \ p< 0.01)\), and fun-seeking \((r = 0.415, \ p< .001)\). These correlations were also present in the final sample recruited into the study \((n = 49, \ all \ p < .03)\) confirming similarities between our sample and clinical populations on these measures. Due to the DAS-24 cut-off, the final groups did not differ on level of depressive symptoms \([F(2, 44) = 2.02, \ p=.146]\), allowing us to selectively examine effects related to susceptibility to hypomania.

3.3.2 REWARD LEARNING TASK

Four participants (two Lo-hyp and two Hi-hyp) did not show evidence for learning the reward contingencies and were excluded. The final sample was therefore as follows: Lo-hyp \((n = 15)\), Mid-hyp \((n = 15)\), and Hi-hyp \((n = 15)\). All participants included in final analyses \((n = 45)\) were able to correctly identify the cues associated with low, medium and high probability of reward when debriefed after the task.

When normalised percentage of optimal bets was entered into a two-way ANOVA with factors: cue (2), block (4) and hypomania group (3), there emerged a main effect of block \([F(3,120) = 51.56, \ p< .001]\). Contrasts showed that the final sample made significantly more optimal bets in block 2 than in block 1 \((p< .001)\), confirming that learning had taken place (Figure 3.1b; mean bet sizes shown in Supplementary Figure 3.1). A block-group interaction \([F(6,120) = 3.23, \ p= .006]\) and a block-cue-group interaction \([F(6,120) = 2.58, \ p= .022]\) also emerged, with a main effect of group approaching significance \([F(2,40) = 2.59, \ p= .065]\). Contrasts for the block-group interaction confirmed that groups differed by optimal choices in block one, with confidence intervals for the marginal means indicating that Hi-hyp
participants made fewer optimal choices in block one than the other groups. The three-way interaction indicated that although Hi-hyp participants showed an increase in optimal choices between block one and two, this increase was steeper for the reward cue than penalty cue, relative to the other groups. A cue-group interaction failed to reach significance for blocks 2-4 \((p \geq .127)\), however, nor were the effect of group or remaining group interactions significant for these blocks \((p \geq .095)\), indicating that all groups reached the same levels of performance after block 1.
3.3.3 ERP-DOMAIN ANALYSIS

Figure 3.2. Average waveforms for all conditions by group. Hi-hyp show reduced (less negative; more gain-like) FRN compared to the other groups.

Consistent with the literature, the FRN deflection was modulated by both expectancy and outcome valence, and exhibited a frontocentral topography (Figure 3.3a). An ANOVA was carried out with two within-group factors, cued reward probability (20%, 50%, 80%) and outcome valence (gain, loss), and one between-groups factor: hypomania group (low, mid, high). Main effects of outcome \( [F(1,42)=40.58, p<.001] \), cue \( [F(2,42)=4.04, p<.03] \) and hypomania group emerged \( [F(2,42)=3.24, p<.03] \), as well as an interaction between outcome and hypomania group \( [F(2,42)=3.71, p<.04] \). There was a trend for a cue-outcome
interaction, but this did not reach significance ($p=.11$). Contrasts across all participants confirmed that the FRN was larger both for losses (relative to gains), and for unexpected outcomes (relative to expected: 20% vs. 80%; $p<.02$), confirming that the task was appropriate for measuring neural responsiveness to reward and punishment.

Figure 3.3. a) Topographical plot of the 50/50 difference wave (loss minus gain; 260-320 ms) shows typical frontocentral distribution of FRN. b) FRN magnitudes for reward (gain) and punishment (loss) across groups. The Lo-hyp group show similar FRN morphology to the Mid-hyp group for losses, but larger FRN for rewards (more loss-like) suggesting reduced reward sensitivity. FRN is reduced in the Hi-hyp group for both gains and losses, suggesting that both outcomes are subjectively experienced as more advantageous (i.e. more gain-like), relative to the other groups.
Between-groups contrasts for the main effect of hypomania group showed that the FRN was significantly reduced in the Hi-hyp relative to Lo-hyp group \((p< .02)\). This confirmed that the Hi-hyp group produced smaller FRNs across task conditions (Figure 3.3b). The outcome-by-group interaction was explored using separate ANOVAs for each group. Whilst a valence effect was significant in the Mid-hyp and Hi-hyp groups \((p\leq .001)\), a trend for reduction in this effect in the Lo-hyp group (Figure 3.3b) did not reach statistical significance in the Lo-hyp group \((p=.081)\). The main effect of group also remained significant \([F(1,43)= 4.02, p< .05]\) when a median split was used to divide the sample into two larger hypomania groups: low \((n=23)\) and high \((n=22)\).

When the 50% outcomes were entered into a repeated measures ANOVA (factors: outcome and group), main effects of outcome \([F(1,42)= 18.5, p< .001]\) and group \([F(1,42)= 2.71, p= .07]\) were again found to be significant or approach significance. To further specify the relationship between hypomania and motivational processing, FRN amplitudes for gain and loss outcomes were entered as predictors of HPS score in the same step of a regression analysis. Outcomes from the 50-50 condition were selected because of equivalent reward probability and magnitude. The resulting model accounted for 14% of the variance \([F(2,42)=3.424, p=.042]\). Whereas the gain FRN accounted for a significant amount of this variance \((p=.031)\), the loss FRN did not \((p=.749)\), suggesting that vulnerability to hypomania is particularly associated with neural sensitivity to reward outcomes.
3.3.4 TIME-FREQUENCY-DOMAIN ANALYSIS

A main effect of valence confirmed greater activity in the theta band for losses than gains \( F(1, 42) = 4.27, \ p = .045 \). A valence-group interaction also reached significance \( F(2, 42) = 6.04, \ p = .0049 \) and was explored by repeating the ANOVA separately for each group. The results showed that the valence effect was present in the Mid-hyp group \( F(1, 14) = 11.1, \ p = .005 \), but not in the Lo-hyp \( (p = .483) \) and Hi-hyp \( (p = .3) \) groups (Figure 3.4).

![Time-frequency spectra](image)

**Figure 3.4.** Time-frequency spectra of the difference in total power (current density; \( \mu V^2 \)) between outcomes (loss minus gain) under the 50-50 condition at Fz electrode. Both Lo-hyp and Hi-hyp groups show reduced valence effect in theta band compared to the Mid-hyp. Topography plots visualise this effect for each group (200 – 600 ms).
3.4. Discussion

In this study, we identify differences in the neural processing of motivational information in individuals vulnerable to hypomania. The results provide further electrophysiological evidence linking reward system alterations to risk-taking and impaired learning in BD.

The hypomania-prone (Hi-hyp) group showed impaired learning of the reward contingencies in the first block, making significantly fewer optimal choices than the other groups and accruing the lowest task earnings. These results are in agreement with decision-making and learning impairments reported in clinical populations (Chandler et al., 2009; Harmon-Jones et al., 2002). Poor performance in the punishment condition may also indicate greater risk-taking predilection (i.e. placing large bets in spite of the odds). Indeed BD is associated with risk-taking clinically (DSM-IV-TR; 2000), perhaps due to reduced sensitivity to modulatory psychological factors when making risky choices (see Chandler et al., 2009). Although we did not collect explicit measures of impulsivity in this study, susceptibility to hypomania was also associated with increased self-report of subjective reward responsiveness and novelty-seeking behaviours (BAS subscales; Carver & White, 1994).

Across all participants, FRN was modulated by outcome valence, appearing larger for losses regardless of how it was measured. This is consistent with previous findings and the view that this component represents the activity of a system evaluating the motivational significance of outcomes (e.g. Wu & Zhou, 2009). Greater theta power for losses (than gains) in the time-frequency analysis also replicates previous findings in healthy controls (HajiHosseini et al., 2012; Marco-Pallares et al., 2008).
In the main FRN analysis the low hypomania group showed reduced neural differentiation of gains and losses, relative to the mid hypomania group. This was driven by increased (i.e. more loss-like) FRN for gains, a finding that has also been reported in a sample exhibiting depressive symptoms (Foti & Hajcak, 2009), and is consistent with a reduced reward response. The hypomania-prone group showed reduced FRN for both outcomes, indicating a tendency to experience both outcomes as more favourable than the other groups (a positive evaluation bias). This effect was particularly pronounced for rewards, consistent with recent electrophysiological evidence of hypersensitivity to immediate reward during a delay discounting task (Mason et al., 2012) and clinical accounts that mania is related to reward hypersensitivity (Johnson, 2005a; Urosevic et al., 2008). In addition, the present finding of reduced FRN for losses fits with the reduced punishment sensitivity hypothesis of impulsivity disorders (Patterson & Newman, 1993) and may help to explain the detrimental behaviours seen clinically in BD, such as unrestrained spending sprees, substance use, unprotected sex and impulsive suicide attempts (DSM-IV-TR; 2000).

Because bet size varied systematically for two of three cues (participants chose smaller bets in the 20% compared to 80% reward condition, confirming learning of the contingencies), FRN differences may also reflect magnitude. Indeed some studies have found that FRN is sensitive to magnitude, particularly for gains (e.g. Cohen et al., 2007), whereas others find it is not (e.g. Hajcak et al., 2006), so we cannot confidently conclude whether the FRN reduction observed in the hypomania-prone group is driven more by expectancy or magnitude. However, group differences in outcomes following the 50% cue, which were equivalent with respect to magnitude, suggest that it is reward expectation that deviates in hypomania. This fits with findings that mania is associated with impaired orbitofrontal representation of expected value - and not magnitude (Bermpohl et al., 2010), and with clinical accounts of grossly increased confidence that goals will be attainable and have favourable outcomes (Johnson, 2005b).
Our results are also consistent with models of risk-taking as arising from an imbalance between striatal activation and ACC control (Ernst et al., 2006; Santesso et al., 2011). Indeed the ACC, a major generator of the FRN (Gehring & Willoughby, 2002), is implicated in both affective processing and performance monitoring (Oliveira et al., 2007) and shows abnormal activation in depression (Pizzagalli, 2010) and mania (Blumberg et al., 2000). When outcome-locked theta band power was compared across groups, both the low- and high-hypomania-prone groups showed reduced differentiation between gains and losses, whereas this effect was not captured in the ERP analysis for the hypomania-prone group. It has been suggested that the theta activity underlying FRN and a related component (the error-related negativity) may reflect a more widespread network than solely ACC (Luu et al., 2003). Hence susceptibility to hypomania may be associated with abnormalities in additional systems implicated in motivational processing and action regulation.

Under reinforcement learning accounts of the FRN, the present findings indicate altered prediction error signalling in groups exhibiting either extremely low or high hypomania traits. This is consistent with neuroimaging evidence of altered striatal prediction error signalling in clinical (Abler et al., 2007c) and analogue (O’Sullivan et al., 2011) samples of mania. In hypomania-prone individuals, reduced FRN for gains and losses implies increased (more positive) prediction error activity (see Holroyd et al., 2008). A similar evaluation bias has been reported in other clinical populations exhibiting impulsive and risky behaviours (e.g. Parkinson’s with impulse control disorders; Voon et al., 2010) and in healthy individuals following administration of a DA-enhancing agent (Pessiglione et al., 2006). In both of these cases it has been suggested that increased positive prediction errors may induce a persistent “better than expected” evaluation, leading to a greater impact of rewards and a reduced impact of punishment (see Voon et al., 2010). This may drive an expectancy bias towards positive outcomes, as we have demonstrated in a separate neuroimaging study of reward learning in hypomania (O’Sullivan et al., 2011). Hence learning deficits and repeated risk-taking may both arise from
inappropriate reinforcement learning signals that fail to update future expectations. This pervasive “rose-tinted” evaluatory bias parallels neuroimaging evidence that trait unrealistic optimism is maintained by a selective failure to update future estimations in the light of undesirable information (Sharot et al., 2011). An alternative interpretation of group differences in the FRN when viewed as indexing a prediction error (Holroyd et al., 2008), is that they are driven by differences in estimation of the expected value of upcoming outcomes rather than evaluation (post-outcome). The two stages of processing are inextricably linked (prediction error updates future expected value) and so cannot be differentiated by the current design. Indeed this represents a conceptual limitation of FRN studies in general.

A strength of this study is that it examined the relationship between hypomaniac symptoms and motivational processing whilst avoiding confounds from depressive symptoms, medication, hospitalisation or comorbidity. However, an intrinsic limitation of this approach is that the sample may not fully represent the range of psychopathology seen in clinical populations (although see Mason et al., 2012, which found a neural bias for immediate rewards in a hypomania-prone sample where depressive symptoms were not excluded). Additionally, whilst we cannot rule out that generalised reduction of the FRN in the hypomania-prone group may be due to reduced task engagement, the elevated traits of drive and responsiveness to reward exhibited by this population (Johnson, 2005b) argues against this interpretation. Our paradigm used free choice to examine risk-taking and, as such, was unable to orthogonalise reward probability and magnitude in all conditions. Also, a relatively low number of unexpected outcome trials were obtained (because they are intrinsically rare in realistic probabilistic tasks). A recent paper advised 20 trials for robust measurement of FRN (Marco-Pallares et al., 2011) - 2 more than in the present study. However, the pattern of results did not differ for the 50-50 gain and loss outcomes, which had the same probability and magnitude as each other, and an ample number of trials to satisfy this criterion. Finally, the positivity preceding the FRN showed some task modulation
In conclusion, we report differences in the neural processing of motivational information in individuals vulnerable to hypomania. The present findings are consistent with accounts that BD is associated with reward dysregulation (Johnson, 2005b; Urosevic et al., 2008) and highlight a common neural mechanism contributing to risk-taking and impaired reward learning. A positive evaluation bias may also explain the elevated motivation, confidence, and goal-striving associated with mania (Johnson, 2005b). In addition, our findings here and elsewhere (Mason et al., 2012; O’Sullivan et al., 2011) demonstrate biological vulnerability markers for BD. These may ultimately lead to more quantifiable risk estimates (Phillips & Vieta, 2007), facilitating early detection and intervention. Our data suggest that appraisal and reflective consolidation of risky events may be a helpful therapeutic approach.
3.5 Supplementary Material

Supplementary Figure 3.1. Mean bet size shown by block and group. Participants alter their bet size after learning the 20% and 80% reward contingencies. Hi-hyp are slower to adjust their bet size in the 20% reward (punishment) condition, consistent with slower learning.
Supplementary Figure 3.2. Frequency spectra showing total power for 50% condition by outcome and group at electrode Fz. All groups show greater theta power (current density, μV^2; vertical colour bar) for losses than gains. Topography plots are provided above their corresponding gain spectra and below for loss spectra (same horizontal colour bar). A frontocentral distribution of this theta effect is demonstrated, consistent with the FRN ERP topography.
CHAPTER 4: I WANT IT NOW! NEURAL CORRELATES OF HYPERSENSITIVITY TO IMMEDIATE REWARD IN HYPOMANIA*

* This chapter was published in Biological Psychiatry:


The results were also presented at International Review of Bipolar Disorders (IRBD; Rome, 10th June 2011) and International Conference on Cognitive Neuroscience (Mallorca, 26th September 2011).
Abstract

Background:
Hypomania is associated with impulsive decision-making and risk-taking, characteristics which may arise from hypersensitivity to reward. To date, the neural dynamics underlying inter-temporal reward processing have neither been characterised clinically nor in the general population. Taking vulnerability to hypomania as a surrogate model of impulsivity, we utilised event-related potentials to study the neural mechanisms of delay discounting.

Methods:
In the first experiment, 32 participants completed an established Two Choice Impulsivity Paradigm in which free choice between immediate and delayed rewards was used to quantify impulsivity behaviourally. In the second experiment, electroencephalography was recorded while 32 separately recruited participants completed a speeded response task involving gains and losses of monetary incentives to be paid at three different delays after the experiment.

Results:
In the first experiment the hypomania-prone group made significantly more immediate choices than the control group. In the second experiment, the hypomania-prone group evidenced greater differentiation between delayed and immediate outcomes in early, attention sensitive (N1) and later, reward sensitive (FRN) components. Proneness to hypomania was also associated with greater N1 amplitude to rewards per se.

Conclusions:
These results indicate steeper delay discounting in hypomania at multiple stages of information processing. The N1 modulation by valence and delay suggests an attentional bias to immediate rewards, which may drive subsequent cognitive appraisal of outcomes (FRN). These results highlight the early influence of attention on reward processing, and provide support for reward dysregulation accounts of bipolar disorder. Potential implications for mindfulness training and other therapeutic interventions are highlighted.
4.1. Introduction

Trait impulsivity is a prominent feature of numerous psychiatric disorders, including alcoholism (Granö et al., 2004), substance dependence (Rogers et al., 2010), bipolar disorder (Swann et al., 2009), attention-deficit hyperactivity disorder (Scheres et al., 2010), pathological gambling (Rogers et al., 2010) and psychopathy (Vitacco & Rogers, 2001). Furthermore, higher impulsivity has also been linked to greater morbidity in many of these disorders, as well as higher rates of relapse in substance users, pathological gamblers and individuals with bipolar disorder (Everitt et al., 2008; Noël et al., 2007; Rogers et al., 2010). Impulsive traits are also linked to habitual relapse into crime (Miner, 2002), particularly aggression (Barratt et al., 1997), violence (Meyer-Lindenberg et al., 2006) and rape (Prentky et al., 1995). The development of interventions that prevent transition into psychopathology and recidivism therefore require a better understanding of the psycho-physiological processes that underpin trait impulsivity.

4.1.1. HYPERSENSITIVITY TO REWARD MAY MEDIATE IMPULSIVITY

Bipolar disorder (BD) is associated with repeated risk-taking and impulsive behaviours with a high potential for damaging consequences, including spending sprees, dubious financial decisions, drinking to excess, substance use, unsafe sex, and suicide attempts (American Psychiatric Association[DSM-IV-TR]; 2000). Whilst risky behaviours are particularly prevalent during manic episodes, impulsivity is also elevated in remission and depressive episodes, highlighting relative independence from clinical state in BD (Swann et al., 2003). Impulsive decision-making may arise from hyperactivity in the behavioural approach system (BAS; Alloy et al., 2009; Gray, 1991) which facilitates approach behaviour, particularly towards sources of reward. Furthermore, our recent electrophysiological (Mason
et al., in press) and neuroimaging (O'Sullivan et al., in press) studies provide support for reward hypersensitivity in individuals vulnerable to mania, as does a study of patients experiencing mania (Abler et al., 2007c).

4.1.2. TEMPORAL DISCOUNTING AS A MEASURE OF IMPULSIVITY

A robust measure of impulsivity is the value individuals ascribe to immediate gratification, relative to delayed outcomes. Delay discounting refers to the subjective devaluation of outcomes (i.e. rewards or penalties) as a function of the duration between a goal-directed action and experiencing the consequence (e.g. Ainslie, 1975). Greater discounting is associated with personality traits of impulsivity (Kirby et al., 1999), extraversion and sensation-seeking (Richards et al., 1999), as well as a wide range of disorders associated with impulsivity and reward-seeking, including attention-deficit hyperactivity disorder (ADHD), alcoholism, substance use disorder and pathological gambling (Petry, 2001a, 2001b; Scheres et al., 2010).

Neural correlates of temporal discounting include greater striatal activity as an indicator of preference for immediate rewards (Hariri et al., 2006) and reduced activity in parietal and dorsolateral prefrontal cortices in response to delayed rewards (Ballard & Knutson, 2009). Clinically, abnormalities in these neural substrates have also been reported in the context of bias toward immediate reward. In ADHD, for instance, there is evidence that delay aversion is related to abnormal striatal activity during processing of delayed rewards (see Plichta et al., 2009). Temporal discounting has been considerably less well characterised in BD, although impulsivity has been broadly established on the Iowa Gambling Task (Adida et al., 2008) and the delayed reward task (DRT; Cherek & Lane, 1999). To date the neural correlates of immediate reward bias have not been demonstrated in this population, however. Furthermore, delay discounting has not been characterised in the general population using event-related potentials (ERPs).
4.1.3. BRAIN POTENTIALS FOR CHARACTERISING IMPULSIVITY

The N1 is an early sensory component involved in selective attention (Luck et al., 2000), particularly for emotionally salient stimuli (Schupp et al., 2007). The N1 is potentiated by visual features that are congruent with internal representations specified *a priori* in top-down processing (Barcelo et al., 2000), and may be involved in facilitating detection of particularly salient events using these perceptual templates. Positive emotional words elicit larger N1 amplitudes than unpleasant ones (Bernat et al., 2001), as do stimuli with high subjective saliency, such as pain-related words in chronic pain patients (Flor et al., 1997). The feedback-related negativity (FRN) is involved in early outcome evaluation, showing larger amplitude for unfavourable outcomes relative to advantageous ones (e.g. Hajcak et al., 2006). FRN has been argued to reflect reward signals originating from mesencephalon (Holroyd et al., 2008) and is sensitive to trait impulsivity in reward contexts (Onoda et al., 2010). Moreover, FRN is found to be abnormal in clinical disorders characterised by impulsivity (e.g. pathological gambling; Hewig et al., 2010), in addition to hypomania-prone populations (Mason et al., in press). The P300 component also encodes motivational significance (Yeung & Sanfey, 2004), and is sensitive to trait positive affect (Yasuda et al., 2004) and individual differences in reward sensitivity (Van den Berg et al., in press). Whilst FRN occurs relatively early, P300 occurs later in the EEG and may reflect higher cognitive processes.

Here we examined the relationship between impulsivity and the motivational processing of delayed outcomes, taking a sample vulnerable to hypomania as a model of impulsivity. This approach avoided confounding factors of clinical state, hospitalisation, task disengagement, and psychotropic medication. This approach is predicated on evidence that (hypo)manic symptoms lie on a spectrum extending
into the general population (Akiskal et al., 2000; Angst & Gamma, 2002) and that psychometric measures reliably identify people meeting the criteria for BD in the general population (Eckblad & Chapman, 1986) and can predict (hypo)mania at thirteen year follow-up (Kwapil et al., 2000).

Given the evidence for an association between steeper temporal discounting and other disorders related to impulsivity, it was predicted that hypomanic traits would be associated with an immediacy bias for rewards. In experiment one, we predicted a greater proportion of choices for small immediate rewards in this group (relative to controls). We postulated that this would be driven by a greater neural differentiation between immediate and delayed rewards. Hence, in experiment two we firstly predicted increased attention to and hedonic impact of immediate rewards (increased N1 and P300, decreased FRN; see above), or the reverse for delayed rewards, in all participants. Second, we predicted that would be more pronounced in hypomania-prone individuals than the controls. We additionally sought to determine at which stage(s) of processing were group differences manifested (e.g. early attentional versus later cognitive systems, as indexed by N1, FRN and P300). This would be informative in identifying factors conferring susceptibility to hypomania and other disorders characterised by impulsive decision-making.
4.2. Methods

For comparable signal-to-noise ratios for between-group ERP analyses, we ensured that both groups had equal numbers of trials for each condition of our main task (i.e. the Fixed Delays task; see 2.2) by not allowing a free-choice between delays. Consequently a separate sample of participants completed an established free-choice task (see 2.1) to confirm that hypomania-proneness is a representative model of impulsivity. Both tasks were approved by the local university research ethics committee and were conducted in accordance with these guidelines and the Declaration of Helsinki.

4.2.1. TWO CHOICE IMPULSIVITY PARADIGM (TCIP)

Participants: 32 participants were selected from a larger pool of 468 Bangor University students that were screened on HPS and Dysfunctional Attitudes Scale (DAS-24; Lam et al., 2004) through completion of an online survey. Low (lower quartile; \( M = 2.13, SD = 1.50 \)) and high (upper quartile; \( M = 16.31, SD = 1.66 \)) hypomania-prone groups were defined based on scores on the HPS short version (HPS-20; Meads & Bentall, 2008). Groups were matched on DAS-24 and therefore did not differ significantly on this measure \([t (30) = .19, p = .849]\).

Stimuli and Task: The TCIP (Dougherty et al., 2005) assesses tolerance for delayed rewards by presenting participants with a binary choice between two shapes, associated with different delay–reward contingencies. One option was associated with a shorter delay but smaller reward (5 points after 5 seconds) than the other option (15 points after 15 seconds). Participants were informed the amount of monetary reinforcement at the end of the task would be proportional to the number of points accrued in the task. After selection the applicable delay is experienced before the reward was delivered and the next trial began. Participants completed 10 training trials and a single block of 50 test trials.
Statistical Analysis: Three independent samples t-tests were separately carried out to compare the total number of immediate choices (1) and the maximum number of consecutive immediate choices (2) and delayed choices (3) between groups.

4.2.2. FIXED DELAYS TASK

Participants: 32 right-handed participants (\(M_{\text{age}} = 20.0\) years, \(SD = 2.29\)) without past or current diagnosis of a psychiatric or neurological disorder, and not receiving psychotropic medication took part in the study. They were recruited from a larger pool of 532 students of the University of Manchester that had completed an online battery of self-report measures (see below).

Self-report measures: Participants completed the 48-item Hypomanic Personality Scale (HPS; Eckblad & Chapman, 1986) and 21-item Depression, Anxiety and Stress Scales (DASS-21; Henry & Crawford, 2005). Whilst the HPS robustly predicts current symptoms (Eckblad & Chapman, 1986) and vulnerability to bipolar disorder (Kwapil et al., 2000), the DASS-21 is regarded as a state measure of depression, anxiety and stress (Henry & Crawford, 2005). We used a median-split to define two groups: high hypomania (Hi-hyp; \(n = 16\)) and low hypomania (Lo-hyp; \(n = 16\)). All groups showed a near-equal distribution of male and female participants and did not differ significantly in age (see Table 4.1). DASS-21 score was significantly higher in the Hi-hyp group (Table 4.1), consistent with the evidence that HPS score identifies individuals with current symptoms of, or vulnerability to, BD (Eckblad & Chapman, 1986; Kwapil et al., 2000). DASS-21 was therefore controlled for in statistical analyses (see below). Two participants did not have 18 trials in all conditions after artefact rejection and were not included in the ERP analyses, leaving 30 participants (15 in each group).
Table 4.1. Demographics and self-report measures. Significantly greater psychometric risk for hypomania and state distress in Hi-hyp group. HPS = Hypomanic Personality Scale, DASS-21 = Depression and Anxiety Stress Scale.

<table>
<thead>
<tr>
<th></th>
<th>Lo-hyp</th>
<th>Hi-hyp</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>19.75 (1.29)</td>
<td>20.25 (3.00)</td>
<td>.545</td>
</tr>
<tr>
<td>Sex (no of males)</td>
<td>7</td>
<td>8</td>
<td>.723</td>
</tr>
<tr>
<td>HPS</td>
<td>12.3 (5.3)</td>
<td>27.8 (5.78)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>DASS-21</td>
<td>14.5 (10.5)</td>
<td>31.9 (18.6)</td>
<td>.003</td>
</tr>
<tr>
<td>Depression</td>
<td>5.00 (3.43)</td>
<td>11.5 (9.73)</td>
<td>.017</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3.25 (2.62)</td>
<td>7.50 (4.53)</td>
<td>.003</td>
</tr>
<tr>
<td>Stress</td>
<td>6.25 (6.02)</td>
<td>12.88 (7.15)</td>
<td>.008</td>
</tr>
</tbody>
</table>

Stimuli and Task: Participants completed a speeded response task. Each trial began with a 500 ms cue signifying the valence (reward: green, penalty: red background) and the delay (alarm clock: no delay, hour glass: one week, calendar: one month) associated with the trial. This was followed by a ‘Go’ cue, prompting participants to respond with either a left or right mouse click (see below) within 500 ms. In the reward condition, participants could gain 5 pence with a correct and timely response, whereas in the penalty condition, they could minimise a large loss of 25 pence and incur a small 5 pence penalty. After 750 ms participants heard a brief tone signifying impending feedback, followed by pictorial representation of the outcome (a bank note; see Figure 4.1) for 2000 ms. The bank note was ringed in green (reward) or red (penalty) and the applicable delay was printed in text (‘Now’, ...
‘1 week’, or ‘1 month). Note that unlike the first experiment, there was no free choice between the delays.

Participants were informed that there were three cumulative totals (‘time pots’), each to be paid at one of three different time points or delays: immediately after the experiment, after one week, or after one month. Both the delay and valence associated with each trial was displayed at the beginning and at the end of the trial. Across six blocks a total of 360 trials were drawn equally and pseudorandomly from each condition. To ensure that outcomes were not fully predictable, a minority of the trials (20%; 12 in each condition) resulted in omission of the reward or penalty anticipated. For statistical reasons these were not analysed, leaving 48 valid trials in each of the six conditions.

After the task, participants were debriefed and immediately reimbursed £10 regardless of performance or which time pot was maximal. The study lasted approximately one hour including breaks. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and University of Manchester local research ethics committee.

![Figure 4.1. Schematic showing stimuli and time course of a trial. The cue was presented for 500 ms and indicated outcome valence (reward, penalty) and the temporal slot (now, one week, one month) applicable. Participants had to provide a rapid correct response to the GO stimulus to obtain reward and minimise penalty. Feedback was delivered after an anticipatory tone and showed a £5 note on green (reward) or red (penalty) background with the applicable delay written underneath. ITI, inter-trial interval.](image-url)
**EEG acquisition, processing and analysis:** We recorded EEG using a 64-electrode ActiveTwo system (BioSemi, Amsterdam, Netherlands) with Actiview® acquisition software (BioSemi, Netherlands). In the BioSemi system, the classical “ground” and “reference” electrodes are replaced with an active and passive electrode, forming a feedback loop which drives the average potential of the subject (the Common Mode voltage) as close as possible to the ADC reference voltage in the AD-box (the ADC reference can be considered as the amplifier “zero”). A detailed description of the BioSemi electrode referencing and grounding convention can be found at http://www.biosemi.com/faq/cms&drl.htm. Brain Electrical Source Analysis 5.2 (BESA; Gräfelfing, Germany) was used for data pre-processing and averaging. Data were re-referenced to an average reference off-line. Vertical and horizontal eye movements were identified using a criterion of ±100 μV, and a high-pass filter of 0.2 Hz (forward phase shift) was used to remove drifts. Epochs were defined as -200 ms to 1000 ms relative to the outcome feedback, with baseline defined as the 200 ms preceding feedback. Averages for participants with fewer than 20 trials (per condition) were not analysed. MATLAB® 6.5 (MathWorks, USA) was used to extract mean amplitudes of ERPs of interest (see below) from individual averages filtered with a low-pass filter of 30 Hz. The N1 peak was extracted in the 170-210 ms latency window from parieto-occipital electrodes (O1, O2, PO7, PO8, P7, P8). The FRN peak was defined as occurring 250-310 ms in frontocentral electrodes (Fz, FC1, FC2, FCz, C1, C2, Cz). P300 was extracted between 300-550 ms in centro-parietal electrodes (CP1, CP2, CPz, P1, P2, Pz).

**Statistical Analysis:** Repeated ANOVA was used to test within- and between-group differences in reaction times and electrophysiological measures across conditions. There were two within-groups factors: valence (reward, penalty), delay (no delay, one week, one month) and one between-groups factor, hypomania group (low, high). Note that the reaction time data correspond to the cue, whereas the ERP data correspond to the outcome. In addition, total score on a 21-item Depression Anxiety Stress Scale (DASS-21) was included as a covariate to control for state distress.
4.3. Results

4.3.1. EXPERIMENT 1: TWO-CHOICE IMPULSIVITY PARADIGM

The hypomania prone (Hi-hyp) group made significantly more immediate choices overall, relative to the control (Lo-hyp) group \([t(30) = 2.34, p = .026]\); see Table 4.2. The maximum number of consecutive delayed choices was also significantly lower for the Hi-hyp participants \([t(30) = 2.84, p = .008]\), with a trend also indicating longer consecutive runs of choosing the immediate outcome \((p = .075)\).

Table 4.2. The hypomania-prone group made significantly more immediate choices overall, as well as more consecutive immediate choices (and fewer consecutive delayed choices) than the low-hypomania group.

<table>
<thead>
<tr>
<th></th>
<th>Hypomania-prone</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of immediate choices</td>
<td>19.25 16.66</td>
<td>8.00 9.69</td>
</tr>
<tr>
<td>Max. no. of consecutive immediate choices</td>
<td>9.06 14.66</td>
<td>2.25 1.84</td>
</tr>
<tr>
<td>Max. no. of consecutive delayed choices</td>
<td>14.62 14.35</td>
<td>29.87 15.99</td>
</tr>
</tbody>
</table>

4.3.2. EXPERIMENT 2: FIXED DELAYS TASK

4.3.2.1. Self-report and Behavioural Results

Since groups differed on DASS-21 scores (Table 4.1), this measure was included as a covariate in subsequent analyses to control for state-related differences in distress. On the task, reaction times following the cue were modulated by valence \((p = .003)\) and delay \((p = .03)\), with contrasts confirming that participants responded faster for rewards than penalties and for immediate outcomes,
compared to those delayed by 1 week \((p = .043)\) or 1 month \((p = .03)\). There were no group differences \((p’s \geq .121; \text{Table 4.3})\).

**Table 4.3.** Across groups, reaction times were faster for reward trials than penalty trials \((p<.01)\), and for immediate outcomes relative to delayed outcomes \((p<.05)\). There were no differences between groups \((p \geq .121)\).

<table>
<thead>
<tr>
<th></th>
<th>Lo-hyp</th>
<th>Hi-hyp</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reward</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Now</td>
<td>231 (48.0)</td>
<td>223 (47.7)</td>
</tr>
<tr>
<td>1 week</td>
<td>246 (54.4)</td>
<td>234 (58.9)</td>
</tr>
<tr>
<td>1 month</td>
<td>253 (50.5)</td>
<td>227 (52.5)</td>
</tr>
<tr>
<td><strong>Penalty</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Now</td>
<td>248 (62.9)</td>
<td>243 (65.0)</td>
</tr>
<tr>
<td>1 week</td>
<td>252 (49.0)</td>
<td>240 (43.5)</td>
</tr>
<tr>
<td>1 month</td>
<td>261 (62.0)</td>
<td>242 (45.8)</td>
</tr>
</tbody>
</table>
4.3.2.2. Electrophysiological Results

N1:
There were effects of valence \([F(1,28) = 7.82, p=.01]\) and delay \([F(2,56) = 17.47, p<.001]\). A larger N1 was observed for rewards relative to penalties, and for immediate outcomes relative to outcomes delayed by 1 week or 1 month \((p’s< .001; \text{Figure 4.2})\). An interaction between hypomania group and delay was observed \([F(2,56) = 4.78, p=.012]\), with the Hi-hyp participants displaying a greater amplitude reduction between immediate outcomes and those delayed by 1 week \((p=.077)\) or 1 month \((p=.006)\), relative to the Lo-hyp participants (see Figure 4.4). A further interaction between hypomania group and valence also reached significance \([F(1,28) = 5.28, p=.03]\), such that the increase in N1 amplitude for rewards (relative to penalties) was greater in the Hi-hyp than the Lo-hyp participants. Finally, a three-way interaction between valence, delay and hypomania group approached significance \([F(1,27) = 3.401, p=.058]\), and was significant when depressive symptoms were entered as a covariate \((p=.045)\). The delay effect differed between hypomania groups in the reward and penalty conditions, such that the Hi-hyp group showed especially pronounced discounting of rewards, but not penalties, relative to the Lo-hyp group \((p=.021)\).
Figure 4.2. N1 indexes temporal discounting. Waveforms collapsed across parieto-occipital electrodes (circled) show greater amplitude for immediate, relative to delayed outcomes. This delay effect is more pronounced in the hypomania-prone group (Hi-hyp) than controls (Lo-hyp), particularly for rewards. Topography of outcomes collapsed across valence and delay is shown for 170-210 ms window extracted.

Feedback-related negativity (FRN):
A main effect of delay emerged \( F(2,56) = 25.59, \ p<.001 \), with contrasts demonstrating that delayed outcomes (1 week, 1 month) elicited a larger (i.e. more negative) FRN than immediate ones \( (p's\leq.001; \ \text{Figure 4.3}) \). A significant interaction was observed between delay and hypomania group \( F(2,56) = 4.95, \ p=.011 \), with contrasts showing that the greater negative deflection for delayed
outcomes (relative to immediate outcomes), was greater in the Hi-hyp than the Lo-hyp group (1 week: \( p = .006 \); 1 month: \( p = .09 \); see Figure 4.4). These effects remained significant when controlling for DASS-21 score, which also interacted with valence \( [F(1,27) = 4.56, p = .043] \) indicating that depressive symptoms may have masked a main effect of valence.

Figure 4.3. The delay associated with motivational feedback is encoded in the human electroencephalograph. Waveforms from fronto-central electrodes to show feedback-related negativity (FRN) collapsed across valence, and topography collapsed across valence and delay.
P300:

P300 was also sensitive to delay \([F(2,5) = 4.96, p=.01]\), with significantly larger amplitudes for immediate outcomes relative to those delayed by one month \((p=.006)\). No group interactions reached significance regardless of covarying DASS-21 score \((p’s ≥ .128)\).

![Graph](image-url)

**Figure 4.4.** Steeper temporal discounting in individuals prone to hypomania. Although both groups show an immediacy preference, this effect is significantly more pronounced in the hypomania-prone (Hi-hyp) group. N1 amplitude reduction for delayed rewards (relative to immediate rewards) is significantly greater in the Hi-hyp group \((p<.05)\). Similarly, FRN amplitude reduction for delayed relative to immediate outcomes (collapsed across valence) was more pronounced in this group \((p<.05)\).
*Regression analyses:*

Regression analyses were conducted to determine whether HPS scores were linearly related to the neural measures of temporal discounting for rewards and penalties (separately). The dependent variable was the amplitude difference between immediate outcomes and outcomes delayed by 1 week (which contrasts identified was driving the delay-by-group interactions already reported). Significant effects were found for N1, for which HPS scores predicted temporal discounting of rewards [standardised $b = .531$, $t(28) = 3.32$, $p = .003$], but not penalties ($p = .639$). Non-planning scores on the BIS-11 also predicted discounting of rewards only [standardised $b = .489$, $t(24) = 2.92$, $p = .007$]. When HPS and BIS non-planning were entered together, the resulting model explained 41.7% of the variance in the temporal discounting of rewards.
4.4. Discussion

In the present study, we identify neural correlates of increased impulsivity in a task emphasising the temporal aspect of motivational feedback. The results provide evidence that vulnerability to mania is associated with a propensity to discount delayed outcomes, and highlight electrophysiological markers of this immediacy bias. The present findings also demonstrate the potential involvement of early attentional mechanisms in mediating temporal discounting and clinical impulsivity.

In the Two-Choice Impulsivity task, the hypomania-prone group showed greater impulsivity, choosing the immediate small reward significantly more than the control group. This finding mirrors behavioural reports in clinical samples of mania (Strakowski et al., 2010; Strakowski et al., 2009) and other impulsivity disorders (Petry, 2001a, 2001b; Scheres et al., 2010), validating the use of our sample as a surrogate model of impulsivity.

The results of the fixed delays experiment are the first to shed light on the neural mechanisms of this immediacy bias. The N1 results demonstrate that both outcome valence and delay are encoded in early neural processing. The N1 component is associated with allocating attentional resources (e.g. Luck et al., 2000) and appears larger for salient (Flor et al., 1997) and pleasant (as opposed to unpleasant) emotional stimuli (Bernat et al., 2001). Hence, the present findings of larger amplitudes for rewards and immediate outcomes plausibly represent preference for these outcomes. This interpretation is further corroborated by the FRN and P300 findings; whilst FRN appears larger for aversive outcomes (e.g. Hajcak et al., 2006) and was more pronounced for delays in the present study, P300 appeared larger for favourable outcomes (e.g. Nieuwenhuis et al., 2004) and was maximal for immediate outcomes. These findings are consistent with existent models of delay discounting (e.g. Ainslie, 1975).
Group comparisons of N1 and FRN indicated an exaggerated preference for immediate outcomes in individuals prone to hypomania. For this group, FRN amplitude indicated substantial discounting of one week delayed outcomes (but no further discounting of one month delayed outcomes), whereas in the low hypomania group only the one month delayed outcomes differed significantly from immediate outcomes in FRN amplitude. This provides support for a steeper delay-discounting function in individuals prone to hypomania.

Reward dysregulation accounts of BD (Alloy et al., 2009) contend that both impulsivity and risk-taking stem from hypersensitivity to BAS-relevant events (i.e. rewards). Both clinical and analogue neuroimaging studies of reward processing implicate mesocortical abnormalities in (hypo)mania (Abler et al., 2007b; O'Sullivan et al., in press). Another study from our group demonstrated that these reward abnormalities are also reflected in the FRN (Mason et al., in press), a putative marker for midbrain activity (see Holroyd et al., 2008). The present delay findings extend this view in two key ways. First, they indicate that impulsive and risky behaviour may be particularly related to hypersensitivity to immediate gratification, rather than to sources of reward per se. This carries important implications for therapeutic intervention. Second, increased reward sensitivity in very early neural processing (N1) points to the involvement of additional mechanisms that precede the involvement of the mesocorticollimbic pathway reflected later, in the FRN component (see Holroyd et al., 2008).

Indeed the N1 component is associated with attention (Hillyard et al., 1995) and is subjected to top-down shaping from prefrontal control structures, particularly dorsolateral prefrontal cortex (Barcelo et al., 2000). Sensitivity to immediate reward may be primarily driven by attentional mechanisms. In this way, top-down prefrontal control could constrain later processing in midbrain reward networks, at least for fully predicted outcomes that do not require behavioural adjustment. Future work will be needed to clarify the interaction between attentional and
reward systems. Prefrontal abnormalities are well documented in mania (Chen et al., 2011) and other impulsivity disorders such as ADHD (Zang et al., 2005), alcoholism (Moselhy et al., 2001), and psychopathy (Raine et al., 2000). Furthermore prefrontal lesions precipitate impulsive and risky decision-making in previously non-impulsive persons (Bechara et al., 2000), as does temporary disruption through TMS (Knoch et al., 2006), warranting further research into the potential utility of the N1 as a marker for impulsivity.

In addition to the delay findings, exaggerated N1 enhancement for rewarding (relative to non-rewarding) outcomes in hypomanics may indicate a greater subjective value of rewards, devaluation of penalties, or both. Whilst the first interpretation is consistent with the view that impulsivity and risk-taking in BD result from hypersensitivity to reward (Alloy et al., 2009), the second interpretation fits with other accounts that reduced punishment sensitivity is causally related to impulsivity (Moeller et al., 2001). In contexts involving risky decisions, it could be speculated that an overvaluation of potential reward(s) may combine with a blunting of the dangers or costs, to increase risky and impulsive choice.

FRN was not sensitive to valence in the present study, contrary to our predictions and extant studies showing greater FRN for unfavourable outcomes (e.g. Hajcak et al., 2006). However, this is the first study to vary temporal (as well as valence) feedback characteristics, and the FRN may encode the most salient aspect of feedback (Nieuwenhuis et al., 2004). The outcomes analysed in the present study were highly expected, further emphasising the delay aspect of feedback and thereby potentially reducing the effect of valence. Indeed, other studies have reported comparable FRN amplitudes for gains and losses that are small and expected (e.g. Figure 2b in Cohen et al., 2007; Figure 2 in Wu & Zhou, 2009). Finally, when both performance (correct/incorrect) and utilitarian (gain/loss) information is available FRN is not larger for losses that are also correct
(Nieuwenhuis et al., 2004). This is the case for the correct-loss trials analysed in the present study, which were preferable to the larger loss imposed for incorrect responses. In this way FRN may be representing the evaluation of outcomes relative to available alternatives, rather than objective value (Nieuwenhuis et al., 2004).

Another possibility is that a valence effect was obscured by depressive symptoms (as indicated by the valence by DASS-21 interaction), which have previously been associated with a reduced difference between FRN elicited by rewarding and non-rewarding feedback (Foti & Hajcak, 2009). Because depressive vulnerability is a key feature of clinical populations of BD, this was not an exclusion criterion in the present study. Finally, the relatively small P300 amplitudes obtained here may also be due to high outcome certainty, and this could have reduced sensitivity to group differences in this component. Future studies manipulating expectancy will be needed to further elucidate the processing of valence and delay information.

In summary, these results show that processing of the temporal characteristics of reward is reflected in both early and late components of the EEG, and provide neural evidence of steeper delay discounting in a non-clinical sample of hypomania. The results indicate two mechanisms of impulsivity and risk-taking: 1) hypersensitivity to reward and/or devaluation of penalties and 2) an immediacy bias, particularly for rewards. Group differences were most pronounced in early processing, suggesting that deficits exist in reflexive or attentional systems, with less evidence for impairment of reflective or higher cognitive systems. This has clinical implications for therapies in BD and other disorders of impulsivity, such as mindfulness training which has been demonstrated to benefit attention (e.g. Jha et al., 2007) or episodic future thinking which may reduce temporal discounting (see Peters & Büchel, 2010).
Chapters 5 and 6 examine motivational decision-making processing in patients with a diagnosis of bipolar disorder during euthymia. To characterise the functional anatomy of the reward network (spatial elements) as well as its evolution over time (temporal elements) and how this may deviate in BD, we acquired both fMRI and EEG recordings. We acquired the two recordings simultaneously, so as to avoid a number of pitfalls associated with separate-session acquisition (see Chapter 2). In particular this allowed us to reduce the burden to the participants and ensure that the phenomena measured by each modality pertained to specific task variables and not other methodological confounds.

Given the novelty of the application, particularly with respect to BD, the two modalities are reported separately. First, Chapter 5 reports the fMRI data and aims to identify the spatial elements of the reward network. Second, the precise evolution of activity in this network over time was probed using the high temporal resolution of EEG, and this is reported in Chapter 6. This also allowed identification of transient electrocortical sources that may be invisible to slower fMRI measurement. Finally, the discussion of Chapter 6 features a theoretical integration or “conceptual fusion” of the two data streams.
CHAPTER 5: TOP-DOWN CONTROL DURING ANTICIPATION REGULATES SENSITIVITY TO REWARD IN BIPOLAR DISORDER*

* This chapter is currently under review in Archives of General Psychiatry.
Abstract

**Background:** Whereas cortico-limbic imbalances are linked to emotional lability in bipolar disorder (BD), the functional neuroanatomy of impulsive and risky decision-making has not been elucidated. We aimed to determine whether BD is associated with a reward hypersensitivity that is related to impaired representation of expected value of response options and reduced executive control.

**Methods:** Patients were 20 euthymic BD patients (not receiving antipsychotic medication) and 20 healthy controls matched for age, gender, and education. Using functional MRI, we assessed brain activity during appraisal, anticipation and outcome of Roulette gambles. Primary outcome measures were response to reward outcomes in nucleus accumbens (NAcc), and trial-wise representation of EV and PE in the wider reward network. We also ascertained whether top-down control in dorsolateral prefrontal cortical (dPFC) predicted subsequent reward response in NAcc.

**Results:** The BD group evidenced a reduced parametric response to EV in the ventral prefrontal cortex during appraisal and, subsequently, an increased response to reward outcomes in NAcc. These effects coincided with reduced dPFC activity during anticipation and with risk perception. Whereas residual manic symptoms reduced the differentiation between expected and unexpected outcomes in NAcc and reduced dPFC activity, residual depression offset the increased reward response in NAcc.

**Conclusions:** Impaired decision-making in risky contexts may be due to a misrepresentation of EV and a core reward hypersensitivity that perseveres in remission. Mood state may differentially modulate this core feature: whereas depressive symptoms dampen it, manic symptoms foster unrealistic expectations and loosen the anticipatory top-down control that keeps the reward response in check. This provides a framework for evaluating therapeutic interventions targeting early appraisal and top-down control in risky contexts.
5.1. Introduction

Abnormalities in motivation and decision-making are central to the clinical profile of bipolar disorder (BD); whilst mania is typified by extreme increases in motivation, confidence, and goal-striving (Johnson, 2005b), depression is characterised by a marked reduction in these variables (Bijttebier et al., 2009). In addition to the costs associated with lost working days, impulsivity and risk-taking in BD have detrimental effects on affected individuals, carers and wider society (APA, 2000). Impulsive and risky decision-making perseveres in remission (Swann et al., 2003) and may be related to residual mood symptoms, but this has not been examined. Whilst an influential conceptual model proposes an imbalance between neural systems governing approach of rewards and executive (“top-down”) control to explain these features (Urosevic et al., 2008), there is currently very little evidence linking the physiology of BD with psychological accounts. In particular, the interplay between reward system function and top-down, higher-order goal systems in governing decision-making and risk-taking remains to be established by neuroimaging.

Whereas decision-making abnormalities in BD have mostly been described in terms of gross constructs such as impulsivity (e.g. Swann et al., 2001; Swann et al., 2009), a refined process-based approach that avails of neuroeconomic and reinforcement learning frameworks may facilitate a more precise characterisation of decision-making in BD. Neuroeconomics fuses economic principles with neurobiological methods to elucidate decision-making processes, and how variables such as risk perception and uncertainty might bias decisions (Glimcher & Rustichini, 2004). Recently, this approach has been fruitfully applied to other disorders in which impulsivity is a characteristic, such as addiction (Monterosso et al., 2012) and attention-deficit hyperactivity disorder (Sonuga-Barke & Fairchild, 2012).
Decisions can be separated into several time stages: an initial appraisal of prospects, subsequent anticipation of an expected outcome(s), followed by evaluation of the actual outcome(s). During appraisal, the desirability of a given prospect is partly determined by its expected value (EV: the combination of probability, valence, and magnitude). Reinforcement learning theory offers a complementary perspective, in which evaluation of outcomes is critical for driving future behaviour. When behaviourally salient outcomes differ from what was expected, prediction error (PE) quantifies the discrepancy between the two, and is used to optimise future predictions and goal-directed behaviour (Sutton & Barto, 1998). Studies have demonstrated that the brain represents EV and PE in dopamine-regulated cortico-limbic circuits including the ventral striatum (nucleus accumbens, NAcc), ventral prefrontal, and right dorsolateral prefrontal cortex (dIPFC) (Corlett et al., 2004; Pessiglione et al., 2006; Schultz, 1998). Trial-wise comparison of these neuroeconomic parameters against neural activity has considerably advanced the understanding of other disorders characterised by reward system abnormalities, including addiction (Park et al., 2010), psychosis (Murray et al., 2007) and impulse control disorders in Parkinson’s Disease (Voon et al., 2010), paving the way for applying this powerful approach in elucidating the pathophysiology of BD. Deficits in any of the decision-making stages outlined above could underlie risky decision-making in BD. On the one hand, a misrepresentation of EV may magnify the desirability of risk-taking by augmenting the probability or magnitude of reward (or by downplaying the costs). Alternatively, differences in the subjective evaluation of realised outcomes may promote future risk-taking by inflating the impact of rewards (‘reward hypersensitivity’), or attenuating the impact of negative consequences (‘punishment insensitivity’). This might be worsened by reduced top-down control during anticipation of these outcomes that would serve to further dysregulate the subsequent response to these outcomes. Indeed a meta-analysis of lesion studies implicates dIPFC in cognitive control (Gläscher et al., 2012) and recent functional imaging studies have demonstrated a top-down mechanism in which dIPFC modulates or reappraises the reward response in NAcc (Staudinger et al., 2009; Staudinger et al., 2011). In BD, reduced prefrontal function is indicated by meta-
analysis (Chen et al., 2011; see also Savitz & Drevets, 2009 for a review) and decreased prefrontal activity has been linked to poorer performance on the Iowa Gambling Task (Jogia et al., 2011). Collectively this suggests that a dlPFC regulatory mechanism may be compromised in BD.

Three other neuroimaging studies have broadly examined reward processing in BD. One found that in acute mania there is an impairment of EV representation in ventral PFC during anticipation of reward and punishment (Bermpohl et al., 2010), consistent with the first decision-making deficit proposed. Another used contrasts between rewarding and non-rewarding outcomes, finding a reduced differential signal between the two in NAcc in mania (Abler et al., 2007c); but the specific parameters contributing to this (valence, expectancy, magnitude, EV or PE) were not isolated. State factors such as mood, arousal, sustained attention, and engagement may also confound group differences, complicating the interpretation of these findings and muddying the water with respect to dissociating trait from state markers of BD. Recent evidence suggest that atypical reward system function perseveres in remission, with euthymic patients showing increased reward anticipatory activity in striatum and ventral PFC compared to controls (Nusslock et al., 2012). Reduced modulatory top-down control might have contributed to this increase; however, this study did not relate activity in dlPFC to striatal and ventral PFC activity. A limitation of the above studies is that patients were in receipt of antipsychotic medication which alters reward-related activity in decision-making tasks (Abler et al., 2007a; Pessiglione et al., 2006), and may also lead to false negatives in studies of BD (Hafeman et al., 2012). To this end we have previously demonstrated reinforcement learning and prediction error differences in at-risk samples not in receipt of medication using neuroimaging (O'Sullivan et al., 2011) and electroencephalography (EEG) (Mason et al., in press). A further EEG study demonstrated the neural correlates of a steeper trajectory of delay discounting that confers hypersensitivity to immediate reward outcomes in this population (Mason et al., 2012). Collectively the existing evidence indicates abnormalities in
the reward system encompassing several stages of processing and spanning both euthymia and mood episodes.

The present study

We applied neuroeconomic principles to characterise decision-making in bipolar disorder during remission (BDR) across multiple stages. Given that learning has previously been documented to be perturbed in BD-related samples (Mason et al., in press; O'Sullivan et al., 2011), removing this variable from the current study allowed an unconfounded elucidation of other decision-making parameters. Given the impact of subclinical symptoms in BD, we sought to dissociate affective state from trait features. We also examined whether responses to rewarding outcomes are shaped by appraisal of value and risk, as well as top-down anticipatory control. We adopted a free-choice Roulette task, previously validated in another clinical population characterised by impulsivity and risk-taking (see van Eimeren et al., 2009). This design allowed assessment of the trial-by-trial coupling between neural activity and objective metrics of 1) expected value (EV) and 2) prediction error (PE), whilst avoiding group differences in learning. Crucially, we also reduced confounding medication effects on dopamine (DA) function by excluding antipsychotic medication (Abler et al., 2007a; Pessiglione et al., 2006).

We hypothesised greater reactivity to rewards as indexed by NAcc activity, and that this would be 1) reduced by residual depressive symptoms and 2) increased by manic symptoms, and low trait appraisal of risk. We additionally predicted poorer representation of EV (in vmPFC) and of PE (in NAcc and right dIPFC) in the BDR group, and that low trait risk appraisal would worsen this deficit. Finally, following evidence that dIPFC mediates self-control over valuation systems (Hare et al., 2009) we probed the efficacy of top-down control during anticipation and outcome evaluation on the reward response. We predicted that reduced dIPFC during anticipation and outcome would be associated with increased response to rewarding outcomes in NAcc and medial PFC.
5.2. Methods

5.2.1. PARTICIPANTS

The bipolar disorder in remission (BDR) group consisted of 22 patients with a diagnosis of bipolar disorder. Inclusion criteria were age 18-45 years, not receiving any antipsychotic medication, and without a current primary alcohol problem (weekly intake not exceeding 25 units per week) or substance use in the past four months. BDR participants were recruited from local mental health trusts and specialist affective disorder clinics within Greater Manchester, United Kingdom. A healthy control (HC) group were case-matched to BDR with respect to age, gender, level of education, and handedness. Data were excluded from 2 BDR participants (one did not complete all runs, and one due to neuroradiological abnormality) and two HC (one did not complete all runs, one due to technical failure). The final sample consisted of 20 participants in each group (see Table 5.1). National Health Service Research Ethics Committee (NRES), and the University of Manchester Senate Ethics Committee approved the study. Informed written consent was obtained from all participants and the study was conducted in accordance with the Declaration of Helsinki.

5.2.2. SCREENING AND ONLINE SELF-REPORT MEASURES

All participants underwent The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 2002). Participants were included if they met the criteria for BD-1 or BD-2, but did not meet the criteria for a mood episode (BD group) or other psychiatric disorder (healthy controls). To ensure a representative sample, anxiety and alcohol and substance use disorders were not exclusion criteria. However, participants were excluded if they had used substances in the
last four months or alcohol in the past 24 hours. Residual symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HAMD) and 12-item Bech-Rafaelsen Mania Scale (MAS). Individual differences in apprehension of undergoing fMRI were assessed immediately before the scan by means of visual analogue scales for state anxiety and sadness.

Participants completed an online battery of self-report measures, including all three parts of the Domain Specific Risk-Taking Scale (DoSpeRT risk-taking behaviours, risk perceptions, and perceived benefits scales; Blais & Weber, 2006) that are reported in this paper. A composite score of attitude to risk-taking was calculated by regressing risk perception and perceived benefits onto risk behaviour and entering these coefficients into the formula below (Blais & Weber, 2006; see supplementary methods). The risk attitude construct arises from the risk-return framework of financial risk-taking in which preferences reflect a subjective trade-off between expected benefit (i.e. EV) and perceived riskiness of the option(s). Hence risk attitude is a metric for assessing how willing people are to take risks (Blais & Weber, 2006).

5.2.3. TASK

Participants played a modified version of a previously validated Roulette task (van Eimeren et al., 2009) comprising three time stages (see Figure 5.1). Initial appraisal and selection (at \( t - 2 \)) was followed by anticipation of an outcome (\( t - 1 \)), and finally outcome evaluation (at \( t = 0 \)). At initial appraisal and selection, the amount of money at stake was presented, and participants made a free choice between four options. The stake was fixed and varied equally between low (£3) and high (£9) magnitude. In a low probability condition (25% reward), the four options were any one of the four colours. In the high probability condition (75% reward), participants chose between different groups of colours, with three colours in each
group (e.g. option 1: blue-red-green, option 2: blue-red-yellow, option 3: blue-green-yellow, option 4: green-yellow-red). In this high probability condition, participants won if the Roulette wheel stopped on any of the three colours in the option they chose. Importantly, the alternatives in each trial did not differ in value or probability, ensuring that all participants had sufficient numbers of trials in each condition and that there were no between-groups differences in trial numbers; thus there was equivalent signal-to-noise ratio in all comparisons. There were eight possible outcomes (*i.e.* gains and losses that were expected or unexpected and either of small or large magnitude).

The duration of the selection phase was tapered over the first trials of each run (5 sec for trials 1-2, 3 sec for trials 3-4 and 2 sec thereafter) to ensure that participants had time to acclimatise and respond. Participants were instructed to respond in this time and informed that if no timely response was issued, a random choice would be made. The duration of both the anticipation and outcome phases were separately jittered between 3-4 seconds. The crosshair was either 1.5 sec (75% of trials) or 4 sec (25%) to facilitate a strong baseline. Participants completed a total of 272 trials over eight runs (approximately six minutes each). Trials were equally distributed between probability (low, high) and stake magnitude (small, large) conditions.
Figure 5.1. Participants made bets on which colour would win in a Roulette gamble. The trial sequence comprised three phases: appraisal/selection (at time $t - 2$); outcome anticipation while the wheel span (at $t - 2$); and outcome evaluation when the ball stopped on one of the colours, signifying the delivery of the reward or loss (time $t$).

5.2.4. FUNCTIONAL MRI DATA ACQUISITION

Echo planar images were acquired over eight runs of 150 volumes, using a Phillips 1.5 T scanner (TR = 2.45 s, TE = 47 ms; flip angle = 90°). Volumes comprised 30 slices (4mm, no gap; in-plane voxel dimensions 1.5 x 1.5 mm), collected in ascending order and with standard field of view.
5.2.5. FUNCTIONAL MRI DATA ANALYSIS

SPM8 (Wellcome Department of Cognitive Neurology, University College London) was used to pre-process and analyse the images. Each participant’s functional images were motion-corrected with realignment to the mean image and time-corrected to the middle slice. The functional images were then coregistered with the structural image, spatially normalised to MNI space, and smoothed with an 8 mm gaussian kernel. The data for all participants were analysed at the first level using the general linear model, as implemented in SPM8 (Friston et al., 1994). Two first-level models were built to assess sensitivity to motivational outcomes 1) parametrically (using EV and PE) and 2) based on reward factors (valence, expectancy, magnitude). Both models are described in greater detail below. Regressors were convolved with a haemodynamic response function and contrast images computed. We anticipated reduced beta values for the initial appraisal event because of the short duration but that this would be offset by the relatively large number of trials. The realignment parameters were included as additional regressors at the first level to reduce residual effects of motion.

Region of interest masks (ROIs) for bilateral nucleus accumbens (NAcc) and the right medial frontal gyrus (MFG) portion of dlPFC were extracted from the Harvard-Oxford probabilistic atlas in the FSL anatomy toolbox (http://www.fmrib.ox.ac.uk/fsl/). For structures not available in the atlas, prior publications were used to generate the following functionally defined ROI masks: bilateral ventral tegmental area (VTA; Abler et al., 2007c), and ventromedial prefrontal cortex (vmPFC; Hare et al., 2009) using 10 mm spheres around the peak coordinates reported by these studies. Based on research reporting more right-lateralised encoding of outcome evaluatory activity in dlPFC (Corlett et al., 2004), the dlPFC ROI was based on the right hemisphere only. The mean beta values in these ROIs were extracted for each contrast using the MarsBaR SPM toolbox (http://marsbar.sourceforge.net/), and entered into repeated measures ANOVAs for each model, as described below. Laterality was entered as an additional factor for bilateral ROIs.
5.2.5.1. Representation of Expected Value and Prediction Error

Expected value (EV) was calculated trial-wise as the arithmetic product of reward probability and magnitude minus the arithmetic product of loss probability and magnitude (\(EV = EV_{\text{Gain}} - EV_{\text{Loss}}\)). The prediction error term (PE) was calculated trial-wise as the difference between EV and the actual outcome (outcome minus total EV). This allowed the model to take into consideration the pattern of neural activity that would be expected based on the relative differences between the parameters of EV and PE terms. Accordingly, three regressors modelled onset of appraisal, anticipation, outcome stages, and a parametric modulator was entered for each; whereas the EV term was entered for pre-outcome stages (appraisal and anticipation), the PE term was entered for the outcome stage. Contrast images were computed for the parametric modulator at each stage (against rest) and entered into a between-group T-test.

5.2.5.2. Separating the contribution of probability, magnitude and valence

To assess sensitivity to reward and punishment per se and (non-parametric) top-down influences, each condition was modelled separately and entered into factorial analysis (see below). This also allowed the relative contributions of valence, probability and magnitude parameters to be dissociated and enabled comparison with previous studies. The four expectation conditions (low and high probability, small and large stake magnitude) were modelled as separate regressors at both the appraisal and anticipation phases (reported as Supplementary Material), along with the eight possible outcomes at the outcome phase. First-level contrast images were computed and entered into separate mixed factorial ANOVAs, one for each phase. For the appraisal and anticipation phases, the within-subjects factors were ‘probability’ (25%, 75%) and ‘magnitude’ (£3, £9).
For the outcome phase, within-subject factors were ‘valence’ (gain, lose), ‘expectancy’ (expected, unexpected), and ‘magnitude’ (small, large). In all cases there was one between-groups factor (group diagnosis: bipolar disorder, healthy control). Additional analysis of covariance (ANCOVA) was used to control for current depressive (HAMD) and manic (MAS) symptoms.

5.2.5.3. Modulation of the reward network by risk-taking

Partial correlations were performed to assess the relationship between real-life risk-taking behaviours and neural activity in the BDR group whilst controlling for HAMD and MAS scores. To reduce the number of comparisons, we correlated on overt risk perception and risk attitude scores summed over subscales, and only in the BDR group given its clinical relevance. Overt risk perception was correlated with activity in regions representing EV (vmPFC, R. dIPFC). Risk attitude was correlated with regions that responded to rewarding outcome, and prediction error (NAcc, R. dIPFC). The mean signal across left and right structures was taken where there was no effect of laterality (NAcc), and the hemisphere with maximum signal otherwise (vmPFC, R. dIPFC). Tests were conducted using Bonferroni adjusted alpha levels of $p < .0125 (.05 / 4)$ per test.

5.2.5.4. Modulation of reward evaluation by initial appraisal of value and top-down control

Extending an established approach (Hare et al., 2009), we evaluated the degree to which activity within the reward network during initial appraisal ($t - 2$) and anticipation ($t - 1$) predicted activity at outcome evaluation (at $t$). In particular, we were interested in how the integrity with which expected value was represented, in addition to top-down control, might shape the reward response. To assess this,
ANCOVA was performed with reward response in NAcc and vmPFC as the dependent variables and group as a fixed factor, with thee covariates based on previous studies: representation of EV (Staudinger et al., 2009) in vmPFC (at $t - 2$), overall anticipatory dIPFC activity (at $t - 1$) (Staudinger et al., 2011), and overall outcome-locked dIPFC activity (at $t = 0$) (Hare et al., 2009; Staudinger et al., 2009). Current symptoms were entered as covariates and group as a fixed factor. Correlations were performed to explore significant differences identified by the ANCOVA.
5.3. Results

5.3.1. CLINICAL AND BEHAVIOURAL DATA

Demographics, clinical variables, medications, and behavioural results are reported in Table 5.1. BDR scored significantly higher on the HAMD and MAS (although all in the low range of ≤ 8); therefore these were entered as covariates for key analyses to control for mood state.
Table 5.1. Demographics and behavioural data. BD patients did not differ from the controls in their response time or proportions of each option chosen.

<table>
<thead>
<tr>
<th>Remitted Bipolar Disorder</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean or Proportion</td>
<td>Mean or Proportion</td>
</tr>
<tr>
<td>Age</td>
<td>35.95</td>
</tr>
<tr>
<td>Female</td>
<td>10/20</td>
</tr>
<tr>
<td>Education (years)</td>
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</tr>
<tr>
<td>Episodes Mania</td>
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</tr>
<tr>
<td>Episodes Hypomania</td>
<td>6.13</td>
</tr>
<tr>
<td>Episodes Depression</td>
<td>7.04</td>
</tr>
<tr>
<td>Primary Diagnosis</td>
<td>BD-I</td>
</tr>
<tr>
<td></td>
<td>BD-II</td>
</tr>
<tr>
<td>Current comorbidity</td>
<td>GAD</td>
</tr>
<tr>
<td>Lifetime diagnoses</td>
<td>Alcohol/SUD</td>
</tr>
<tr>
<td></td>
<td>Panic disorder</td>
</tr>
<tr>
<td></td>
<td>GAD</td>
</tr>
<tr>
<td></td>
<td>OCD</td>
</tr>
<tr>
<td>Medications</td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td>Valproate</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
</tr>
<tr>
<td></td>
<td>SSRI</td>
</tr>
<tr>
<td></td>
<td>SNRI</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepine</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td>HAMD-17</td>
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</tr>
<tr>
<td>MAS-12</td>
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</tr>
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<td>VAS-Sadness</td>
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</tr>
<tr>
<td>Response Time (ms)</td>
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</tr>
<tr>
<td>Response (%)</td>
<td></td>
</tr>
<tr>
<td>Choice 1</td>
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</tr>
<tr>
<td>Choice 3</td>
<td>24.3</td>
</tr>
<tr>
<td>Choice 4</td>
<td>17.8</td>
</tr>
</tbody>
</table>

* SUD, substance use disorder; GAD, Generalised Anxiety Disorder; OCD, Obsessive-Compulsive Disorder; HAMD, Hamilton Depression Score; MAS, Bech-Rafaelsen Mania Score; VAS, Visual Analogue Scale Score (-50 to +50)
5.3.2. FMRI FINDINGS

This section focuses on the a priori ROI analyses. A complete list of activated foci for whole-brain analysis is provided in Supplementary Tables 5.1 and 5.2. For clarity, the subheadings of each analysis reported here correspond to those of the descriptions in the Method section.

5.3.2.1. Representation of Expected Value and Prediction Error

Initial Appraisal (t - 2):

Parametric modulation by EV was found in clusters in R. Posterior Parietal and R. dIPFC at whole-brain level (see Figure 5.2). The ROI analysis confirmed this parametric modulation in a priori hypothesised structures: R. dIPFC \( F(1, 39) = 7.99, \ p = .007 \), and vmPFC \( F(1, 39) = 6.88, \ p = .012 \). There were main effects of group for R. dIPFC \( F(1, 38) = 4.11, \ p = .05 \) and R. vmPFC \( F(1, 38) = 4.67, \ p = .037 \), indicating a reduced parametric response to EV in the BDR group for both structures.

Anticipation (t – 1):

Parametric modulation by EV was observed bilaterally in posterior parietal cortex and dIPFC, with larger clusters in the right hemisphere at the whole-brain level (Supplementary Table 5.1). ROI analysis confirmed effects in R. dIPFC \( F(1, 38) = 9.0, \ p = .005 \), with no effects being evident in R. vmPFC or NAcc (\( p \geq .414 \)). There were no group differences in either ANOVA or ANCOVA analyses (\( p \geq .155 \)).
Outcome (at t = 0):

The whole-brain analysis revealed clusters responding parametrically to PE in bilateral NAcc, R. dIPFC, and ventral ACC at FWE-corrected $p = .05$ (see Figure 5.3). The ROI analysis demonstrated a significant positive parametric response in bilateral NAcc [$F(1, 38) = 51.4$, $p < .001$], VTA [$F(1, 38) = 11.0$, $p = .002$], and dIPFC [$F(1, 38) = 17.7$, $p < .001$], with a larger effect in the right than in the left dIPFC [$F(1, 38) = 3.24$, $p = .08$]. Contrary to our hypotheses, groups did not differ in their parametric response in the NAcc ($p = .3$), but main effects of group were observed for VTA and DLPFC, and these signified an increased parametric response in BDR relative to HC participants.

Figure 5.2. Evolution of the reward network over time. Trial-wise expected value (EV) is represented by ventromedial and right dorsolateral prefrontal cortex (dIPFC) at initial appraisal and is maintained in dIPFC and posterior parietal cortex during anticipation. At outcome, prediction error is represented by nucleus accumbens and dIPFC. Outcome map thresholded at the whole-brain level at $p \leq$
0.05; appraisal and anticipation maps voxel thresholded at $p \leq 0.02$, with a minimum capacity of 50 voxels.

5.3.2.2. Separating the contribution of probability, magnitude, and valence

Outcome (at $t = 0$):

The NAcc ROI showed main effects of valence $[F(1, 38) = 53.7, p < .001]$, magnitude $[F(1, 38) = 5.51, p = .024]$, and group $[F(1, 38) = 4.51, p = .04]$, as well as valence-expectancy $[F(1, 38) = 7.71, p = .008]$ and valence-magnitude $[F(1, 38) = 4.05, p = .051]$ interactions. These effects indicated greater activity for gains than losses (see Figure 5.3), and for large compared to small outcomes. As expected, the interactions confirmed that 1) unexpected and 2) large magnitude outcomes increased NAcc activity for gains, but reduced activity for losses (valence-expectancy and valence-magnitude interactions).
Figure 5.3. a) Experiencing reward in the nucleus accumbens (NAcc) and the ventromedial prefrontal cortex. Gain>Loss contrast across all subjects \([p<.05, \text{familywise error corrected}]\). b) Patients with remitted bipolar disorder (BDR) may be more susceptible to the “feel-good” highs of risky choices and less to the hazards. Following a Roulette gamble, patients show a hyper-hedonic response to reward outcomes in NAcc, and a smaller response to losing, following a Roulette gamble. Asterisk indicates significant group difference \((p\leq .05)\)

The main effect of group confirmed that overall NAcc activity was greater in BDR than HC with an effect size of partial \(\eta^2 = .106\). This effect was increased when HAMD score was covaried \([F(1, 37) = 7.95, p = .008; \text{partial } \eta^2 = .177, \text{large effect}]\) and there was a trend for a main effect of this covariate \([F(1, 37) = 3.20, p = .082]\), which had a negative relationship with NAcc activity. Figure 5.4a shows NAcc activity for low and high HAMD subgroups of BDR. When MAS score was covaried, the main effect of group was no longer significant \((p = .1)\), and instead a valence-group interaction emerged \([F(1, 37) = 4.32, p = .045]\). This trend showed that the increased activity in BDR relative to HC group was more pronounced for gains than
losses (see Figure 5.4b). Finally, when both HAMD and MAS scores were covaried, a valence-expectancy-MAS interaction was significant $[F(1, 36) = 6.04, p = .019]$, which indicated that increased levels of manic symptoms were associated with a reduced distinction between gains on the basis of their objective probability.

**Figure 5.4.** Modulation of reward outcomes in NAcc of BDR participants by residual mania and depression. **a)** Group-by-Valence interaction: Depressive symptoms dampen reward response and enhance response to loss. **b)** Group-Valence-Expectancy interaction: Manic symptoms impair the distinction between outcome expectancies which may relate to the increase in self-efficacy and unrealistic goal-striving associated with mania. Subgroups defined by median-split of BDR group.
5.3.2.3. Modulation of the reward network by risk-taking

Correlations were performed for BDR participants with an adjusted significance threshold of $p < .0125$, Bonferroni corrected for multiple comparisons (see methods).

At initial appraisal ($t - 2$), parametric activity associated with EV was positively correlated with overt risk perception in R. dlPFC [$r(16) = .678, p = .004$; Figure 5.5a] and NAcc [$r(16) = .54, p = .031$, although this did not reach the Bonferroni-corrected significance threshold].

During outcome evaluation ($t$), there were trends for positive correlations between overt risk-taking perception and the parametric response to PE in both R. dlPFC [$r(16) = .554, p = .026$] and bilateral NAcc [$r(16) = .515, p = .041$], but these did not reach Bonferroni-corrected threshold and so should be interpreted with caution. Finally, risk attitude was negatively correlated with dlPFC activation for reward outcomes [$r(16) = -.629, p = .005$; Figure 5.5b]. No other correlations reached significance.
Figure 5.5. Right dorsolateral prefrontal cortex (dPFC) function in bipolar disorder group  

- **a)** Recruitment of dPFC (during outcome-locked reward response) linearly increases perception of risk \( r = .678, p = .004 \) whereas  

- **b)** Risk Tolerance (willingness to take risk) is increased by poor representation of expected value in dPFC (during appraisal) \( r = -.629, p = .005 \). fMRI signal represents the change from baseline in the blood-oxygen-level-dependent signal (mean of dPFC ROI).
5.3.2.4. Modulation of reward hypersensitivity by initial appraisal of value and top-down control

ANCOVA assessed the degree to which activity within the reward network during initial appraisal (parametric representation of EV in vmPFC at \( t - 2 \)), anticipation (dIPFC activity at \( t - 1 \)) and outcome (dIPFC activity at \( t \)) predicted the reward response in NAcc and in vmPFC (at \( t \)) (see methods). Significant effects were followed up with correlations.

For the NAcc response to rewards, there emerged a main effect of group \([F(1,35) = 4.43, p = .043]\), and initial representation of EV in vmPFC \((t - 2)\) \([F(1,35) = 4.37, p = .044]\). Group additionally interacted with initial representation of EV \([F(2,35) = 5.09, p = .012]\), and anticipatory R. dIPFC activity \((t - 1)\) \([F(1,35) = 6.84, p = .014]\). There were no interactions with HAMD or MAS scores \((p \geq .514)\). The directionality of these effects was explored with correlations.

Within the BD group, the parametric response to EV in vmPFC at initial appraisal \((t - 2)\) was negatively correlated with the response to gain outcomes in bilateral NAcc \((at t)\) \([r(20) = -.436, p = .055]\). This correlation was absent in HC \((p = .44)\). For HC, anticipatory activity in R. dIPFC \((t - 1)\) predicted an increased bilateral NAcc response when subsequently experiencing gain outcomes \((at t)\) \([r(20) = .448, p = .048]\). For BDR the directionality was reversed \([r(20) = -.440, p = .052]\). No other correlations approached significance \((p \geq .15)\).

For the reward response in vmPFC, there emerged main effects of initial EV representation \((t - 2)\) \([F(1,35) = 6.71, p = .014]\), as well as a trend for outcome-locked dIPFC activity \((at t)\) \([F(1,35) = 3.13, p = .086; \text{trend approaching significance}]\). Group interacted with initial EV representation \([F(2,35) = 11.4, p < .001]\), as with the NAcc ANCOVA reported above,. There was also a trend for a main effect of MAS \([F(1,35) = 3.04, p = .094]\) and MAS additionally interacted with initial EV
representation \[F(1,35) = 8.37, p = .008\] and anticipatory dlPFC activity \[F(1,35) = 3.23, p = .085\]. There were no effects or interactions with HAMD score \(p \geq .263\).

As per NAcc findings above, the parametric response to EV in vmPFC at initial appraisal \((t - 2)\) was negatively correlated with the response to gain outcomes in bilateral NAcc (at \(t\)) \([\text{across groups: } r(20) = -.426, p = .006; \text{the same correlation emerged within separate groups } p \leq .079\]. When experiencing gain outcomes (at \(t\)), outcome-locked activity in dlPFC was positively correlated with activity in vmPFC in HC \([r(20) = .704, p < .001]\), but negatively in BDR group \([r(20) = -.478, p = .033]\). There was a trend for vmPFC reward response to be positively correlated with MAS score \([r(40) = .293, p = .066]\). Furthermore, MAS contributed to the negative correlation between outcome-locked dlPFC activity and the vmPFC response in the BDR group: the interaction term between MAS and outcome-locked dlPFC was negatively correlated with the vmPFC response \([r(40) = -.327, p = .039]\). Similarly, MAS modulated the negative correlation between the parametric response to EV \((\text{in vmPFC, } t - 2)\) and the subsequent reward response \([\text{interaction term: } r(40) = -.682, p < .001]\). No other correlations reached significance.
5.4. Discussion

In this study we took a neuroeconomic approach to characterise the abnormalities in decision-making and motivational processing in euthymic BD not in receipt of antipsychotic medication. We found that misrepresentation of expected value, and a trait hypersensitivity to rewarding outcomes were related to 1) reduced top-down control, and 2) lesser real-life perception of risk. We also found that mood state additionally interacted with these core features: whereas residual depression brought about anhedonic representation of reward value, mania brought about unrealistic representation of reward likelihood, and also reduced anticipatory top-down control. We reduced a common confound of clinical neuroimaging studies – disruption of reward processing by DA antagonists – by excluding patients in receipt of antipsychotic medication.

5.4.1. CORE REWARD HYPERSENSITIVITY AND MISREPRESENTATION OF EXPECTED VALUE

The parametric representation of EV was decreased in both the dlPFC and vmPFC in the BD group relative to case-matched healthy controls. This finding indicates that patients were less able to weigh the likelihood and value of reward against that of loss, which may hinder adaptive levels of effort being expended on real-life goals. The accuracy of patients’ representation of EV was negatively correlated with real-life perception of risk, consistent with behavioural reports showing a link between reduced representation of EV and risk-taking in BD-related samples (Adida et al., 2011; Brambilla et al., 2012). Brought together with the elevated anticipatory VTA activity in the present study, this suggests that BD patients were swayed more towards the potential reward on offer, a conclusion reached by a
neuroimaging study demonstrating impaired orbitofrontal representation of EV during mania (Bermpohl et al., 2010). This fits with clinical accounts of extreme goal-setting and inflated confidence in patients’ ability to obtain unrealistic goals (Johnson et al., 2009).

At outcome, the nucleus accumbens (NAcc) and vmPFC response to gains and losses was greater in the BD group compared to healthy controls. This ‘hyper-hedonic’ response may further serve to foster risk-taking, through an increased subjective impact of rewards as well as a less aversive (i.e. more “reward-like”) impact of losses. This parallels a “rose-tinted” evaluation bias that has been reported in other clinical populations characterised by impulsive and risky decision-making (e.g. Parkinson’s Disease with impulse control disorders; Voon et al., 2010) and unrealistic optimism about outcomes (Sharot et al., 2011). Our finding in euthymic patients suggests that it is a core feature of BD, adding to a recent study reporting NAcc hyperactivity during anticipation of reward (Nusslock et al., 2012) and behavioural evidence that impulsive and risky decision-making is elevated in all phases of the disorder (Jollant et al., 2007; Swann et al., 2001; Swann et al., 2009). Increased sensation-seeking is a feature of BD, and there is some evidence that this trait is associated with accentuated dopaminergic responses in healthy controls (Zald et al., 2008).

Trait reward hypersensitivity was separately modulated by affective symptoms. Whereas residual depression somewhat dampened the NAcc response, residual mania reduced its specificity by 1) producing the favourable (reward-like) response to losses and 2) impairing discrimination between expected and unexpected outcomes. An elevated NAcc response to non-rewards has previously been reported in mania (Abler et al., 2007c) and may maintain risky behaviours by dampening the impact of aversive consequences. Alternatively, this response may represent increased frustration at not obtaining the desired reward, consistent with the view that irritable mania may arise from reward-obstruction (Urosevic et al., 2008) and that anger is generated by the approach system (Carver & Harmon-Jones, 2009). Residual depressive symptoms reduced the NAcc reward response which may offset risk-taking, but could also have the opposite effect by reducing...
the intrinsic value of everyday activities and thereby increasing the pull from more intense sources of reward. Further work will be needed to examine the causal relationship between risk-taking and affective self-regulation in BD.

5.4.2. MODULATION OF REWARD HYPERSENSITIVITY BY INITIAL APPRAISAL OF VALUE AND TOP-DOWN CONTROL

The magnitude of the NAcc response to reward outcomes (at \( t \)) was negatively correlated with the parametric response to EV in vmPFC (\( t - 2 \)). This suggests that patients that more accurately represent EV show a less exaggerated reward response, providing a potential target for interventions. Indeed, cognitive interventions may be more efficacious when focusing on precedent appraisal rather than subsequent evaluation of risky behaviours.

In addition, when experiencing reward outcomes, activity in dIPFC was positively correlated with that of vmPFC in HC group but negatively in BDR group. Whereas controls appeared to keep increases in affective valuation in check by proportionally recruiting top-down self-control (Hare et al., 2009), patients showed dominance of the reflexive valuation system. This complements an existing finding of reduced frontopolar cortical activity and increased vmPFC in euthymic BD (Jogia et al., 2011), and may signify a reduced vigilance over novel or exciting outcomes, consistent with a vulnerability to these kinds of experiences with respect to triggering episodes of mania. Similarly, the reward response in NAcc and vmPFC (at \( t \)) negatively correlated with anticipatory dIPFC activity (\( t - 1 \)), indicating that patients with BD vary in their ability to prospectively modulate their response to rewarding outcomes (see also supplementary discussion). Of clinical relevance, we additionally found that manic symptoms increased the reward response in vmPFC and modulated the relationship between anticipatory dIPFC and vmPFC. This latter finding is in accordance with a recent meta-analysis that found reduced prefrontal activity as a state marker for acute mania (Chen et al., 2011). In this way dIPFC
function may be critical for maintaining euthymia (e.g. Strakowski et al., 2012) and cognitive interventions that target effortful and reflective control may be particularly useful for preventing relapse. In support of this, there is recent evidence that cognitive reappraisal can effectively modulate anticipation and evaluation of rewarding outcomes, and does so via dIPFC (Staudinger et al., 2009; Staudinger et al., 2011).

5.4.3. PREDICTION ERROR SIGNALLING

Interestingly and despite the above deficits, prediction error signalling was intact in BD patients who showed equivalent parametric response to PE in NAcc and enhanced response in VTA and dIPFC. This enhancement suggests that patients with BD track motivational outcomes more intently, at least when euthymic, a finding consistent with our previous study in which non-clinical and high functioning hypomania (O'Sullivan et al., 2011). One possibility is that the steeper parametric response is driven by an enhanced response to unexpected and large rewards (compared to small and predictable ones). This enhancement may amplify the perceived value of novel outcomes over more predictable and commonplace rewards from everyday behaviours, potentially fuelling pursuit of more intense and riskier sources of reward. An apparent discrepancy is how prediction error is represented accurately, given impaired representation of EV. A possibility is that although the distribution of prediction error signals is comparable between the BD and control groups, the level of neural activation in the patients is “shifted up” towards the higher end of the neural activation distribution, corresponding to a more positive interpretation of outcomes. This may maintain unrealistic expectations in the future by potentiating the impact of positive outcomes and dampening the impact of aversive or disconfirmatory evidence (Sharot et al., 2011; Voon et al., 2010). It seems likely that the ability to track outcomes more precisely diminishes with increased mania, given that residual manic symptoms were associated with reduced discrimination of expected from unexpected outcomes. In
support of this there is evidence of altered striatal prediction error signalling in mania, although this was assessed by individual contrasts rather than parametrically (Abler et al., 2007c).

A strength of the study is that patients were not in receipt of DA antagonists which are known to alter reward processing (Abler et al., 2007a; Pessiglione et al., 2006). Whilst meta-analysis across various tasks suggest that medication ameliorates rather than introduces anomalous group differences (Hafeman et al., 2012), this represents as serious methodological challenge for researchers as it may mask important pathophysiological mechanisms. However, an intrinsic limitation of our approach is that patients not in receipt of antipsychotics may not be representative of BD populations. Also, although our paradigm was useful for controlling for previously identified differences in learning (O'Sullivan et al., 2011; Pizzagalli et al., 2008b), this may have prevented the detection of some differences that are important as learning occurs.

In summary, we report evidence of a core impairment to expected value and hypersensitivity to rewarding outcomes in euthymic BD, providing insight into risk-taking in this population. We additionally identify distinct neural mechanisms by which affective state interacts with this core feature. These findings suggest that reward hypersensitivity may be amenable to interventions that bolster prefrontal function and foster more accurate perception of risk.
5.5. Supplementary Material

5.5.1. SUPPLEMENTARY METHODS

5.5.1.1. Self-report measures

In addition to the DoSpeRT, participants completed the Impulsivity and Sensation-Seeking Subscale (ImpSS) from the Zuckerman Personality Scale (Zuckerman, 1996), Baratt Impulsivity Scale (BIS-11; Patton et al., 1995), and BIS/BAS (Carver & White, 1994). Comparison on these measures was to establish between-groups differences in impulsivity, reward-sensitivity and risk-taking.

Overall attitude to risk-taking was calculated from the three forms of the 30-item DoSpeRT according to the formula below (see also Blais & Weber, 2006):

\[ \text{Risk Attitude} = a(\text{Expected Benefits}) + b(\text{Perceived Risk}) + c \]

The coefficients \(a\) and \(b\) were obtained by regressing the scores on the “Expected Benefits” and “Risk Perception” on “Risk-Taking” sections of the Domain-Specific Risk-Taking questionnaire (Blais & Weber, 2006).

5.5.1.2. Functional MRI modelling of initial appraisal and anticipation

Four expectation conditions (low and high probability, small and large stake magnitude) were modelled as separate regressors at both the appraisal and anticipation phases, along with the eight possible outcomes at the outcome phase (reported in main results). First-level contrast images were computed and entered into separate mixed factorial ANOVAs, one for each phase. For the appraisal and anticipation phases, the within-subjects factors were ‘probability’ (25%, 75%) and ‘magnitude’ (£3, £9). For the outcome phase, within-subject factors were ‘valence’
(gain, lose), ‘expectancy’ (expected, unexpected), and ‘magnitude’ (small, large). Group (BD, HC) was entered as a between-groups factor in each ANOVA and additional analysis of covariance (ANCOVA) was used to control for current depressive (HAMD) and manic (MAS) symptoms.

5.5.2. SUPPLEMENTARY RESULTS

5.5.2.1. Self-report measures

BDR scored higher on ImpSS \[t(1, 38) = 3.76, p = .001\], BIS [total score: \[t(1, 38) = 5.86, p < .001\]; motoric subscale: \[p = .06\]; non-planning: \[p = .089\]], BAS reward responsiveness \[t(1, 38) = 2.53, p = .016\], BAS fun \[t(1, 38) = 2.08, p = .044\], BAS drive \[t(1, 38) = 2.23, p = .03\]. BDR also scored higher scores on total DoSpeRT risk-taking behaviours \[t(1, 38) = 2.13, p = .04\] and lower on risk perception \[t(1, 38) = -2.63, p = .013\].

5.5.2.2. fMRI measures

Reported below are the results of the second model which separated the contribution of probability, magnitude and valence (described above) for the appraisal, anticipation and outcome stages. See Supplementary Tables 5.1 and 5.2 for activated foci in the whole-brain analyses.

*Initial Appraisal:*

At whole-brain level, the probability contrast revealed clusters in R. Posterior Parietal Cortex and R. dIPFC, L. dorsal NAcc, the affective subdivision of the ACC, and R. lateral OFC were found for the probability-magnitude interaction (see
Supplementary Table 5.1). No clusters survived statistical threshold for contrast of unsigned magnitude. In the ROI analysis, there were no main effects or interactions for NAcc ($p \geq .13$).

Anticipation:

At whole-brain level, reward probability activated bilateral dlPFC and posterior parietal cortex with greater activation in right hemisphere (see Supplementary Table 5.1). The dlPFC ROI showed main effects of probability [$F(1, 38) = 12.64, p < .001$] and magnitude [$F(1, 38) = 6.91, p = .012$] as well as a probability-group interaction [$F(1, 38) = 4.1, p = .05$]. Across all participants dlPFC activity increased with reward probability and magnitude, but the probability effect was reduced in BDR (relative to HC). The probability-group interaction was no longer significant when HAMD score was covaried ($p = .5$).

In NAcc, there was a trend for main effect of magnitude [$F(1, 38) = 2.85, p = .1$] such that larger values resulted in more activity, irrespective of reward probability. A group-probability-laterality interaction also approached significance [$F(1, 38) = 3.81, p = .058$], which indicated that in L. NAcc, the increase in activity for high probability rewards (relative to low) was more pronounced in the BDR compared to HC group. When HAMD was covaried, this effect approached significance bilaterally (probability-group two-way interaction; [$F(1, 37) = 3.07, p = .088$]) and the main effect of probability was significant [$F(1, 37) = 5.04, p = .03$].

Activity in VTA did not show any within-subject task effects ($p \geq .41$) but did show a laterality-group interaction [$F(1, 38) = 4.04, p = .05$] and a trend for main effect of group [$F(1, 38) = 3.43, p = .07$]. These effects indicated that, regardless of task parameters, the BDR group showed increased activity in this structure compared to HC group, and that this effect was more pronounced in left hemisphere.
Outcome:

In the factorial analysis, dlPFC showed effects of valence \[ F(1, 38) = 19.2, p < .001 \], laterality \[ F(1, 38) = 6.16, p = .018 \], and a trend for magnitude approached significance \[ F(1, 38) = 3.55, p = .067 \]. These indicated that dlPFC showed greater deactivation for 1) losses than gains and 2) small than large outcomes, and that this signal change was more pronounced in left hemisphere than right. Valence-Expectancy-Group \[ F(1, 38) = 4.96, p = .03 \] and Valence-Laterality-Group \[ F(1, 38) = 6.61, p = .014 \] interactions also emerged. These indicated that whereas HC showed a greater valence effect for expected outcomes compared to BDR, BDR showed a greater valence effect than HC for unexpected outcomes. This was driven by a greater dlPFC deactivation for unexpected losses in BDR relative to HC. An overall increased effect of valence in BDR (relative to HC) was more pronounced in left hemisphere than right.

5.5.3. SUPPLEMENTARY DISCUSSION

At initial appraisal, NAcc activity in the BDR group differentiated small bets by reward probability (showing increase for likely gains as seen in the healthy control group), but showed indiscriminately high activity for large bets, irrespective of reward probability (three-way interaction when depressive symptoms controlled for). A possibility is that when the stakes are high, patients with BD are drawn more to the possible reward payoff and somewhat blinded to the loss – that is, appraisals are influenced more by an affective response to reward and fail to be moderated by the objective likelihood of its attainability (Johnson, 2005b). This ‘reward-value inflation bias’ was obscured by depressive symptoms, suggesting the involvement of state-dependent modulatory factors such as pessimism (i.e. negative outcome-expectancy bias; Eisner et al., 2008). BDR also showed reduced parametric coupling between EV and activity in right dlPFC, indicating inaccurate neural appraisal of EV. This replicates findings in mania (Bermpohl et al., 2010) and
again fits with psychological (Johnson, 2005b) and neuroimaging (O'Sullivan et al., 2011) reports of hyperoptimistic predictions about goal outcomes in BD.

During anticipation of impending outcome, VTA was more active in BDR over all conditions, indicative of an overall increase in attending to the potential reward on offer. Reward probability modulated activity in dIPFC and posterior parietal cortex (particularly in right hemisphere), consistent with roles in appraising the likelihood of goal-directed behaviours (e.g. Plassmann et al., 2007) and maintaining a representation in working memory (Honey et al., 2000), respectively. In line with our hypothesis that dIPFC indexes cognitive control, we present an interpretation of this finding as signifying the need for increased control when it is likely that a reward will occur (see main discussion). The probability effect was reduced in dIPFC in the BD group, who failed to show as large an increase in activation for likely rewards. This may signify that, like manic symptoms (see main results) depressive symptoms reduce top-down control over limbic circuits. An alternative interpretation of the dIPFC modulation by probability is that this region tracks the probability of reward and allocates attentional resources according to the probability of reward. By this view, the group difference may signify a negative-outcome expectancy bias in the BD group, a possibility that is supported by the finding that the group difference was no longer significant when controlling for depressive symptoms. We also found that reduced anticipatory dIPFC was associated with increased NAcc response to rewarding outcomes (see main findings). This could alternatively be explained as signifying variability in expectancy violation across patients. That is, for patients failing to activate dIPFC for high probability rewards the receipt of a rewarding outcome is more unexpected, leading to greater NAcc response. However, a negative-outcome-expectancy bias is not consistent with the increased anticipatory VTA activity found in the BD group (see above). Further work will be needed to clarify the role of the dIPFC during reward expectancy.
Across both groups, NAcc showed a main effect of magnitude, suggesting that this structure tracks the potential reward on offer irrespective of its likelihood (whether it is more likely to be a loss). It is possible that a distinct system tracks the potential loss, as already suggested (e.g. Yacubian et al., 2006), although our analyses did not address this. The BDR group showed greater anticipatory NAcc, particularly when rewards were likely and especially when depressive symptoms were controlled for, indicating greater engagement and subjective valuation of rewards in this group. This replicates the findings in another report of euthymic BD (Nusslock et al., 2012), and additionally demonstrates that this tendency is modulated by state symptoms.

At outcome, activity in NAcc across groups was consistent with reports in the literature that this structure responds to valence, magnitude and expectancy (Elliott et al., 2003; Knutson & Cooper, 2005). Parametric modulation by prediction error was also found in this region, along with right dIPFC, medial PFC and emotional portion of ACC, replicating previous reports (Corlett et al., 2004; van Eimeren et al., 2009). Contrary to our hypotheses, there were no group differences in the coupling between NAcc and prediction error. More surprisingly, increased coupling was observed the VTA and dIPFC for the BDR group. We previously reported a similar finding in an analogue sample of hypomania for representation of prediction errors in dorsal striatum (O'Sullivan et al., 2011) and this may represent increased tracking of motivational goals, which are overly valued in BD ((Johnson, 2005b; Johnson et al., 2012); see also main discussion).
Supplementary Figure 5.1. Patients with bipolar disorder show increased reward response when evaluating gain outcome compared to healthy controls [Contrast: BDR_{(Gain>baseline)} > HC_{(Gain>baseline)}] when controlling for depressive symptoms; p≤.001, k=20 voxels.
**Supplementary Table 5.1.** Activated foci for main whole-brain analysis. EV, expected value; PE, prediction error. Main effects and interactions with group did not reach statistical threshold and are not reported.

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CHAPTER 6: EVOLUTION OF REWARD NETWORK
ABNORMALITIES OVER TIME: EEG-FMRI INTEGRATION
IN BIPOLAR DISORDER
Abstract

Background:
Impulsive and risky decision-making in bipolar disorder (BD) may arise from attentional, motivational and cognitive differences. We sought to characterise whether abnormalities manifest across these stages of processing and their underlying neural systems.

Methods:
EEG was recorded concurrently with fMRI from 20 euthymic BD patients and 19 matched controls engaged in a Roulette task. A conventional ERP analysis quantified attentional (N1), motivational (FRN) and cognitive (P300) processing of gains and losses separately. We additionally employed electrocortical source analysis to detail the generators and relate them to the fMRI findings. We hypothesised that patients would show potentiated processing of gain outcomes across the time course of outcome evaluation.

Results:
Both groups showed potentiation of N1 for gain outcomes, but this was greater in the BD group and correlated with real-life risk-taking. Source analysis revealed that this N1 enhancement was driven by increased activity in precuneus and dorsomedial prefrontal cortex. In BD participants, FRN was reduced for both outcomes despite anterior cingulate hyperactivity for gains. A delayed latency of both ERPs and their sources was observed in patients.

Conclusion:
FRN amplitude correlated with striatal activity, supporting a dopaminergic origin. In BD, deviation in early attentional systems may drive the subsequent hypersensitivity to rewards by increasing the recruitment of mesocorticolimbic and associated motivational systems. Reduced processing efficiency may result in important peripheral information being processed in risky reward contexts. There may be potential for psychological interventions that target attention processes, such as mindfulness.
6.1. Introduction

A major strength of electrophysiological measurements is their direct measurement of neural activity and optimal temporal resolution. This aspect makes EEG well suited to the study of motivational processing which comprises multiple stages of processing that may evolve too quickly to be captured by current fMRI techniques. It has been proposed that distinct properties of motivational stimuli are encoded sequentially, with basic representation of outcome valence (good/bad) encoded earlier by the FRN (260-320 ms) and more elaborate representations of value and motivational significance encoded later by the P300 (300-600 ms) component (Sato et al., 2005; Wu & Zhou, 2009). Furthermore, the first evidence of even earlier modulation, in the sensory-attentional N1 component (~180 ms), was recently documented (Mason et al., 2012; Chapter 4), exemplifying the rapidly evolving dynamics of motivational processing. Accordingly, characterising the evolution of the reward-motivation network across early attentional (N1), later evaluative (FRN) and cognitive (P300) stages of processing enables a more precise characterisation of decision-making in BD. With the exception of the FRN however, these components have not yet been localised in motivational processing contexts, and the understanding of how sensory, motivation and cognitive systems interact has not been established. This gap in the literature precludes additional insight into the functional significance of these components and how they relate to findings from other imaging modalities, particularly fMRI. The gap is especially pronounced for studies of motivational decision-making in psychiatric populations, limiting our understanding of their pathophysiology and identification of targets for novel interventions. For example, there is evidence that early attentional (N1) deficits respond to mindfulness interventions (Jha et al., 2007), and behavioural and pharmacological interventions may be warranted by altered sensitivity in the reward system. Similarly, deviation in later cognitive processes (P300) may be more amenable to cognitive interventions.
When the visual N1 is elicited by target detection tasks it has been primarily localised to extrastriate cortex in the occipital lobe (Hillyard et al., 1995; Luck et al., 2000), and primarily represents the activity of the visual pathways. ACC has been implicated as an additional N1 generator, particularly for difficult (“high motivation”) stimuli, albeit in an auditory task (Esposito et al., 2009). In addition, the role of PFC in attentional modulation of the N1 has been established by a combined ERP-lesion study (Barcelo et al., 2000). Whilst there have been very few studies to examine N1 modulation in BD, there has been interest in establishing whether the visual processing deficits documented in schizophrenia (Foxe et al., 2001) also manifest in BD. There is preliminary evidence for early sensory deficits in clinical BD (reduction in both P1 and N1 amplitude) during target detection (Yeap et al., 2009). However, we have recently reported the opposite pattern in a motivational (delay-discounting) context (Mason et al., 2012; Chapter 4). Enhanced N1 was found for gains relative to losses, and this enhancement was greater in a hypomania-prone group. Because of its very early latency, the higher-level (i.e. non-sensory) information of valence and delay of outcomes can only modulate N1 through top-down modulation of the bottom-up sensory input (e.g. through prefrontal cortex; Barcelo et al., 2000). However, source analysis was not performed by Mason et al. (2012) study and so it cannot be determined whether the increased N1 found in the hypomania-prone group argues against the basic visual pathway deficiency identified by Yeap et al. (2009). It is possible that there is a hyper-attentional bias towards reward that overrides a basic visual pathway deficit, or that the visual pathway deficit is secondary to onset of the disorder and not detectable in at-risk groups. The present study sought to test these possibilities by examining N1 sources in a clinical population of BD.

The FRN has been directly linked to activity in the mesocorticolimbic network (Holroyd & Coles, 2002) and as such represents a critical bridge to the fMRI literature and the findings in (Chapter 5). Numerous studies localise the FRN to an anterior cingulate source (e.g. Bellebaum & Daum, 2008; Christie & Tata, 2009; Marco-Pallares et al., 2008), a region centrally involved in performance monitoring, response conflict, and compensatory adjustment of goal-directed behaviour.
Botvinick et al., 2004; Bush et al., 2002; Kerns et al., 2004). A dominant view is that this structure uses prediction error signalling to guide goal-directed behaviour (Holroyd & Coles, 2002) and FRN measurements in a hypomania-prone sample have indicated a positive (“rose-tinted”) bias when evaluating gains and losses (Mason et al., in press; Chapter 3 of this thesis). This was subsequently confirmed by a very recent study examining FRN in remitted BD patients (Ibanez et al., 2012).

Neuroimaging studies of ACC function in BD have produced equivocal results. During mania, increased ACC has been reported both at rest (Blumberg et al., 2000) and, of particular relevance here, during a decision-making task (Rubinsztein et al., 2001). However, studies during euthymia have yielded varied findings: whereas increased activity has been reported in an emotion task (Wessa et al., 2007), decreased ACC was reported during a study eliciting response conflict (Gruber et al., 2004). Because of the task differences, these results may not be contradictory; whereas on the one hand increased ACC response to emotional stimuli fits with affective lability, reduced ACC in conflicting situations may relate to the role of this structure in inhibiting risk-taking (Campbell-Meiklejohn et al., 2008). Collectively it seems that BD is associated with ACC hyperactivity in emotional and motivational contexts, but may be underactivated in situations requiring cognitive control or resolution of goal-conflict.

The P300 has a late latency and represents a conscious, cognitive evaluation of the motivational significance of outcomes (e.g. Branston et al., 2005) but its sources remain to be demonstrated in motivational contexts. In visual and auditory target detection tasks, its generators are widespread and have included dIPFC, ACC, posterior cingulate and inferior parietal lobe (Halgren et al., 1995; Winterer et al., 2001), as well as supplementary motor cortex in superior parietal cortex, superior temporal gyrus and the precuneus (Linden, 2005; Mulert et al., 2004). A clue to the underlying generators during motivational processing comes from a reward study that established a positive correlation between with P300 amplitude and frontal cortical volumes in OFC, ACC and dIPFC (assessed by structural MRI; Parvaz et al., 2012). Hypofrontality has been theorised in BD when processing emotional (e.g. Strakowski et al., 2012) and motivational (see section 1.1)
information, predicting reduced prefrontal activity during P300 latency. Psychophysiological studies provide some evidence for this, with reduced P300 amplitude during auditory target detection (O'Donnell et al., 2004), although other studies find that delayed P300 latency better characterises BD populations (Souza et al., 1995). However, limitations of these studies are that the patients were either in manic or mixed episode (O'Donnell et al., 2004) or clinical state was not described (Souza et al., 1995). A very recent report in euthymic patients found enhanced P300 discrimination between small and large outcomes (irrespective of valence), but this conflicted with their source analysis findings which found the contrary (Ibanez et al., 2012). Collectively it would seem most plausible that frontal sources are reduced in activity in reward contexts, consistent with decreased cognitive control in BD.

The present study aimed to characterise the evolution of the reward network during outcome evaluation. We focused on functionally defined windows spanning during early sensory-attentional (N1), prediction evaluation (FRN) and later cognitive (P300) stages. Despite a paucity of motivational processing studies in BD, the following predictions were formed for this group. First, at the early sensory stage we predicted that rewards would elicit potentiation of N1 and its extrastriate cortical sources, and that this would be more pronounced in patients (Mason et al., 2012). Second, we predicted a reduced dACC response during FRN-locked outcome evaluation for both gains and losses, consistent with previous reports of a “rose-tinted” evaluation bias (Mason et al., in press; Chapter 3 of this thesis). Finally, during later cognitive appraisal (P300) it was predicted that this group would evidence reduced prefrontal cortical activity, consistent with compromised effortful control in BD (Chapters 1 and 5).
6.2. Methods

6.2.1. PARTICIPANTS, SELF-REPORT MEASURES AND TASK

The demographics of the participants and the Roulette task are described in (Chapter 5; see Figure 5.1 for trial schematic). In this paper we focus on the outcome phase of the task. EEG data from one healthy control were unusable despite extensive cleaning of the fMRI artifacts. The final group sizes were therefore 20 euthymic patients diagnosed with bipolar disorder (BDR) and 19 healthy controls (HC). Scores from the online battery described in (Chapter 5) were correlated with ERP amplitudes (see below). In addition to the 20-item Hypomanic Personality Scale (Eckblad & Chapman, 1986; Meads & Bentall, 2008), we focussed on the 30-item Domain-Specific Risk-Taking (DoSpeRT) scale, which gives an indication of real-life risk-taking behaviours across financial, social, recreational, health and ethical domains (Blais & Weber, 2006). These allowed the relationship between risk-taking and reward- and attention- related ERPs to be quantified (DoSpeRT) and also allowed comparison to previous studies (Mason et al., 2012; Mason et al., in press; Chapters 3 and 4 of this thesis) exploring the relationship between these ERPs and hypomanic traits (HPS).

6.2.2. JOINT EEG-FMRI RECORDING

An fMRI-compatible EEG cap (Braincap MR; Brain Products GmbH; Gilching, Germany) with 63 Ag/AgCl electrodes was used. Impedances at each electrode were below 5 kOhm (scalp) and 30 kOhm (ECG) at the time of entering the scanner. A high sampling rate of 5000 Hz was used to aid characterisation of the gradient artefact for its subsequent removal (see below). The electrodes were routed to amplifiers by means of short cables to reduce the amount of interference, and the amplifiers were placed directly in the scanner bore (see 2.4).
6.2.3. REMOVAL OF FMRI ARTIFACTS

BrainVision Analyzer 2.0 (Brain Products GmbH; Gilching, Germany) was used for pre-processing, including cleaning of the gradient (GA) and ballistocardigram (BCG) artefacts.

To remove the GA a high-pass filter of 0.1 Hz was first applied to reduce the effect of drifts on the subsequent correction steps. Because the fMRI volume duration (i.e. time to repeat; TR) of 2400 ms was not integer divisible by the sampling rate of 0.2 ms, slice artefact detection and merging of micro-volumes was performed (see section 2.4). An automatic detection of slice-based artifacts (criterion: voltage acceleration > 800 /ms) yielded the correct number of slices based on the preset number of slices per volume and total number of volume acquisitions (plus dummy volumes). Slices were merged into 3-slice micro-volumes and a local average artifact subtraction (AAS; Allen et al., 2000; see also section 2.4 of this thesis) was performed with a sliding window of 21 samples. The data was high-pass filtered at 80 Hz and downsampled to 250 Hz.

To reduce the BCG artefact, automatic detection of the QRS cardiac cycle was performed on the ECG channel. Accurate placement of markers for the ‘R’ wave were checked and amended by visual inspection to ensure that the onset of each heart beat was accurately detected. AAS was performed with 21 samples per local average.

6.2.4. PREPROCESSING AND ERP AVERAGING

A maximum amplitude criterion of 200 μV was used to reject muscular movement and residual fMRI artifacts. Independent components analysis (ICA) was used to detect and remove blink artifacts. Data were re-referenced to an average reference, segmented into epochs around the presentation of outcome feedback
stimuli (-200 to 1000 ms post-stimulus). To ensure a sufficient number of trials in each condition, and to reduce the number of comparisons made in the source domain, the original task factors of expectancy and magnitude were collapsed before averaging. This also facilitated comparison with the fMRI analysis of this dataset. All participants had at least 50 trials per condition in the final averages, which were low-pass filtered to 30 Hz and exported to MATLAB® 6.5 (MathWorks, USA) for ERP extraction.

Event-related potentials were extracted by averaging the activity in each of the latency windows at the electrodes showing maximal activity (N1: PO7, PO8; FRN: FCz; P300: Pz). To address groups differences in the onset of N1 and FRN components (see Figures 6.1 and 6.2), different latencies were selected. For N1 the latencies were 200-280 ms (for HC) and 220-300 ms (for BDR). For FRN, latency windows 210-280 ms (HC) and 300-370 ms (BDR) were extracted. Finally, for P300 there was no between-groups latency shift and so a common window of 400-600 ms was selected.

6.2.5. ERP ANALYSIS

ERPs were compared across groups and conditions by means of a mixed ANOVA with factors valence (gain, loss) and group (HC, BDR). In addition, correlations were performed separately for each group to test the relationship between the 1) HPS and 2) DoSpeRT scores and amplitudes of N1, FRN and P300 components (gain and loss outcomes). To reduce the number of comparisons, only the recreational and financial risk-taking subscales were selected (which were found to be significant; see Chapter 5, Supplementary Material).
6.2.6. SOURCE ANALYSIS

The cortical generators of the N1, FRN and P300 were estimated for each subject and for gains and losses separately (see below). So as not to lose valuable information about potential differences in the chronometry of motivational processing between the two groups we extracted, for both groups, the sources from the FRN latency of the HC group ("early FRN") and the BDR group ("late FRN"). We argue that this is superior to making a single between-group comparison of their peak FRN latency, which would essentially be adjusting for the latency difference and therefore obscure useful insights into the putative differences with regards to onsets of each processing stage.

For source analysis we availed of a cross-validated Low Resolution Electromagnetic Tomography (cLORETA) (see Pascual-Marqui, 2002; Trujillo-Barreto et al., 2004). This approach constrains sources to cortical grey matter areas which comprise the dominant contribution to scalp potentials because of the macro-columnar organisation of this tissue that allows potentials to summate along a superior-inferior gradient (e.g. Nunez & Srinivasan, 2006; see general methods). Because of the inverse problem, the number of potential solutions (collections of neuronal sources) that could explain the scalp potentials approaches infinity (e.g. Trujillo-Barreto et al., 2004). LORETA solves this problem by selecting the sources that are spatially smoothest and accomplishes this estimate by means of a cross-validation function (Pascual-Marqui, 2002). Because of this, and the cortical constraint (above), this technique achieves relatively high localisation accuracy (within 14–16 mm of those identified through fMRI; e.g. Mulert et al., 2004).

The averaged time-domain (ERP) data for each of the latencies above were separately converted to images of current density magnitude within a three-dimensional head model defined by the MNI probability atlas (Mazziotta et al., 2001). Normalisation was performed to reduce inter-subject differences in global activity levels that could otherwise bias statistical testing. This involved subject-wise adjustment by the standard deviation in the baseline period (200 ms prior to
feedback). For each contrast of interest (gain versus loss, BDR versus HC), difference images were obtained through voxel-wise subtraction of the magnitudes of the solutions for the two conditions being contrasted for each participant. A Statistical Parametric Map was obtained by means of a voxel-by-voxel Hotelling $T^2$ test. To correct for multiple comparisons, a global activation threshold based on the expected type I error rate, according to the False Discovery Rate (Benjamini & Hochberg, 1995). We set this threshold to $p<.05$. 
6.3. Results

6.3.1. EVENT-RELATED POTENTIALS

All components were modulated by outcome valence (see Figures 6.1 – 6.3). Whereas the N1 \( [F(1,37) = 4.92, p=.03] \) and P300 \( [F(1,37) = 7.47, p=.01] \) were more pronounced for gains than losses, the opposite pattern was observed for the FRN \( [F(1,37) = 4.74, p=.04] \).

The N1 additionally showed a main effect of group \( [F(1,37) = 4.97, p=.03] \), with the BDR group showing a tendency for a larger N1 deflection compared to HC. There was also a valence-laterality interaction \( [F(1,37) = 4.97, p=.03] \) such that the difference between gains and losses was pronounced in the right hemisphere. The three-way interaction did not reach significance \((p=.21)\).

For FRN, there was a main effect of group \( [F(1,37) = 12.5, p=.001; \text{partial } \eta^2 = .252] \) such that this component was reduced (i.e. more positive) in BDR compared to controls. This corresponded to a large effect size \((\text{partial } \eta^2 > .13; \text{ Cohen, 1988})\).

There were no effects of group or interactions for the P300 component \((p\geq .3)\).
Figure 6.1. N1 at occipital electrodes. Healthy controls (top) and bipolar disorder in remission (bottom). Patients show a greater N1 amplitude at this laterality compared to controls ($p=.03$). Topography shows the difference (loss minus gain) at the shaded latency that was extracted for source analysis.
Figure 6.2. FRN at electrode FCz. Healthy controls (HC), bipolar disorder in remission (BD). Patients showed a substantially smaller (less negative) feedback-related negativity ($p=.001$), with delayed latency. Nevertheless, the topography plot shows a more pronounced difference (loss minus gain) at the shaded latency.

Figure 6.3. P300 at centroparietal electrode Pz. Healthy controls (HC), bipolar disorder in remission (BD). Topography shows the difference (loss minus gain) at the shaded latency that was extracted for source analysis.
Correlations in patients:

N1 amplitude was negatively correlated with HPS for both outcomes [gain: $r(20) = -.406$, $p=.07$, trend approach significance; loss: $r(20) = -.442$, $p=.051$] and with DoSpeRT recreation domain for gains [$r(20) = -.449$, $p=.047$]. P300 amplitude was positively correlated with DoSpeRT score in the financial [$r(20) = .478$, $p=.033$] and recreational domains for losses [$r(20) = .392$, $p=.088$; trend approaching significance], but not for gains. No other correlations reached significance ($p\geq.21$).

6.3.2. CROSSMODAL (FRN-BOLD) CORRELATIONS

Across groups, there was a positive correlation between gain-locked FRN voltage and BOLD signal in NAcc [$r(39) = .441$, $p = .005$] and vmPFC/vACC [$r(39) = .333$, $p = .038$] ROIs. Correlations for loss outcomes did not reach significance [$p \geq .19$].

![Figure 6.4](image)

**Figure 6.4.** Activity in nucleus accumbens (NAcc), as measured by fMRI, correlates with the feedback-related negativity brain potential (FRN, measured by EEG). Note that increased voltage corresponds to a smaller FRN (i.e. a lesser negative deflection).
6.3.3. SOURCE DOMAIN

6.3.3.1. N1 window

For the Gain>Loss contrast, both groups showed increased activity in bilateral extra-striate visual cortex (ESV). Only healthy controls (HC) showed increased left ventrolateral PFC as well as decreases in right ventrolateral PFC, supplementary motor area (SMA) and right medial temporal cortex. Only the BDR group demonstrated increased precuneus, as well as decreased dorsomedial PFC (dmPFC, bordering BA 9 and BA 10) and medial orbitofrontal cortex in this contrast.

HC showed greater activity than BDR in ESV and lesser activity in precuneus regardless of outcome valence (see Figure 6.5). HC also showed less activity than BDR in dmPFC/Frontal Eye Fields (BA 8) for gains, and right dmPFC for losses.
Figure 6.5. Generators of the N1. A) Across groups, gains (top) activate visual cortex and precuneus more than losses (bottom). B) Between-groups contrast maps for gains and losses. For both outcomes, patients with bipolar disorder show lesser activity than controls in visual areas, consistent with a visual processing deficit. However, greater activity than controls in attention areas; precuneus and dorsal prefrontal cortex may compensate for this deficit. This group difference in precuneus is more pronounced for losses than gains because controls show lesser precuneus activity for losses than gains, whereas bipolar participants show equivalent activation for both outcomes.
Whereas gains (compared to losses) elicited greater ESV in HC, the opposite pattern was observed in BDR. Furthermore, whereas HC activated superior temporal cortex but deactivated dmPFC/SMA in this contrast, BDR activated precuneus and SMA.

Between-group comparisons for gains confirmed that the BDR group showed reduced left ESV than controls, but greater dmPFC (BA 9; see Figure 6.6). For losses, the BDR group showed greater ESV activity than the HC group.

**Figure 6.6.** Sources during early FRN window. A) Across groups, losses (bottom) activate an anterior midline cortical source more than gains (top). B) Between-groups contrast maps for gains and losses. For losses, patients with bipolar disorder (BDR) show less activity than controls in a midline dorsal cortical area encompassing supplementary motor area, but the opposite pattern for gains. Relative to controls, patients also continue to activate precuneus more for gains.
6.3.3.3. Late FRN window

In HCs, gains elicited greater ESV and lesser dmPFC (extending into SMA). As with the early FRN window BDR showed the opposite pattern to HCs, and additionally showed greater precuneus activity for gains than losses.

Between-group comparisons confirmed that HCs showed lesser ACC and precuneus than BDR for gains (see Figure 6.7). For losses, HC showed lesser ESV and bilateral superior temporal cortex than BDR. In addition, there was dissociation in dmPFC activity for losses; HC showed greater activity in a more posterior portion (BA 9), whereas BDR showed greater activity in a more anterior portion of dmPFC (BA 10).
Figure 6.7. Sources during late FRN window. A) Across groups, the regions recruited are similar to that of the early FRN window, with losses (bottom) activating an anterior midline cortical source more than gains (top). B) Between-groups contrast maps for gains and losses (note that “relative $T^2$ value” refers to the size of the difference of the [positive] $T^2$ values between-groups). For losses, patients with bipolar disorder show lesser activity than controls in dorsomedial prefrontal / paracingulate cortex, consistent with lesser evaluative activity, but the opposite pattern for gains. For gains, a more anterior source is active which may indicate contribution from additional sources, such as ventral anterior cingulate (see main text).
In HCs, gains activated ESV, left precuneus extending into SMA, right superior temporal cortex and left dmPFC (relative to losses). A similar pattern of activations was observed in BDR group.

Between-groups comparisons confirmed greater gain-locked SMA activity in HC (compared to BDR) but lesser activity in midline dmPFC and precuneus (see Figure 6.8). The same pattern emerged for losses, although the greater dmPFC activation in BDR was more right-lateralised.

Figure 6.8. Sources during P300 window. A) Across groups, a fronto-temporo-occipital network is recruited with more frontal activity for gains (top) than losses (bottom). B) Between-groups contrast maps for gains and losses. For gains but not losses, patients with bipolar disorder show greater activity than controls in dorsomedial prefrontal, consistent with preferential evaluation of rewards.
6.4. Discussion

6.4.1. ERP AND SOURCE-DOMAIN ANALYSES

Here we uncovered both early attentional and later evaluation differences in patients with euthymic BD. Consistent with our predictions we found a highly substantial reduction in the FRN as measured by mean voltage, corroborating our previous report of FRN reduction in non-clinical hypomania (Mason et al., 2012; Mason et al., in press). This suggests that BD is underpinned by a sensitivity of the mesocorticolimbic pathway to reward, which may contribute to risky reward-seeking behaviours (APA, 2000) and extreme goal-striving (Johnson, 2005b). We also demonstrate that hypomanic symptoms and real-life recreational risk-taking behaviours potentiate an early attentional bias toward motivational outcomes, as indexed by the N1 component. This may potentiate the recruitment of the mesocorticolimbic pathway for gains, as indexed by marked FRN reduction in patients. Finally, an information processing delay, in concert with biases in these selection mechanisms, may lead to important periphery information from being dropped before conscious awareness (P300 latency).

We have previously demonstrated that the N1 is potentiated for gain outcomes, and that this effect is exaggerated in hypomania-prone individuals (Mason et al., 2012). In the present study, we extend this finding by demonstrating that rewards elicit increased activity in extra-striate visual cortex (ESV), relative to losses. However, whilst we replicate an increased gain-locked N1 ERP in BD, this group demonstrated reduced ESV activity (compared to controls), contrary to our hypotheses and the ERP domain results reported here and previously (Mason et al., 2012). Importantly, our N1 source network also incorporated dmPFC (BA 8; see below), which is consistent with an influential lesion study demonstrating prefrontal augmentation of the N1 component. By this view, top-down attentional...
processes maintain a “sensory template” that is compared with incoming visuosensory information, facilitating matches (Barcelo et al., 2000). In this way, our finding extends a previous report of a core visual processing deficit in BD (Yeap et al., 2009) suggesting that this can be ameliorated or offset by stimuli with high motivational significance by increased attentional tracking. BA 8 incorporates the frontal eye fields and has previously been linked to contexts of high uncertainty (Volz et al., 2005) and hope (Chew & Ho, 1994), which presumably warrant increases in visual attention. The greater activation in precuneus in patients relative to controls further supports this view of attention (Fliessbach et al., 2007; Le et al., 1998).

However this early facilitation of reward outcomes did not manifest in later anterior midline systems involved in performance-monitoring and outcome evaluation. Whereas this system differentiated loss outcomes from gains in controls, discrimination of valence was reduced in the BD group at both early and late FRN windows. This is again in accordance with a previous FRN study in non-clinical hypomania, and may represent a dampening of the aversive impact of losses or “rose-tinted” evaluation bias (Mason et al., in press). In the present study we hypothesised that this reduction in FRN in the BD group would be accompanied by less ACC activity. However, we found that anterior midline activity was increased in patients, at least for gains. This may be driven by an exaggerated affective response that fails to be modulated by the objective value of feedback (see next section for an integration with the fMRI findings from this dataset). It should be noted that the major FRN source extended outside of ACC to more superior areas, including SMA and dorsomedial PFC. A similar source has been implicated by other studies (e.g. Bellebaum & Daum, 2008), and this may result from the relatively poor spatial accuracy of EEG source localisation techniques (typically around 10-20 mm; Liu et al., 2002). Alternatively, dorsal PFC also subserves evaluation across a range of tasks (e.g. Northoff & Bermpohl, 2004) and frequency-domain EEG studies have uncovered a more distributed frontal network associated with the FRN (Christie & Tata, 2009).
At the later FRN stage, the anterior region responding to valence in the controls was more posterior, compared to the early FRN time point. This shift towards premotor cortex could reflect the relay of an initial evaluation in ACC to premotor regions for behavioural adjustment, which is in line with performance monitoring accounts (Gehring & Willoughby, 2002; Holroyd et al., 2008) and the finding that these structures coactivate in fMRI studies (Holroyd et al., 2004c). Conversely, patients showed greater activity in a source that resembled the earlier ACC source seen in controls, indicating a lag in propagating the signal to premotor regions and slower information processing in the patient group. This is corroborated by the delayed FRN-ERP latency (see Figure 6.2) and by previous reports of delayed ERP latency in BD (Bruder et al., 2009; Muir et al., 1991; Schulze et al., 2008; Souza et al., 1995). This was further corroborated by the subsequent pattern of source activity in the P300 stage, where the patient group showed continued activation the ACC source seen earlier in controls, but extending more diffusely into right dorsomedial PFC. This again resembles the pattern of source activity seen earlier in controls, particularly that of a frequency domain decomposition which typically occurs earlier in processing (Christie & Tata, 2009; see above). It has been proposed that the extremely large amount of incoming visual information is too vast for it all to be processed, resulting in a “bottle-neck” in which the most salient and goal-relevant information is selected for (Pashler, 1994). Impulsivity may result in an accentuation of this mechanism, causing peripheral information to be discarded, which has been demonstrated clinically (e.g. in psychopathy; Baskin–Sommers et al., 2011). The general inefficiency in information processing identified in BD here and elsewhere could plausibly lead to frequent “bottle-necks” that cause relevant information to be dropped in favour of subjectively salient information, such as that pertaining to reward. Although speculative at this point, this is consistent with the early attentional bias to this information. It is worth noting that the temporal resolution of fMRI is unable to detect this perturbation to the chronometry of information processing, highlighting the additive value of EEG for identifying disorder pathophysiology. Furthermore, source-domain analysis was able to uncover important differences that were not visible at the ERP-domain.
Contrasting with previous reports of delayed P300 latency in BD (Bruder et al., 2009; Muir et al., 1991; Schulze et al., 2008; Souza et al., 1995), we found intact latency in this component. This may be due to differences in stimuli: whereas these studies utilised an auditory target detection task, our study involved visual feedback of high motivational significance, pointing towards a context-specific deficit akin to the N1 findings. The present findings also demonstrate how the study of processes in clinical populations can inform understanding of the mechanisms in the general population. The traditional view is that ERPs proceed sequentially, with an initial and primitive FRN evaluation of valence followed by a subsequent and elaborated P300 evaluation incorporating reward value or other information from working memory (Wu & Zhou, 2009). Our findings challenge this hierarchical or “serial progressive” view of processing and suggest that processing can proceed in parallel: BD patients demonstrated preserved P300 latency despite delayed FRN. This is in keeping with numerous reports that FRN is sensitive to additional higher-level parameters such as value (e.g. Kamarajan et al., 2009; Kreussel et al., 2012; San Martín et al., 2010), and delay (Mason et al., 2012). Alternatively, the decoupling of these components in BD patients may mean that the lagging FRN information does not make it into conscious representation (P300). A consequence would be that decisions are governed by an incomplete appraisal of all factors, which may explain impulsive, risky and later regretted decisions in BD (APA, 2000). Further work will be needed to test this possibility.

6.4.2. INTEGRATION OF EEG AND FMRI FINDINGS

This section provides a conceptual fusion of the present EEG source findings with the concurrently acquired fMRI findings (Chapter 5), highlighting the similarities and differences. A particular focus is on the methodological and theoretical implications for performance-monitoring and motivational; particularly in addressing ongoing questions on the functional significance of the FRN component.
6.4.2.1. Is the dorsal anterior cingulate the single source of the feedback-related negativity?

Functional MRI is an invaluable tool for characterising motivational processing, because of the central involvement of subcortical structures (midbrain, limbic and basal ganglia) which contribute minimally to the EEG signal (Luck, 2005; see section 2.2 of this thesis). However, an influential ERP account asserts that the FRN component is generated in dACC after receiving subcortical dopaminergic afferents (Holroyd & Coles, 2002; Holroyd et al., 2008), providing a theoretical interface for fMRI and EEG studies. However, fMRI studies do not support the classical FRN pattern of greater ACC activity for losses compared with rewards (the opposite is generally found; Carlson et al., 2011; at least in ventral portions of ACC). The present study is well placed to contribute to the debate on the relationship between the FRN and mesocorticolimbic network and to provide a more definitive framework for integrating different measures of pathophysiology in BD and other disorders.

Through EEG, we replicate previous findings of a dACC source that activates more for losses than gains. However, the fMRI findings failed to find this pattern and instead found the reverse (Figure 9). Rather than highlighting sources that are “invisible” in one modality, or “extra” in another, these findings appear harder to reconcile. A major consideration for this discrepancy is the heterogeneity of the ACC, which is implicated in target selection, novelty detection, response selection, performance monitoring, response conflict, and working memory (see Bush et al., 2002). Indeed, in the macaque homologue, the rostral cingulate motor area, some cells respond to rewards and others to errors (Procyk et al., 2000) and fMRI studies demonstrate similar heterogeneity between adjacent ACC clusters in humans (Bush et al., 2002; Fujiwara et al., 2009). Bush et al. (2000) proposed functional
subdivision of the ACC into “affective” (ventral) and “cognitive” (dorsal) portions, with this latter section implicated in conflicting situations requiring behavioural adjustment (Botvinick et al., 2004; Holroyd & Yeung, 2012). In line with this, there is some fMRI evidence that errors activate the cognitive portion with rewards activating the more ventral-affective subregion (Fujiwara et al., 2009). Our findings are in accordance with this possibility.

A recent EEG study that decomposed the FRN using principle component analysis (PCA; Dien et al., 2003) offers additional insight into this. Foti et al. (2011) found that the traditional negative deflection (“default FRN”, largest for losses) is offset by a reward-related subcomponent (“reward positivity”). Whilst these authors used dipole-fitting to argue that striatum was the primary source, this has been heavily criticised (Cohen et al., 2011) on the grounds that deep, non-laminar sources contribute minimally to scalp potentials (see also section 2.2 of this thesis). Accordingly the ventral ACC is a more plausible source, given that it is adjacent to striatum, explained the second most amount of variance of the scalp potentials (Foti et al., 2011) and was implicated by separately collected fMRI data of the same task (Carlson et al., 2011). Our findings provide support for the possibility that the mesocorticolimbic pathway generates the “reward positivity”. We found that following reward outcomes, the BOLD response in NAcc and vACC correlated with FRN voltage (Figure 6.4). By this view, the significantly reduced (i.e. more positive) FRN observed in the patient group may reflect a dominance of vACC, rather than the dACC source observed by electrocortical localisation. In support of this, the exact spatial location of the dACC source differed between groups, particularly for gains. It can be speculated that the estimated source was more anterior in patients because of a greater vACC contribution in this group (see Figure 6.9). Future studies deconstructing the FRN contributions will be needed to shed light on the relative involvement of these two neural generators.

Another source of the intermodality discrepancy may be the low temporal resolution of fMRI (typically 1-2 seconds) and so the gain-related activity it detects could be a later and more sustained response than the early EEG-FRN dACC activity. This possibility is made tenable by ERP studies that have shown that the
FRN is succeeded by functionally distinct positivity that arises from the same source and has a long latency (Endrass et al., 2007; San Martín et al., 2010; Veen & Carter, 2002). Furthermore, the P300 has previously been linked to dACC (see Linden, 2005) and in the present study showed a sustained response that was larger for gains than losses: both in the ERP domain and in an underlying anterior midline source.

Figure 6.9. Reward>Loss contrast ($p<.0001$, 100 voxel extent threshold) from the fMRI analysis (see Chapter 5). Whereas controls (left) recruit dorsal (“cognitive”) anterior cingulate cortex (ACC) and right dorsolateral prefrontal cortex, patients with bipolar disorder preferentially recruit ventral (“affective”) ACC.
Figure 6.10. Reduced dACC-FRN in patients may arise from a relative dominance of affective (ventral) portion of ACC. This may be due to the mesocorticolimbic hyperactivity (yellow arrow) established by the fMRI findings. By this view, hyperactivity in ventral ACC occurs at the same time as in dACC (controls) and may bias estimation of sources in the anterior direction (patients). dACC = [dorsal] anterior cingulate cortex; FRN = feedback-related negativity

6.4.3. LIMITATIONS OF ELECTROCORTICAL SOURCE ANALYSIS

The present study demonstrates the additive value of source space analysis. However, whilst we reported “snapshots” averaged across established and functionally defined ERP latencies, a reconstruction of the full ERP time-course in the source domain would facilitate better characterisation of the time course of deficits. Second, a typical pre-stimulus baseline was selected for both for ERP averaging and for normalising the source maps (scaling by each individual’s own range of activity). However, during this period participants viewed the rotating roulette wheel in anticipation of the outcome (Figure 5.1; ‘Anticipation’ stage),
which elicited a steady-state visually evoked response at the constant frequency of the wheel rotation (e.g. Lovegrove et al., 1990), observable in the ERPs (Figures 6.1 - 6.3). Although the steady-state response did not differ between conditions or groups, we cannot completely rule out that differences in this baseline of neuronal activity affected both ERP and source analysis procedures. Finally, the statistical analysis of the source maps could be extended by future work. Whilst we used FDR-corrected Hotelling $T^2$-tests for each source map, a factorial ANOVA treatment of the source maps would have allowed valence and group interactions to be explicitly tested, as well as to reduce the number of comparisons (although the results were unchanged when FDR $p$ values were further Bonferroni corrected for the number of $T^2$-tests).

6.4.4. CONCLUSION

In conclusion we report electrophysiological source-space evidence of hypersensitivity in reward networks that converges with the accompanying fMRI findings (reported in Chapter 5). We replicate an early attentional bias to motivational information in a hypomania-prone sample (Mason et al., 2012) and showed that this overcompensates for a basic visual processing deficit and subsequently leads to over-recruitment of reward circuitry (FRN window). In concert with a delayed information processing deficit, this may lead to important peripheral information being dropped from conscious awareness. Integration with fMRI findings highlights a potential dual-source account of the FRN, which may account for the substantial inter-study variability in the exact sources (and topography) of the FRN. In the BD group, a potential dACC-vACC imbalance may further fuel reward hyper-responsivity and down-regulate error processing, akin to the ERP findings from (Chapter 3). Decomposing the FRN into its subcomponents may be a useful approach for shedding further light on this.
CHAPTER 7: GENERAL DISCUSSION

Abstract

This thesis aimed to characterise the neural systems underpinning motivational dysregulation in bipolar disorder (BD) by availing contemporary neuroscience techniques, theory and paradigms. In particular the goal was to better understand the neural mechanisms involved in impulsive and risky decision-making. We hypothesised that these behaviours are causally related to a core hypersensitivity to reward as instantiated by abnormalities in the mesocorticolimbic pathway. In this final chapter the findings from the previous chapters are summarised and evaluated in relation to the hypotheses and predictions made at the outset. The main themes are teased apart and lead to an updated model of reward dysregulation in BD.
In Chapters 3 to 6 of this thesis, findings from converging modalities (behaviour, EEG, fMRI) have been presented that collectively indicate disruptions in motivational processing and decision-making in BD. These are summarised below.

In Chapter 3, reinforcement learning and outcome evaluation were probed in relation to hypomanic traits. Behaviourally, a hypomania-prone group demonstrated impaired acquisition of the reward contingencies. Through EEG, this study replicated findings that the FRN brain potential represents the activity of an evaluatory system. Specifically, that signifies rewarding outcomes (gains) elicited reduced FRN amplitude as compared to aversive (loss) outcomes. Consistent with the hypothesis of increased reward sensitivity in the hypomania-prone group, these participants evidenced a more pronounced amplitude reduction for the FRN elicited by gains. Losses also elicited a reduced (more gain-like) FRN in the hypomania-prone group; a profile consistent with the decreased punishment sensitivity reported in impulsivity (Hall et al., 2007). Given that FRN has been argued to reflect a corollary of dopamine-dependent prediction errors impacting on the ACC (Holroyd & Coles, 2002; Holroyd et al., 2008), the FRN differences detected in the hypomania-prone group may account for the learning deficits that are manifested behaviourally. Indeed, a tendency to evaluate negative outcomes more positively could lead to the maintenance of maladaptive and risky behaviours by failing to update future expectations of those behaviours.

In Chapter 4, the proposal that hypomania is associated with impulsive decision-making was tested using the delay discounting framework. Behaviourally, hypomania-prone participants chose immediate reward more often than the low hypomania group in a free-choice task, indicating steeper discounting of delayed rewards. The electrophysiological findings converged with this immediacy bias; in an adapted task the hypomania-prone group showed greater neural differentiation
between immediate and delayed rewards (a steeper discounting gradient for increasingly delayed rewards), relative to the low hypomania group. These findings arose both in an early, attention-sensitive (N1) and a later, outcome evaluation (FRN) component, raising the possibility that an attentional bias may be a key driver both of the discounting profile and of the differences in reward system functionality inferred from the FRN.

In Chapter 5, fMRI was used to deconstruct reward and loss processing into more specific constructs borrowed from neuroeconomics and learning theory (valence, probability, magnitude, expected value and prediction error parameters). Neural activity in euthymic patients diagnosed with bipolar disorder and matched controls was sampled at three time points during each bet of a Roulette game, permitting separate characterisation of 1) initial appraisal of value, 2) top-down anticipatory processes and 3) outcome evaluatory processes. Relative to controls, patients showed evidence of impaired encoding of expected value and hyper-optimism when anticipating outcomes, combined with an increased striatal response. Weaker top-down control, both during anticipation and during outcome evaluation, was associated with potentiation of the reward response, consistent with a previous report of reduced prefrontal function during a reward task (Jogia et al., 2011). There was evidence that representation of prediction error was intact but either biased towards positive evaluation, or towards a tendency to attach more motivational significance to unexpected and large rewards. Finally, mood state modulated these traits features in two notable ways: whilst residual depressive symptoms blunted the reward response, residual manic symptoms may have enhanced it by further dysregulating the loosened anticipatory top-down control of the nucleus accumbens.

The work in Chapter 6 availed of the superior temporal resolution of EEG, which was recorded simultaneously during the Roulette fMRI task, to more carefully examine the evolution of the reward and attention networks during outcome evaluation. The ERP-domain analysis replicated the early attentional bias to reward and demonstrated that this was modulated both by level of hypomanic personality traits and by predilection for recreational risk-taking. The source-space
analysis revealed that a visual processing deficit is offset by increases in cortical regions implicated in attentions (precuneus and frontal eye fields), consistent with top-down shaping of the N1 (Barcelo et al., 2000). In addition, the marked reduction of the FRN component observed in our hypomania-prone sample was replicated in BD patients. Both findings may be related to an imbalance in its underlying dorsal and ventral anterior cingulate sources: particularly an up-regulated reward response in the ventral frontostriatal pathway. This was accompanied by a delayed latency of these processes relative to the control group, highlighting disrupted chronometry of information processing in BD.
7.2. Synthesis and relationship to hypotheses

7.2.1. HYPOTHESIS 1: IMPULSIVITY AND RISK-TAKING IN BIPOLAR DISORDER ARISE FROM INCREASED SENSITIVITY TO REWARD

Findings from Chapters 1, 3 and 5 support this view, providing converging theoretical, electrophysiological and functional neuroimaging evidence for reward hypersensitivity in bipolar disorder. The evidence for each specific prediction is detailed below.

7.2.1.1. Prediction 1a: Reward hypersensitivity will manifest in early, reflexive processing

Emotion, cognition and decision-making may be strongly influenced by rewarding stimuli because of their impact at an early, pre-conscious level, and patients with BD may be particularly susceptible to these stimuli (Urosevic et al., 2008). Understanding more about the reflexive processing of motivational stimuli may inform therapies that either target these processes directly (e.g. pharmacological interventions) or indirectly via regulatory or reappraisal processes at the cognitive level (psychological interventions).

To probe early stages of motivational processing, the work in Chapters 3, 4 and 6 availed of the high temporal resolution of EEG and utilised the FRN (and activity in its underlying neuronal sources) as the primary physiological marker of reward sensitivity. Attenuated FRN for rewards and losses was observed in both clinical (Chapter 6) and non-clinical (Chapters 3 and 4) samples, consistent with a tendency to positively evaluate outcomes in early processing. In addition, biases towards immediate rewards were manifest at this early pre-conscious stage, as
signalled by a steeper increase in FRN amplitude for delayed outcomes in the hypomania-prone sample (Chapter 4). Collectively this suggests that patients and non-clinical at-risk samples respond strongly to rewarding stimuli before they are consciously aware of them. This response plays a role in the rapid upward cycle of risky reward-seeking behaviours seen clinically; perhaps especially in situations where there is pressure or desire to make decisions rapidly and spontaneously. When the chain of decisions evolves rapidly, the exaggerated reflexive impact of rewards (and dampened impact of losses) may govern behaviour more than slower, effortful cognition, posing problems for cognitive-level interventions.

An unexpected finding arising from Chapter 4 (replicated in Chapter 6) was that motivational processing abnormalities were manifested even earlier, at the sensory processing level, preceding the FRN. In both the at-risk and clinical populations the processing of reward-related visual information was facilitated, as indexed by potentiation of the N1 and its underlying sources. In spite of this enhancement, source-domain analysis revealed a extra-striate visual processing deficit in patients (Chapter 6), consistent with a previous report in a target detection task (Yeap et al., 2009). In the ERP-domain however, this previous study reported N1 attenuation in patients – the opposite of our findings. In reward-related contexts, it would appear that a core deficit in extra-striate visual processing can be ameliorated by increased recruitment of precuneus and dorsomedial prefrontal attentional systems. This is the first demonstration of how attentional systems drive both sensory and reward processing in healthy and BD samples. Importantly, it highlights the potential for therapies that intervene at the attentional stage (such as mindfulness), which may be effective in ameliorating abnormalities “downstream” in later stages of processing.

This also highlights an important methodological consideration when utilising early sensory components as biomarkers for sensory processes (e.g. in studies of schizophrenia; Foxe et al., 2001; Koychev et al., 2010). It will be important to bear in mind that finding (or not-finding) abnormality in clinical populations may be domain-specific and dependent on the task stimuli used. More generally, the finding that a steeper discounting trajectory is manifested in the N1
highlights that complex reward representations are selected for early in sensory processing (in this case, temporally discounted value; i.e. valence combined with delay). This is subtly different from, and extends, the classical delay discounting interpretation which predicts that reward value is discounted – instead, it suggests that it is the amount of attentional resources that is “devalued” by delay. This may precede, or at least interact with, the way in which incentive salience is signalled by dopamine activity (Berridge & Robinson, 1998). Future work will be needed to examine the interaction between these mechanisms, and to clarify the role of attention in selecting for and amplifying clinically relevant visual cues, such as those associated with illicit substances and paraphernalia.

A limitation is that we did not examine the role of attention during anticipation of outcomes. A possibility is that greater facilitation of reward outcomes in patients (N1 potentiation) is related to the positive-outcome-expectancy bias revealed through fMRI (increased VTA activity during anticipation; Chapter 5). The stimulus-preceding negativity has been shown to differentiate anticipation of painful from non-painful stimulation (Brown et al., 2010), and could similarly be used to establish whether patients show increased attention and arousal when anticipating rewards.

7.2.1.2. Prediction 1b: Reward hypersensitivity has its pathophysiological roots in the mesocorticolimbic network

Whereas Prediction 1 dealt with identifying deviations in temporal processing of motivational information, Prediction 2 is focused on identifying the neural bases of those differences spatially, within a neurobiological framework. Importantly, this allows the findings from both EEG and fMRI modalities to be discussed in a common domain. It may additionally provide insight into the therapeutic mechanisms of current pharmacotherapies, and could highlight targets for novel compounds. Whereas in Chapters 3 and 4 dysfunction in the wider
mesocorticolimbic (MCL) network was inferred from an electrophysiological marker of the dorsal ACC, the findings in Chapters 5 and 6 offered insight into the interface of the dorsal ACC with the ventral ACC and subcortical MCL components. The evidence from each is summarised and discussed below.

Through fMRI, Chapter 5 provided the most direct evidence for MCL hyperactivity in BD. Patients activated ventral tegmental area (VTA), nucleus accumbens (NAcc) and ventromedial prefrontal cortex (vmPFC, which encompassed ventral ACC) to a greater degree than matched controls, connecting clinical symptoms of motivational dysregulation and risk-taking to specific physiological abnormalities. This is timely given that the DSM-V research priorities emphasise the value of physiological markers for improving diagnostic and treatment outcomes (APA, 2000). Importantly, Chapter 5 extends findings of MCL abnormality during acute mania (Abler et al., 2007c) by demonstrating that this is a core feature that perseveres in remission. This converges with another recent report in euthymic BD (Nusslock et al., 2012) but whilst this other study found deviation in reward anticipation but not outcome, our findings suggest perturbation in both phases. This discrepancy may relate to differences in the sample tested: whereas our study excluded antipsychotic medication, theirs did not, potentially masking key pathophysiological differences in the dopaminergic mesolimbic system (e.g. Hallahan et al., 2011).

Based on theoretical accounts that dACC is the principle neural generator of the FRN (Gehring & Willoughby, 2002) and that this structure receives inputs from midbrain dopaminergic projections (Holroyd & Coles, 2002), this thesis was also able to infer MCL differences in reinforcement learning (Chapter 3), delay discounting (Chapter 4) and outcome evaluation (Chapter 6) contexts. This provides converging electrophysiological evidence for hyperactivity in dopaminergic pathways across non-clinical at-risk and clinical samples. One exception was observed: in spite of reduced FRN in the ERP domain, the EEG
source-space analysis in Chapter 6 nonetheless revealed greater dACC activity in BD patients, specifically for reward outcomes. In light of recent source localisations of the FRN (Carlson et al., 2011; Foti et al., 2011), it is concluded that a second, reward-specific source in ventral ACC contributes to this anomalous finding. Chapter 6 proposes that FRN reduction in patients represents a dominance of this ventral contribution over that of dACC, which results in estimation of a single source that is located between these true sources (see Figure 6.10 and section 7.2.1.3).

This dual-source conceptualisation of the FRN has theoretical implications for the motivational decision-making literature at large. Whereas a dominant theory asserts that the FRN is singly generated by dACC and inhibited by dopaminergic efferents (Holroyd & Coles, 2002; Holroyd et al., 2008), this mechanism was not supported by the above finding in patients. The combined EEG-fMRI findings instead indicate a second source in vmPFC, which may be better placed to modulate the FRN on reward trials due to dense innervation from dopaminergic efferents. However, further studies involving intracranial electrodes capable of resolving electrical sources with higher spatial accuracy will be needed to better establish or refute this possibility. It is noteworthy that this general mechanism was revealed through comparison with the patient group, illustrating how clinical neuroscience can inform scientific understanding of motivational processes in the general population.

Related to the discrepancy across neuroimaging modalities, it has been proposed that fMRI recordings fail to identify greater activity in dACC for losses because of the task typically used. Because simple gambling tasks generally do not elicit substantial intra-goal conflict, they only require recruitment of ventral frontostriatal circuits involved in stimulus-response learning (Holroyd & Yeung, 2012). These authors propose a hierarchical systems view in which dACC can suppress frontostriatal learning of actions when it is adaptive to do so. Specifically, when these actions lead to immediate reinforcement but ultimately contravene an overall goal or, conversely, when actions bear initial cost but yield success more distally. Reduction in this capacity may also be related to bias towards immediate
rewards, highlighted in Chapter 4. Studies utilising more complex tasks may further elucidate the dorsal-ventral division of anterior cingulate systems, as well as the putative imbalance in BD. In addition to their validity for real-life decision-making, their clinical relevance is highlighted by the dysregulated goal-pursuit (Johnson, 2005b) and goal-conflict (Mansell et al., 2007) that are central to BD.

7.2.1.3. Prediction 1c: There is an imbalance between reflective prefrontal and reflexive limbic impulses

Current diagnostic conceptualisations of BD based on the biomedical model emphasise fixed and vague neural deficits that do not take account of psychological factors and relegate the patient to a passive vector for disease processes (Sonuga-Barke & Fairchild, 2012). A neurobiological model that specifies how cognitive control processes can impact on the more automatic and unconscious impulses would advance current conceptualisation of the disorder and provide a common framework within which the mechanisms of pharmacological and psychological interventions can be understood and evaluated.

The work in Chapter 5 made use of fMRI to holistically examine both reflexive (bottom-up) and reflective (top-down) processes. Consistent with Prediction 1c, BD patients increased activity in the ventral frontostriatal pathway was related to decreased anticipatory and outcome-locked top-down control (dIPFC). Hence, two distinct but interacting mechanisms may contribute to impulsivity and risk-taking in BD: a reflexive “hot” impulse to approach rewards (in spite of objective value and likelihood that they will be obtained; see Hypothesis 3), coupled with a lesser reflective (“cool”) influence that modulates the “hot” impulse. This may lead to difficulties in maintaining long-term goals and considering other, superior options, as has been proposed by a neuroeconomics
account of ADHD (Sonuga-Barke & Fairchild, 2012). In addition, a previous report linked reduced frontopolar cortical efficiency to both reward and working memory impairment in euthymic BD (Jogia et al., 2011). However, causality cannot be inferred at this stage and studies directly manipulating dIPFC activity through intervention (e.g. by instructing participants to reappraise outcomes; Staudinger et al., 2009) will be needed to confirm or disprove this potential mechanism.

The finding that MCL network abnormalities were additionally modulated by residual mood symptoms is in accordance with neurobiological accounts of emotional dysregulation in which prefrontal dysregulation leads to greater limbic reactivity to affective stimuli (e.g. Phillips et al., 2008; Strakowski et al., 2012). This shared neural mechanism can account for how goal-attainment and goal-failure can trigger relapse into mania and depression, respectively (Johnson et al., 2008). In particular, there was evidence that manic symptoms exacerbated the prefrontal control deficit, which dovetails with a meta-analysis identifying reduced PFC as a state marker for mania (Chen et al., 2011). Longitudinal designs that examine PFC fluctuation between euthymic and prodromal states of BD will be needed to establish causality, but there is initial evidence that stabilising a “regulatory” or “supervisory” system is effective in preventing mood swings (e.g. Searson et al., 2011). Ultimately this may also be accomplished by novel pharmacological agents that enhance prefrontal cortical function, or by neurofeedback training.

Implications for the BAS dysregulation theory

The BAS dysregulation theory of BD (Alloy et al., 2009; Urosevic et al., 2008; see section 1.1 of this thesis) remains the dominant account of mood swings and has shaped important clinical interventions (e.g. Nusslock et al., 2009). The BAS dysregulation account has a number of limitations, however, and these are summarised below, along with the additive value offered by the current model.
First, despite being proposed as a brain-based system since its conception, a lack of physiological research has left the model disconnected from current cognitive neuroscience perspectives of motivation and emotion, and as such the BAS remains an overly broad concept (Johnson et al., 2012). Just as the understanding of other disorders has been enriched by the application of neuroeconomic and cognitive neuroscience frameworks (e.g. Monterosso et al., 2012; Sonuga-Barke & Fairchild, 2012), consideration of these parameters offers an opportunity to better specify the biopsychological mechanisms involved in motivation and emotion in BD.

Second, the BAS model does not provide an adequate account of mixed episodes, in which patients experience high levels of both negative and positive affect simultaneously (Meyer & Hofmann, 2005). The model supported by the current thesis can account for mixed states as the simultaneous oscillation of limbic systems mediating appetitive and aversive stimuli (see Chapter 1.1).

Third, the BAS account has been criticised for failing to acknowledge cognitive perspectives (Lam, 2009), including higher-order goals. Indeed, current BAS-informed interventions for depression and prodromal mania are predominantly behavioural: either increasing BAS through behavioural activity or decreasing it through behavioural deactivation (Cuypers et al., 2007; Lam & Wong, 1997). The model supported by this thesis can account for efficacy of both behavioural (Figure 7.1, path b) and cognitive (Figure 7.1, path a) psychological interventions, and specifies how they might converge with pharmacological interventions (Figure 7.1; ‘Remission’). It has been speculated that the greater long-term efficacy of cognitive therapy in preventing relapse in unipolar depression (e.g. Butler et al., 2006) may be due to bolstering PFC function (DeRubeis et al., 2008). However, current cognitive-behavioural therapy for BD shows only modest effect sizes (Szentagotai & David, 2010) and was concluded to be ineffective for severe and recurrent BD (Scott et al., 2006). One possibility is that prefrontal function progressively worsens (Chang et al., 2004), making behavioural and pharmacological interventions more effective (Scott et al., 2006). Alternatively, there has been increasing interest in using transdiagnostic approaches to treat BD,
which emphasise a reflective mindset and the resolution of conflict between different life goals (e.g. Mansell et al., 2007; Searson et al., 2011). The therapeutic mechanisms may be elucidated by future intervention studies correlating clinical improvement with change in the neurobiological systems presented here.

Limitations

Whereas the present thesis established a relationship between manic symptoms and prefrontal control, it did not uncover a similar link with depressive symptoms. This is surprising given that a case for hypofrontality has been made in the literature for depressive episodes in unipolar (Harvey et al., 2005) and bipolar (Ketter et al., 2001) presentations. Indeed, effortful control is conceptualised not only as a “brake” on approach or reward-seeking (e.g. knowing to stop after several alcoholic drinks), but also as an “override” on withdrawal impulses (e.g. forcing oneself to get up and out of the house when feeling low or anxious) (Carver et al., 2008). Hence in contrast to mania it might be expected that anhedonia and amotivation in depression result from a diminished reward response that is further “dysregulated” by a lack of a cognitive override. In support of this, hypofrontality has been conceptualised as a state rather than trait feature in unipolar depression (e.g. DeRubeis et al., 2008). However, the studies in the present thesis focussed on vulnerability to mania and so may have missed important neural correlates of depression. Indeed, Chapters 3 and 4 controlled for depressive symptoms in analogue samples and Chapters 5 and 6 recruited euthymic patients. Although effects of residual depressive symptoms were considered, it may be that our sample did not exhibit sufficient levels of symptomatology to detect an association with prefrontal function. On the other hand, dysregulation over amygdala hyperreactivity may be the critical mechanism, as has been suggested in unipolar depression (e.g. DeRubeis et al., 2008) and indicated by psychological research in BD linking depressive symptoms to sensitivity to threat and failure (Carver &
Johnson, 2009). Top-down control over amygdala function was not demonstrated by this thesis and remains an area for investigation.

Figure 7.1. Psychological and pharmacological interventions may accomplish the same end-goal via distinct biopsychological mechanisms. In relapse, low activity in prefrontal cortical (PFC) results in reduced modulation of the limbic system. Therapeutic interventions may address this imbalance by reducing limbic activity directly (b) or indirectly by bolstering PFC function and increasing control over limbic impulses (a). Adapted from DeRubeis et al. (2008).
7.2.2. HYPOTHESIS 2: REWARD PROCESSING ABNORMALITIES REPRESENT AN ENDOPHENOTYPE OF BIPOLAR DISORDER THAT PRECEDES ONSET OF THE DISORDER

7.2.2.1. Prediction 2a: Individuals vulnerable to bipolar disorder show increased impulsivity and risk-taking

This was assessed in Chapters 3 and 4 with tasks tapping risk-taking and reward impulsivity (delay discounting; see 2.2.1), respectively. In Chapter 3, we assessed risk-taking by the bet size selected in the conditions associated with low (20%) and 50-50 reward probability. Consistent with our prediction, the high trait hypomania (non-clinical at-risk) group selected larger bets in these conditions, relative to the low and mid hypomania groups. However, the at-risk group made smaller bets in the high reward (80%) condition, implying poorer learning of the reward contingency in this condition. Accordingly, it is equally possible that the pattern of behaviour in the 20% and 50-50 conditions was due to a failure to learn these contingencies. Whilst we are unable to conclude elevated risk-taking in the at-risk population based on these findings, several other behavioural studies have contributed evidence that supports this possibility (e.g. Hirshfeld-Becker et al., 2003; Hirshfeld-Becker et al., 2006; Nurnberger et al., 1988). Further work with specialised paradigms will be needed to conclusively address this.

In Chapter 4 we were able to detect increased reward impulsivity in a (separate) at-risk sample, as indexed by the number of times an immediate reward was chosen over a delayed but larger reward. This adds to similar findings in clinical populations (Strakowski et al., 2010; Strakowski et al., 2009) and provides evidence that a steeper delay discounting trajectory may be an intrinsic feature that predates onset of BD. This was mirrored by the electrophysiological findings (see 7.2.2.2).
7.2.2.2. Prediction 2b: Reward hypersensitivity will be present in individuals vulnerable to mania

Chapters 3 and 4 revealed that differences can be found in early neural measures of attention (N1) and outcome evaluation (FRN) in non-clinical at-risk individuals. Taken together these findings suggest that hypersensitivity to reward, perhaps particularly immediate reward, is a vulnerability marker that precedes BD diagnosis. In the context of Prediction 1b, an underlying neural mechanism for this trait was proposed to involve perturbation to dorsal and ventral ACC systems (see 7.2.1.2). For example, the greater aversive response to delayed rewards could arise either from an increased dACC-conflict response, or from a decreased vACC-reward response, relative to the low risk group. Although it cannot be concluded on the basis of these data, the latter possibility is consistent with reports that the immediacy bias in a closely related disorder, ADHD, is related to a blunted striatal reward response to delayed outcomes (Plichta et al., 2009; Scheres et al., 2010). This reduction “upstream” in the MCL pathway would plausibly result in lesser vACC activity and therefore a larger dACC-mediated (“default”) FRN to delayed outcomes.

There has been considerable interest in recent years of establishing endophenotypes for psychiatric disorders, especially for improving diagnostic accuracy in DSM-V (Charney et al., 2002). Endophenotypes are hereditary and state-independent biological markers that are associated with specific features of a disorder, rather than the more complex overall presentation (Gottesman & Gould, 2003). Deficient face emotion labelling represents one established endophenotype in BD, and has been linked to abnormalities in ventral frontolimbic circuits including dlPFC, amygdala and striatum rosen (e.g. Rosen & Rich, 2010), further highlighting the overlap between affective and motivational processing (Chapter 1). The present thesis offers the possibility that reward system hypersensitivity, as indexed by reduced FRN, may be a candidate endophenotype for BD given that it is found as a trait feature during euthymia (Chapter 5) and in non-clinical at-risk
populations (Chapters 3 and 4). However, a number of criteria remain unfulfilled and so this speculation cannot be confirmed at this point. First, our at-risk population were selected based on psychometric rather than genetic vulnerability; whilst hypomanic and sensation-seeking traits are themselves heritable (Nurnberger et al., 1988) and our samples may have had first-degree relatives with a bipolar diagnosis, this was not assessed.

Second, the disorder specificity of reward hypersensitivity and in particular, FRN attenuation has not been established. Trait BAS and sensation-seeking are associated with greater activity in ventral striatum and vmPFC (Hahn et al., 2009; Simon et al., 2009) and higher frequencies of certain polymorphisms of genes coding for dopamine receptor function are more common in extrovert individuals (Cohen et al., 2005; and Golimbet et al., 2007, who additionally found an association with hypomania). Furthermore, FRN reduction has previously been associated with trait impulsivity (e.g. Onoda et al., 2010) and other psychiatric disorders, notably pathological gambling (e.g. Hewig et al., 2010). Combining biomarkers has been suggested as way of increasing specificity (e.g. Moeller et al., 2004) and our finding of reward-N1 potentiation has not been reported in other disorders as of yet. On the other hand, the overlap between BD and other impulsivity disorders (e.g. ADHD; Chapter 1.1) suggests the possibility of a transdiagnostic endophenotype which may be more useful than the “disorder-specific” endophenotype espoused by (Gottesman & Gould, 2003). This point notwithstanding, future studies will need to assess the potential of the FRN and N1 as biomarkers. Specifically, are perturbations evident in the first-degree relatives of BD patients? Also, does FRN amplitude normalise in response to treatment?
7.2.2.3. Prediction 2c: The degree of reward hypersensitivity is positively correlated with vulnerability to mania

In a similar way to how high psychometric risk has been defined by hypomanic trait scores falling two standard deviations above the mean (Eckblad & Chapman, 1986), it may be that this measure could be combined with FRN measurement to identify people at highest risk and need of early intervention. In Chapter 3, a regression analysis demonstrated that level of hypomanic traits positively predicted FRN amplitude, particularly for rewarding outcomes, providing initial evidence that the FRN may be an electrophysiological vulnerability marker that varies across a spectrum.

A recent survey found that the gap between first experiencing problems and receiving a BD diagnosis averages 13.2 years, with patients enduring a raft of other diagnoses and inappropriate pharmacotherapies in the interim (RCP, 2012) at great cost to the individual and possibly their long-term clinical outcome. An ongoing challenge facing clinicians is correctly distinguishing bipolar from unipolar depressive episodes (where diagnosis of BD has not been established). Whereas this thesis demonstrated that BD is associated with FRN attenuation (and increased activity in the MCL pathway), unipolar depression is linked to reduced mesocorticolimbic activity (Elliott et al., 1998; Pizzagalli et al., 2009) and increased FRN (especially for losses; Oliveira et al., 2007). However the possibility that affective state may modulate (or even reverse) the trait FRN reduction reported in this thesis needs to be addressed; whilst Chapter 6 reported no effect of residual depressive symptoms on the FRN, in Chapter 5 an association with reduced reward response in NAcc was found. Recent evidence demonstrating FRN enhancement in remitted unipolar depression (Santesso et al., 2008) suggests that this measurement may be relatively state-independent. Future research comparing unipolar and bipolar depressed groups will be needed to examine the potential for using the FRN as a clinical tool for differentiating these two presentations. The limitations outlined in 7.2.2.2 are also relevant here, and the possibility that the FRN shows poor disorder specificity may limit its diagnostic utility.
7.2.3. Hypothesis 3: In bipolar disorder there is misrepresentation of the probability and value associated with actions and behaviours

7.2.3.1. Prediction 3a: There is an appraisal bias towards expecting rewarding outcomes that fails to be moderated by objective probability

Through fMRI, we were able to show a positive expectancy bias using objective economic metrics such as representation of the expected value (EV) term and anticipatory activity in reward regions (Chapter 5). Perceiving an unrealistically high likelihood of positive consequences can go some way to explaining the engagement in maladaptive and risky behaviours frequently seen clinically in BD (APA, 2000). Psychological interventions may benefit from targeting antecedent cognitions and appraisals more than subsequent evaluation. It has been shown experimentally in healthy controls that cognitive reappraisal (distancing oneself or reframing a situation) can effectively offset mood induction (Heilman et al., 2010) and modulates reward anticipation through recruitment of dIPFC (Staudinger et al., 2011). Hence it might be possible to leverage cognitive control to offset initial ‘affective’ appraisals of reward, in line with the reward dysregulation model.

A limitation of the studies in this thesis is that the relative contributions of probability and magnitude were not conclusively identified: do patients overestimate the likelihood of reward, or the value of that reward? Chapter 3 was unable to orthogonalise probability and magnitude because the task allowed free choice on bet size, but Chapter 5 accomplished this by equating the probability and magnitude for all options within a given trial. Whilst group did not interact with probability or magnitude, patients tended to hyperactivate the reward system in anticipation of all outcomes (irrespective of objective reward probability), suggesting an expectancy bias rather than inflation of perceived reward magnitude. Interactions with mood state also arose in NAcc, with depressive
symptoms reducing the effect of probability on anticipatory activity, consistent with a negative-outcome-expectancy bias. At outcome, manic symptoms impaired expectancy but not magnitude, suggesting that mania is associated more with impaired estimation of outcome likelihood than an overrepresentation of reward value. This fits with psychological accounts that conceptualise mania in terms of increased confidence in the ability to bring about positive outcomes (Johnson et al., 2009).
7.2.4. HYPOTHESIS 4: IMPAIRED REINFORCEMENT LEARNING UNDERLIES PERSISTENT ENGAGEMENT IN MALADAPTIVE BEHAVIOURS IN BIPOLAR DISORDER

7.2.4.1. Prediction 4a: Prediction errors are incorrectly calculated

7.2.4.2. Prediction 4b: Prediction errors are not utilised to guide future behaviour and expectations

Using FRN as a marker for prediction error, Chapter 3 provides evidence for a positive outcome evaluation bias in which gains and losses were restricted more to the positive end of the spectrum (see Figure 7.2). This “rose-tinted evaluation bias” may serve to amplify rewards and attenuate losses, maintaining unrealistic optimism about subsequent outcomes (Sharot et al., 2011) and maladaptive or risky behaviours (Hall et al., 2007). It has been hypothesised that this narrowing of the dynamic range of FRN-PE signals may be related to increased tonic dopamine (DA) concentrations (Olvet & Hajcak, 2008). In support of this, DA agonists decrease FRN amplitude in controls (Jocham & Ullsperger, 2009) and mania is widely conceptualised as a hyperdopaminergic state (Berk et al., 2007) for which DA antagonists are commonly prescribed (e.g. Lage & Hassan, 2009).
In contrast to the data reported in Chapter 3, intact representation of PE was found in patients (Chapter 5). An obvious difference between the studies is the population tested, but if this were to play a role then the opposite pattern might be expected: the clinical sample showing greater impairment than the high-functioning non-clinical sample (Chapter 3). This inconsistency may be better explained by two key task differences between the studies. First, in Chapter 3 participants needed to acquire novel stimulus-response-outcome associations, and the finding of learning impairment in the hypomania-prone group led to this variable being removed in Chapter 5 (by making the reward contingencies explicit). It may be that a prediction error deficit is only exposed in highly demanding contexts, something that makes sense from a clinical perspective; whereas BD patients are not impaired at routine or highly learned everyday tasks – at least during euthymia – they might be expected to struggle more in novel and unexpected contexts. Similarly, whilst Chapter 3 required choices between different bet sizes, the stake was fixed in Chapter 5, reducing the demand on cognitive, learning and conflict-resolution processes. Indeed, decisions that generate conflict between two or more goals may be most problematic for people with BD (Mansell et al., 2007; Searson et al., 2011), and reinforcement learning deficits have been demonstrated behaviourally with more complex tasks (Pizzagalli et al., 2008b). Future work will be needed to tease out the additional factors
involved in learning deficits, and one possibility might relate to the early attentional differences identified in Chapters 4 and 6. However, an important methodological implication is that overly simplistic tasks may obscure deficits in psychiatric and neurological populations (i.e. false negatives). This thesis advocates using a range of tasks that cover both complex, ecologically valid tasks in concert with simplified designs that allow more precise and unconfounded characterisation of deficits.

Convergence between the two studies comes from the finding that, in both cases, future decisions were not being optimally updated by prediction error. In Chapter 3, this was manifested behaviourally as impairment in acquiring the reward contingencies (taking longer to learn and adopt the optimal betting strategy). In Chapter 5, it manifested as impairment in representing expected value: the PE from trial \( n \) did not drive updating of expectation for the subsequent trial \( n+1 \). Both phenomena may be related to a positive outcome evaluation bias, which maintains unrealistically optimistic predictions about chances on the subsequent gamble. Whilst trial-wise representation of PE has not previously been examined in BD, a general outcome evaluation deficit has been reported in acute mania (Abler et al., 2007c). A possibility is that, following repeated manic and mixed episodes, the efficacy of this learning mechanism may decrease. Studies establishing a relationship between learning and number of episodes would be needed to validate this supposition.

A theoretical comment on interpreting prediction errors

Whilst the validity of the FRN as an index of dopamine-dependent prediction error remains an on-going issue (Jocham & Ullsperger, 2009), a broader issue is what can legitimately be inferred from group differences in PE per se. Because PE represents a comparison between 1) what was expected and 2) the actual outcome, we cannot say whether group differences reflect the “expectancy” or the “actuality” part of the PE term. This is not widely acknowledged in the literature but has important implications for interpreting decision-making differences. In the
current thesis, FRN reduction in Chapter 3 could alternatively be interpreted in terms of an expectancy bias; smaller FRN-PE for loss outcomes, for example, could be driven by pessimism about outcome likelihood which is subsequently met with confirmation of that prediction. This emphasises the importance of considering other relevant factors. In this case, although both negative and positive affect frequently co-occur, BD is generally defined by a positive outcome-expectancy bias rather than pessimism (Johnson et al., 2009; O'Sullivan et al., 2011). Furthermore in unipolar depression which is associated with a pessimistic bias (Mineka et al., 1998), the conceptually problematic finding of FRN enhancement for losses ("worse than expected") is explained in terms of hypersensitivity to these outcomes (e.g. Oliveira et al., 2007). This underscores the value of examining several stages of processing when drawing inferences about expectancy and evaluation.

In sum, repeated engagement in risky behaviours despite their negative consequences (APA, 2000) may be driven both by unrealistically optimistic expectations about risky situations and a failure to update future expectations after experiencing aversive consequences.
In Chapter 1, a model was proposed which produced hypotheses to be tested by the experimental work. Here this model is revisited and updated in light of the findings. The model, summarised in Figure 7.3, highlights a core reward hypersensitivity that manifests as increased activity in the ventral frontostriatal pathway (Chapters 3 – 6). This path has been termed “affective” and “hot” by different authors (Bush et al., 2000; Sonuga-Barke & Fairchild, 2012) to emphasise its reflexive and somewhat automatic nature. In addition to a stronger hedonic impact of rewards in ventral striatum (Chapter 5), activity in the ventral tegmental area (VTA) and ventromedial cortical valuation systems fails to be modulated by the objective probability and expected value of outcomes (Chapter 5), fostering a positive-outcome expectancy bias (Johnson et al., 2009; O’Sullivan et al., 2011). In line with this possibility, the present thesis additionally highlighted the involvement of attentional bias (Chapters 4 and 6) mediated by precuneus and dorsomedial prefrontal systems (Chapter 6). These systems act to increase visual attention when there is the possibility of obtaining reward, perhaps especially grabbed by prospects associated with immediate gratification (Chapter 4). Following receipt of outcome, prediction error may be perturbed by a “rose-tinted” evaluation bias (Chapters 3 and 5) which maintains maladaptive and risky behaviours in spite of negative repercussions. Contrary to the original model (see Figure 1.2), hypersensitivity to threat and loss was not supported by the experimental work, nor was there evidence for greater activation in amygdala and insula. Hence these factors were dropped from the revised model.

In remission, this pathway is sufficiently modulated by a dorsal network, particularly dorsolateral prefrontal cortex (dPFC; Chapter 5) but also including the dorsal anterior cingulate cortex (Holroyd & Yeung, 2012). Dorsal ACC has been proposed to govern intra-goal control, and may offset activity in the ventral pathway that favours immediate gratification (Plichta et al., 2009; e.g. substance use) to foster preference for delayed but larger rewards (e.g. staying well, not
relapsing). In addition to modulating the ventral pathway, the dlPFC coordinates higher-order goals (e.g. Holroyd & Yeung, 2012) and impairment may relate to goal dysregulation in BD (Johnson, 2005b; Mansell et al., 2007), dominance of reflexive impulses (Figure 7.3; “hot” pathways in yellow) and, ultimately, relapse (Figure 7.1). Whilst not explicitly tested, the results of this thesis are consistent with this account.
Figure 7.3. Dorsal and ventral pathways in the reward network in healthy individuals (top) and BD (bottom).
7.4. Limitations of this thesis

In addition to the specific limitations to each of the conclusions of this chapter, a number of broader issues should be acknowledged.

First, a potential selection bias may apply to these studies, particularly those involving EEG and fMRI. Because these kinds of studies could be perceived as aversive, it may be that the subpopulation of patients and non-clinical at-risk participants that volunteered for them were not representative of the population as a whole. It could even be speculated that by virtue of their novelty and public perception, neuroimaging studies preferentially attract a subpopulation of novelty-seekers, who are inclined to try new experiences. This poses a general methodological consideration for this type of study. In addition, the non-clinical at-risk participants may have been motivated to volunteer because of concern of their mental state, potentially resulting in a threshold-clinical rather than high-functioning sample. However, the research volunteering advertisements did not mention BD or vulnerability to psychiatric disorder (instead they were more generally described in terms of studies of personality, mood and brain activity). Also, whilst we called for participants without history of psychiatric problems or psychotropic medication, we did not perform a diagnostic interview and so cannot rule out that participants already met the criteria for BD (but were not yet in treatment). Ordinarily, the high functioning associated with students in higher education might suggest against this possibility, but goal-striving and achievement in early life is a feature of BD (Johnson & Carver, 2006), making this defence less tenable than for other populations at risk to psychiatric disorder. The alternative is that these findings relate to psychological processes in early and untreated BD, which is a valuable contribution in its own right given exclusion of variables that confound clinical samples (effects of psychiatric intervention, hospitalisation, stigmatisation etc). Future studies will be needed to more conclusively characterise the neurobiological factors conferring vulnerability to BD and at least exclude current BD illness by means of diagnostic interview.
There are also conceptual issues of making comparisons between non-clinical (analogue) and clinical samples of BD. The inherent assumption is that, contrary to the Kraepelinian dichotomy (see e.g. Bentall, 2006; and Craddock & Owen, 2010 for a discussion and critique), psychiatric symptoms lie on a continuum that extends into the normal population. Accordingly, the same biopsychological processes are manifested in the non-clinical population (but are likely attenuated compared to patients). Whilst this assumption is not unequivocally accepted, it is supported by cross-sectional (Eckblad & Chapman, 1986), longitudinal (Kwapil et al., 2000) and factor analytic (Meads & Bentall, 2008) studies of the Hypomanic Personality Scale used for recruitment. The linear relationship between HPS and electrophysiological measures (Chapters 2 and 6) further vindicates the spectrum approach and suggests that psychometric vulnerability is mirrored by neurobiological vulnerability.

In Chapters 5 and 6 we purposefully recruited patients not in receipt of dopamine antagonists, because of the impact of this class of medication on reward-related activity (Abler et al., 2007a; Pessiglione et al., 2006). Whilst this represents a strength and may have allowed us to uncover deficits normally masked or altered by medication, an intrinsic limitation is that our subpopulation may not be representative of the wider BD population. Future studies could recruit patients who discontinue use of antipsychotics days or weeks before the study may be warranted, bearing in mind the additional ethical and methodological issues of this approach. Alternatively, the specific contribution of antipsychotics may be isolated by a correlational design recruiting patients in receipt of a wide dosage range of antipsychotic medication (controlling for severity and other clinical variables) with a view to examining the relationship with neural activity. Patients were in receipt of other medications, particularly mood stabilisers, and so we cannot establish the specificity of our findings to the intrinsic pathophysiology of BD. Future studies with unmedicated samples will be needed, again controlling for severity.
### 7.5. Future Research

The work of the current thesis forms a foundation for researching reward system function in BD and can be extended in a number of important ways.

First, this thesis emphasised how tendencies toward mania influence or reflect decision-making and motivational processing. The rationale was that there is already an extensive and rapidly evolving research effort into understanding reward system function in (unipolar) depression, and mania represents the key defining feature between unipolar and bipolar affective disorders. This approach is further justified by evidence that mania and depression lie on somewhat orthogonal axes (Carver & Johnson, 2009; Johnson et al., 2011). However, there remains debate as to the overlap between unipolar and bipolar depression, warranting a more concerted focus on the depressive phase of BD. We found that residual depressive symptoms in BD euthymia confer anhedonic symptoms and a negative outcome expectancy bias but, unexpectedly, no evidence that they increase threat sensitivity or aversive response (e.g. in amygdala or insula). Future work will be needed to establish whether depressive symptoms are associated with a separate mechanism involving these aversive processing regions, rather than simply modulating a core hypersensitivity in the reward network as per manic symptoms. In particular, how does activity in serotonergic systems relate to motivational, affective and cognitive tendencies towards bipolar depression?

Second, the current conceptualisation of BD would be enriched by a greater consideration of cognitive factors. Currently, the dominant view stems from the biomedical model; BD arises from a neurobiological defect without acknowledgement of the active role that patients’ cognitions play in their experience. This is an overly simplistic view, particularly for BD, which is an extremely heterogenous and dynamic disorder. Whilst dysregulation over reflexive processes offers a plausible mechanism for the profile of BD, and fits reasonably well with psychological models (e.g. Johnson et al., 2012; Mansell et al., 2007), it perhaps loses sight of the patient’s ability to self-determine and actively influence
these processes. Indeed, it is not simply a passive, automatic and unconscious drive that draws people to approach rewards, even risky or objectively maladaptive ones. Rather, these drives arise from complex and often conflicting goal hierarchies, which are themselves dynamic and changeable (perhaps especially so in BD). A recent account of ADHD highlights the importance of personal agency and representations-of-self in explaining normal and atypical behaviours. To quote this view, the individual is “an active agent, expressing tastes and preferences and attempting to implement and adjust plans to secure desired outcomes, based on judgments regarding expected utility, in the light of their current states, past experience, and future expectations” (Sonuga-Barke & Fairchild, 2012; pp. 126). It will be important that diagnostic conceptualisations and future research into BD and other psychiatric disorders also consider this “agency” view. The fusion of economic modelling with neuroimaging methods (Glimcher & Rustichini, 2004) is a powerful approach that may more empathically characterise the personal goals and utility functions that people are attempting to maximise. Of particular relevance may be the consideration of how the mesocorticolimbic pathway interacts with wider brain networks, such as those involved in maintaining stable value and goal hierarchies Johnson (e.g. medial prefrontal cortical regions; Johnson et al., 2005), and how this relates to disruptions in self-referential thought and sense of self (e.g. the default mode network; Gusnard et al., 2001).
7.6. Conclusion

This thesis provided strong evidence for reward system abnormalities in bipolar disorder and was able to map these neuronal differences using motivational decision-making paradigms. Converging evidence from electrophysiological and functional neuroimaging measures indicated hyperactivity in the mesocorticolimbic network, compounded by reduced reappraisal from higher cortical regions (dorsolateral prefrontal cortex). A consequence is that behaviour and decisions may be more guided by reflexive impulses than by longer-term goals. Lamentably this phenotype confers susceptibility to impulsive, risky and ultimately self-destructive behaviours that are often highly distressing to the individual because of their consequences. There is scope for novel interventions to build on this foundation, however. In particular, we hope that the work of this thesis will pave the way for psychological interventions that strengthen the integrity of top-down systems, thereby bolstering cognitive reappraisal of impulsive drives and sustaining pursuit of longer-term goals and aspirations. The application of cognitive neuroscience techniques with frameworks from clinical psychology offers a promising path forward to achieve this vision.
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Euthymic Bipolar Disorder or Attention-Deficit/Hyperactivity Disorder (ADHD). *PloS one*, 7(5), e37306.


RCP. (2012). *Challenges to bipolar disorder diagnosis* o. Document Number


APPENDICES

Appendix A: Self-report Measures

1. HYPOMANIC PERSONALITY SCALE (HPS)*


This questionnaire consists of statements to which you can respond true or false. In each case, please record your answer by circling the appropriate response. Please answer honestly. There are no right or wrong answers and we expect there to be variation in the way different people respond to the items.

Thank you for your participation.

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<tr>
<th>No.</th>
<th>Item</th>
<th>Please circle a response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>I seem to have an uncommon ability to persuade and inspire others.</td>
<td>TRUE         FALSE</td>
</tr>
<tr>
<td>2.</td>
<td>I often get into moods where I feel like many of the rules of life don’t apply to me.</td>
<td>TRUE         FALSE</td>
</tr>
<tr>
<td>3.</td>
<td>Sometimes ideas and insights come to me so fast that I cannot express them all.</td>
<td>TRUE         FALSE</td>
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<td>4.</td>
<td>I seem to be a person whose mood goes up and down easily.</td>
<td>TRUE</td>
</tr>
<tr>
<td>5.</td>
<td>There are often times when I am so restless that it is impossible for me to sit still.</td>
<td>TRUE</td>
</tr>
<tr>
<td>6.</td>
<td>I often feel excited and happy for no apparent reason.</td>
<td>TRUE</td>
</tr>
<tr>
<td>7.</td>
<td>I often have moods where I feel so energetic and optimistic that I feel I could outperform almost anyone at anything.</td>
<td>TRUE</td>
</tr>
<tr>
<td>8.</td>
<td>In unfamiliar surroundings I am often so assertive and sociable that I surprise myself.</td>
<td>TRUE</td>
</tr>
<tr>
<td>9.</td>
<td>I am frequently in such high spirits that I can’t concentrate on any one thing for too long.</td>
<td>TRUE</td>
</tr>
<tr>
<td>10.</td>
<td>I very frequently get into moods where I wish I could be everywhere and do everything at once.</td>
<td>TRUE</td>
</tr>
<tr>
<td>11.</td>
<td>A hundred years after I’m dead, my achievements will probably have been forgotten.</td>
<td>TRUE</td>
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</tr>
<tr>
<td>12.</td>
<td>I am so good at controlling others that sometimes it scares me.</td>
<td>TRUE</td>
</tr>
<tr>
<td>13.</td>
<td>I am usually in an average sort of mood, not too high and not too low.</td>
<td>TRUE</td>
</tr>
<tr>
<td>14.</td>
<td>I do most of my best work during brief periods of intense inspiration.</td>
<td>TRUE</td>
</tr>
<tr>
<td>15.</td>
<td>I am considered to be a kind of ‘hyper’ person.</td>
<td>TRUE</td>
</tr>
<tr>
<td>16.</td>
<td>Many people would consider me to be amusing but kind of eccentric.</td>
<td>TRUE</td>
</tr>
<tr>
<td>17.</td>
<td>I have often felt happy and irritable at the same time.</td>
<td>TRUE</td>
</tr>
<tr>
<td>18.</td>
<td>I frequently find that my thoughts are racing.</td>
<td>TRUE</td>
</tr>
<tr>
<td>19.</td>
<td>When I feel an emotion, I usually feel it with extreme intensity.</td>
<td>TRUE</td>
</tr>
</tbody>
</table>
2. BIS/BAS SCALES*


Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Please respond to all the items; do not leave any blank. Choose only one response to each statement. Please be as accurate and honest as you can be. Respond to each item as if it were the only item. That is, don't worry about being "consistent" in your responses. Choose from the following four response options:

- 1 = very true for me
- 2 = somewhat true for me
- 3 = somewhat false for me
- 4 = very false for me

1. A person's family is the most important thing in life. [  ]
2. Even if something bad is about to happen to me, I rarely experience fear or nervousness. [  ]
3. I go out of my way to get things I want. [  ]
4. When I'm doing well at something I love to keep at it. [  ]
5. I'm always willing to try something new if I think it will be fun. [  ]
6. How I dress is important to me. [  ]
7. When I get something I want, I feel excited and energized. [  ]
8. Criticism or scolding hurts me quite a bit. [  ]
9. When I want something I usually go all-out to get it. [  ]
10. I will often do things for no other reason than that they might be fun.

11. It's hard for me to find the time to do things such as get a haircut.

12. If I see a chance to get something I want I move on it right away.

13. I feel pretty worried or upset when I think or know somebody is angry at me.

14. When I see an opportunity for something I like I get excited right away.

15. I often act on the spur of the moment.

16. If I think something unpleasant is going to happen I usually get pretty "worked up."

17. I often wonder why people act the way they do.

18. When good things happen to me, it affects me strongly.

19. I feel worried when I think I have done poorly at something important.

20. I crave excitement and new sensations.

21. When I go after something I use a "no holds barred" approach.

22. I have very few fears compared to my friends.

23. It would excite me to win a contest.

24. I worry about making mistakes.
3. DOMAIN-SPECIFIC RISK-TAKING SCALE*


Risk Taking Behaviours

For each of the following statements, please indicate the likelihood that you would engage in the described activity or behavior if you were to find yourself in that situation. Provide a rating from Extremely Unlikely to Extremely Likely, using the following scale:

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely Unlikely</td>
<td>Moderately Unlikely</td>
<td>Somewhat Unlikely</td>
<td>Not Sure</td>
<td>Somewhat Likely</td>
<td>Moderately Likely</td>
<td>Extremely Likely</td>
</tr>
</tbody>
</table>

1. Admitting that your tastes are different from those of a friend. (S)
2. Going camping in the wilderness. (R)
3. Betting a day’s income at the horse races. (F)
4. Investing 10% of your annual income in a moderate growth mutual fund. (F)
5. Drinking heavily at a social function. (H/S)
6. Taking some questionable deductions on your income tax return. (E)
7. Disagreeing with an authority figure on a major issue. (S)
8. Betting a day’s income at a high-stake poker game. (F)
9. Having an affair with a married man/woman. (E)
10. Passing off somebody else’s work as your own. (E)
11. Going down a ski run that is beyond your ability. (R)
12. Investing 5% of your annual income in a very speculative stock. (F)
13. Going whitewater rafting at high water in the spring. (R)
14. Betting a day’s income on the outcome of a sporting event. (F)
15. Engaging in unprotected sex. (H/S)
16. Revealing a friend’s secret to someone else. (E)
17. Driving a car without wearing a seat belt. (H/S)
18. Investing 10% of your annual income in a new business venture. (F)
19. Taking a skydiving class. (R)
20. Riding a motorcycle without a helmet. (H/S)
21. Choosing a career that you truly enjoy over a more prestigious one. (S)
22. Speaking your mind about an unpopular issue in a meeting at work. (S)
23. Sunbathing without sunscreen. (H/S)
24. Bungee jumping off a tall bridge. (R)
25. Piloting a small plane. (R)
26. Walking home alone at night in an unsafe area of town. (H/S)
27. Moving to a city far away from your extended family. (S)
28. Starting a new career in your mid-thirties. (S)
29. Leaving your young children alone at home while running an errand. (E)
30. Not returning a wallet you found that contains £200. (E)

Note. E = Ethical, F = Financial, H/S = Health/Safety, R = Recreational, and S = Social.
Risk Perception

People often see some risk in situations that contain uncertainty about what the outcome or consequences will be and for which there is the possibility of negative consequences. However, riskiness is a very personal and intuitive notion, and we are interested in your gut level assessment of how risky each situation or behavior is.

For each of the following statements, please indicate how risky you perceive each situation. Provide a rating from Not at all Risky to Extremely Risky, using the following scale:

<table>
<thead>
<tr>
<th>1</th>
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<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all Risky</td>
<td>Slightly Risky</td>
<td>Somewhat Risky</td>
<td>Moderately Risky</td>
<td>Risky</td>
<td>Very Risky</td>
<td>Extremely Risky</td>
</tr>
</tbody>
</table>

Risk Benefits

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>No benefits at all</td>
<td>Moderate Benefits</td>
<td>Great benefits</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>