THINKING, PERCEIVING AND REGULATING FEELING: AN INVESTIGATION OF NEUROCOGNITION, SOCIAL COGNITION AND EMOTION REGULATION IN BIPOLAR DISORDER

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"If I can't feel, if I can't move, if I can't think, and I can't care, then what conceivable point is there in living?"

— Kay Redfield Jamison[1], An Unquiet Mind: A Memoir of Moods and Madness

[1] Professor Redfield Jamison is a highly regarded clinical psychologist diagnosed with bipolar disorder. Her book *An Unquiet Mind: A Memoir of Moods and Madness* tells of her experiences with the disorder from the perspective of both the healer and the healed. This quote reflects the everyday feelings of many people with bipolar disorder and exemplifies the need for continued research in the field.

Abstract

Bipolar disorder (BD) is a serious mood disorder, the aetiology of which is still unclear. The disorder is characterised by extreme mood variability in which patients fluctuate between markedly euphoric, irritable and elevated states to periods of severe depression. The current research literature indicates that BD patients show compromised neurocognitive, social cognitive and emotion regulation ability in addition to these mood symptoms. However, the precise nature of these abnormalities is not well-established.

This thesis comprehensively explores neurocognitive, social cognitive and emotion regulation features in BD. It aims to better characterise the profiles of these domains of function and provide an improved understanding of the intricate processes within them, as well as exploring their genetic aetiology, shared relationships, and their psychosocial consequences. Specifically this thesis i) examines neurocognitive, theory of mind and emotion regulation deficits in BD abilities using novel measures, ii) characterises facial emotion processing deficits by controlling for a number of potential confounds, and iii) explores whether patients with BD demonstrate emotional prosody processing and auditory abnormalities. Further, it iv) examines the influence of viable dopamine and serotonin candidate genes on neurocognition, social cognition and emotion regulation, v) explores the influence of neurocognitive ability in relation to social cognition and emotion regulation in the disorder, and vi) determines the importance of these domains in influencing psychosocial outcome.

A group of BD patients and healthy control participants completed a battery of measures that assessed neurocognition, social cognition (emotion processing and theory of mind), emotion regulation and psychosocial function, in addition to providing a sample of blood for genetic analysis. The results indicated that BD patients show impairments in three broad processes; basic neurocognition, social cognition (primarily facial emotion processing and theory of mind, with specific deficits evident for emotional prosody processing) and emotion regulation. The genetic analyses revealed that the influence of a dopaminergic gene

on components of neurocognition was modulated by BD diagnosis, but there was no impact from a gene linked to the serotonin system. Further analyses in the BD group revealed that neurocognition explained a significant proportion of the variance in social cognition, but neither neurocognition nor social cognition had any effect on emotion regulation. Of these constructs, neurocognition and to a lesser degree emotion regulation, were found to be the most important predictors of objectively measured psychosocial functioning, whilst emotion regulation was found to be the most important predictor of subjectively measured psychosocial functioning.

These findings support assertions that patients with BD experience cognitive and emotion regulation deficits that meaningfully contribute to psychosocial dysfunction. They also suggest that there may be inherent overlap in brain processes underlying neurocognition and social cognition in BD. This work is discussed in terms of methodological and research implications as well as treatment advances for the disorder.

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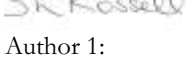
General Declaration

In accordance with the Swinburne University Higher Degree's by Research Committee regulations, I hereby declare that this thesis:

i. Contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution.
ii. To the best of my knowledge contains no material previously published or written by another person except where due reference is made in the text of this thesis.
iii. Where work is based on joint research or publications, full disclosure of the contributions of the relative authors are made; this thesis includes six papers published in peer reviewed journals, three papers in the review process and seven traditional thesis chapters. The ideas, development, and writing of all papers/chapters in the thesis were the principal responsibility of me, the candidate, working under the supervision of Professor Susan L. Rossell and Professor Greg Murray.

In the case of all chapters in this thesis, including those comprising articles published / in press/ accepted or submitted, my contribution to the work was the following:
project design (in consultation with my supervisors and co-authors), review of appropriate literature; securing ethics approval; recruitment of participants; data collection; conducting data analysis; writing of manuscripts/chapters. Supervisors and co-authors provided input into completed manuscript drafts (for specific information on contribution to papers, see page vi-vii).

In order to maintain a consistent style of presentation I have included the published/ in press/ accepted/ submitted articles in the relevant chapters of this thesis. Please note that in this electronic version of the thesis, all appendices containing these articles in their published journal format have been removed to avoid copyright infringements.

Thesis chapter	Citation	Authors (in order of authorship)	Co-author input	Publication status	Nature and extent of contributions	Signatures
2	Van Rheenen, T. E., & Rossell, S. L. (2013). Genetic and neurocognitive foundations of emotion abnormalities in bipolar disorder. Cognitive Neuropsychiatry, 18, 168-207. doi: 10.1080/13546805.2012.690938	Author 1:TE Van Rheenen Author 2: S.L Rossell	SR provided supervisory input into completed manuscript draft	Published 2013	Author 1: 95% Author 2: 5%	Author 1:  Author 2: 
3	Van Rheenen, T. E., & Rossell, S. L. (2013). Is the non-verbal behavioural emotion-processing profile of bipolar disorder impaired? A critical review. *Acta Psychiatrica Scandinavica, 128*, 163-178. doi: 10.1111/acps.12125	Author 1:TE Van Rheenen Author 2: S.L Rossell	SR provided supervisory input into completed manuscript draft	Published online 2013	Author 1: 95% Author 2: 5%	Author 1:  Author 2: 
5	Van Rheenen, T. E. & Rossell, S. L. (in Press, September 2013). Phenomenological predictors of psychosocial function in bipolar disorder: is there evidence that social cognitive and emotion regulation abnormalities contribute? *Australian and New Zealand Journal of Psychiatry,* DOI: 10.1177/0004867413508452	Author 1:TE Van Rheenen Author 2: S.L Rossell	SR provided supervisory input into completed manuscript draft	Published online 2013	Author 1: 95% Author 2: 5%	Author 1:  Author 2: 
8	Van Rheenen, T. E., & Rossell, S. L. (In press). An Empirical Evaluation of the MATRICS Consensus Cognitive Battery in Bipolar Disorder. doi: 10.1111/bdi.12134	Author 1:TE Van Rheenen Author 2: S.L Rossell	SR provided supervisory input into completed manuscript draft	Published online 2013	Author 1: 95% Author 2: 5%	Author 1:  Author 2: 
9	Van Rheenen, T. E., & Rossell, S. L. (In submission). Let's face it: facial emotion processing is impaired in bipolar disorder	Author 1:TE Van Rheenen Author 2: S.L Rossell	SR provided supervisory input into completed manuscript draft	In submission	Author 1: 95% Author 2: 5%	Author 1:  Author 2:

10	Van Rheenen, T. E., & Rossell, S. L. (2013). Auditory-prosodic processing in bipolar disorder; from sensory perception to emotion. *Journal of Affective Disorders, 151*, 1102-1107.	Author 1:TE Van Rheenen Author 2: S.L Rossell	SR provided supervisory input into completed manuscript draft	Published online 2013	Author 1: 95% Author 2: 5%	Author 1: SK Rossell Author 2: SK Rossell
11	Van Rheenen, T. E., & Rossell, S. L. (2013). Picture sequencing task performance indicates theory of mind deficit in bipolar disorder. *Journal of Affective Disorders, 151*, 1132-1134. doi: http://dx.doi.org/10.1016/j.jad.2013.07.009	Author 1:TE Van Rheenen Author 2: S.L Rossell	SR provided supervisory input into completed manuscript draft	Published online 2013	Author 1: 95% Author 2: 5%	Author 1: Author 2: SK Rossell
12	Van Rheenen, T.E., Murray, G., and Rossell, S.L. An examination of the emotion regulation profile of bipolar disorder.	Author 1:TE Van Rheenen Author 2: G. Murray Author 3: S.L Rossell	SR and GM provided supervisory input into completed manuscript draft	In submission	Author 1: 90% Author 2: 5% Author 3: 5%	Author 1: Author 2: Author 3: SK Rossell
13	Van Rheenen, T.E., Bozaoglu, K., and Rossell, S.L. The influence of Catechol-O-methyltransferase on cognition is modulated by bipolar disorder diagnosis	Author 1:TE Van Rheenen Author 2: K. Bozaoglu Author 3: S.L Rossell	SR provided supervisory input into completed manuscript draft. KB extracted DNA for genetic analysis and provided specialised genetic advice.	In submission	Author 1: 90% Author 2: 5% Author 3: 5%	Author 1: Author 2: Author 3: SK Rossell

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List of Common or Important Abbreviations

ANOVA	Analysis of Variance	*MATRICS*	Measurement and Treatment Research to Improve Cognition in Schizophrenia
BD	Bipolar Disorder	*MCCB*	MATRICS Consensus Cognitive Battery
CBT	Cognitive Behavioural Therapy	*MDD*	Major Depressive Disorder
COMT	Catechol-O-methyltransferase	*Met*	Methionine
d'	d prime	*Ms*	Millisecond
dB	Decibel	*PoFA*	Pictures of Facial Affect
DSM	Diagnostic and Statistical Manual of Mental Disorders	*Rs/rs*	Reference SNP ID
fMRI	Functional Magnetic Resonance Imaging	*SD*	Standard Deviation
GWAS	Genome Wide Association Study	*SNP*	Single Nucleotide polymorphism
Hz	Hertz	*SPSS*	Statistical package for the Social Sciences
IQ	Intelligence Quotient	*ToM*	Theory of Mind
ISBD	International Society for Bipolar Disorders	*TPH2*	Tryptophan-hydroxylase-2
M	Mean	*Val*	Valine
MANCOVA	Multivariate Analysis of Covariance	*5HT*	Serotonin 5-hydroxytryptamine (serotonin)
MANOVA	Multivariate Analysis of Variance		

Note: This list is not exhaustive and contains only important or common abbreviations mentioned in text. Abbreviated names of measures are specified in Table 4.

List of Peer Reviewed Publications (In Press or Published) During Candidature

i. **Van Rheenen, T. E.,** & Rossell, S. L. (2013). Genetic and neurocognitive foundations of emotion abnormalities in bipolar disorder. *Cognitive Neuropsychiatry*, 18:168-207 (Presented in Chapter 2)

ii. **Van Rheenen, T. E**. & Rossell, S. L. (2013). Is the nonverbal behavioural emotion processing profile of bipolar disorder impaired? A critical review. *Acta Psychiatrica Scandinavica ,* 128, 163-178 (Presented in Chapter 3)

iii. **Van Rheenen, T. E.** & Rossell, S. L. (in Press, September 2013). Phenomenological predictors of psychosocial function in bipolar disorder: is there evidence that social cognitive and emotion regulation abnormalities contribute? *Australian and New Zealand Journal of Psychiatry,* DOI: 10.1177/0004867413508452 (Presented in Chapter 5).

iv. **Van Rheenen, T.E.** and**.** Rossell, S.L., (In press, July 2013). An Empirical Evaluation of the MATRICS Consensus Cognitive Battery in Bipolar Disorder. *Bipolar Disorders,* DOI: 10.1111/bdi.12134 (Presented in Chapter 8)

v. **Van Rheenen, T. E.** & Rossell, S. L. (In Press, August 2013). Auditory-prosodic processing in bipolar disorder; from sensory perception to emotion. *Journal of Affective Disorders*, 151, 1102-1107 (Presented in Chapter 10).

vi. **Van Rheenen, T. E.** & Rossell, S. L. (2013). Picture Sequencing Task Performance Indicates Theory of Mind Deficit in Bipolar Disorder. *Journal of Affective Disorders,* 151-1132-1134 (Presented in Chapter 11)

vii. Rossell, S.L., and **Van Rheenen, T.E.** (2012). Theory of mind performance using a story comprehension task in bipolar mania compared to schizophrenia and healthy controls. *Cognitive Neuropsychiatry*, 18, 409-421.

viii. Kulkarni, J., Gavrilidis, E., Worsley, R., **Van Rheenen, T.E**., and Hayes, E.H (2012). The Role of Estrogen in the Treatment of Men with Schizophrenia. *International Journal of Endocrinology and Metabolism,* 11,129-136

ix. Rossell, S.L., **Van Rheenen, T.E.,** Groot, C., Gogos, A., & Joshua, N.R. (In press, August 2013). Investigating affective prosody in psychosis: A study using the Comprehensive Affective Testing System. *Psychiatry Research,* DOI:10.1016/j.psychres.2013.07.037

List of Manuscripts under Review during Candidature

i. **Van Rheenen, T. E.** & Rossell, S. L. (in submission). Let's face it: facial emotion processing is impaired in bipolar disorder (Presented in Chapter 9).

ii. **Van Rheenen, T. E.** & Rossell, S. L. (in submission). A comprehensive examination of the emotion regulation profile of bipolar disorder (Presented in Chapter 12).

iii. **Van Rheenen, T.E.**, Bozaoglu, K., and Rossell, S.L. (in submission). The influence of Catechol-*O*-methyltransferase on cognition is modulated by bipolar disorder diagnosis (presented in Chapter 13).

List of Conference Presentations during Candidature

Published conference proceedings

i. **Van Rheenen, T.E.,** and Rossell, S. (2013). The influence of Catechol-O-methyltransferase on cognition is modulated by bipolar disorder diagnosis. Forthcoming paper presented at the Australasian Cognitive Neuroscience Society annual conference, Melbourne Australia: to be published in *Frontiers in Human Neuroscience*.

ii. Rossell, S.L., **Van Rheenen, T.E.,** Joshua, N.R., O'Regan, A., and Gogos, A. (2013) Facial Affect Perception in Psychosis: Recent evidence. Forthcoming paper presentation at the Australasian Cognitive Neuroscience Society annual conference, Melbourne Australia: to be published in *Frontiers in Human Neuroscience* (20% contribution)

iii. **Van Rheenen**, T.E., Rossell, S. and Murray, G., (2013). Let's face it: facial emotion processing impaired in bipolar disorder. Paper presented at Winter Workshop in Psychosis, Marrakesh, Morocco: to be published in the *International Clinical Psychopharmacology*

iv. **Van Rheenen**, T.E., and Rossell, S. (2013). Vulnerability to bipolar disorder is associated with emotion dysregulation and poor quality of life. Paper presented at Winter Workshop in Psychosis, Marrakesh, Morocco: to be published in the *International Clinical Psychopharmacology*.

v. **Van Rheenen T. E,** Rossell S. L, Murray G. (2012). Face facts: BD patients show impairments in emotion processing. Paper presented at the Australian Cognitive Neuroscience Society annual meeting; Brisbane, Australia: *Frontiers in Human Neuroscience. DOI: 10.3389/conf.fnhum.2012.208.00167*

vi. Rossell, S., **Van Rheenen**, T.E., and Groot, C., (2012). Affective Prosody in Psychosis. Recent evidence and future directions. Paper presented at the Australian Cognitive Neuroscience Society annual meeting; Brisbane, Australia: *Frontiers in Human Neuroscience*, *DOI: 10.3389/conf.fnhum.2012.208.00182* (20% contribution)

Oral presentations

i. **Van Rheenen, T.E.,** and Rossell, S. (forthcoming, Nov 2013). The influence of Catechol-O-methyltransferase on cognition is modulated by bipolar disorder diagnosis. Oral presentation at the *Australasian Cognitive Neuroscience Society annual conference, Melbourne Australia.*

ii. **Van Rheenen, T.E.,** and Rossell, S. (forthcoming, Dec 2013). COMT is associated with cognition in bipolar disorder. Oral presentation at the *Australasian Society for Psychiatric Research annual conference, Melbourne Australia.*

iii. **Van Rheenen, T.E.,** and Rossell, S. (2013). An investigation of auditory-prosodic emotion processing in bipolar disorder. Oral presentation at the *Australasian Society of Bipolar and Depressive Disorders annual conference, Melbourne Australia.*

iv. **Van Rheenen**, T.E., and Rossell, S. (2013). Auditory-prosodic processing in bipolar disorder; from sensory perception to emotion. Oral presentation at the *Australasian Schizophrenia Conference, Melbourne, Australia.*

v. **Van Rheenen**, T.E., Rossell, S. and Murray, G., (2013). Let's face it: facial emotion processing impaired in bipolar disorder. Oral presentation at the *Winter Workshop in Psychosis, Marrakesh, Morocco.*

vi. Gurvich, C., Louise, S., **Van Rheenen, T.E**., Neill, E. and Rossell, S.L. (2013). DRD1 rs4532 polymorphism interacts with schizotypy to influence cognition. *Australasian Schizophrenia Conference*, *Melbourne, Australia* (20% contribution)

vii. **Van Rheenen T. E,** Rossell S. L, Murray G. (2012). Face facts: BD patients show impairments in emotion processing. Oral presentation at the *Australian Cognitive Neuroscience Society annual meeting; Brisbane, Australia*

viii. Rossell, S., **Van Rheenen**, T.E., and Groot, C., (2012). Affective Prosody in Psychosis. Recent evidence and future directions. Oral presentation at the *Australian Cognitive Neuroscience Society annual meeting; Brisbane, Australia* (20% contribution)

ix. Rossell, S., **Van Rheenen**, T.E., and Joshua, N., (2012). Neuropsychology of bipolar disorder. Oral presentation at the *East Asia Bipolar Forum, Fukuoka, Japan* (10% contribution).

x. **Van Rheenen, T.E.,** Rossell, S. and Murray, G., (2011). Emotion abnormalities in bipolar disorder. Presented at the *Australasian Society for Psychiatric Research conference, Dunedin, New Zealand.*

xi. **Van Rheenen, T.E.,** and Murray, G., (2010). Exploring vulnerability to bipolar disorder; the role of cognitive self-concept clarity. Presented at the *Australasian Society for Psychiatric Research conference, Sydney*, *Australia.*

Poster presentations

i. **Van Rheenen, T.E.,** and Rossell, S. (forthcoming, Dec 2013). Picture sequencing task performance indicates theory of mind deficit in bipolar disorder. Poster presentation at the *Australasian Society for Psychiatric Research conference*, *Melbourne, Australia*

ii. Reynolds, M., **Van Rheenen, T.E.,** and Rossell, S. (forthcoming, Dec 2013). Theory of mind deficits found in first-degree relatives of bipolar disorder probands. Poster presentation at the A*ustralasian Society for Psychiatric Research conference*, *Melbourne, Australia* (30% contribution).

iii. **Van Rheenen**, T.E., and Rossell, S. (2013). An empirical evaluation of proposed International Society for Bipolar Disorders - Battery for the Assessment of Neurocognition in Bipolar Disorder (ISBD-BANC). Poster presentation at the *International review of Bipolar Disorders, Seville, Spain.*

iv. **Van Rheenen**, T.E., and Rossell, S. (2013). Vulnerability to bipolar disorder is associated with emotion dysregulation and poor quality of life. Poster presentation at the *Winter Workshop in Psychosis, Marrakesh, Morocco.*

v. **Van Rheenen**, T.E., and Rossell, S. (2013). Vulnerability to bipolar disorder is associated with emotion dysregulation and poor quality of life. Poster presentation at the *International Review of Bipolar Disorders, Seville, Spain.*

vi. **Van Rheenen**, T.E., and Rossell, S. (2013). An empirical evaluation of the MCCB-EF+ in Bipolar Disorder. Poster presentation at the *Australasian Schizophrenia Conference, Melbourne, Australia.*

vii. Gurvich, C., Louise, S., **Van Rheenen, T.E.,** Neill, E. and Rossell, S.L (2013). The Influence of Prefrontal and Striatal Dopaminergic Genes on Cognitive Control in High

and Low Schizotypy, Poster presentation at *Society of Biological Psychiatry, California, USA* (20% contribution).

viii. **Van Rheenen**, T.E., Rossell, S. and Murray, G., (2012). Is neurocognitive ability related to facial emotion processing in bipolar disorder? Poster presentation at *the Australasian Society for Psychiatric Research conference, Perth, Australia.*

ix. **Van Rheenen**, T.E., Rossell, S. and Murray, G., (2012). Vulnerability to bipolar disorder is associated with emotion dysregulation and poor quality of life. Poster presentation at the *Australasian Society for Psychiatric Research conference, Perth, Australia.*

x. **Van Rheenen**, T.E., Rossell, S. and Murray, G., (2012). Facial emotion recognition specificity in bipolar disorder. Poster presentation at the *Australasian Society for Psychiatric Research conference, Perth, Australia.*

xi. **Van Rheenen, T.E.,** and Rossell, S. (2012). COMT in cognition: pilot findings. Poster presentation at *CCS symposium, Melbourne, Australia.*

xii. **Van Rheenen**, **T.E.,** and Rossell, S. (2012). COMT and cognition: pilot findings. Poster presentation at the *Students of Brain Research Conference, Melbourne, Australia.*

xiii. **Van Rheenen, T.E.,** and Rossell, S. (2012). COMT in cognition and emotion abnormalities. Poster presentation at *Alfred Week Research, Melbourne, Australia.*

xiv. **Van Rheenen**, **T.E.,** and Rossell, S. (2012). COMT and cognition: pilot findings. Poster presentation at the *Biological Psychiatry Australia conference, Melbourne, Australia.*

xv. **Van Rheenen, T.E.,** and Rossell, S.L. (2012). Theory of mind in bipolar mania. Poster presentation at the *CCS ECR symposium, Melbourne, Australia.*

xvi. **Van Rheenen, T.E.,** and Rossell, S.L. (2011). Theory of mind in bipolar mania. Poster presentation at the *Australasian Society for Psychiatric Research conference, Dunedin, New Zealand.*

CHAPTER 1: INTRODUCTION AND THESIS OVERVIEW

The general aim for this body of work was to provide insight into neurocognitive, social cognitive and emotion regulation abnormalities in bipolar disorder (BD), with a view to better characterising each domain of functioning and understanding the relationships shared between them, genetic influences on them, and their psychosocial consequences. This is a worthy avenue of research given that the efficacy of psychopharmacological treatments for the disorder is limited. Certainly, a better understanding of these processes is therefore necessary in providing data that will enhance insight into the core features, aetiology and/or mechanisms of the disease. Ultimately, this work may potentially inform the development of new psychological treatments that will improve the outcomes of people with the disorder.

This thesis presents a series of important reviews and investigations that reflect this general aim. It is a hybrid thesis, in which many of its chapters comprise published/in press/submitted papers. Thus, there is some unavoidable repetition between them, for example there is repetition of background information in each chapter, and in parts of the method sections for each empirical study. However, each chapter does present unique information, theory or findings. Further, it should be noted that there is also some inevitable fragmentation in the text. For example, unlike traditional thesis formats, the introduction does not comprise a single chapter in which the entire rationale for the empirical investigations that follow is explicitly laid out. Rather it comprises a series of distinct, yet related review papers that form chapters organised along a common theme. Nonetheless, the reader will note that the work is collated in a manner consistent with the general aim of gaining a better and more holistic understanding of the aforementioned core processes and their relationships in BD. A guide will precede each chapter to provide necessary clarification, linkage, and to ensure that the contents of the thesis are established as a substantial and coherent body of work.

Although data for this research was collected at one time point in a single, large scale, multi-aim study, this thesis is presented as a series of short, concise chapters to reduce confusion and increase readability. Six of the chapters comprise manuscripts that have been

published or are in press in recognised scientific journals, three of them comprise manuscripts that are currently under review, and seven of them reflect more traditional thesis chapters that have not been submitted as journal articles. All of the chapters of this thesis were researched and written during the course of candidature as per Swinburne University's higher degree by research requirements. All research to which these chapters pertain was carried out in accordance with the Alfred Hospital and Swinburne University Human Ethics Review Boards and abided by the Declaration of Helsinki (see Appendix A).

The remainder of this introductory chapter will present a general overview of the disorder to provide a summary of the diagnosis, course, epidemiology, psychosocial burden and treatment of BD for the reader. It should be noted that despite recent changes to the official diagnostic system produced by the American Psychiatric Association, this thesis focusses on BD as defined by the fourth, text revised edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000). There are only minor changes to diagnostic criteria for BD in the most recent, fifth edition of the manual (DSM-5; American Psychiatric Association, 2013). These changes have not affected the description of the disorder, nor the aims or design of the body of work presented here. Thus, the following section describes BD as per its DSM-IV-TR description and a summary of changes between editions four and five can be found in section 1.2.

Following this chapter are four review chapters, three of which are published and one that represents a more traditional thesis chapter. Collectively, the aim of these review chapters is to introduce the reader to the three domains of BD research relevant to this thesis; neurocognition, social cognition and emotion regulation. It should be noted that although these four chapters provide a general overview of these topics in the context of their genetic aetiology, inter-relationships and potential influence on outcomes in BD, for practicality, they do not explicitly outlay the rationale for every single empirical investigation carried out as part of this research project. Rather, the *precise* background pertaining to each investigation is presented in each of the later empirical chapters.

Specifically, Chapter 2 presents a published review introducing the idea that neurocognitive deficits underlie deficits in social cognition and emotion regulation in BD. It also asserts that two particular genes linked to the dopamine and serotonin neurotransmitter

systems may be implicated in these deficits. Chapter 3 presents a published review providing a systematic overview of the non-verbal emotion processing literature in BD and discusses its methodological shortcomings. Chapter 4 reviews literature on emotion regulation, and introduces the idea that social cognition may impact emotion regulation in BD, while Chapter 5 provides a published theoretical review of potential predictors of psychosocial dysfunction in the disorder.

Chapter 6 follows with a short summary of the key points of interest in the previous introductory review chapters, and provides an overview of the general aims and objectives for the following empirical chapters. Chapter 7 provides a detailed methodological section that can be referred to for further details regarding particular measures used within each of the empirical investigations. The eight chapters that follow present detailed empirical investigations with an aim to first characterise neurocognitive, social cognitive and emotion regulation deficits in BD, *and then* assess potential genetic influences on them, interactions between them, and the impacts that they have on psychosocial functioning in the disorder.

Chapter 8 is the first of these empirical chapters and comprises a published manuscript that investigates the neurocognitive profile of BD using a novel cognitive battery. Chapters 9 and 10 contain submitted and /or published manuscripts that detail complex investigations of facial and prosodic emotion processing in BD respectively. Chapter 11 comprises a published manuscript that presents findings of impaired theory of mind in BD, whilst Chapter 12 describes a submitted manuscript detailing an investigation of emotion regulation in the disorder.

Chapter 13 is broader in scope and describes investigations of the influence of the COMT and TPH2 genes on neurocognition, social cognition and emotion regulation in patients with BD. Chapter 14 follows with an investigation of relationships between processes that were the focus of the preceding empirical chapters, namely neurocognition, social cognition and emotion regulation. Specifically, Chapter 14 details inter-relationships amongst these processes in an attempt to systematically identify whether neurocognition underpins social cognition and emotion regulation, and whether social cognition acts as a mediator of emotion regulations' relationship with neurocognition in BD. Chapter 15 is the final of the

empirical chapters, and presents an investigation of neurocognitive, social cognitive and emotion regulatory predictors of psychosocial function in BD.

Finally, the thesis concludes with an integrative discussion of the findings from the empirical studies (Chapter 16). Chapter 16 also examines the clinical implications of these findings and provides suggestions for future research.

Given the inevitable fragmentation in this type of hybrid thesis, the reader is advised to consult Table 1 and Figure 1 for further clarification around its content. These are provided as a quick reference to assist the reader to understand the development of the thesis as it unfolds. The reader should also note that some terminology has been used interchangeably across the chapters of this thesis. Specifically, the term *theory of mind* is also referred to as mentalising; the term *emotion recognition* is also referred to as emotion identification or emotion labelling; the term *affect* is also referred to as emotion; and the term *features* is also referred to as processes or abilities. Further, it should be noted that the term *social cognition* refers to both emotion processing and theory of mind.

Table 1. *Overview of thesis content*

Chapter number	Chapter content	Notes on overarching chapter aims
1	A general overview of BD is provided	Introduction to thesis and overview of BD
2	Literature is reviewed suggesting that in BD, i) neurocognition, social cognition and emotion regulation are impaired, ii) impairments in neurocognition impede the capacity for good social cognition and emotion regulation and iii) specific genes linked to the dopamine and serotonin system may be involved in these processes.	General review chapters introducing neurocognitive, social cognitive and emotion regulation deficits in BD, in the context of an overarching argument for genetic influences on them, inter-relationships between them and their psychosocial consequences
3	Literature is reviewed focussing on impairment in the non-verbal emotion processing profile of BD.	
4	Literature is reviewed focussing on emotion regulation difficulties in BD, and proposing that deficits in social cognition (as catalysed by poor neurocognition) may impact the capacity for good emotion regulation in the disorder.	
5	Literature is reviewed suggesting that in BD, psychosocial functioning may be impacted by social cognition and emotion regulation difficulties, in addition to poor neurocognition and mood symptomatology (processes that have traditionally been associated with outcomes in the disorder).	
6	The general aims and research objectives for the study is provided	Aims and methods chapters
7	The methodology of the study is provided	
8	The neurocognitive profile of BD is established using a standardised battery with established validity in a related clinical disorder	Empirical profiling chapters with an overarching aim to characterise neurocognitive, social cognitive and emotion regulation impairments in BD in the context of specific research objectives
9	Facial emotion processing impairments are examined by taking a range of potential confounds into account	
10	The potential for prosodic emotion processing impairments to exist in BD is investigated in light of factors that might contribute to these potential impairments	
11	The capacity for theory of mind in BD is explored	
12	The emotion regulation profile of BD is examined using a measure that considers its multiple dimensions	
13	Specific genetic influences on neurocognition, social cognition and emotion regulation are assessed in BD	Empirical chapters assessing genetic influences, inter-relationships and consequences of neurocognition, social cognition and emotion regulation in BD
14	Inter-relationships between neurocognition, social cognition and emotion regulation in BD are assessed	
15	The impact of neurocognition, social cognition and emotion regulation on subjective and objective psychosocial functioning in BD is assessed.	
16	A general discussion is provided	Discussion of findings, including implications, limitations and future directions

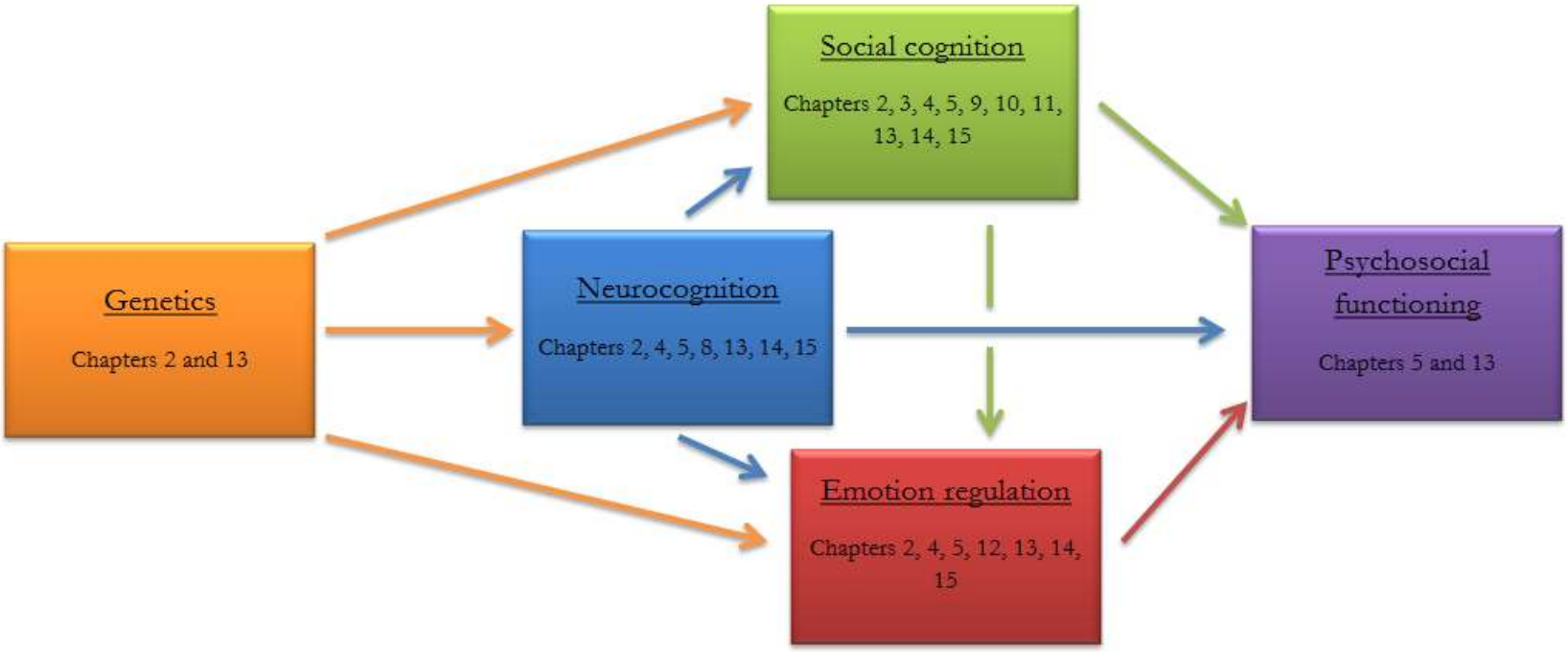

Figure 1. Thesis components and structure

Note: The coloured squares represent the topics covered in the thesis. The empirical chapters conducted in reference to the topics in the three central squares investigate the neurocognitive, social cognitive and emotion regulation profiles of BD patients across chapters 8-12. The arrows to and from the outer boxes, and within the model, show associations that are discussed in the introductory chapters (2-5) and tested in the latter empirical chapters (13-15) of the thesis.

1.1 General introduction to bipolar disorder

Bipolar disorder (BD), formerly known as manic-depression, is a debilitating mental illness thought to affect approximately 1.2% of the general population. The disorder has been found to decrease health, shorten life span and reduce involvement in important life activities, with some 30-60% of BD sufferers experiencing impairment in psychosocial functioning (Coryell et al., 1993; Goodwin & Jamison, 1990; MacQueen, Young, & Joffe, 2001). BD is a chronic psychopathology and the prolonged maladaptive functioning associated with its onset also contributes to its maintenance (Coryell, et al., 1993; Keller, Lavori, Coryell, & Endicott, 1993; Robins, 1984; Weissman & Myers, 1978). Even with optimal pharmacological treatments, relapse rates remain unacceptably high (Gitlin, Swendsen, Heller, & Hammen, 1995). The severity of the disorder has lead Goodwin and Jamison (1990) to estimate that 25-50% of sufferers will attempt suicide at least once in their lifetime. These outcomes have encouraged vast research efforts to determine both sources of and treatments for the illness. However, the aetiological roots of BD remain uncertain (Potash & DePaulo Jr, 2000).

BD is a complex affective disorder characterised by extreme mood variability. It's prevalence is equal across genders with the peak age of onset typically falling between 15-24 years (Goodwin & Sachs, 2010). The DSM-IV-TR (American Psychiatric Association, 2000) defines BD by the presence of at least one manic or one hypomanic episode. These episodes refer to markedly euphoric, irritable or elevated mood states that last for at least four days (hypomania) to periods of a week or longer (mania). Manic and hypomanic episodes are characterised by the presence of at least three of the following symptoms during the specified time periods; decreased need for sleep, inflated self-esteem or grandiosity, pressure of speech, flight of ideas, distractibility, psychomotor agitation or increases in goal directed activity and excessive involvement in pleasurable behaviours with no account for negative consequences.

During a hypomanic episode these symptoms are associated with an uncharacteristic change in functioning that does not significantly impair social or occupational ability, but that may be observable by others (American Psychiatric Association, 2000). In full-blown mania these symptoms are magnified, and are often accompanied by psychotic symptoms that cause a marked social or occupational impairment, or necessitate hospitalisation. In some cases,

patients experience concurrent periods of elevation and depression, known as mixed states. In addition to meeting core criteria for full-blown mania during these states, patients also experience at least five of the following symptoms that define a major depressive episode; depressed mood, anhedonia, weight loss or loss of appetite, changes in sleeping patterns, psychomotor abnormalities, fatigue or energy reductions, feelings of worthlessness, poor concentration and/or suicidal ideation (American Psychiatric Association, 2000).[2]

Typically, a clinical course characterised by one or more full-blown manic or mixed episodes leads to a diagnosis of bipolar disorder I (BD I). Episodes of depression are also almost always present within this subtype but are not required for its diagnosis. At least one major depressive episode, in addition to at least one hypomanic episode (but with no history of manic or mixed episodes), is however required for the diagnosis of bipolar disorder II (BD II).

Research investigating whether BD I and BD II represent distinct forms of mood disorder is limited, although there is some evidence to suggest that clinical and neuropsychological markers may differ between the two. For example, relative to BD II, BD I is associated with lower glucose uptake in the prefrontal cortex, slowed binocular rivalry rates and greater neurocognitive impairment (Kessler et al., 2013; Li et al., 2012; Nagamine, Yoshino, Miyazaki, Takahashi, & Nomura, 2009). BD II appears to cluster more within families, may be more common in females, is later in onset than BD I and carries greater suicide risk and incidence of mixed states, rapid cycling and seasonality (Baek et al., 2011; Baldessarini et al., 2010; Berk & Dodd, 2005; DePaulo Jr, Simpson, Gayle, & Folstein, 1990; Peselow, Dunner, Fieve, Deutsch, & Rubinstein, 1982).

Whilst those diagnosed as having BD II do not experience psychotic symptoms, approximately 50% of BD I patients experience positive symptoms, including formal thought disorder, delusions and hallucinations (Dunayevich & Keck, 2000; Goodwin & Sachs, 2010). The most common of these symptoms are mood-congruent delusions, the content of which is often grandiose, with patients tending to over-estimate their self-worth in terms of attractiveness and intelligence (Black & Nasrallah, 1989; Dunayevich & Keck, 2000; Goodwin

[2] See Table 1, section 1.2 for a detailed description of DSM-IV-TR diagnostic criteria for BD.

& Jamison, 1990; Goodwin & Sachs, 2010). Nevertheless, there are cases in which psychosis in BD is mood-incongruent, although this has been associated with greater impairments in outcome and a poorer clinical course (Fennig, Bromet, Karant, Ram, & Jandorf, 1996; Strakowski et al., 2000; Tohen, Tsuang, & Goodwin, 1992). As mood-incongruent psychosis in BD parallels that seen in schizophrenia, patients presenting with such symptoms are often misdiagnosed (Gonzalez-Pinto et al., 1998). However, if these symptoms subside with the remission of mood symptoms then a diagnosis of BD should be made (Goodwin & Sachs, 2010).

Indeed, BD is a disorder thought to share biological and phenomenological features with schizophrenia. Current evidence even suggests the need for a shift away from dichotomous categorisations of each disorder toward a continuum approach (Craddock & Owen, 2010). In particular, genetic studies show evidence for shared susceptibility across nosological boundaries (Cichon et al., 2011; Craddock, O'Donovan, & Owen, 2006; Craddock, O'Donovan, & Owen, 2009; Lichtenstein et al., 2009; Purcell, 2009) and there are growing accounts that the two disorders have overlapping features (Altshuler et al., 2004; Zalla et al., 2004). For example, both schizophrenia and BD patients exhibit neurocognitive (albeit quantitatively different), social cognitive and psychosocial impairments (Dickerson, Sommerville, Origoni, Ringel, & Parente, 2001; Krabbendam, Arts, van Os, & Aleman, 2005; Rossell, Van Rheenen, Groot, Gogos, & Joshua, In Press; Rowland et al., 2013b). BD also shares some genetic overlap with unipolar depression, and there is growing consensus that it sits on a mood spectrum comprising BD I and BD II, recurrent unipolar depression, minor depressions and sub-threshold symptomatology (Akiskal & Benazzi, 2003; Angst, 2007; Angst & Cassano, 2005; see Benazzi, 2007 for a review; Judd et al., 2003; Kelsoe, 2003). A wide body of research supports this contention, with evidence suggesting that many patients diagnosed with unipolar major depressive disorder go on to develop BD in the long term (Angst, Sellaro, Stassen, & Gamma, 2005; Cassano et al., 2004; Fiedorowicz et al., 2011; Goldberg, Harrow, & Whiteside, 2001).

BD is so severe a disorder that it is considered to be one of the top ten leading causes of years lost to disability (World Health Organization, 2004). Currently, first line treatments for the disorder include pharmacological interventions in the form of mood stabilisers such as

lithium carbonate or sodium valproate, and a host of other standard antipsychotic (mostly atypical), and anti-depressant medications (Baldessarini, Henk, Sklar, Chang, & Leahy, 2008; Fountoulakis et al., 2005; Kessing, Hellmund, Geddes, Goodwin, & Andersen, 2011; Sachs & Thase, 2000). Whilst these treatments have proven efficacy in reducing symptomatology, adherence can be low and there is evidence that psychosocial dysfunction remains beyond clinical remission (Coryell, et al., 1993; Gitlin, et al., 1995; Sajatovic, Valenstein, Blow, Ganoczy, & Ignacio, 2006; Tohen et al., 2000). Indeed, the disorder tends to be highly recurrent, with more than 70% of individuals who have experienced a full manic or depressed episode estimated to experience relapse within five years (Gitlin, et al., 1995). Thus, the use of adjunctive physical and psychological treatments may be necessary to effectively and holistically treat the disorder (Colom, Vieta, Tacchi, Sánchez-Moreno, & Scott, 2005; Zaretsky, 2003). There is emerging evidence that some novel brain stimulation techniques including electro-convulsive therapy and more recently, repetitive transcranial magnetic stimulation, are efficacious in its treatment (see Loo, Katalinic, Mitchell, & Greenberg, 2011 for a review). Various forms of psychotherapy and psycho-education also show promise (Miklowitz, 2008; Swartz, Frank, Frankel, Novick, & Houck, 2009; Tundo, Cavalieri, Navari, & Marchetti, 2011; Vieta & Colom, 2004). Moreover, relatively novel treatments including cognitive and functional remediation may be usefully applied to BD, but further research into the mechanisms of action in the disorder is necessary before these treatments become valuable (Martínez-Arán et al., 2011).

The prevention of future episodes is a major goal of current treatments but progress toward this end is slow and is further complicated by common comorbidities within primary BD. Many patients with the disorder also frequently meet criteria for anxiety, substance abuse/dependence, impulse control disorders (i.e., attention deficit and hyperactivity disorder, intermittent explosive disorder) and personality disorders (Altindag, Yanik, & Nebioglu, 2006; Bauer et al., 2005; Garno, Goldberg, Ramirez, & Ritzler, 2005; Goodwin & Sachs, 2010; Krishnan, 2005; Perugi et al., 2013). BD thus remains a disorder associated with inadequate treatment and misdiagnosis (Rybakowski, Suwalska, Lojko, Rymaszewska, & Kiejna, 2005). For example, an Access Economics report for SANE Australia (2003) showed that average treatment levels for BD were less than one quarter of what is considered to be best practice; it

was estimated that 33% of patients don't receive treatment, 40% don't receive medication and only 17% are involved in some form of rehabilitation. Of the completed suicides associated with the illness, 60% were estimated to be the result of inadequate treatment. Moreover, there was a greater than 66% chance that BD was wrongly diagnosed, with the average time from illness onset to correct diagnosis being approximately 10 years. The suffering, disability and death caused by the disorder was estimated to be similar to schizophrenia, and greater than that of rheumatoid arthritis, ovarian cancer, or HIV/Aids (Access Economics: Sane Australia, 2003).

Consequently, BD is associated with an increased economic burden; the financial impact of the disorder in Australia amounts to over $1.5 billion (Access Economics: Sane Australia, 2003). Almost $3 million is spent directly on hospital, medical and residential care and medications per annum, and indirectly, the costs are even greater; the disorder amounts to over $220 million in lost tax revenue, over $460 million in lost earnings due to occupational incapacity, over $230 million in welfare payments and over $20 million in legal, police and prison costs.

At a personal level, the financial and psychosocial burden of BD is substantial. Almost half of the overall financial impact of the disorder in Australia is borne by patients and their carers (Access Economics: Sane Australia, 2003). One study of the US population reported that the disorder amounted to 65.5 lost days per worker annually, which translated to a personal income loss of over $9000 (Kessler et al., 2006). Certainly, patients with BD have reduced occupational functioning *and* interpersonal functioning, and report poorer quality of life in comparison to the general population (Brissos, Dias, Carita, & Martinez-Aran, 2008a; Dean, Gerner, & Gerner, 2004; Malhi et al., 2007a; Michalak, Yatham, & Lam, 2005; Michalak et al., 2007). Continued symptomatic and psychosocial dysfunction in the disorder is of grave concern given the risk of suicide in BD is 6.2 times greater than for that of other Axis I disorders (Chen & Dilsaver, 1996). Thus, the early diagnosis and treatment of the disorder should be considered an urgent matter, and further research examining the aetiological and phenomenological mechanisms involved in BD should be a top priority in the research agenda.

1.2 Supplementary information

Table 2. *Summary of DSM-IV-TR criteria for BD I and II diagnoses, manic, hypomanic and major depressive episodes, and relevant changes in DSM-5*

	DSM-IV-TR	DSM-5-changes
Diagnoses	**BD I;** A. Criteria are currently (or most recently) met for a manic, hypomanic, mixed, or major depressive episode B. There has previously been at least one manic episode or mixed episode. C. The mood symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. D. The mood symptoms in criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified. E. The mood symptoms in criteria A and B are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism)	Mixed episodes are no longer used to diagnose BD I. Thus, only the presence of a current (or past) manic, hypomanic, or major depressive episode is needed to fulfil criterions A and B.
	BD II; A. Presence (or history) of one or more major depressive episodes. B. Presence (or history) of at least one hypomanic episode. C. There has never been a manic episode or a mixed episode. D. The mood symptoms in criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified. E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.	There has been no change to this diagnosis.
Manic Episode	A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary)	This criterion now includes an emphasis on changes in activity and energy as well as mood.
	B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree:	These criteria remain the same

	DSM-IV-TR	DSM-5-changes
	1. increased self-esteem or grandiosity 2. decreased need for sleep (e.g., feels rested after only 3 hours of sleep) 3. more talkative than usual or pressure to keep talking 4. flight of ideas or subjective experience that thoughts are racing 5. distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli) 6. increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation 7. excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)"	
	C. The symptoms do not meet criteria for a mixed episode	This criterion has been removed
	D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features	This criterion remains the same
	E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatments) or a general medical condition (e.g., hyperthyroidism).	This criterion remains the same
	Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of BD I.	This note remains the same
Hypomanic Episode	A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual non depressed mood	This criterion now includes an emphasis on changes in activity and energy as well as mood.
	B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only 1. irritable) and have been present to a significant degree: 2. inflated self-esteem or grandiosity 3. decreased need for sleep (e.g., feels rested after only 3 hours of sleep) 4. more talkative than usual or pressure to keep talking 5. flight of ideas or subjective experience that thoughts are racing 6. distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli) 7. increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation 8. excessive involvement in pleasurable activities that have a high potential for painful	These criteria remain the same

	DSM-IV-TR	DSM-5-changes
	consequences (e.g., engaging in 9. unrestrained buying sprees, sexual indiscretions, or foolish business investments)	
	C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic	This criterion remains the same
	D. The disturbance in mood and the change in functioning are observable by others	This criterion remains the same
	E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.	This criterion remains the same
	F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).	This criterion remains the same
	Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of BD I.	This note remains the same
Depressive Episode	Major depressive disorder requires two or more major depressive episodes	
	A. Depressed mood and/or loss of interest or pleasure in life activities for at least 2 weeks and at least five of the following symptoms that cause clinically significant impairment in social, work, or other important areas of functioning almost every day 1. Depressed mood most of the day. 2. Diminished interest or pleasure in all or most activities. 3. Significant unintentional weight loss or gain. 4. Insomnia or sleeping too much. 5. Agitation or psychomotor retardation noticed by others. 6. Fatigue or loss of energy. 7. Feelings of worthlessness or excessive guilt. 8. Diminished ability to think or concentrate, or indecisiveness. 9. Recurrent thoughts of death	These criteria remains the same
	B. The symptoms do not meet criteria for a mixed episode	This has been removed
	C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning	This is now listed as criterion B
	D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).	This criterion remains the same

	DSM-IV-TR	DSM-5-changes
	E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterised by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.	This criterion has been removed
Mixed Episode	A. The criteria are met for both a manic episode and for a major depressive episode (except for duration) nearly every day during at least a 1-week period. B. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features. C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).	A new specifier, "with mixed features," has been added that can be applied to episodes of mania or hypomania when depressive features are present and to episodes of depression in the context of major depressive disorder or BD when features of mania/hypomania are present.
Notes		• DSM-5 now permits categorisation of individuals with a past history of a major depressive disorder who meet all criteria for hypomania except the duration criterion under the diagnosis "other specified Bipolar and Related Disorder"., Individuals in which too few symptoms of hypomania are present to meet criteria for the full BD II are also eligible for classification under this diagnosis. • An "anxious distress" specifier appears in the DMS-5 and is intended to identify patients with anxiety symptoms that are not part of the bipolar diagnostic criteria.

Note: This information is taken directly from online information publications provided by the American Psychiatric Association (2012) and Intermountain Healthcare (2005) in reference to the DSM-IV-TR (American Psychiatric Association, 2000) and DSM-5 (American Psychiatric Association, 2013).

CHAPTER 2: GENETIC AND NEUROCOGNITIVE FOUNDATIONS OF SOCIAL COGNITION AND EMOTION REGULATION IN BIPOLAR DISORDER

2.1 Chapter guide

Van Rheenen, T. E., & Rossell, S. L. (2013). Genetic and neurocognitive foundations of emotion abnormalities in bipolar disorder. *Cognitive Neuropsychiatry, 18*, 168-207.

Chapter 2 is the first of the review chapters and comprises a version of the above mentioned article, which can be found in Appendix B in its published form.[3] This chapter introduces the idea that neurocognition, social cognition and emotion regulation are impaired in bipolar disorder (BD). It also asserts that there may be potential links between impairments in these processes, and that genes linked to the serotonin and dopamine systems may contribute susceptibility to BD by influencing them. This chapter is particularly relevant to empirical Chapter's 8, 13 and 14. A glossary of common molecular genetic terminology has been provided in Appendix C to assist in the comprehension of this chapter (and that of Chapter 13).

[3] The reader will note some wording differences between the contents of the manuscript presented in this chapter and the published version. This is because the published version refers to emotion perception and theory of mind as 'emotion processing' and at times does not explicitly distinguish between emotion processing and emotion regulation, rather referring to them collectively as socio-emotional processing. For clarity, and to maintain consistency with the rest of the thesis (where these processes are referred to separately), the term emotion processing has been changed to *social cognition* in this chapter, and the terms social cognition *and* emotion regulation are no longer referred to collectively. Other than these terminology changes, no core content has been altered.

2.2 Abstract

Introduction: Bipolar disorder (BD) is a serious mood disorder, the aetiology of which is still unclear. The disorder is characterised by extreme mood variability in which patients fluctuate between markedly euphoric, irritable and elevated states to periods of severe depression. The current research literature shows that BD patients demonstrate compromised neurocognitive, social cognitive and emotion regulation ability in addition to these mood symptoms. Viable candidate genes implicated in these processes may be involved. Additionally, links between deficient neurocognition, and impaired social cognition and emotion regulation complement genetic explanations of BD pathogenesis. This review examines associations between cognition indexing prefrontal neural regions, and impairments in social cognition and emotion regulation. A review of the effect of COMT and TPH2 on these functions is also explored.

Methods: Major computer databases including PsycINFO, Google Scholar and Medline were consulted to conduct a review of the genetic, neurocognitive, social cognitive and emotion regulation literature in BD.

Results: This review determines that COMT and TPH2 genetic variants contribute susceptibility to abnormal prefrontal neurocognitive function, which may oversee social cognition and the regulation of emotion in BD. This provides for greater understanding of some of the emotion and cognition relevant symptoms in BD.

Conclusions: Current findings in this direction show promise although the literature is still in its infancy and further empirical research is required to investigate these links explicitly.

2.3 Introduction

Social cognitive and emotion regulation abnormalities represent primary functional disturbances in bipolar disorder (BD), an illness typified by impairment in psychosocial functioning (e.g., Coryell, et al., 1993; Goodwin & Jamison, 1990). Persons with BD signify a complicated clinical sample that are disabled by their symptoms, and prone to relapse despite optimal pharmacological treatment (Gitlin, et al., 1995). Although primarily a disorder of affect, there is little clarity around the aetiological development of the mood symptoms that characterise BD. The disorder is complex and is therefore likely to be underpinned by several biological and psychological processes. An extensive literature has documented abnormalities in neurochemical, genetic and neurocognitive processes which may directly translate to both the disorder itself and its associated deficits in social cognition, emotion regulation, insight and psychosocial functioning (e.g., Bora, Yucel, & Pantelis, 2009a; Getz, Shear, & Strakowski, 2003; Inoue et al., 2010; Martino, Strejilevich, Fassi, Marengo, & Igoa, 2011b; Soeiro-de-Souza et al., 2012a; Strakowski et al., 2011; Wolf, Brüne, & Assion, 2010). This review intends to briefly examine some of the existing literature and identify appropriate avenues for future study in the area.

2.3.1 *Social cognitive and emotion abnormalities in BD*

Broadly speaking, *social cognition* describes our ability to perceive and process emotion from the environment. Emotive entities comprise a wide variety of stimuli including emotionally charged words and pictures, and stimuli that allow us to decode and understand the social world. Our understanding of other people is an important aspect of human nature that facilitates the creation of a social context in which our own emotional reactions occur. For the purposes of this review we define social cognition as comprising *theory of mind*; our ability to understand the emotional and mental state of a communicator, and as *emotion perception*; the ability to identify, recognise and distinguish facial and prosodic emotional expressions in others (Addington & Addington, 1998; Getz, et al., 2003; Olley et al., 2005). Emotional expressions are a significant component of nonverbal communication that permits

rapid inferences about the emotional state of the communicator (Batty & Taylor, 2003). Effective processing of emotion signifies our human ability to perceive emotional representations and make inferences about them. An impairment of emotion processing reduces our capacity to make social hypotheses that can lead to a range of maladaptive psychosocial contingencies.

Filtering emotional responses to control and cope with such contingencies, commonly referred to as *emotion regulation*, is also critical to adaptive human functioning. Emotion regulation is an umbrella term for various abilities that allow us to initiate, inhibit or modulate internal states, cognitions, behaviours and physiological reactions in response to emotion inducing environmental stimuli (Gross, 2011). Emotion regulation is heavily dependent on social context and may be crucially influenced by inherent cognitive processes including flexibility and decision making (Green & Malhi, 2006). When effective, it maintains a healthy emotion system that allows us to recognise, understand and accept our emotional responses, manage behaviours and access strategies that reduce/increase emotion as needed (Gratz & Roemer, 2004).

Social cognitive processes in BD groups are abnormal, with impairment in the ability to perceive affect in faces (Bozikas, Tonia, Fokas, Karavatos, & Kosmidis, 2006b; Lembke & Ketter, 2002) and spoken expressions (Murphy & Cutting, 1990) observed in a number of samples. Patients with BD also have reduced theory of mind ability that limits their capacity to make inferences about the emotional state of others (Bora et al., 2005; Olley, et al., 2005; Rossell & Van Rheenen, 2013). Emotional attention biases as well as deficits in emotionally relevant inhibitory control processes and difficulty in regulating emotions in themselves and in their relationships with others have also been identified as features of BD (Burdick et al., 2011; Murphy et al., 1999). Neurocognitive and genetic functions may explain this.

2.3.2 *Neurocognitive profile*

There is growing evidence to suggest that higher order prefrontal cognition is impaired in the BD population, as patients have been reported to exhibit persistent abnormalities across a range of measures indexing prefrontal functions including memory, learning and executive

processes relating to attention, flexibility, planning and control (e.g., Clark, Iverson, & Goodwin, 2002; Clark, Kempton, Scarnà, Grasby, & Goodwin, 2005a; Gourovitch et al., 1999; Keri, Kelemen, Benedek, & Janka, 2001; Sobczak et al., 2002).[4] There has even been suggestion that cognitive functioning in BD should be conceptualised similarly to that of classical cognitive disorders like mild cognitive impairment (Osher, Dobron, Belmaker, Bersudsky, & Dwolatzky, 2011).

Neurocognition is often equated with IQ, where neurocognition refers to specific cognitive abilities and IQ describes global intellectual ability. BD patients generally tend to exhibit similar levels of premorbid IQ in comparison to controls, whereas their current IQ levels appear to differ in a negative direction (Bora, et al., 2009a; Getz, et al., 2003; Murphy et al., 2001; Murphy, et al., 1999). This indicates a rate of decline as the disorder progresses, and suggests that environmental and disease related factors have a direct effect on the disorder (Burdick, Gunawardane, Woodberry, & Malhotra, 2009). Interestingly, IQ does not appear to underpin social cognitive abilities, as case/control differences in these processes are evident in early diagnostic or at risk groups where the effects of the disorder on IQ are absent, or at least less pronounced (Brotman et al., 2008a). This is further confirmed by a number of studies indicating the presence of social cognitive abnormalities in BD, using experimental designs in which patients are matched on levels of premorbid IQ (Getz, et al., 2003; Schenkel, Pavuluri, Herbener, Harral, & Sweeney, 2007). The information we review below suggests that it is higher order abilities governed by the central executive specifically, and not global IQ that includes language, motor or sensory perceptual abilities that affects social cognition and emotion regulation in BD. Therefore, it should be noted that for the remainder of this review, the term neurocognition refers to higher order cognitive functions including memory, attention, learning, and executive functions.

Altered neurocognitive ability has been reported in both bipolar disorder I (BD I) and bipolar disorder II (BD II) subtypes across manic and depressed states (e.g. Fleck et al., 2003; Larson, Shear, Krikorian, Welge, & Strakowski, 2005; Xu et al., 2012; Y.L. Hsiao et al., 2009).

[4] It should be noted that currently there is no well-validated standardised battery of neurocognition in BD, although this would seem important for better characterising cognitive impairments across cohorts.

Impairments during remission have also been demonstrated across various behavioural measures purporting to quantify these abilities (see Arts, Jabben, Krabbendam, & van Os, 2008 for a review). Given that impairments are evident across a range of tasks that tap different aspects of neurocognition, it is becoming increasingly apparent that cognitive processes indexed by prefrontal neural functioning have some trait-like qualities that are globally disturbed in the disorder, with some worsening during the depressed or manic state (Dixon, Kravariti, Frith, Murray, & McGuire, 2004; Martinez-Aran et al., 2004b).

BD is traditionally conceptualised as an emotional illness, although it is becoming clear that this emotionality may be manifested by impaired social cognition and emotion regulation. As mentioned earlier, these terms relate to the way that people process and use information drawn from interactions with each other and their environment. This is reflected in the human ability to identify, recognise and distinguish facial emotional expressions in others, create a representation of others' emotion states, and regulate internal emotions by inhibiting inappropriate responses, initiating appropriate responses and modulating affect (Gross, 2011).

There is a growing literature that suggests that social cognition and emotion regulation are impaired in severe psychiatric disorders (e.g., Bora, Yucel, & Pantelis, 2009b; Getz, et al., 2003; Urosevic, Abramson, Harmon-Jones, & Alloy, 2008), and it is certainly plausible that these phenomena are at least partially representative of underlying neurocognitive dysfunction in BD (Bora, Yucel, & Pantelis, 2009c; Green, Cahill, & Malhi, 2007; Wolf, et al., 2010). For example, attention, verbal, spatial and language abilities are required to organise and process affect-related sources and maintain focus on relevant information, while flexibility and inhibition of impulsive responses are required for effective emotional monitoring and initiation (Clark, Sarna, & Goodwin, 2005b; Ferrier, Chowdhury, Thompson, Watson, & Young, 2004; Kohler, Bilker, Hagendoorn, Gur, & Gur, 2000). Further to this, a growing body of evidence suggests that social cognitive and emotion regulation abnormalities reflect activity in brain regions thought to be responsible for neurocognitive processes (e.g., D'Esposito et al., 1998; Lawrence et al., 2004; YurgelunTodd & Yurgelun, 2000).

We thus postulate that neurocognitive function plays a fundamental role in social cognition and emotion regulation, and that impairment in the neurocognitive profile of BD is

partially reflected in deficits in these processes. A discussion of this relationship within various indices of prefrontal function is presented below.

2.3.2.1 Executive function

Executive functions are top down processes that reflect neural efficacy in the prefrontal cortical region (Fuster, 2001). They are involved in the organisation of other functions such as attention and memory, and fundamentally influence psychosocially valuable abilities including self-regulation, decision making and planning, perspective taking and adaptation to shifting environmental conditions.

There are frequent reports of abnormal responses in behavioural and neurobiological indicators of executive function in the BD population (e.g., Blumberg et al., 2003; Frangou, Kington, Raymont, & Shergill, 2008; Murphy, et al., 2001; Olley, et al., 2005). Deficits are pervasive, as evidenced across numerous measures including the Wisconsin Card Sorting Task (Arts, et al., 2008; Frantom, Allen, & Cross, 2008; van Gorp, Altshuler, Theberge, Wilkins, & Dixon, 1998; Zubieta, Huguelet, O'Neil, & Giordani, 2001), Stroop test (e.g., Frangou, Donaldson, Hadjulis, Landau, & Goldstein, 2005; McGrath, Scheldt, Welham, & Clair, 1997; Torrent et al., 2006), Trail Making Test B (e.g., Goswami et al., 2006; Nehra, Chakrabarti, Pradhan, & Khehra, 2006) and the Stockings of Cambridge Task (Maalouf et al., 2010). These deficits have been associated with reduced academic aptitude and imply poorer cognitive flexibility, abstract thinking and inhibitory control in people with BD (Biederman et al., 2011; Murphy, et al., 1999). This chronic dysfunction may signify that problems within the central executive are related to the social cognitive and emotion regulation abnormalities that are characteristic of the illness (Becerra et al., 2013; Green, et al., 2007; Martino, et al., 2011b).

For example, Gopin, Burdick, DeRosse, Goldberg and Malhotra (2011) recently demonstrated impairment in BD I patients' ability to discriminate and respond accurately to positive and negative emotional stimuli in an executive task requiring the inhibition of a prepotent response. Interestingly, Brand and colleagues (2012) found similar results in a group of unaffected BD siblings, where a response bias to negative emotional cues was observed. These results support that of McClure et al., (2005) who found that paediatric BD patients impaired on a task of facial affect recognition, were also impaired on tasks requiring the

inhibition of a prepotent response. Similarly, Bora et al. (2005) reported that the ability to conceptualise another's mental/emotional state was positively correlated with measures of flexibility in a euthymic BD sample. Impairment in the ability to understand another's mental state has also been associated with executive processes (Brüne, 2005; Ozonoff, Pennington, & Rogers, 1991), emotion recognition (Buitelaar & van der Wees, 1997) and poor psychosocial functioning (Brüne, 2005; Inoue, Yamada, & Kanba, 2006) in a variety of psychopathological populations with overlapping symptom profiles. There is limited research investigating theory of mind in BD, although emotion recognition difficulties have been associated with mentalising ability in the disorder on at least one occasion (Bora, et al., 2005).

The influence of the executive system extends beyond emotion perception and theory of mind because executive impairments are believed to affect the ability to regulate emotion efficiently as well (Green & Malhi, 2006). For example, to maintain socially appropriate responses to environmental contingencies and reduce enacting potentially risky behaviours, the inhibition of impulsive actions and the ability to shift attention from emotionally laden stimuli is important. Similarly, the capacity to make adaptive self-regulatory changes in the face of environmental contingencies including rewards requires flexibility (Blair, Peters, & Granger, 2004). Heightened reward orientation and impulsive behaviour are a common feature of the illness, and findings of impairment in flexibility and inhibitory control suggest that a dysfunctional executive processing system may be responsible for this (Christodoulou, Lewis, Ploubidis, & Frangou, 2006; Dickstein et al., 2007; Dickstein et al., 2004; Johnson et al., 2000b; Joormann & Gotlib; Najt et al., 2007). Of note, there is a large body of literature demonstrating impairment on emotional go/no go and stroop tasks indexing emotional inhibition and attentional shifting/flexibility in patients and at risk groups (Bentall & Thompson, 1990; French, Richards, & Scholfield, 1996; Kerr, Dunbar, & Bentall, 2003; Kerr, Scott, & Phillips, 2005; Lyon, et al., 1999; Malhi, Lagopoulos, Sachdev, Ivanovski, & Shnier, 2005; Murphy, et al., 1999; Rubinsztein, Michael, Paykel, & Sahakian, 2000). For example, Strakowski et al. (2011), found that BD patients responded significantly slower to neutral and negative emotional stimuli than healthy controls on a task measuring emotional inhibition; and Mueller and colleagues (2010) found increased errors on a reward processing eye movement task indexing cognitive control in a sample of youth with BD.

It is likely there exists an influence of cognition on social understanding and so it seems fitting that the collective evidence suggests that emotion recognition, representation and regulation reflect common underlying neurocognitive functions. It is thus certainly plausible that poor emotion regulation in response to socio-emotional dilemmas can be accounted for by deficits and discordant integration of prefrontal executive processes that permit inferences about others emotional states, from which these dilemmas stem. Thus, the appropriate and accurate perception of emotion and mental state of another would be required to initiate and regulate an appropriate internal and/or social response. This interaction is likely to be impaired in BD.

2.3.2.2 Learning and memory

The ability to retain, recall and recognise information and experiences is referred to as memory. Memory supports the attainment of knowledge and skills by facilitating the storage of visual and verbal environmental inputs that contribute to learning. The ability to learn and the ability to retain information are largely interdependent and can affect the efficiency of planning, appropriate adjustment of behaviour and the ability to make informed decisions about important events.

Visual learning and memory tasks require participants to acquire, maintain or retain information from stimuli perceived visually. These tasks oblige the participant to view and reproduce an image or distinguish targets faces from distracters following observation. Deficits in visual learning functions have been evidenced with the Rey-Osterrieth Complex Figure Test (Deckersbach et al., 2004a; Ferrier, Stanton, Kelly, & Scott, 1999), the Biber Figure Learning Recall Test, the Faces subtests I and II of the Wechsler Memory Scale III (WMS; Frantom, et al., 2008) and the Brief Visual Memory Test (Schretlen et al., 2007) in BD samples.

In contrast, measures of verbal learning and memory commonly require participants to repeat a list of words recited by a trained administrator at different time intervals. Although there is some variation between measures, BD versus control differences in verbal learning have been elicited using the Hopkins Verbal Learning Test-Revised (HVLTR; Schretlen, et al., 2007), the California Verbal Learning Task (Altshuler, et al., 2004; Cavanagh, Van Beck, Muir,

& Blackwood, 2002; Deckersbach et al., 2004b; Fleck, et al., 2003; Martinez-Aran, et al., 2004b; van Gorp, et al., 1998) and the Rey Audio Visual Memory Task (Ferrier, et al., 1999; Goswami, et al., 2006; Krabbendam et al., 2000) across immediate recall, delayed recall and delayed recognition discrimination.

Learning and memory difficulties may underlie social cognitive and emotion regulation disturbances because the ability to store information 'on-line', and recall information without bias subserves the ability to remember an emotion or integrate past positive and negative emotional experiences (Showers, 1992; Showers & Zeigler-Hill, 2007). Accordingly, visual and verbal working memory impairments in BD have been reported across a variety of measures including the computerised Spatial Span (Allen et al., 2009; Martinez-Aran, et al., 2004b; Thompson et al., 2005; Thompson et al., 2006) and the Digit Span Forwards and Backwards (Ferrier, et al., 1999; Goswami, et al., 2006; Martinez-Aran, et al., 2004b; Torrent, et al., 2006).

Memory capacity may play an important contributing role in social cognition and emotion regulation because smaller memory span could reduce the aptitude to learn, to analyse different perspectives concurrently or to carry out tasks or make immediate decisions. Hence, reduced memory capacity has been directly related to difficulties in emotion processing (Schneider, Gur, Gur, & Shtasel, 1995) and to poor psychosocial function (Glahn et al., 2006; Martinez-Aran et al., 2004a; McGrath, Chapple, & Wright, 2001). For example, Summers and colleagues (2006) have reported that BD patients impaired in visual and verbal memory domains were also impaired in recognising facial expressions. Similarly, Addington and Addington (1998) have reported the co-occurrence of impaired performance on a task of visual learning and on a task of facial emotion discrimination, where an explicit association between the two was apparent.

Other evidence shows that verbal memory and learning ability is related to emotion recognition in disorders with similar emotion perception abnormalities to those seen in BD (Buitelaar, Wees, Swaab-Barneveld, & Gaag, 1999). For example, in schizophrenia populations, verbal and non-verbal learning deficits have been associated with the ability to differentiate emotional intensity in faces (Kohler, et al., 2000; Sachs, Steger-Wuchse, Kryspin-Exner, Gur, & Katschnig, 2004), and there is a large literature that suggests that children with learning disabilities experience emotion perception difficulties (Dimitrovsky, Spector, Levy-

Shiff, & Vakil, 1998; Holder & Kirkpatrick, 1991; Petti, Voelker, Shore, & Hayman-Abello, 2003; Sisterhen & Gerber, 1989).

Episodic forms of memory are also abnormal in BD and might be expected to impact emotion regulation. Persons with the disorder demonstrate a reduced tendency to recall specific as opposed to broad-spectrum memories (Mansell & Lam, 2004; Scott, Stanton, Garland, & Ferrier, 2000). Overgeneralised autobiographical memory recall is associated with abnormal cognitive ability (processing speed, attention, inhibition and working memory) and poor social problem solving ability (Beaman, Pushkar, Etezadi, Bye, & Conway, 2007; Evans, Williams, O'Loughlin, & Howells, 1992; Mowlds et al., 2010) which is thought to take effect by reducing one's capacity to recall coping strategies used in previous situations to facilitate current mood management (Scott, et al., 2000).

BD patients have been reported to demonstrate a greater tendency to recall distressing personal memories, where the content of these memories relate to depressed experiences and failed goals (Mansell & Lam, 2004). Heightened goal pursuit is a well-recognised feature of BD and is thought to contribute to its aetiology. It has been hypothesised that abnormal responding to environmental reward cues (i.e., potential goals) in those vulnerable to BD can differentially lead to mania or depression; when the reward goal is reached the regulation of the experience of intense positive affect is insufficient and contributes to the manic ascent. If the goal is thwarted the ineffective management of the experience of negative affect contributes to the depressive spiral (Johnson, 2005b; Meyer, Johnson, & Winters, 2001). Autobiographical memories may play a role in maintaining these emotions because memory for events is thought to be tied up with goals for the self (Conway & Pleydell-Pearce, 2000). Thus it has been argued that upon striving for new goals, distressing personal memories of related instances are triggered, which if considered to be a reflection of the current situation, prompts socially excessive and inappropriate goal oriented behaviour to avoid failure (Mansell & Lam, 2004).

Learning and memory difficulties are particularly evident when tasks indexing reward based learning are used in BD studies. Manic patients have been reported to show an increased tendency to choose the less likely of two outcomes despite explicit information about the favourability of these outcomes (Murphy, et al., 2001). Similarly, blunted reward learning has been found in BD patients on response reversal tasks (Dickstein, et al., 2007;

Dickstein, et al., 2004; Gorrindo et al., 2005; McKirdy et al., 2009) and when using tasks in which one stimulus is more frequently rewarded than another (Pizzagalli, Goetz, Ostacher, Iosifescu, & Perlis, 2008). As mentioned previously, reward based learning is particularly relevant to the BD phenotype given that patients exhibit excessive reward based orientations in situations in which behavioural withdrawal would be more adaptive (Johnson, 2005b). This increased risk taking behaviour is highlighted in findings that show BD patients prefer to take a less favourable response option to obtain a reward (Murphy, et al., 2001) and become unrealistically confident by seeking out difficult goals following an initial success (Johnson, 2005b).

2.3.2.3 Processing speed

Processing speed is a measure of cognitive efficiency and relates to a functional ability to fluently and automatically process information. Slowed processing speed reduces the capacity to capture, process and respond to complex information and has been reported in a number of BD studies using the Controlled Word Association Test (Altshuler, et al., 2004; Balanzá-Martínez et al., 2008; Frangou, et al., 2005; Martinez-Aran, et al., 2004b), the Trail Making Test A (e.g., Martinez-Aran, et al., 2004b; Nehra, et al., 2006; Thompson, et al., 2005), the Digit Symbol Substitution Test (e.g., Goswami, et al., 2006; McIntosh, Harrison, Forrester, Lawrie, & Johnstone, 2005; Thompson, et al., 2005; Varga, Magnusson, Flekkøy, Rønneberg, & Opjordsmoen, 2006), the Animal Naming Test (e.g., Torrent, et al., 2006; Zubieta, et al., 2001) and the processing speed index measures of the WISC-V (Mattis, Papolos, Luck, Cockerham, & Thode).

There is some evidence to suggest that processing speed is sensitive to differences in emotion processing in the healthy population (De Sonneville et al., 2002). Because rapid dynamic facial expressions naturally place an increased burden on mental processing, inherent deficits in mental speed which are commonly found in BD are likely to make some contribution to emotion processing abnormalities. Studies supporting this assertion indicate that slowed reaction times (which are thought to reflect reduced processing speed) and impaired early information processing ability are related to facial emotion processing tasks in the disorder (Addington & Addington, 1998; Getz, et al., 2003; Marchand et al., 2011). For

example, Sokhadze, Tasman, Tamas and El-Mallakh (2011) found that when BD patients were asked to respond to only female faces, reaction time was significantly slower for stimuli depicting an emotional expression than for stimuli that did not depict emotion.

At this stage it is unclear whether the effect of processing speed on emotion perception abnormalities occurs directly by limiting what is perceived or responded to in any given emotional context, or indirectly by maladaptively affecting other cognitive abilities that are implicated in emotion perception. Evidence in the latter direction however, suggests that deficits in processing speed reduce the efficiency of learning and memory functions (e.g., Bryan & Luszcz, 1996; Kieseppa et al., 2005).

2.3.2.4 Attention

Attention refers to the selection and allocation of processing resources for the purpose of concentration on an aspect of the environment. Attention modulates processing ability by controlling which material enters awareness, and is vital for the construction of visual and auditory experiences which include those related to emotional state (Kanwisher & Wojciulik, 2000). Poor ability to perceive, be selective and/or sustain attention translates to distractibility and diminished concentration, and may lead to social cognitive problems including reduced facial emotion recognition accuracy and increased sensitivity to emotionally valanced stimuli. Reduced perceptual attention has been found in psychotic manic patients, and there is considerable evidence to show that BD patients across all phases are impaired in their ability to sustain attention (Bora, Vahip, & Akdeniz, 2006b; Bora, et al., 2009a; Maalouf, et al., 2010; Robinson et al., 2006; Strauss, Prescott, Gutterman, & Tune, 1987).

A common task used to measure sustained attention is the Continuous Performance Test (CPT), which requires participants to maintain focus on a repetitive stimulus for a period of time (usually between 7-10 minutes), responding only to target stimuli. Although variations of the task have been used, there is consistent evidence that such measures elicit attention deficits in BD populations. For example, Clark et al., (2002) used the rapid Visual Information Processing Task (RVIP) in a group of euthymic BD patients and found that attention diminished over the duration of the task. Patients were also significantly impaired in their detection of targets and significantly slower to respond than a healthy control group. In a later

study, Clark, Kempton and colleagues (2005a) again reported that euthymic BD patients show impaired sustained attention in comparison to controls. Similarly, Natj et al.(2005) reported significantly reduced attention in a BD population using the CPT-Identical Pairs Version and Ancin and colleagues (2010) reported deficits in a large group of euthymic patients when using the Degraded Stimulus CPT.

Relationships between attention and social cognition have been demonstrated in BD groups and show that sustained and early visual attention are related to facial emotion identification and discrimination (Addington & Addington, 1998). Attentional biases for affect have thus been reported in studies using emotion relevant task designs (Rich et al., 2010). For example, Murphy et al., (1999) reported a bias toward sad stimuli in depressed patients and a bias toward happy stimuli in manic patients using an affective go/no go task. Similarly, Lyon, Startup and Bentall (1999) and Harmer, Grayson and Goodwin (2002) have demonstrated that depressed and manic patients are biased towards negative stimuli as opposed to positive stimuli in an emotional Stroop and facial affect recognition task respectively.

2.3.2.5 Effects of medication

Medication effects on neurocognition have not been regularly studied in BD, although growing available evidence indicates that neurocognitive, social cognitive and emotion regulation abnormalities are not affected by medication (Addington & Addington, 1998; Brotman, et al., 2008a; Getz, et al., 2003; Roiser et al., 2009; Schenkel, et al., 2007; Strakowski, Adler, Holland, Mills, & DelBello, 2004). There are exceptions however, and it may be that it is only certain types of medications (i.e., antipsychotics as opposed to mood stabilisers) that negatively impact these abilities (Frangou, et al., 2005; Robinson, et al., 2006; Strakowski, et al., 2011). For example, in a recent meta-analysis Bora, Yucel and Pantelis (2009a) found that studies reporting higher incidences of antipsychotic medication usage had larger processing speed impairments. This is in line with reports that mood stabilisers, anticonvulsants and antidepressants have minimal to no effects on cognition in comparison to antipsychotic medication use, although it is difficult to ascertain the exact effects of any of these medications without significantly more empirical research (Arts, Jabben, Krabbendam, & van Os, 2011;

Goswami et al., 2002). We therefore suggest that the information presented in this review should be interpreted with caution.

2.3.3 *Genetic research in BD*

BD has long been conceptualised as a heritable disorder, but the specific mechanisms of its genetic transmission are not known. Numerous isolated studies have identified genetic variants thought to be implicated in the disorder, yet their effect sizes are small and replications across samples are frequently unsuccessful. Recently, genetic studies of BD have utilised the genome wide association (GWAS) approach in which thousands of Single Nucleotide Polymorphisms (SNPs) are genotyped to examine their association with the BD phenotype. While this approach permits hypothesis-free analysis of a large number of genes fairly rapidly, it also means that the many varied symptoms in a fairly heterogeneous disorder are effectively 'shoved into one basket'. GWAS studies in BD have generated some important findings that show the potential involvement of cell migration, calcium and sodium channel genes such as CACNA1C, NCAN and ANK3. However, these studies have generally yielded inconsistent results with genetic associations failing to replicate across most studies and no meta analyses confirming the involvement of any of these genes (Baum et al., 2008; Burton, 2007; Cichon, et al., 2011; Ferreira et al., 2008; Hattori et al., 2009; Lee et al., 2011; McMahon et al., 2010; O'Donovan et al., 2008; Scott et al., 2009; Sklar et al., 2008; Smith et al., 2009). Even evidence for CACNA1C, which demonstrates the strongest statistical association with the disorder, is preliminary (Sklar, et al., 2008).

An alternative approach involving the examination of associations between identified candidate genes and a given "intermediate" phenotype in a case/control design has also presented promising findings. The key principle of the endophenotype approach is that genes are selected for study based on their biological underpinnings when the pathophysiology of the disorder is at least partially understood (Kwon & Goate, 2000). In BD, abnormalities in neurocognition, social cognition and emotion regulation may be quantifiable intermediate phenotypes, because they are considered to be features that may exist across the bipolar spectrum and mediate between genotype and phenotype. They are thought to be involved in

BD pathophysiology because there is demonstrated evidence that they are associated with BD, are not state dependent, may influence mood symptoms that characterise the disorder (Addington & Addington, 1998; Bozikas, et al., 2006b; Carver & Johnson, 2009; Johnson, 2005b; Vederman et al., 2012), and are found within BD families (Antila et al., 2007b; Brotman, et al., 2008a; Glahn, Bearden, Niendam, & Escamilla, 2004). For example, cognitive and emotional impairments have been demonstrated in both clinical samples (Getz, et al., 2003; Gopin, et al., 2011) and siblings of BD patients (e.g., Antila et al., 2007a; Brand, et al., 2012; Brotman et al., 2008b).

Examining abnormalities in neurocognition, social cognition and emotion regulation is therefore a valuable method to facilitate understanding of BD's genetic basis in comparison to the use of broad categorical diagnostic variables as is the case in GWAS (Antila, et al., 2007b; Bevilacqua & Goldman; Mier, Kirsch, & Meyer-Lindenberg, 2010; Potash et al., 2007). Such a method serves to reduce heterogeneity issues in genetic studies as it is certainly plausible that these abilities have distinct genetic causes, such that a given gene contributes to some, but not all of BD's features.

The endophenotype approach is an advocated approach that adopts a practical method of exploring the genetic basis of BD based on targeted inquiry of specific candidate intermediate phenotypes (e.g., neurocognition, social cognition and emotion regulation) in relation to specific genes (Tabor, Risch, & Myers, 2002). This approach eliminates the need for multiple comparisons (as in GWAS) that increase the power needed to uncover genetic effects. It is possible that genes identified using the candidate gene approach will therefore not be represented in GWAS results. BD is a disorder likely to result from the additive nature of multiple genes demonstrating small effects (Langenecker, Saunders, Kade, Ransom, & McInnis, 2010). GWAS studies are broad in scope and require enormous power due to the necessary statistical correction needed for the many multiple comparisons used to examine associations within the genotype of a given BD sample. Small genetic effects on intermediate phenotypes would not survive this statistical correction. Thus, GWAS studies are missing out on important information about the genetics of BD.

The endophenotype approach however, has greater statistical power to detect genes of small effect, and would permit refinement of knowledge around abilities that may be involved

in the aetiology and maintenance of the disorder (Risch & Merikangas, 1996). Thus, emotion regulation abnormalities and neurocognitive and social cognitive dysfunction may mediate the relationship between certain genes and BD itself. These functions may be pathophysiologically influenced by the dopamine and serotonin neurotransmitter circuits (Canli & Lesch, 2007; Meneses, 1999) and their trait-like qualities indicate an underlying genetic component (Antila, et al., 2007b). Dopamine and serotonin circuits are known to be heavily involved in the pathogenesis of BD (Burdick et al., 2007; Cichon et al., 2008; Cousins, Butts, & Young, 2009; Mahmood & Silverstone, 2001). A small number of SNPs with origins from these circuits have been separately documented as viable candidate genes for neurocognition, social cognition and emotion regulation, as well as for the BD phenotype itself. Two of these genes are becoming increasingly recognised as being involved in the degradation of dopamine and the synthesis of serotonin, and will be of focus in the current review.

2.3.3.1 Dopamine and serotonin genes involved in neurocognition and emotion in BD

2.3.3.1.1 Dopamine /COMT

There is general consensus that irregularities in the dopamine system are involved in the symptomatology of BD. The COMT gene codes for a protein that catabolises a range of catechol chemicals including dopamine, and is implicated in its synaptic degradation. It is located in a BD candidate region on chromosome 22, and is well recognised as a candidate gene for severe psychiatric illnesses including schizophrenia and major mood disorders (e.g., Kelsoe et al., 2001; Lachman et al., 1997; Li et al., 1997; Ohara, Nagai, Suzuki, & Ohara, 1998; Wonodi, Stine, Mitchell, Buchanan, & Thaker, 2003). There is good evidence to suggest that COMT is involved in the pathogenesis of BD (Burdick, et al., 2007; Jones & Craddock, 2001; Lee et al., 2010; Shifman et al., 2004; Zhang et al., 2009).

A SNP occurring at COMT gene codon 158 results in a G→A Valine (Val) to Methionine (Met) substitution that occurs relatively frequently. The Val allele manifests as higher COMT activity and reduced synaptic dopamine availability, whereas the Met allele manifests as reduced COMT activity and increased synaptic dopamine availability (Lachman et al., 1996b).

The Val^{158}Met polymorphism has been the subject of great research interest and a variety of studies have uncovered promising findings. Given that dopamine excess has a well-recognised involvement in BD it is not surprising that the low activity allele has been implicated in its susceptibility (Li, et al., 1997). For example, Craddock and colleagues (2001) found that the low activity Met allele confers vulnerability to the disorder in a large meta-analyses of 13 case control studies comprising 910 bipolar cases and 1069 controls.

COMT has also been associated with particular clinical subtypes, symptom groups and demographics of the BD illness. Lachman et al., (1996ab), Kirov et al., (1998), and Papolos et al., (1998) have all independently established that the low activity allele increases susceptibility to rapid cycling, and Rotondo et al. (2002) found a higher frequency of Met homozygotes in BD patients not comorbid for panic disorder. The low activity allele has been found to be preferentially transmitted in females (Mynett-Johnson, Murphy, Claffey, Shields, & McKeon, 1998) and is associated with greater positive symptomatology in schizophrenia and BD groups (Goghari & Sponheim, 2008). Lee (2010) found that Met allele carriers were on average less likely to respond to mood stabiliser treatment in mania, suggesting a possible gene effect on therapeutic response in BD.

The high activity Val allele has also been linked with depression in affective psychoses (McClay et al., 2006) and a (non-significant) trend for increased psychotic symptoms in BD patients (Basterreche et al., 2008). Moreover, there is evidence to indicate its increased distribution in BD patients with a history of attempted suicide (Massat et al., 2004). Collectively these findings appear to indicate that increased synaptic dopamine availability leads to excesses in affective symptomatology (i.e., rapid cycling, positive symptomatology) whereas reduced synaptic dopamine availability is associated with severe negative symptoms.

Although these findings show promise, the picture remains complicated with a range of molecular genetic studies failing to find an association between COMT and BD (Gutierrez et al., 1997; Kunugi et al., 1997; Lachman, Kelsoe, Moreno, Katz, & Papolos, 1997; Ohara, et al., 1998). It is possible these inconsistencies are related to the genetic and phenotypic heterogeneity of the illness or the ethnicity of sample cohorts. Effect sizes for the significant Val^{158}Met polymorphism-BD results have also generally been small and suggest that the SNP may act as a modifier, affecting associated BD features rather than the disorder itself (Lelli-

Chiesa et al., 2010). The mechanism for this is unclear, although abnormalities in dopamine transmission appear to be a critical contributor to affective disturbances, as they may play a role in biasing the functional reactivity of brain areas involved in social cognition and emotion regulation (i.e., neurocognitive brain regions). Given the critical role that dopamine plays in the prefrontal cortex, a neural brain region central to the acquisition and representation of information (Miller, Freedman, & Wallis, 2002), COMT is indeed one of the most promising genes implicated in these functions (Mattay & Goldberg, 2004).

Recently, Farrell, Tunbridge, Braeutigam and Harrison (2012) demonstrated the effects of COMT on cognition and emotion-related responses. They conducted a placebo controlled trial to test the effects of a COMT inhibiting agent, tolcapone, on working memory and risk aversion. In the placebo group, Met homozygotes performed significantly better than Val homozygotes and tended to be more averse to risk. Interestingly, in the experimental groups, memory performance was improved for Val homozygotes and worsened for Met alleles. Similarly, risk taking behaviour was increased in Met homozygotes and decreased in Val homozygotes.

The COMT gene has been found to play a critical role in reactivity related to neurocognitive circuitry that may mediate responses to arousal and the processing of emotion-relevant stimuli (Domschke et al., 2008; Drabant et al., 2006). A recent meta-analysis of all available and relevant imaging studies demonstrated a strong effect of COMT on prefrontal activity, with reduced efficiency for Val carriers on cognitive tasks and reduced efficiency for Met carriers on emotion relevant tasks (Mier, et al., 2010). Yacubian et al. (2007) have also reported that COMT Met activity in the ventral striatum and prefrontal cortex modulates reward anticipation. Similarly, Bishop and colleagues (2006) found the COMT Met genotype to be associated with reduced activity in the ventrolateral prefrontal cortex and orbitofrontal cortex when presented with negative, as opposed to neutral distracters during a matching task. These regions are associated with controlled attentional processing and suggest the Met allele is implicated in weakened attentional focus on task stimuli, and reduced regulation of distraction from negative stimuli.

The Val^{158}Met genotype has been associated with neurocognitive performance in both healthy and schizophrenia populations (Bevilacqua & Goldman; Egan et al., 2001; Malhotra et

al., 2002; Wirgenes et al.). The single study examining this in a BD population reported negative findings, where a related COMT SNP (rs165599) was implicated instead (Burdick, et al., 2007). Given the effect of COMT is likely the result of a complex interaction with other factors including stress and genetic background, this lack of effect can again be explained by the relative heterogeneity of the disorder and the background in which Val^{158}Met exerts its effect (see Tunbridge, Harrison, & Weinberger, 2006 for a detailed explanation of this theory). Nevertheless there is growing evidence to support the claim that COMT is associated with neurocognition, social cognition and emotion regulation (e.g., Bevilacqua & Goldman, 2011; Farrell, et al., 2012; Sheese, Voelker, Posner, & Rothbart, 2009; Witte & Flöel, 2011). For example, Weiss and colleagues (2007) found people homozygous for the Met allele to be slower and less accurate at processing negative facial expressions. Herrmann et al., (2009), Smolka et al., (2007) and Williams et al., all found that Met homozygotes had significantly increased brain activation for emotionally negative stimuli which may be related to increased dopamine availability. Swart and colleagues (2010) too, found that Met homozygotes reported higher levels of alexithymia, thus demonstrating greater difficulties in verbalising their feelings, which is an aspect of emotion regulation. These processes are often found to be impaired in BD. Thus, understanding their genetic basis may present a novel method of understanding the genetic basis of the disorder.

2.3.3.1.2 Serotonin/TPH2

Serotonin (5HT) is a monoamine neurotransmitter that has been critically implicated in a variety of functions relevant to BD aetiology. BD has been associated with abnormal levels of 5HT and given that Tryptophan Hydroxylase 2 (TPH2) is the first and rate limiting enzyme in the biosynthesis of 5HT, it has been considered to be a viable candidate gene in the disorder (Walther & Bader, 2003; Walther et al., 2003; Wiste, Arango, Ellis, Mann, & Underwood, 2008). TPH2 is located in a BD candidate region on chromosome 12q21 (Ewald, Flint, Kruse, & Mors, 2002; Shink, Morissette, Sherrington, & Barden, 2004) and has been associated with a variety of related psychiatric disorders (Manor et al., 2008; Zill et al., 2004a). Findings linking the gene to BD are inconsistent however, with some studies failing to find an

association (e.g., Campos et al., 2010; Choi, Yoon, & Kim, 2010; Mann et al., 2008; Serretti et al., 2011) and several others reporting clear links (Cichon, et al., 2008; De Luca, Likhodi, Van Tol, Kennedy, & Wong, 2005; Harvey et al., 2004; Lin et al., 2007; Lopez, Detera-Wadleigh, Cardona, Kassem, & McMahon, 2007; Roche & McKeon, 2009; Van Den Bogaert et al., 2006). Despite this discrepancy, there is a general consensus that serotonin genes control a broad range of biological functions thought to be involved in BD (Lucki, 1998) and further study of the TPH2 gene is warranted to ascertain its role (if any) in the disorder.

Although BD has been associated with TPH2 in several ethnically distinct samples (Lin, et al., 2007; Van Den Bogaert, et al., 2006), the mechanism of involvement for this gene is unclear. It has however been noted to play a fundamental role in the modulation of neurocognition and emotion (Cichon, et al., 2008; Strobel, 2007; Waider, Araragi, Gutknecht, & Lesch, 2011). For example, Inoue (2010), reported that a TPH2 polymorphism is related to greater levels of reward dependence, an emotional construct relating to the tendency for positive responses to signals of reward.

There is also growing evidence that negative emotional traits are associated with TPH2 (Reuter, Kuepper, & Hennig, 2007a). For example Jacob et al., (2010) reported a TPH2 risk allele association with personality disorders from the B (emotional or dramatically inclined) and C clusters (anxious-avoidant) which are often comorbid in BD (Altindag, et al., 2006; George, Miklowitz, Richards, Simoneau, & Taylor, 2003). Similarly, Gutknecht (2007) reported that TPH2 polymorphisms were associated with harm avoidance and neuroticism which are overlapping dimensions reflecting proneness to psychological distress, temperamental sensitivity to negative stimuli and reduced risk tasking propensity (Cloninger et al., 1998; Costa & McCrae, 1992). These are common features of different BD episodes (Blairy et al., 2000; Engstrom, Brandstrom, Sigvardsson, Cloninger, & Nylander, 2004; Young et al., 1995). Experimental results pointing to an association between TPH2 SNPs and lowered risk taking behaviour on implicit and explicit tasks compliments these findings (Juhasz et al., 2010) and contribute to an emerging hypothesis that TPH2 may influence features common to severe emotional disorders.

Studies examining the neural relationship between TPH2 and social cognition have also presented promising results. For example, TPH2 polymorphisms G844T and G703T have

been linked to the amygdala, a neural structure implicated in the processing of emotion (Adolphs, 2002; Adolphs, Cahill, Schul, & Babinsky, 1997; Adolphs, Tranel, Damasio, & Damasio, 1994; Morris et al., 1998; Phillips, Drevets, Rauch, & Lane, 2003). Brown et al., (2005) reported greater amygdala activity in response to an affective face matching task in healthy carriers of the 844T allele. Similarly, Canli et al. (2005) and Furmark et al. (2009) reported that carriers of the 703T allele showed greater amygdala reactivity in response to emotional face stimuli using two different psychophysiological methods.

In fact, the TPH2 polymorphism (rs4570625) occurring at promoter region 703 and resulting in a guanine to thymine substitution has been frequently linked with other neural areas thought to be involved in the sensory encoding and regulation of affect (Phillips, et al., 2003; Phillips, Ladouceur, & Drevets, 2008; Schupp, Markus, Weike, & Hamm, 2003). For example Hermann (2007) reported that carriers of the 703T allele show a trend for greater posterior neural activity in response to emotionally arousing stimuli; and Canli and others (2008) reported that in response to fearful faces, the putamen was more activated in carriers of the T allele than non-carriers.

Other experimental behavioural data shows genotype differences, with Osinsky et al., (2009) reporting that homozygous carriers of the T allele performed slower in a low conflict condition on an emotional response inhibition task than in the high conflict condition. This suggests that as well as having some role in emotion processes, TPH2 is involved in emotion relevant aspects of neurocognitive function.

There are identified links between TPH2 and disorders characterised by attentional deficits (De Luca, et al., 2005; Manor, et al., 2008; Sheehan et al., 2005; Walitza et al., 2005) and a growing literature demonstrates that the G703T allele is implicated in various higher order cognitive processes related to attention, working memory and response control (Stoltenberg et al., 2006). For example, Reuter et al.(2007b) demonstrated an effect of the 703T allele on an executive attention task in which healthy carriers of the allele displayed more errors and poorer executive control. Other neurocognitive methodologies have revealed similar results, with Strobel (2007) reporting greater response variability and increased error rate on a continuous performance task in those with the T allele; and Osinksy et al. (2009) reporting that

homozygous T allele carriers performed substantially slower on congruent stroop trials that are generally considered low conflict and tend to index faster reaction times.

On cognitive tasks the polymorphism has also been found to differentiate between neural responses. Stronger activations in the prefrontal cortex have been reported during a working memory task in healthy T homozygotes (Reuter et al., 2008), and abnormal responses to a cognitive inhibition task have been found in healthy GG allele carriers, and in those with attention deficits (Baehne et al., 2009).

Collectively, these studies demonstrate that at least two identified TPH2 SNPs may be involved in emotion regulation, social cognition and neurocognition, of which one (G703T) appears to have a consistent effect. There is good indication that the 703T allele is implicated in emotional and cognitive performance deficits, however, neural studies indicate that TT carriers display *increased* neural activity in response to emotional and cognitive stimuli. These findings appear somewhat conflicting; however, Reuter et al. (2008) argue that increased neural activation may be a compensatory index of effort as opposed to ability. This is in line with the neural efficiency hypothesis (Haier, Siegel, Tang, Abel, & Buchsbaum, 1992; Haier et al., 1988) and prompts us to suggest that carriers of the homozygous T allele find emotion and cognitive tasks more difficult, and thus they exert a stronger degree of effort which increases brain activation. In contrast, heterozygous or homozygous G allele carriers may find cognitive/emotion relevant tasks easier, expending lesser effort and hence lower levels of brain activation. At this time it is too early to make any clear predictions as to the way in which TPH2 enacts its effect. However, it is becoming increasingly evident that a demonstrable link between TPH2, neurocognition, social cognition and emotion regulation exist.

Indeed, TPH2 has been consistently linked to maladaptive emotional behaviours and psychopathologies that share common symptoms and embody strong emotional or cognitive components. For example, higher levels of TPH2 have been found in the post mortem brains of BD patients and depressed suicide victims (Bach-Mizrachi et al., 2005; Bach-Mizrachi et al., 2008; De Luca, et al., 2005) and SNPs from the TPH2 gene have been associated with major depressive disorder (e.g., Haghighi et al., 2008; Tsai et al., 2009; Van Den Bogaert, et al., 2006; Zill, et al., 2004a), attention deficit and hyperactivity disorder (e.g., Manor, et al., 2008;

Walitza, et al., 2005), anxiety disorder (Zhou et al., 2005), bipolar disorder (e.g., Harvey, et al., 2004; Van Den Bogaert, et al., 2006) and suicide (De Lara et al., 2007; Zill et al., 2004b).

This broad association amongst TPH2 and several severe psychiatric disorders suggests that the gene may act by exerting influence over common features, not clinical phenotype. Thus features generally representative of these disorders (i.e., abnormal neurocognitive function, social cognition and emotional dysregulation) may signify building blocks in the understanding of their genetic aetiology.

In sum, it appears that both serotonin and dopamine genes control a broad range of biological functions thought to be involved in BD (Canli & Lesch, 2007; Coldman-Rakie, Castner, Svensson, Siever, & Williams, 2004; Hariri & Holmes, 2006; Laviolette, 2007; Lucki, 1998; Takahashi et al., 2005). Interestingly the genes have not reached GWAS significance, possibly due to the issues with genetic effects and power discussed earlier. Nevertheless, the literature we have reviewed here suggests a role for both COMT and TPH2 in the pathogenesis of neurocognitive, social cognitive and emotion regulation abnormalities. These abnormalities are common to the disorder and suggest a genetic link that may provide insight into its biological basis.

Of course there are other genes that have been implicated in BD, yet research examining their influence over neurocognition, social cognition and emotion regulation is less extensive, and does not permit inferences regarding aetiological hypotheses at this early stage. Many of these genes (e.g., BDNF and NRG1) are involved in biological processes such as cell growth and neuronal migration. We chose to examine genes from the dopamine and serotonin system due to growing evidence for their role in neurocognition, emotion processing and regulation ability (Bevilacqua & Goldman; Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009; Herrmann, et al., 2007; Reuter, Schmitz, Corr, & Hennig, 2006), deficits of which are core features of the disorder that may indirectly contribute to its maintenance.

2.3.4 *Gene-cognition effect on social cognition and emotion regulation in BD*

Human social cognition is contextualised by emotion. Perceptual skills including acuity for identifying and distinguishing emotions from others, and regulatory skills which facilitate

the initiation and management of emotional responses are vital for adaptive social interaction. The current literature suggests that the processing of emotion, and the subsequent ability to interpret another's emotional state, entails the integration of a variety of higher order brain functions that permit rapid emotional inferences, orient attention, and assimilate past representations and experiences of affect. Similarly, the ability to initiate, monitor and flexibly alter emotions necessitates attention to important situational features, maintenance of goal relevant behaviours, emotionally impartial memory storage and recall, learning capabilities that assist in regulating responses, impulse inhibition and cognitive response flexibility. Thus, top down neurocognitive functions are likely to underlie deficits in social cognition and emotion regulation, and may represent underlying neural dysfunction in regions of the brain localised to these processes. Effectively, neurocognitive ability may represent a distinct aetiological basis from which these BD features stem (Green & Malhi, 2006).

Further to this, two genetic variants involved in the synthesis of serotonin and the degradation of dopamine may be causally implicated in these neurocognitive, social cognitive and emotion regulation abnormalities in the disorder, as genes from both neurotransmitter systems are thought to have a fundamental role in the modulation of cognition and affect (Cichon, et al., 2008; Drabant, et al., 2006; Strobel, 2007). TPH2 and COMT have been associated with neurocognitive performance, personality traits related to emotional instability and brain circuitry mediating responses to arousal and processing affectively relevant stimuli (Bishop, et al., 2006; Drabant, et al., 2006; Gutknecht, et al., 2007; Reuter, et al., 2007b; Wichers et al., 2007; Yacubian, et al., 2007). Their behavioural expressions have also been frequently associated with the BD phenotype (Shifman, et al., 2004; Van Den Bogaert, et al., 2006).

Collectively, we interpret this information as suggesting a possible pathway of illness pathology in which genetic variants from within the serotonin and dopamine systems contribute susceptibility to abnormal prefrontal neurocognitive function which oversees social cognitive processing and regulation of emotion. We suggest that these genes confer susceptibility for BD by disturbing neurocognitive, social cognitive and/or emotion regulation abilities in the illness.

This hypothesis would go some way in explaining the overlap of features amongst several psychiatric illnesses, as interactions amongst COMT or TPH2 and other disorder specific genetic risk factors may account for disparities in phenotypic expression. For example, circadian rhythm disruption is another candidate intermediate phenotype for BD and related mood disorders (Lenox, Gould, & Manji, 2002). Glycogen synthase kinase 3-beta (GSK3-B) is involved in the regulation of circadian rhythms and has been implicated in the action of lithium (Kaladchibachi, Doble, Anthopoulos, Woodgett, & Manoukian, 2007). It has also been consistently tied to BD, but there is no good evidence for an association with disorders such as autism, which are exemplified by social cognitive deficits, but lack the expression of severe mood symptoms or disruptions in circadian cycles (American Psychiatric Association, 2000; Benedetti et al., 2004; Carter, 2007; Le-Niculescu et al., 2009; Serretti & Mandelli, 2008). Thus it may be that the interaction amongst COMT, TPH2 and GSK3B contributes to the phenotypic expression of BD, whereas the interactions amongst TPH2, COMT and some other gene contribute to the phenotypic expression of autism.

Although our model of the aetiology of social cognitive and emotion regulation abnormalities in BD is a defensible interpretation of the literature, we acknowledge that it is probable that not all social cognitive and emotion regulation abilities directly interact with neurocognition, and may not necessarily be genetically influenced by the hereditary variants we have specified in this review. For example, schizophrenia samples show impaired processing of general facial information such that difficulties in emotion perception may be the direct result of bottom up perceptual complexities as opposed to top down cognitive impairments (Kerr & Neale, 1993). It appears that this is not the case in BD; however, other mediating factors may be involved instead (Addington & Addington, 1998; Getz, et al., 2003). These include the potential indirect influences of personality traits (Canli, Sivers, Whitfield, Gotlib, & Gabrieli, 2002; Canli et al., 2001), gender (Bearden et al., 2006) and family mental illness history (Gogos, van den Buuse, & Rossell, 2009; Vaskinn et al., 2007) which have been independently linked to neurocognitive, social cognitive and emotion regulation processes.

In sum, social cognition and emotion regulation are very specific and unique abilities. There appears to be a great deal of overlap amongst them, prefrontal neurocognition and dopamine and serotonin genetics, but given the lack of explicit experimental designs to test

these relationships it is too early to confidently determine the extent to which COMT, TPH2 and neurocognition explains variance in social cognition and emotion regulation in BD.

2.4 Conclusions

Taken together, it is apparent that clarity around genetic and neurocognitive underpinnings in BD is still in its infancy. However, it would appear that the social cognitive and emotion regulation deficits commonly seen in the disorder are at least partially underpinned by neurocognitive difficulties. Furthermore, it may be that these cognitive and emotion-related abnormalities are influenced by variations in the COMT and TPH2 genes.

Given that BD is a fairly heterogeneous disorder, studying the genetic origins of phenotypic features (i.e., intermediate phenotypes) may be more informative than looking at genome variability based on nosologically recognised categories. This review suggests that our understanding of the pathophysiology of BD may be facilitated by examining gene variations that impact the effectiveness of neurocognition, and subsequently social cognition and emotion regulation. A direct investigation of such a conjecture is yet to be conducted but will surely provide further insight into the biological basis of BD.

Such an investigation would have extensive clinical implications. Pharmacologically, better understanding of the effects of allele variation could influence the provision of medications based on genotype, as carriers of different alleles may respond better to some medications than others. It could also provide the basis for developing new or improved medications that directly target cognition (Tunbridge, et al., 2006). In the same vein, greater knowledge about the relationship shared between deficits in neurocognition, social cognition and emotion regulation in BD could assist in the development of cognitive remediation and psychological therapies to improve psychosocial contingencies resulting from deficiencies in emotion-related cognition.

CHAPTER 3: NONVERBAL EMOTION PROCESSING IN BIPOLAR DISORDER

3.1 Chapter guide

Van Rheenen, T. E., & Rossell, S. L. (2013). Is the non-verbal behavioural emotion-processing profile of bipolar disorder impaired? A critical review. *Acta Psychiatrica Scandinavica*, 128, 163-1785

Chapter 3 is the second of the review chapters, and comprises the above mentioned article which can be found in Appendix D in its published form. In the previous chapter, the reader was informed that neurocognitive, social cognitive and emotion regulation processes are impaired in BD, and an argument for the impact of deficits in neurocognition on social cognition and emotion regulation was made. This chapter delves deeper into one aspect of social cognition; nonverbal emotion processing. Here we present a background review on the behavioural facial, prosodic and multi-modal processing literature in BD, and discuss methodological issues in the context of this evidence. This review is particularly relevant to empirical Chapters 9 and 10.

3.2 Abstract

Objective: Growing evidence suggests that bipolar disorder (BD) patients are impaired in their ability to process nonverbal emotion, although few comprehensive reviews of the behavioural literature exist and there has been little consideration of methodological issues that may account for discrepant empirical findings. This review examines the behavioural facial, prosodic and multi-modal processing literature in BD and discusses methodological issues in the context of this evidence.

Method: Major computer databases including Google scholar and PsychINFO were consulted to conduct a comprehensive review of quantitative behavioural differences in the emotion processing literature in BD. Articles were accepted only if the target population sample met criteria for a DSM-III, DSM-IV or ICD-10 diagnosis and they contained a healthy control group.

Results: The current literature suggests that facial emotion processing is impaired, and there is preliminary evidence for some behavioural impairment in the processing of emotional prosody.

Conclusions: The specificity or generalisability of impairments in facial emotion processing and the effects of mood state are unclear. Similarly, the lack of clarity around the impact of auditory processes on emotion prosody processing warrants a comprehensive examination of the auditory profile in BD.

3.3 Introduction

Bipolar disorder (BD) is a severe mental disorder characterised by persistent and relapsing fluctuations in mood (Goodwin & Jamison, 1990). The disorder is psychosocially debilitating; evidence indicates that the capacity for effective employment, meaningful and long term interpersonal relationships and good psychological adjustment is significantly reduced in BD (Australian Bureau of Statistics, 2007). Even with optimal pharmacological intervention relapse rates for the disorder remain unacceptably high (Gitlin, et al., 1995). This can have substantial negative effects, with some authorities estimating that 25 - 50% of persons with the disorder will attempt suicide at least once in their lifetime (Goodwin & Jamison, 1990). In the context of such statistics it is imperative that understanding factors that may contribute to such disability are thoroughly investigated.

It is well recognised that nonverbal skills facilitate healthy social interactions and influence the development of important social relationships (Leppänen, 2001; Martino, et al., 2011b; Rich et al., 2008b; Yoo, Matsumoto, & LeRoux, 2006). Such relationships prosper on the basis of shared emotionally significant social interactions derived from the understanding and interpretation of, amongst others, facial and prosodic expressive cues. These nonverbal cues carry emotional value and feed into a well-developed system of personally relevant meanings. Their accurate recognition and interpretation is therefore crucial for effective social activity; inability to process emotion is likely to impede on adaptive social behaviour. As BD is associated with emotional impairments including those related to the processing of nonverbal emotional information (e.g., Bozikas, et al., 2006b; Lembke & Ketter, 2002; Murphy & Cutting, 1990), it is highly plausible that such impairments are important contributors to the disorders' psychosocial outcome.

A great deal of empirical research in BD has focussed on patients' ability to encode, process and recall information of an emotional nature and there is a large literature that has investigated forms of implicit emotion processing including emotional attention, memory, and inhibition (Malhi, et al., 2005; Murphy, et al., 1999; Van Rheenen & Rossell, 2013b, Chapter 2). Whilst this literature has been useful in unpacking the cognitively driven nature of impairments for the processing of linguistic emotional information, it has not addressed the processing of

socio-emotional information. Understanding whether BD patients have sufficient skills to accurately interpret emotion from body language is arguably even more important than understanding other implicit or verbal forms of emotion processing, because emotional cues from the body are of the most readily encountered in everyday life. Thus, their accurate processing is of direct relevance to the development of social communication skills, largely because nonverbal emotion processing is a primary sensory-perceptual function that provides a crucial first-line means of acquiring information from which rapid inferences about others emotional and mental states can be drawn. For this reason, we have chosen to focus the current review on facial and prosodic nonverbal emotion processing in BD.

Recent reviews in this domain reveal that the neurobiological facial emotion processing profile of BD is characterised by abnormal limbic and prefrontal neural functioning (Delvecchio et al., 2012; Townsend & Altshuler, 2012; Wessa & Linke, 2009), with meta-analyses of behavioural research estimating small to medium effect sizes for impairment (Kohler, Hoffman, Eastman, Healey, & Moberg, 2011; Samamé, Martino, & Strejilevich, 2012). Whilst these summary articles have made substantial headway in defining deficits in BD, they are also limited by their respective foci; some have emphasised only the psychophysiological basis of emotion processing in the disorder (Townsend & Altshuler, 2012) or analysed behavioural manifestations of such impairment on only facial emotion processing tasks (Rocca, 2009) or in only euthymic BD samples (Samamé, et al., 2012). Others have grouped studies of both BD and Major Depressive Disorder (MDD) populations together, making it difficult to draw any firm conclusions about the specificity of results (Kohler, et al., 2011). None have thoroughly reviewed studies of prosodic emotion processing ability despite this playing a critical role in human social understanding and being an area of emerging interest in BD. These articles have also failed to comprehensively and critically discuss confounds and methodological variables in behavioural tasks that that may influence findings in the nonverbal emotion processing literature in BD. Review of such factors is especially important for identifying potential hindrances to current understandings of the nature of the nonverbal processing profile of BD, and may even provide some headway into asserting hypotheses about the underlying nature of the deficits that exist in the disorder. A broader and more precise quantitative review of the nonverbal behavioural emotion processing literature in BD

specifically, is therefore warranted. Without it, the implications that nonverbal emotion processing deficits have in the context of social behaviour in the disorder will be difficult ascertain. In this paper we present such a review, with a view to identifying appropriate and useful avenues for future psychological treatments that can have direct implications for psychosocial outcome in the disorder.

3.3.1 *Aims of the study*

Our review focuses on studies which have used behavioural tasks to examine emotion processing in BD; we present the methodological issues related to facial emotion processing and discrepancies in findings from differing diagnostic subtypes, address phase related impairment, state versus trait effects, generalised or specific abnormalities, prosodic processing and multi-modal processing and discuss discrepant results in the context of each theme. We conclude with a discussion of directions for future research.

3.4 Material and methods

Major computer databases (Google scholar, EBSCOhost, PsychINFO, PubMed) were consulted to conduct a comprehensive review of the behavioural emotion processing literature in BD. The following terms were used in varying combinations; "behavioural"" bipolar", "mani*", "euthymi*", "depress*", "bipolar disorder", "mood disorder", "emotion processing" "face processing", "affect*", "auditory", "prosody", "linguistic", "integration", "modality" ,"dominance", "recognition", discrimination", "sensitivity", "at-risk" and "prone" to generate articles central to the purposes of the review. Articles were accepted only if they were a) quantitative behavioural studies, b) the target population sample met criteria for a DSM-III, DSM-IV or ICD-10 diagnosis, c) they contained a healthy control group and d) used perceptual measures of facial or prosodic recognition or discrimination to assess nonverbal emotion processing. Given that there is inconsistency in reporting behavioural data in neuroimaging studies of emotion processing in BD, and that studies of this type often use unusual tasks that focus on implicit emotion processing, we did not include neuroimaging articles that also reported behavioural findings. Accepted articles were generally those that had

completed empirical investigations of emotion processing in a BD sample although five articles including at-risk BD groups were also included. Given that early onset of BD is relatively common, articles using both adult and paediatric populations were accepted (e.g., Chengappa et al., 2003; Faedda et al., 1995; Hirschfeld, Lewis, & Vornik, 2003; Moreno et al., 2007). However, findings from the latter should be interpreted with caution. Two additional unpublished studies that were communicated to us personally were included due to their substantial relevance to the topic at hand. Overall, 34 articles were used in this review (see Table 3 for an overview)

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Table 3.*Overview of accepted articles including assessment measures and key results*

Reference	Mode	Participants	Diagnosis & Diagnostic Measures	Current Mood & Mood Symptom Measures	Relevant Key Measures	Assessed Emotions and Exposure time (ms)	Relevant Key Results
(Addington & Addington, 1998)	F-EP	40 BD patients 40 SCZ patients 40 HC	BD subtype not specified SCID- DSM-III-R	Euthymic (N=40) Assessment measures not stated	Experimental: FED & FER Control: BFRT	Angry, Disgust, Happy, Fear, Neutral, Sad, Surprise 500ms	FER: BD=HC FED: SCZ<BD<HC BFRT: BD = HC
(Bellack, 1996)	F-EP A-P	25 SCZ patients 10 Schizoaffective patients 11 BD patients 19 HC	BD subtype not specified SCID- DSM-III-R	All patients in latter stages of acute hospitalisation Assessment measures not stated	Experimental: FED & FER Control(Facial): BFRT Control(Auditory): SSPT	Anger, Fear, Happy, Sad, Shame, Surprise 15000ms	FER: SCZ = BD = HC FED: SCZ = BD =HC BFRT: SCZ & BD<HC SSPT:BD<HC
(Brotman, et al., 2008a)	F-EP	52 paediatric BD patients *(Age M=13.3yrs) 24 at-risk youths 78 HC	BDI (N=41) K-SADS-PL	Euthymic(N=34) Depressed (N=3) Hypomanic/ manic or mixed (N=15) CDRS YMRS	Experimental: FER Control: None	Anger, Fear, Happy, Sad 2000ms	FER: BD & at risk <HC
(Brotman, et al., 2008b)	F-EP	37 paediatric BD patients*(Age M=14.2) 25 genetically at-risk youths 36 HC	BD subtype not stated K-SADS-PL	Euthymic(N=17) Depressed (N=5) Hypomanic / manic or mixed (N=15) CDRS YMRS	Experimental: FCM, sensitivity Control: None	Disgust, Fear, Happy, Sad, Surprise Morph time not specified	FCM, sensitivity: BD&AR<HC BD and at risk patients required higher emotional intensity before correctly identifying the emotion

Reference	Mode	Participants	Diagnosis & Diagnostic Measures	Current Mood & Mood Symptom Measures	Relevant Key Measures	Assessed Emotions and Exposure time (ms)	Relevant Key Results
							being displayed.
(Bozikas, et al., 2006b)	F-EP	19 BD patients 30 HC	BDI(N=19) MINI	Euthymic(N=19) MADRS YMRS	Experimental: KAMT Control: KIMT	Anger, Disgust, Fear, Happy, Sad, Surprise No limit on exposure	KAMT: BD<HC KIMT: BD = HC
(Langenecker, et al., 2010)	F-P & P-EP	122 BD patients 34 HC	BDI(N=104) BDII(N=12) Schizoaffective BD (=5) BDNOS (N=1) DIGS	Euthymic (N=66) Depressed(N=43) Hypomanic/mixed (N=13) HAM-D YMRS	Experimental: FER & PER Control: None	FER: Anger, Fear, Happy, Sad 300ms PER: Anger, Fear, Happy, Sad, neutral 4000-5000ms	Latent emotion processing score derived from FER&PER: Depressed<HC
(Bozikas et al., 2007)	P-EP	19 BD patients 22 HC	BD subtype not stated MINI	Euthymic(N=19) MADRS YMRS	Experimental: PER Control: None	Anger, Fear, Happy, Neutral, Sad, Surprise	PER: BD<HC (specific to females)
(Derntl, Seidel, Kryspin-Exner, Hasmann, & Dobmeier, 2009)	F-EP	62 BD patients 62 HC	BDI(N=26) BDII(N=36) MINI	Unclear although it was stated that there were mild depressive symptoms in the sample and N=60 with manic symptoms within normal range	Experimental: FER Control: Emotional memory task	Disgust, Fear, Neutral 2750ms	FER:BD I<HC & BD II=HC Emotional memory: BD I &BD II=HC

Reference	Mode	Participants	Diagnosis & Diagnostic Measures	Current Mood & Mood Symptom Measures	Relevant Key Measures	Assessed Emotions and Exposure time (ms)	Relevant Key Results
				MADRS (scores ranging from 0-18) YMRS			
(Edwards, Pattison, Jackson, & Wales, 2001)	F-EP P-EP	23 Affective Psychosis patients (AP;13 BD &10 MDD) 29 SCZ patients 28 Other psychotic disorder patients 40 HC	BD subtype not specified RPMDIP	BD patients in affective psychosis group were: Mixed (N=4) Manic(N=9) HRDS MRS	Experimental (Facial): FED & FER Experimental (Prosody): PER Control (Facial): inverted faces (FACT1) & faces right-side up (FACT2) Control (Prosody): LP	FED/FER: Anger, Disgust, Fear, Happy, Neutral, Sad, Surprise 500ms Affective prosody task: Angry, Fear, Neutral, Sad, Surprise	FED: AP=HC FER: AP=HC PER:AP=HC FACT 1 & 2: AP=HC LP: AP=HC
(Force, Venables, & Sponheim, 2008)	A-P	18BD patients 25 BD relatives 19SCZ patients 37 SCZ relatives 36HC	Subtypes not stated DIGS	Mood state and measures not stated	Auditory pitch processing task	N/A	Pitch processing: BD=HC
(Getz, et al., 2003)	F-EP	25 BD patients 25 HC	BD subtype not stated SCID–P	Manic/mixed (N=25) HAM-D YMRS	Experimental: FED & FER Control: BTFR & a novel computerised facial recognition task	Anger, Fear, Disgust, Happy, Sad, Surprised 500,700,1000 ms	FER:BD < HC FED: BD = HC BTFR: BD=HC Computerised facial recognition: BD=HC

Reference	Mode	Participants	Diagnosis & Diagnostic Measures	Current Mood & Mood Symptom Measures	Relevant Key Measures	Assessed Emotions and Exposure time (ms)	Relevant Key Results
(Gray et al., 2006)	F-EP	17 BD patients 21 HC	BD subtype not stated SCID-I	Depressed (N=9) Manic (N=14) HAM-D YMRS	Experimental: FCM, accuracy and sensitivity Control: BTFR	Anger, Disgust, Happy, Sad, Surprise 3100ms	FCM, accuracy: Depressed<HC & Manic=HC FCM, sensitivity: Depressed = HC & Manic = HC BTFR: BD=HC Depressed patients were differentially less sensitive to happy than to negative expressions
(Guyer et al., 2007)	F-EP	42 paediatric BD patients* (Age M=12.8yrs) 39 SMD youth 44 ANX/MDD patients 35ADHD patients 92 HC	BDI(N=33) BDII(N=9) K-SADS-PL	Euthymic (N=25) Hypomanic (N=11) Mixed(N=3) YMRS CDRS	Experimental: FER, child and adult facial expressions Control: None	High and low intensity Anger, Fear, Happy, Sad 2000ms	FER: BD=SMD<HC Euthymic BD=symptomatic BD The impact of face-age or emotion on errors did not differ across groups
(Harmer, et al., 2002)	F-EP	20 BD patients 20 HC	Subtype not stated SCID-IV	Euthymic (N=20) HAMD YMRS	Experimental: FER Control: Famous face classification	Anger, Disgust, Fear, Happy, Neutral , Sad 500ms	FER: BD>HC(disgust only) BD=HC (all emotions except disgust) Famous face classification: BD<HC
(Hofer et al., 2010)	P-EP	44BD patients 33SCZ patients	BDI (N=60)	Euthymic(N=60)	Experimental: PER Control: None	Happy, Sadness,	PER: BD<HC

Reference	Mode	Participants	Diagnosis & Diagnostic Measures	Current Mood & Mood Symptom Measures	Relevant Key Measures	Assessed Emotions and Exposure time (ms)	Relevant Key Results
		40HC	MINI	MADRS YMRS		Anger, Fear, Neutral	
(Joshua, 2010)	F-EP	30 BD patients 29 HC	Subtype not stated SCID-IV	Euthymic (N=19) MRS	Experimental: FED & FER Control: Scrambled faces (1'st order configural processing) & Spacing Manipulation Tasks(2nd order configural processing)	Anger, Fear, Happy, Neutral, Sad 2000ms	FER: BD=HC FED: BD<HC Scrambled: BD=HC Spacing: BD<HC
(Lembke & Ketter, 2002)	F-EP	24 BD patients 10HC	BDI (N=16) BDII (N=8) SCID-IV	Euthymic (N=16) Manic (N=8) HAM-D YMRS	Experimental: FER	Anger, Disgust, Fear, Happy, Surprise No limit on exposure	FER: Manic < HC Manic < Euthymic (BD I & II) Euthymic = HC Manic patients did not make one single error in recognising happy faces
(McClure, Pope, Hoberman, Pine, & Leibenluft, 2003)	F-EP	11 paediatric BD patients(Age M=13.7yrs) 10ANX patients 11 HC	BD subtype not stated K-SADS-PL	Mood state and measures not stated	Experimental: FER child and adult facial expressions Control: Facial memory task	High and low intensity Anger, Fear, Happy, Sad 2000ms	FER, child faces: BD<HC FER, adults: BD=HC FER, Low intensity expression: BD<HC FER, High intensity expression: BD=HC Facial memory: BD= HC
(McClure, et al., 2005)	F-EP	40 paediatric BD patients* (Age	BDI (N=32) BDII (N=8)	Euthymic (N=20) Symptomatic (N=14)	Experimental: FER child and adult facial	High and low intensity	FER: BD<HC

Reference	Mode	Participants	Diagnosis & Diagnostic Measures	Current Mood & Mood Symptom Measures	Relevant Key Measures	Assessed Emotions and Exposure time (ms)	Relevant Key Results
		M=12.9yrs) 22 HC	K-SADS-PL	CDRS YMRS	expressions Control: None	Anger, Fear, Happy, Sad 2000ms	
(Murphy & Cutting, 1990)	P-EP	15 manic patients 15 depressive patients 15 SCZ patients 15 HC	BD subtype not specified RDC	Mood state and measures not stated	Experimental: PER Control: LP	Anger, Neutral, Surprised, Sad	PER: Manic & Depressed< HC LP: Manic<HC
(Rich, et al., 2008b)	F-EP	31 paediatric BD patients *(Age M=14yrs) 31 SMD youth 36HC	KSADS-PL	Euthymic (N=19) Depressed(N=1) Hypomanic(N=13) Mixed(n=6) CDRS YMRS	Experimental: FCM, sensitivity Control: None	Anger, Disgust, fear, Happy, Sad, Surprise 3900ms	FCM, sensitivity: BD=SMD<HC Hypomanic/mixed BDs have face-labelling deficits across all emotions, whereas euthymic BDs have face-labelling deficits on disgusted and happy faces
(Rock, Goodwin, & Harmer, 2010)	F-EP	32 high MDQ group (comprising 12 BD participants and 3 MDD as well as those without DSM-IV diagnosis). 30 low MDQ group	BDII (N=7) BDNOS(N=5) MINI-PLUS	Euthymic (N=32) HAM-D YMRS	Experimental: FCM, accuracy Control: None	Anger, Disgust, Fear, Happy, Sad, Surprise 500ms	FCM, accuracy: HMD>LMD(surprised & neutral) & HMD <LMD (disgust; trend only)
(Rossell, et al.,	P-EP	43 BD patients	BDI (N=43)	Euthymic(N=20)	Experimental: PER &		PED: BD=HC

Reference	Mode	Participants	Diagnosis & Diagnostic Measures	Current Mood & Mood Symptom Measures	Relevant Key Measures	Assessed Emotions and Exposure time (ms)	Relevant Key Results
In Press)		54 SCZ patients 11 Schizoaffective patients 112 HC	SCID-IV	Depressed(N=23) BDI MRS	PED Control: None		PER: BD<HC
(Schenkel, et al., 2007)	F-EP	86 paediatric BD patients (Age M=12yrs) 28 HC	BDI (N=86) K-SADS-PL	Euthymic (N=29) Manic (N=29) YMRS CDRS-R	Experimental: SFES & SFED Control: None	Happy, Neutral, Sad Exposure time not stated	SFES: manic/ mixed & euthymic: BD<HC (BD patients judged extreme happy & sad expressions as milder in intensity) SFED: Manic/mixed BD<HC & Euthymic BD = HC (manic/mixed BD patients had difficulty differentiating subtle sad & happy expressions)
(Schaefer, Baumann, Rich, Luckenbaugh, & Zarate Jr, 2010)	F-EP	21 BD 34MDD 24 HC	BDI(N=9) BDII(N=12) SCID-IV	Depressed (N=21) MADRS YMRS	Experimental: FCM, accuracy & sensitivity Control: None	Angry, Disgust, Fear, Happy, Neutral, Surprise 3900ms	FCM, accuracy: MDD=BD & BD=HC FCM, sensitivity: MDD=BD & BD<HC BD>HC(Disgusted faces)
(Summers, et al., 2006)	F-EP	36 BD patients 30 HC	BDI (N=25) BDII (N=11) SCID-IV	Euthymic (N=15) Depressed(N=13) BDI	Experimental: FCM, accuracy and sensitivity Control: None	Anger, Disgust, Fear, Happy, Neutral, Surprise	FCM, accuracy: BD I=BD II<HC (Surprise only) & BD I=BD II>HC(Disgust only) FCM, sensitivity: BD=HC

Reference	Mode	Participants	Diagnosis & Diagnostic Measures	Current Mood & Mood Symptom Measures	Relevant Key Measures	Assessed Emotions and Exposure time (ms)	Relevant Key Results
						Rapid morph for measuring accuracy Slow morph for measuring sensitivity	
(Vaskinn, et al., 2007)	F-EP P-EP	21 BD patients 31 SCZ patients 31 HC	BDI(N=21) SCID-IV	Euthymic (N=23) Depressed (N=8) YMRS IDS-C	Experimental(Facial): FER Experimental(Prosody): PER Control: None	Anger, Fear, Happy, Sad, Shame Exposure Time Not Stated	FER: BD=HC PER: BD=HC
(Vederman, et al., 2012)	F-EP P-EP	119 BD patients 78 MDD patients 66 HC	BD subtype not stated SCID-IV and DIGS	Euthymic(N=119) HAM-D YMRS	Experimental(Facial): FER Experimental(Prosody): PER Control: None	FER: Angry, Fear, Happy, Neutral, Sad (note that there was no neutral as a response option to invoke response bias) 300ms PER: Angry, Fear, Happy, Neutral Sad 4000-5000ms	FER:BD<HC PER: BD=HC

Reference	Mode	Participants	Diagnosis & Diagnostic Measures	Current Mood & Mood Symptom Measures	Relevant Key Measures	Assessed Emotions and Exposure time (ms)	Relevant Key Results
(Venn et al., 2004)	F-EP	17 BD patients 17 HC	BDI (N=14) BDII (N=3) SCID-IV	Euthymic(N=17) HAM-D YMRS	Experimental: FCM, accuracy & sensitivity Control: BFRT	Anger, Disgust, Fear, Happy, Sad, Surprised 3100ms	FCM, accuracy: BD<HC (fear only) FCM, sensitivity: BD=HC BFRT: BD=HC

Note: F-EP; Facial Emotion Processing, P-EP; Prosodic Emotion Processing, A-P; Auditory Processing, BD; Bipolar Disorder, HC; Healthy Control, BDNOS: BD not otherwise specified, SCZ; Schizophrenia, YMRS; Young Mania Rating Scale, MRS; Bech Rafaelson Mania Rating Scale, BDI; Beck Depression Inventory, MADRS; Montgomery Asberg Depression Rating Scale, HAM-D, Hamilton Depression Rating Scale, CDRS; Child Depression Rating Scale, K-SADS-PL; Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version,, SCID; Structured Clinical Interview For Diagnosis, MINI; Mini International Neuropsychiatric Inventory, RPMDIP; Royal Park Multi-Diagnostic Instrument for Psychosis, FER; Facial Emotion Recognition task, FED; Facial Emotion Discrimination task, PER; Prosodic Emotion Labelling task, PED; Prosodic Emotion Discrimination task, FCM; Facial Emotion Computer Morphing task, SFES, Static Face Emotion Sensitivity, SFED, Static Facial Emotion Discrimination, BFRT; Benton Facial Recognition Task, SSPT; Speech Sounds Perception Test, KAMT; Kinney's Affect Matching Task, KIMT; Kinney's Identity Matching Task, FACT; Facial Affect Computer Tasks, LP; Linguistic Prosody task *Narrow phenotype BD

3.5 Results

3.5.1 *Facial emotion processing*

The ability to process emotion from facial expressions is vital to social interaction. Facial expressions facilitate the understanding of others' underlying states and permit appropriate social communication. There is growing evidence to suggest that the processing of emotional information from faces is impaired in BD. Such impairment is likely to have many detrimental effects on psychosocial functioning and quality of life (Hoertnagl et al., 2011; Martino, et al., 2011b). A greater understanding of their occurrence could thus potentiate developments of remedial treatments and improve the lives of those living with the disorder.

Patients with BD have been found to have difficulty in recognising (identifying/labelling; Getz, et al., 2003; Lembke & Ketter, 2002), discriminating (matching; Addington & Addington, 1998; Bozikas, et al., 2006b; Joshua, 2010) and discerning subtle variations in emotional expression (Schenkel, et al., 2007) in comparison to controls. These effects are evident in both adult (Getz, et al., 2003) and paediatric populations (Brotman, et al., 2008a; Schenkel, et al., 2007) and in symptomatic (Gray, et al., 2006; Lembke & Ketter, 2002), euthymic (Bozikas, et al., 2006b; Vederman, et al., 2012) and at risk groups (Brotman, et al., 2008b; Rock, et al., 2010). Impairments occur for faces of all ages (Brotman, et al., 2008a; Guyer, et al., 2007; McClure, et al., 2005) and do not appear to be secondary to general visuoperceptual or face memory difficulties (Addington & Addington, 1998; Bozikas, et al., 2006b; Getz, et al., 2003; Gray, et al., 2006; McClure, et al., 2003). Preliminary evidence in which manic BD I patients experiencing psychosis (Lembke & Ketter, 2002) were found to have difficulty in recognising facial emotion, coupled with numerous reports of facial emotion processing deficits in schizophrenia (Addington & Addington, 1998; Hooker & Park, 2002; Kohler, et al., 2000) suggest that these impairments are not specific to non-psychotic BD.

Although results demonstrating impairment are growing, there have been some reports of contradictory findings where differences are reported to exist between symptom subtypes (Derntl, et al., 2009), symptomatic patients have shown mood congruent facial emotion processing biases during depression but not mania (Gray, et al., 2006) and some BD groups in

general have not performed differently to controls on facial emotion recognition and discrimination tasks at all (Bellack, 1996; Edwards, et al., 2001; Lembke & Ketter, 2002; Vaskinn, et al., 2007). Some researchers have reported that paediatric patients have difficulty recognising low intensity emotions in children but not adults emotional expressions (McClure, et al., 2003), whereas others have found face age to make no difference to paediatric facial emotion processing performance (Guyer, et al., 2007). Others still have reported differential effects, in which discrimination but not recognition is impaired (Joshua, 2010).

These conflicting findings may be in part, attributable to different task designs. For example, some of the studies reporting null findings used tasks in which facial expression exposure times were (often substantially) longer than 2000ms. In contrast, a number of studies reporting case/control differences used exposure times of 2000 ms or less (with some exceptions). Discrepant results corresponding to this disparity in exposure time appears to indicate that it is sensitivity to emotional information rather than explicit problems with accuracy that are at the crux of BD facial processing difficulties. Given that there is substantial evidence to indicate that speed of information processing is slowed in BD (e.g., Goswami, et al., 2006; Malhi et al., 2007b; Nehra, et al., 2006; Zubieta, et al., 2001), perhaps shorter exposure durations actually limit patients' capacity to attend to subtle emotional variations which they would otherwise have time to acknowledge if the emotional stimulus presentation were longer in duration. This is particularly pertinent considering that a number of studies explicitly measuring sensitivity to emotional expressions have demonstrated that BD patients need increased intensity to detect emotion (Brotman, et al., 2008b; Schaefer, et al., 2010). Nevertheless, discrepant exposure times do not explain the null findings of studies in which stimulus presentation approximates real life (Harmer, et al., 2002).

3.5.1.1 Diagnostic Subtypes.

To the best of our knowledge there are two known studies in which comparisons between largely stable BD I and BD II subtypes have been explicitly conducted in relation to emotion processing. Summers et al., (2006) reported that both BD I and BD II patient groups underperformed in comparison to controls, while Derntl (2009) reported that it was only BD I patients that demonstrated deficits in identifying emotional expressions.

Disparities in task measures that differentially facilitate the magnitude of neurocognitive skills may go some way in explaining these disparities. Summers' et al., employed a multimorph emotion recognition task whereas Derntl et al., employed a static emotion recognition task. Accuracy rates for facial emotion recognition have been found to be higher for dynamic versus static stimuli designs in healthy participants and suggest that motion facilitates the perception of affect (Ambadar, Schooler, & Cohn, 2005). If this is true, it would suggest that Derntl et al.'s task design is more difficult due to the lack of temporal cueing, which may increase demands on executive processes that are often reported to be more impaired in BD I than BD II (Glahn et al., 2005; Martinez-Aran, et al., 2004b; Simonsen et al., 2008; Torrent, et al., 2006). For example, increased impairment in appropriately allocating attentional resources in the BD I relative to BD II group may explain why Derntl and colleagues found that only BD I patients were impaired relative to controls. To further support this we note that Lembke and Ketter (2002) used a stimuli design similar to that of Derntl et al., to demonstrate that psychotic manic patients significantly underperform in comparison to euthymic BD II or control participants. Again it is plausible that these results reflect increased task difficulty due to additional task dependence on neurocognitive attentional abilities which are significantly more impaired during episodes of mania (Dixon, et al., 2004).

In keeping with this idea, the facilitation effect of temporal cueing in the Summers et al.', task design may reduce its difficulty and lessen reliance on neurocognitive abilities such as the appropriate direction of attention to certain affective cues. This theory is poignant given that there is preliminary evidence to show that euthymic BD I patients have an impaired ability to detect subtle changes in the spacing of facial features (Joshua, 2010). As variations in expressed emotions simply reflect variations in the spacing of facial features, their accurate processing would require the appropriate and equal allocation of attention to all features of the face. It is therefore plausible that the dynamic task reduces dependence on the attentional resources that may initially differentiate subgroups and could therefore account for the similarity that Summers and colleagues observed in performance between groups. Given that dynamic expressions approximate real-life situations in which emotion is often expressed rapidly and patients are not afforded the luxury of extended fixation periods, it is also arguable

that morphing task designs such as those used by Summers and colleagues are more ecologically valid. However, more research is clearly needed to substantiate these possibilities.

3.5.1.2 Mood State Related Impairment.

As previously mentioned, facial emotion processing has been found to be impaired in patients during the active phases of the disorder. For example, Getz et al., (2003) found a general reduction in accuracy on an affective recognition task in patients during manic or mixed episodes. Lembke and Ketter (2002) also reported that manic patients had greater difficulty in recognising fear and disgust than euthymic BD I and BD II patients or controls. Comparable phase relationships have been identified by Schaefer et al., (2010) who found decreased sensitivity to facial expressions in depressed patients with BD, while Langenecker, Saunders, Kade, Ransom and McInnes (2010) reported poorer emotion recognition in depressed BD rather than euthymic BD or control participants.

There is some indication of a differential valence processing deficit during these active phases as three of the aforementioned studies generally report accurate recognition of or normal sensitivity to positive emotions, but significant difficulty in recognising the negatively valenced expressions of fear, sadness or anger. This initially appears to indicate a bias away from negative expressions such that acutely ill BD patients show reduced responsiveness or recognition of negative emotion in proportion to normal sensitivity or recognition of positive emotion.

Despite this the picture remains complicated with conflicting evidence indicating that depressed patients are worse at differentiating between subtle variations in both positive *and* negative emotions (Summers, et al., 2006) and require greater emotional intensity to recognise positive expressions than to recognise negative ones (Gray, et al., 2006). Such evidence suggests that emotion recognition operates, at least in part, as an independent process from mood. This notion is supported by reports from Schaefer (2010) that suggest that emotion recognition performance does not discriminate controls from currently depressed MDD patients but does discriminate them from depressed BD patients. A differential effect would surely not have been observed if depressed mood was in fact largely influential over task performance. Further to this, comparable performance on positive but not negative emotional

expressions is also evident in mania which adds to the proposition that there is more to valence processing than a straightforward influence of mood (Gray, et al., 2006; Lembke & Ketter, 2002).

These abnormalities may instead be attributed to the differing complexity of facial expressions. In the healthy population, happy emotional expressions have been found to be easier and faster to process than others (e.g., Calvo & Lundqvist, 2008; Hess, Blairy, & Kleck, 1997; Leppänen & Hietanen, 2004). This may be due to the salience and uniqueness of the configuration of facial muscles during positive expressions (i.e., mouth upturned, arched eyebrows etc.) or because facial information processing strategies for positive emotions differ from that of negative (Kirita & Endo, 1995; Leppänen & Hietanen, 2004). For example, happy faces are posited to be processed holistically and rely on higher order cognitive processes such as those integrated by the central executive (i.e., executive functions), whilst negative faces are posited to be processed analytically and rely on lower-order feature based integration of configural information. There is preliminary evidence to indicate that first order configural processes are relatively intact in BD and that top down neurocognitive functions better account for problems in facial emotion processing (Joshua, 2010) . In light of this it is possible that comparable case/control performance on happy emotions reflect a general facilitation of intact holistic processing, whereas deficits in processing negative expressions reflect top down impairments such as reduced processing speed or attentional allocation, and reduced integration or processing of the relationship between local facial information.

Further evidence for the independence of facial emotion processing deficits from mood is apparent in a number of studies reporting the persistence of such impairments during remission (Addington & Addington, 1998; Vederman, et al., 2012). For example, Bozikas and colleagues (2006b) found that euthymic patients performed worse than controls when matching emotional expressions to affect laden situations, Schenkel et al., (2007) found paediatric euthymic patients made significantly more errors than control participants on a test of emotional intensity recognition and discrimination, and Venn and colleagues (2004) reported that euthymic patients were impaired in their recognition of fear on a multimorph test of facial emotion accuracy.

3.5.1.3 State or trait impairments?

Evidence is currently mixed in regard to state versus trait impairments. Some researchers have demonstrated state like impairments during symptomatic but not euthymic BD phases (Langenecker, et al., 2010; Venn, et al., 2004) whereas others have demonstrated trait-like impairments during remission (e.g., Addington & Addington, 1998). It would be reasonable to expect that if emotion processing deficits are a stable feature of BD, they would exist in those who are vulnerable to develop the disorder.

To date, five separate studies have investigated facial emotion processing in at risk groups. Brotman and colleagues (2008a) demonstrated that case/control deficits on a test of emotion recognition using static face stimuli in children with a first degree relative with BD was similar to that of a mixed group of manic, depressed and euthymic youths with the disorder. Comparable results were reported by Brotman and others (2008b) in a separate study in which both a mixed group of manic, depressed and euthymic paediatric BD patients and unaffected genetically at risk participants equally underperformed in comparison to controls on a test of sensitivity to emotions using dynamic stimuli. Similarly, Guyer et al., (2007) investigated a group of predominantly euthymic youths with BD and youths with chronic irritability and hyper-arousal (i.e., those with severe mood dysregulation; *SMD*) thought to represent a potential risk syndrome for the disorder. These groups were both significantly impaired in recognising facial emotions in comparison to controls and other psychiatrically disordered groups, but demonstrated no differences between them. In another study comparing paediatric BD patients, SMD youths and controls performance on a facial emotional sensitivity task, Rich and others (2008b) reported no difference between the mixed group of euthymic, hypomanic and mixed BD patients and the SMD group on sensitivity to emotional expressions. Again, both groups were found to be significantly less sensitive to facial emotions than controls. Finally, Rock et al. (2010) reported a trend level reduction in the recognition of disgust in young people presenting with a BD phenotype identified by high self-reported mood elevation symptoms. This sample had enhanced recognition of surprised or neutral faces in comparison to those in the low mood elevation group.

When this literature is considered in relation to facial emotion processing impairments observed during periods of euthymia, the findings collectively appear to indicate that abnormalities in facial emotion processing are not state dependant. That is, subtle facial emotion processing deficits are likely to have a trait-like and enduring quality although mood symptomatology may exert further influence by affecting the magnitude and extent of the abnormality. For example, Schenkel and colleagues (2007) found that both symptomatic and euthymic paediatric patients had difficulties in accurately judging the intensity of emotionally extreme facial expressions, however only symptomatic patients were impaired in their ability to identify slight variations in emotional intensity.

3.5.1.4 Emotion specific or generalised abnormality.

There have been various mixed reports of emotion specific processing differences in BD. For example, some studies report that paediatric patients show impairment in the accuracy of recognising all basic emotions (Brotman, et al., 2008b; Guyer, et al., 2007), others report trends for abnormalities that are specific to certain emotions (Summers, et al., 2006) and some report that impairments differ across mood states (Gray, et al., 2006; Rich et al., 2008a). Some researchers have reported poorer recognition of or sensitivity to fear (Lembke & Ketter, 2002; Vederman, et al., 2012) whilst others have reported poorer recognition of sadness (Derntl, et al., 2009; Schenkel, et al., 2007; Summers, et al., 2006; Vederman, et al., 2012) and happiness (Schenkel, et al., 2007; Summers, et al., 2006). The evidence is conflicting however, with some groups reporting intact processing of neutral (Schenkel, et al., 2007) and sad stimuli (Rich, et al., 2008b) and others reporting an enhancement effect in which disgust (Harmer, et al., 2002; Summers, et al., 2006), surprise and neutral expressions (Rock, et al., 2010) are recognised even more accurately by BD patients than controls. Others still have reported that happy faces are the most accurately recognised of all the basic emotions, that anger may be the hardest to recognise (Edwards, et al., 2001; Guyer, et al., 2007; Lembke & Ketter, 2002; Summers, et al., 2006) and that expressions displaying extreme emotional intensity are misinterpreted as displaying a lesser degree of intensity in sad expressions (Schenkel, et al., 2007).

When taken together it remains unclear as to whether processing deficits are generalised or specific although it is possible that certain methodological parameters place confounds within the results. For example, our review of the literature has found that many studies have used stimulus expressions of negative emotional valence (i.e., sadness, anger, fear or disgust) 50%-75% more than they have used expressions of positive valence (i.e., happiness, surprise) (Addington & Addington, 1998; Bozikas, et al., 2007; Brotman, et al., 2008b; Getz, et al., 2003). This as a result may generate a heightened contrast between stimuli, making positive emotional expressions significantly easier to process. Moreover, some studies have omitted neutral face stimuli which reduce the degree to which patients have a valid point of comparison during the course of the task (Bellack, 1996; Bozikas, et al., 2006b; Brotman, et al., 2008a; Guyer, et al., 2007; McClure, et al., 2003; Vaskinn, et al., 2007).

3.5.1.5 Influence of Clinical and Demographic Variables.

In general, there is little evidence to suggest that performance on facial emotion processing tasks are correlated with IQ or age (Rich, et al., 2008a), gender (Addington & Addington, 1998; Schaefer, et al., 2010) or number or type of medication (Addington & Addington, 1998; Brotman, et al., 2008a; see Derntl, et al., 2009 for an exception). There is however conflicting evidence as to whether number of hospitalisations (Derntl, et al., 2009; Vederman, et al., 2012), age at illness onset (Derntl, et al., 2009; Schenkel, et al., 2007) or psychotic and mood symptomatology is involved (Derntl, et al., 2009; Edwards, et al., 2001; Getz, et al., 2003; Lembke & Ketter, 2002; Vederman, et al., 2012). Further study is needed to ascertain the roles that these variables may play.

3.5.1.6 Disorder specificity.

Of the studies that have directly compared BD and schizophrenia, two have reported greater impairment in schizophrenia patients relative to those with BD (Addington & Addington, 1998; Vaskinn, et al., 2007) and two have failed to find a difference between the groups (Bellack, 1996; Edwards, et al., 2001). Similar inconsistency is evident in comparisons of BD and MDD, with one study finding no difference (Schaefer, et al., 2010) and the other reporting that BD patients are less accurate than their MDD counterparts at labelling fear

(Vederman, et al., 2012). Despite the lack of clarity with regards to the comparative magnitude of impairment between these groups, the large body of research independently indicating facial emotion processing impairments in each of these populations suggests that they are not specific to BD, but rather generalised across a number of psychiatric illnesses (Bourke, Douglas, & Porter, 2010; Edwards, Jackson, & Pattison, 2002).

3.5.2 *Prosodic processing*

Prosodic emotion processing describes one's ability to understand nonverbal variations in the intonation of speech patterns. That is, to understand emotion from spoken expressions. Accurate prosodic comprehension is vital to non-verbal communication because it facilitates understanding of others and permits appropriate and potentially rewarding interpersonal interactions. BD patients have many difficulties in social functioning which may be caused by difficulties in the accurate perception of emotional prosody. Thus, greater understanding of prosodic processing in BD could assist in understanding the origin of psychosocial dysfunction in the disorder.

This has not been a focus in the current behavioural research literature, with only seven studies having examined the topic in BD thus far. The lack of attention is noteworthy given that prosodic deficits have been found in disorders with overlapping symptom profiles. That is, in samples of unipolar depression and schizophrenia patients who appear to share similar biological and phenomenological profiles with BD. For example, there is suggestion that patients with depression and schizophrenia share genetic characteristics (e.g., Blackwood et al., 2007; Craddock, O'Donovan, & Owen, 2005). Additionally these patient groups show comparable cognitive and facial emotion processing impairments (e.g., Addington & Addington, 1998; Fossati, Amar, Raoux, Ergis, & Allilaire, 1999; Gur et al., 1992; Hooker & Park, 2002; Surguladze et al., 2004; Weiland-Fiedler et al., 2004).

Currently, within both unipolar depression and schizophrenia, there is consistent evidence for impairment in the ability to recognise emotional prosody (Bozikas et al., 2006a; Emerson, Harrison, & Everhart, 1999; see Giannakou et al., 2008 for an exception; Hoekert, 2007; Huang et al., 2009; Kan, Mimura, Kamijima, & Kawamura, 2004; Kerr & Neale, 1993;

Leentjens, Wielaert, van Harskamp, & Wilmink, 1998; Luck & Dowrick, 2004; Péron et al., 2011; Scholten, Aleman, & Kahn, 2008; Uekermann, Abdel-Hamid, Lekhmkamper, Vollmoeller, & Daum, 2008). Further to this both schizophrenia and unipolar depression have been associated with overt deficits in auditory processing (Bellack, 1996; Javitt, Shelley, & Ritter, 2000; Kerr & Neale, 1993 see Hooker & Park, 2002 for an exception) as well as psychophysiological brain responses on the N100 and P200 event related potentials (ERP) that are thought to index early sensory processing (Kähkönen et al., 2007; O'Donnell, Vohs, Hetrick, Carroll, & Shekhar, 2004). These difficulties have been found to impact emotional prosody comprehension in schizophrenia and suggest that early sensory impairments form a basis for difficulties in the processing of emotional prosody (Leitman et al., 2005; Leitman et al., 2010). This hypothesis is certainly in need of empirical attention in BD.

At present there are only a handful of studies that have investigated prosodic processing in BD. Results have been mixed with four studies reporting evidence for impairment in prosodic comprehension (Bozikas, et al., 2007; Hofer, et al., 2010; Murphy & Cutting, 1990; Rossell, et al., In Press) and three failing to find differences between BD groups and controls (Edwards, et al., 2001; Vaskinn, et al., 2007; Vederman, et al., 2012). It should be noted that some of these studies were not initiated to measure prosodic emotion processing explicitly in BD, instead using patients as psychiatric controls. This lack of explicit investigation of BD prosodic processes, and the limited number of studies available, indicates the narrow status of knowledge in the area. For example, mood related impairment or the impact of psychosis is at this stage far from clear. While Rossell et al., (In Press) and Murphy and Cutting (1990) found depressed and manic patients to be impaired on recognising emotional intonation, Edwards et al., (2001) reported that manic and mixed patients with first episode affective psychosis performed in the same way as controls on a similar task. Of note, Edwards et al.'s, sample comprised both BD patients and MDD patients during a depressive phase, making it difficult to ascertain exactly which diagnosis drove the results.

Mood state effects aside, two of the four studies reporting impairment in prosody have observed this in patients during the euthymic phase of illness (Bozikas, et al., 2007; Hofer, et al., 2010). This would initially appear to suggest at least partial independence of prosodic processing from mood state. However, these results should be considered with caution given

that a recent large scale investigation of affective prosody in euthymic patients revealed no evidence of impairment (Vederman, et al., 2012).

Explanations for these conflicting prosody findings are unclear at present, particularly because most studies used similar task designs in which participants were asked to name the emotional intonations of semantically neutral sentences. Despite this, it is possible that other subtle disparities in task elements contributed to differences in results. For example, the use of more than one actor could introduce variability in pronunciation (e.g., Edwards, et al., 2001) as could actor accents that differ from the sample population (Hofer, et al., 2010).

3.5.2.1 Influence of Hearing Acuity and Linguistic Stress in BD.

Prosodic emotional information is conveyed via variations in pitch, amplitude and durational components of speech, yet none of the aforementioned studies used hearing tests to assess early auditory processing (Merewether & Alpert). Although behavioural information investigating hearing in BD is mixed (Bellack, 1996; Force, et al., 2008), there is growing psychophysiological research reporting abnormalities in N100 and P200 ERP's in euthymic and symptomatic patients (Fridberg et al., 2009; Lijffijt et al., 2009). To our knowledge, the relationship between early auditory processing and emotion prosody processing in BD has not yet been examined. Control tasks that measure early auditory processing would seem important given that auditory processing of emotion is likely to rely heavily on early acoustic abilities that allow for the decoding of sound components.

Further to this, linguistic prosody, which refers to the application of non-emotional propositional stress to alter semantic meaning, was assessed in only two of the six aforementioned prosody studies in BD. Murphy and Cutting (1990) found that manic patients ability to comprehend stress was reduced, whereas Edwards et al., (2001) failed to find a difference between their affective psychosis and control groups. As linguistic prosody is involved in decisions about the semantic content of an expression, control tasks to assess for potential difficulties in stress comprehension will assist researchers in separating out semantic impairments in comparison to emotional impairments in BD. Such a measure is particularly appropriate given there is some evidence to indicate that BD patient have difficulty in understanding the semantic meanings of stories and difficulty generating responses on tasks

assessing semantic fluency (e.g., Arts, et al., 2008; Robinson, et al., 2006; Rossell, et al., In Press).

3.5.3 *Multi-modal processing*

Effective emotion processing relies on perceptions from both visual (facial) and auditory (prosody) domains. Although this may occur in isolation, it is the integration of visual and auditory emotional information that most greatly assists one to understand a communicator (Paulmann & Pell, 2011; Paulmann, Titone, & Pell, 2012). That is, that multiple sources of information are used to understand other's emotions. Ultimately, the effective identification of an emotional expression results from higher order integration of visual and auditory modalities occurring within a general multi-modal system that is independent of modality (Borod et al., 2000). Psychosocial difficulties in BD may thus not only reflect difficulties in unimodal processing, but may also reflect underlying impairment in the integration of emotional information received from each modality (Borod et al., 1998). There is some preliminary evidence to suggest that sensory audio-visual integration in BD I patients is impaired relative to controls (Negash, 2004). Yet, to our knowledge there has been no published investigation of the interactional relationship between facial and prosodic emotion processing in BD. Needless to say, it would be of use to examine for integration difficulties during the simultaneous reception of emotion information, given that difficulties in integrating emotional information can detrimentally influence the perception of an emotional event. Investigation of any potential modality dominance in BD would also be useful in understanding the magnitude of benefit that audio-visual integration of information offers for emotion identification in the disorder.

3.5.4 *Influence of medication on emotion processing*

Despite pharmacological therapy being the treatment of choice in BD, its effects on emotion processing have not been regularly studied. Nevertheless there is some evidence to indicate that neurocognitive performance is inversely influenced by antipsychotic treatments (Arts, et al., 2011; Bora, et al., 2009a). Given that intact emotion processing performance may

be heavily weighted on neurocognitive ability, it is certainly possible that medication effects can account for some of the variance in nonverbal emotion processing performance. Generally though, facial emotion processing studies that have reported medication analyses have failed to find significant differences on task performance for patients on and off medication (e.g., Addington & Addington, 1998; Bellack, 1996; Brotman, et al., 2008b; Derntl, et al., 2009; Getz, et al., 2003) although it is not clear how far this can generalise to prosodic emotion processing performance.

3.6 Discussion

Our review of the behavioural emotion processing literature in BD strongly indicates abnormalities in the processing of facial emotional expressions. However, at present there are inconsistencies regarding 1) the specificity or generalisability of such impairments; 2) our understandings of their neurocognitive underpinnings and 3) the effects of mood state. Although limited, research in the area of prosodic emotion processing provides at least some preliminary evidence to suggest there may be existence of a prosodic emotion processing deficiency in BD. However, substantial future research efforts are required to investigate this phenomenon more comprehensively in the disorder.

From a clinical perspective, the information generated from this review suggests that the assessment of nonverbal emotion processing skills in patients with BD is important in the therapeutic setting. In order to provide the best care, clinicians must be aware of patients' impairments in nonverbal emotion processing skills. Clinicians that acknowledge such impairments will have a better understanding of the difficulties faced by patients in emotional contexts within the therapeutic relationship. They can use this information to inform patients of potential shortcomings in their ability to process emotion from facial or prosodic expressions; time spent increasing patient awareness and discussing appropriate strategies to manage impairments may assist the patient to adjust their behaviours on this basis. The development of clinician administered treatment interventions that aim to retrain these abilities may also improve the interactional outcomes and coping abilities of BD patients, in turn facilitating functional psychosocial recovery (Colom, 2012). Social cognitive intervention

programmes have indeed shown efficacy in schizophrenia populations, but currently no such treatments have been validated for use with persons with BD (Sachs et al., 2012). Given that emotion processing impairments are not disorder specific, with deficits having been reported for facial and prosodic emotion processing in schizophrenia too; it is possible that similar remediation strategies will be applicable to BD.

At present there has been no research conducted to examine potential modality dominance or whether the multi-modal integration of facial and prosodic emotion perception is impaired. This would seem important given the insights such information would provide for the development of psychological treatments. For example, understanding modality integration and whether one sensory modality is dominant over the other in BD would allow treatment programs a point of focus. That is, a precise understanding of the nature of emotion processing impairments in the disorder would allow a good starting point from which psychological interventions can be defined. For example, should modality integration be impaired, it may need to be the focus of intervention in comparison to targeting each modality individually. Moreover, initial intervention at the level of the dominant modality, should there be one, could lead to greater and faster improvements in social functioning.

To build on the aforementioned behavioural findings of emotion processing in BD we make a number of recommendations for future study that will address discrepancies and limitations in the current research. Specifically we recommend that future studies examine the relationship between emotion processing, both facial and prosodic, and behavioural measures of neurocognition in BD. Behavioural abilities, rather than brain abnormalities per sé, have direct clinical relevance because they can be potentially remediated via training techniques. Remediation at the behavioural level may subsequently lead to recovery in brain function (e.g., Kraus et al., 1995; Temple et al., 2003). The current review raises reasonable cause to suspect that the magnitude of neurocognitive ability has subsequent effects for facial emotion processing. Thus, future research could specifically look at comparing BD subtypes on cognitive and emotion processing measures to determine the effects that disparities in neurocognitive ability have on emotion perception in these two groups. Studies that make explicit comparisons between facial emotion stimuli presentation times could also assist in determining whether difficulties in information processing speed account for the observed

deficits that have often been found in tasks using shorter inspection intervals. Further to this, comparisons between dynamic and static emotion processing tasks will assist in defining whether motion does have a facilitatory effect on facial emotion perception by reducing cognitive load.

Of primary importance, future studies need to address whether a deficiency in prosodic emotion processing actually exists by conducting investigations of emotional prosody perception using well defined BD groups. Research examining the auditory profile of BD (hearing acuity and linguistic prosody comprehension) and its relationship to prosodic emotion processing will also assist in deciphering the basis of deficits in the auditory domain. Future research will also do well to examine the effects of mood state on emotion processing and to examine the interaction between visual and auditory modes of emotion perception.

Broadly speaking, the nonverbal emotion processing impairments that we have discussed here are likely to have detrimental influences for emotion regulation in BD. That is, misinterpretation of others' nonverbal emotion expressions and therefore their emotional states may produce difficulties in initiating and regulating adaptive emotional reactions, with detrimental consequences. For example, intact nonverbal emotion processing ability facilitates empathic and pro-social behaviours, whilst misperception of nonverbal emotion degrades socially appropriate responses and contributes to social withdrawal (Lopes, 2005; Marsh, Kozak, & Ambady, 2007; Martino, et al., 2011b). Appropriate emotional functioning, both processing and regulation, are thus important to healthy clinical and psychosocial function in BD (Goldstein, Miklowitz, & Mullen, 2006; Hoertnagl, et al., 2011; Lopes, Salovey, & Straus, 2003). In view of this, it is likely that using early emotion processing impairments as targets for intervention will be a useful method of facilitating the remediation of both emotion dysregulation and psychosocial disability alike. This may also serve to reduce the rate of relapse in the disorder.

CHAPTER 4: THE ASSOCIATION BETWEEN SOCIAL COGNITION AND EMOTION REGULATION IN BIPOLAR DISORDER

4.1 Chapter guide

In previous chapters we have outlined detailed literature indicating that neurocognitive and social cognitive processes are impaired in bipolar disorder (BD). We have also discussed evidence for the assertion that impairments in neurocognition, social cognition and emotion regulation are associated, with deficits in neurocognitive processes potentially underpinning poor social cognitive and emotion regulation processes in the disorder. In the discussion of the preceding chapter we alluded to the idea that a third relationship, between social cognition and emotion regulation, may exist in BD. The purpose of this brief chapter is to overview the current emotion regulation literature of the disorder, and explore this hypothesis in more detail. This chapter contributes toward the rationale for empirical Chapters 12 and 14. It has not been submitted to a journal and therefore takes on a more traditional format.

4.2 Introduction

Bipolar disorder (BD) is a serious psychiatric disorder characterised by a distinct pattern of mood fluctuations. Although there is general agreement that abnormalities in the regulation of emotion contribute to this symptom profile (e.g., Gruber, Eidelman, Johnson, Smith, & Harvey, 2011; Johnson, 2005b), comprehensive understandings of the psychopathological mechanisms that lead to difficulties in emotion regulation remain unclear. Emotion regulation is a broad umbrella term describing the ability to monitor and modulate one's emotions, emphasising the use of cognitive and behavioural strategies to adaptively moderate emotional experience. Current evidence suggests that poor regulation of emotion may represent a stable, trait-like characteristic of the BD phenotype, which may contribute to the maintenance of symptoms and consequent difficulties in psychosocial functioning in the disorder (Becerra, et al., 2013; Hoertnagl, et al., 2011; Houshmand et al., 2010; Johnson, 2005b; Meyer, et al., 2001; Rucklidge, 2006; Urosevic, et al., 2008).

We have previously argued that one process by which the capacity for effective emotion regulation may be impacted in BD is through impaired neurocognition (Van Rheenen & Rossell, 2013b- Chapter 2). However, a second and related process, social cognition, may impact the capacity for emotion regulation as well, perhaps as a mediator of neurocognition itself. Social cognition focusses on the social aspects of emotion, including the ability to identify and distinguish emotion using verbal and visual information, theory of mind (ToM), and the consequent ability to understand the emotional state of another (collectively referred to as social cognition). The current evidence suggests that the ability to process social and emotional information including emotional expressions and mental states is impaired. That is, patients with BD appear to have difficulty in accurately perceiving emotion in faces (e.g., Bozikas, et al., 2006b; Lembke & Ketter, 2002) and in spoken expressions (Bozikas, et al., 2007; Hofer, et al., 2010; Murphy & Cutting, 1990) as well as difficulty in theorising about others' mental or emotional states (Bora, et al., 2005; Rossell & Van Rheenen, 2013; Samamé, et al., 2012).

In the literature to date, these processes have been considered relatively separately, and the possible implications of one for the other have not been systematically considered. It is however likely that they share significant overlap: a-priori, it would seem that healthy emotional equilibrium requires both the ability to process social cognitive information and to regulate emotions arising from this processing. Here we discuss the hypothesis that deficits in emotion regulation may be impacted by impairments in social cognition in BD. We begin by briefly reviewing the literature on emotion regulation in BD. We follow by discussing the potential impact of social cognition on emotion regulation in the disorder, and finish by addressing some of the implications that the possible outcomes of this testable hypothesis may have for its treatment.

4.2.1 *Emotion regulation in BD*

A large body of research suggests that BD is associated with a variety of impairments that fall under the term emotion regulation (e.g., Green et al., 2011; Mansell, Morrison, Reid, Lowens, & Tai, 2007). This umbrella term describes various abilities involved in monitoring, inhibiting, initiating and modulating emotions, behaviours, physiological reactions, internal states and cognitions. Adaptive emotion regulation requires emotional acceptance, awareness, understanding, control and the appropriate use of regulation strategies (Gratz & Roemer, 2004; Gross, 2011). Thus, emotion regulation involves both overt and covert cognitive, physiological and motivational components.

The ability to regulate the experience and expression of emotion is critical to healthy emotional functioning. Indeed, the regulation of emotion is important for reducing common, transient depressive and sometimes elevated feelings, to circumvent their manifestation into pathological mood states (Gross & Muñoz, 1995). Emotional regulation may thus occur via an array of active and passive processes, including the inhibition of negative information and the use of coping strategies including that involving the reappraisal of social information, the ability to rapidly switch behaviours in response to changing environmental conditions, and the

ability to access and employ adaptive upward mood regulation strategies (Ochsner & Gross, 2005).

Typically mood and emotion are very changeable in BD and this is reflected by recurrent and persistent fluctuations between (hypo) manic, euthymic and depressive states (Frank, Swartz, & Kupfer, 2000). As people with BD tend to exhibit chronic and heightened trait-like emotional reactivity to reward and threat stimuli, this observed changeability in mood is proposed to occur as a consequence of an inability to regulate emotional arousal arising from this emotional reactivity (Depue & Iacono, 1989; Gratz & Roemer, 2004; Johnson, et al., 2000b). Certainly, difficulties in the regulation of emotional arousal may represent a common feature of BD; abnormalities in various aspects of emotion regulation have been reported across various measures in both at risk groups and BD patients (Becerra, et al., 2013; Chang, Steiner, & Ketter, 2000; Cichon, et al., 2011; Green, et al., 2011; Grigoroiu-Serbănescu et al., 1989; Hayden et al., 2008; Jones, Tai, Evershed, Knowles, & Bentall, 2006; Salavert et al., 2007). That is, BD patients have been reported to have difficulty regulating attentional control, exhibit negative cognitive styles, poor decision making and response flexibility when faced with changing rewards and punishments, and have difficulty inhibiting emotional responses or enacting adaptive regulation strategies (Bora, et al., 2006b; Doyle et al., 2005; Goldstein, et al., 2006; Green, et al., 2011; Kerr, et al., 2005; Lam & Wong, 1997; Maalouf, et al., 2010; Van der Gucht, Morriss, Lancaster, Kinderman, & Bentall, 2009). There is also some preliminary evidence indicating that euthymic patients with BD are less accepting of their emotions and have difficulty in understanding the types of emotions experienced, compared to their control counterparts (Becerra, et al., 2013). These difficulties have been associated with maladaptive interpersonal stress responses and depression (Flynn & Rudolph, 2010; Gohm & Clore, 2002; Salovey, Mayer, Goldman, Turvey, & Palfai, 1995; Tull & Roemer, 2007).

Indeed, there is reasonable evidence to indicate that people with BD engage in greater ruminative behaviour compared with the normal population (Gruber, et al., 2011; Johnson, McKenzie, & McMurrich, 2008; Van der Gucht, et al., 2009). This unproductive regulation strategy has been associated with hypomania and depression vulnerability as well as with increased frequency of clinical episodes in BD (Alloy et al., 2009a; Gruber, et al., 2011;

Johnson, et al., 2008; Thomas & Bentall, 2002). Other behaviours such as reduced sleep, setting highly challenging goals and embracing risk taking opportunities also reflect poor regulation strategies that may contribute to, or maintain, BD symptomatology (Mansell & Lam, 2003; Mansell, et al., 2007). For example, Green and colleagues (2011) found that both BD patients, and their unaffected relatives use rumination and self-blame to a far greater extent than their healthy control counterparts when faced with stressful life events. Similarly, Gruber, Harvey and Gross (2012) found that BD patients used more emotionally suppressive strategies in response to happy and sad stimuli, and Rucklidge (2006) found that BD patients were more likely to use insufficient methods to regulate stress related emotions, including using alcohol, screaming and taking their frustrations out on others.

Effective emotion regulation also involves the ability to deliberately return to baseline emotional functioning following an emotional event (Davidson, 1998). In BD, mood recovery time appears to be abnormally prolonged in comparison to controls. For example, Goplerud and Depue (1985) reported that BD spectrum patients exhibited prolonged periods of emotion recovery following stressful events; and Farmer (2006) reported that BD patients demonstrated a sustained increase in happiness response following a mood induction procedure. Negative regulation strategies including rumination likely serve to uphold arousal levels and prolong emotion recovery time. This is consistent with findings in which patients with BD show increases in manic symptomatology two months following a positive emotional life event (Johnson, et al., 2000b). Collectively, this suggests that BD patients have a tendency to spiral into increasing positive or negative affect because of difficulty in shifting their emotional focus, where the normal population would alternatively regulate their emotional experience to return to baseline (Gruber, 2011).

Taken together, this literature demonstrates that a range of factors contribute to the dysregulation of emotion in BD, including those relating to the non-acceptance of emotion and the use of unproductive coping strategies to modulate mood. Given that emotion dysregulation has strong implications for emotional/clinical outcomes in the disorder, further research to better characterise the profile of these difficulties, and the underpinning mechanisms from which these difficulties stem is certainly necessary.

4.2.2 *A novel hypothesis suggesting that social cognition impacts mechanisms for emotion regulation.*

It has previously been suggested that aberrations in neurocognitive function may be important for perpetuating deficits in emotion regulation in BD, given that impaired executive processes (i.e., those that bind together processing, memory and attention systems, monitor conflict and configure cognitive control in BD) appear to underpin distraction from goals, increase impulsive actions and reduce flexibility when responding to a changing environment (Bora, et al., 2005; Botvinick, Braver, Barch, Carter, & Cohen, 2001; Gopin, et al., 2011; Green, et al., 2007; Van Rheenen & Rossell, 2013b - Chapter 2). However, converging evidence suggests that impaired neurocognition may be integral to social cognition in BD as well (Green, et al., 2007; Van Rheenen & Rossell, 2013b - Chapter 2). Thus, there is potential for deficits in emotion regulation to be indirectly impacted by poor neurocognition through social cognition itself. In other words, there is potential that poor social cognition mediates the impact of neurocognitive deficits on emotion regulation in BD.

Indeed, emotion regulation is conceptualised as a process by which emotional experiences occurring in response to external stimuli are monitored and modulated (Gratz & Roemer, 2004; Gross, 2011; Gross & Thompson, 2011). These emotional responses may be formed, at least in part, on the recognition of basic emotional expressions (emotion processing) as well as an understanding of the needs and intentions of others (theory of mind). Thus, the accurate processing of emotion is necessary to the regulation of emotion (Brackett, Rivers, Shiffman, Lerner, & Salovey, 2006; Mayer, Salovey, Caruso, & Sitarenios, 2001).

In BD, the misinterpretation of others' emotional states (as catalysed by deficient neurocognitive functioning) may produce difficulties in initiating and regulating appropriate emotional reactions. For example, a pleased or cheerful emotional expression conveys warmth and encouragement, whereas an intimidating or hostile expression communicates threat and risk. The resulting judgements about the communicator's state of mind will thereby not only affect one's own emotional arousal but also the treatment of the communicator. In the above example the judgement could either foster affection or dislike for the communicator.

Mismanagement of emotion in response to the latter could lead to a variety of negative consequences.

Inaccuracy in perceiving emotions may thus affect the understanding of others' emotional states and the subsequent management of socially relevant physiological and cognitive emotional responses. Misidentification of emotion in BD is particularly pertinent given that patients exhibit heightened reactivity to signals of reward or failure, which may be represented by positive or negative social cognitive information. This reactivity can trigger emotional behaviours that when ineffectively regulated, detrimentally influence mood-related outcomes (Alloy, Abramson, Urosevic, Bender, & Wagner, 2009b; Urosevic, et al., 2008). Thus, inaccurate processing of social cognitive information is likely to have negative implications for the generation and appropriate regulation of emotional responses in BD (Green, et al., 2007).

The notion that poor social cognition impacts the capacity for adaptive emotion regulation is consistent with the neurobiological literature. This literature suggests that emotion dysregulation in BD results from dysfunction in a complex neural network in which there is reduced prefrontal (involved in cognition) inhibition of limbic system (involved in emotion) activity (Green, et al., 2007; Townsend & Altshuler, 2012). Dysfunction in this same network has also been associated with impaired neurocognitive and social cognitive processes in the disorder, and speaks to the proposition that social cognition and emotion regulation are inherently related (Cusi, Nazarov, Holshausen, MacQueen, & McKinnon, 2012; Green, et al., 2007; Townsend & Altshuler, 2012).

While empirical testing of the hypothesis that poor social cognition contributes to difficulties in emotion regulation, and thus, acts as a mediator of the impact of neurocognition on emotion regulation has not been adequately explored in BD groups as yet; the primacy of social cognition to emotion regulation has been independently recognised in other clinical samples characterised by core emotion difficulties. For example, in anorexia, decreased ToM ability is associated with greater difficulties in regulating emotions (Harrison, Sullivan, Tchanturia, & Treasure, 2009). In samples characterised by poor emotional awareness; a component of emotion regulation, there are also reports of reduced ToM (Moriguchi et al.,

2006) and emotion processing ability, such that poorer emotion perception is associated with poorer regulation of emotion (Lane, Sechrest, Riedel, Shapiro, & Kaszniak, 2000; Mann, Wise, Trinidad, & Kohanski, 1994).

There is indeed a possibility that aberrations in social cognition impede mechanisms for emotion regulation in BD as well, and we are aware of at least one other group investigating this same hypothesis (Rowland, et al., 2013b). Certainly, dedicated empirical attention to the potential impact of social cognition on emotion regulation represents a promising avenue of future research in the disorder. Given that maladaptive emotional regulation may be important to clinical and subsequently, psychosocial outcomes in BD (Goldstein, et al., 2006; Hoertnagl, et al., 2011; Lopes, et al., 2003), examining potential predictors of emotional regulation may ultimately elucidate potential targets for intervention. Uncovering pathways involved in clinical and psychosocial outcomes is therefore crucial to understanding mechanisms of the disorder and for establishing useful psychological interventions that may address core impairments at their source.

4.3 Future directions

The idea that impaired social cognition impedes adaptive emotion regulation in BD, possibly as a result of underlying neurocognitive impairments, is only one among many in the circuits that may impact emotion regulation, and subsequently emotional outcomes. It is unlikely to be specific to BD alone. However, one way forward is to make the specific concrete prediction specified above, to form the basis of focused empirical investigations for the future. Indeed, if social cognition does prove to be a mediator of the impact of neurocognition on emotion regulation in BD, or even it is associated with emotion regulation independently, these findings will have practical implications for the psychological treatment of BD. For example, new interventions that emphasise the importance of accurate emotion processing could be developed. Such treatment, in adjunct to cognitive remediation *and* treatments emphasising strategies to appropriately modulate emotions could assist in improving both mood symptomatology and functional outcomes in the disorder. Future

research would do well to empirically investigate this contention by employing experimental designs that consider the potential relationships between these variables appropriately, including using regression based analyses to model relationships between these processes in BD groups.

CHAPTER 5: PHENOMENOLOGICAL PREDICTORS OF PSYCHOSOCIAL FUNCTION IN BIPOLAR DISORDER

5.1 Chapter guide

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The previous chapters highlighted the idea that deficits in neurocognition, social cognition and emotion regulation may be related in BD. Thus, there is potential for each of these processes to impact psychosocial outcomes in the disorder. To date, only neurocognition and mood symptomatology have been *empirically* considered as key contributors to psychosocial outcomes. The documented effect of these processes on such outcomes has led the impact of other, potentially intermediate factors such as social cognition and emotion regulation, to be empirically ignored. This chapter (containing a published article that can be found in its final form in Appendix E) specifically aims to emphasise the importance of considering social cognition and emotion regulation alongside neurocognition and mood in studies of psychosocial functioning in the disorder.

A supplementary table comprising a comprehensive summary of studies that have investigated the relationship between neurocognitive, social cognitive or emotion regulation and psychosocial functioning in an explicit BD population can be found in Appendix F. This chapter is the final of the review chapters and provides the background to empirical Chapter 15.

5.2 Abstract

Objectives: Neurocognitive ability and mood have often been discussed as contributing mechanisms to the severe psychosocial dysfunction experienced in bipolar disorder (BD). In contrast there has been little discussion on the contribution of social cognition or emotion regulation. This paper aims to assert a potential role for these constructs in psychosocial functioning in BD, with an overarching goal to highlight the necessary importance of considering them in future research examining psychosocial outcomes in the disorder.

Methods: This paper provides a theoretical synthesis of available and indirect evidence for an influence of i) social cognition and ii) emotion regulation on psychosocial functioning; it acknowledges important clinical questions that need addressing, and discusses how current research might be translated to improve the treatment of psychosocial dysfunction in BD.

Results: Given their assumed roles in facilitating social interactions and modulating behaviours, it is certainly plausible that abnormalities in social cognition and emotion regulation are detrimental to psychosocial functioning. Currently, there is only minimal direct evidence examining their influence however, although existing BD studies are preliminarily supportive of relationships between these constructs.

Conclusions: There are reasonable theoretical grounds, supported by indirect and preliminary evidence, to suggest that social cognition and emotion regulation may be important in the prediction of psychosocial outcome in BD. However, this proposition is limited by the paucity of empirical research directly examining this matter.

5.3 Introduction

Bipolar disorder (BD) is a severe mood disorder characterised by problems in psychological, social and interpersonal functioning (e.g., Coryell et al., 1998; Godard, Baruch, Grondin, & Lafleur, 2012; Judd et al., 2005; Keenan-Miller & Miklowitz, 2011; MacQueen, et al., 2001; Rosa et al., 2009; Sanchez-Moreno et al., 2009; Serretti et al., 1999). For patients diagnosed with BD the capacity for effective employment, meaningful and long term interpersonal relationships and good psychological adjustment is significantly reduced (Australian Bureau of Statistics, 2007). Such impairment can have detrimental effects, with lifetime risk for suicide in people with BD estimated to be as high as 15% (Black Dog Institute, 2012). Indeed, BD disrupts life to the same degree as chronic medical illnesses such as multiple sclerosis and rheumatoid arthritis, with psychological wellbeing, family and social relationships and employment being the life domains most affected (Robb, Cooke, Devins, Young, & Joffe, 1997).

Many people with BD have difficulty in carrying out work functions (Judd et al., 2008), and in some cases are unable to work (Dion, Tohen, Anthony, & Waternaux, 1988). They report difficulties in social activities (Morriss et al., 2007) and social skills performance (Goldstein, et al., 2006), as well as maladjustment in marital or romantic relationships (Blairy et al., 2004; Tsai, Lee, & Chen, 1999). People with BD also consistently demonstrate lower scores on subjective psychosocial functioning (i.e., quality of life) scales (Cramer, Torgersen, & Kringlen, 2010; Freeman et al., 2009; Gutiérrez-Rojas et al., 2008; Saarni et al., 2010; Srivastava, Bhatia, Sharma, Rajender, & Kumar, 2010) and have reduced or labile self-esteem (Blairy, et al., 2004; Knowles et al., 2007; Serretti, et al., 1999).

Traditionally, clinical symptomatology has been implicated as a primary predictor of psychosocial outcome in BD; residual depressive symptoms occurring independently of mood episodes are often found in BD patients (Goossens, Hartong, Knoppert-van der Klein, & Van Achterberg, 2008; Keitner et al., 1996) and this depressive symptomatology appears to exacerbate psychosocial difficulties. However, even when it is attenuated, psychosocial

impairment remains (Bauer, Kirk, Gavin, & Williford, 2001; Bonnín et al., 2010; Godard, et al., 2012; Simon, Ludman, Unützer, Operskalski, & Bauer, 2008; Tabarés-Seisdedos et al., 2008; Wingo, Harvey, & Baldessarini, 2009).

At the phenotype level, BD is characterised by a compromised neurocognitive profile (e.g., Arts, et al., 2008; Balanzá-Martínez et al., 2005). Meta-analytic studies indicate large effect size deficits for patients with BD, even during remission (e.g., Bora, et al., 2009a). It is now becoming increasingly clear that patients' ability to develop new skills, respond flexibly to a changing environment and create complex understandings of life are constrained. Consequently, neurocognitive ability has been associated with objective, and to a lesser degree, subjective psychosocial functioning in the disorder in multiple studies, including consistently in those examining euthymic samples (Altshuler, Bearden, Green, van Gorp, & Mintz, 2008; Atre-Vaidya et al., 1998; Bonnín, et al., 2010; Bowie et al., 2010; Brissos, et al., 2008a; Brissos, Dias, & Kapczinski, 2008b; Burdick, Goldberg, & Harrow, 2010; Dickerson et al., 2010; Dickerson et al., 2004; Dittmann et al., 2007; Fujii, Wylie, & Nathan, 2004; Jabben, Arts, Van Os, & Krabbendam, 2010; Jaeger, Berns, Loftus, Gonzalez, & Czobor, 2007; Laes & Sponheim, 2006; Lahera et al., 2009; Malhi, et al., 2007a; Martínez-Arán et al., 2002; Martinez-Aran, et al., 2004a; Martinez-Aran et al., 2007; Martino, Igoa, Marengo, Scápola, & Strejilevich, 2011a; Martino et al., 2009; Mur, Portella, Martinez-Aran, Pifarre, & Vieta, 2009; Sánchez-Morla et al., 2009; Simonsen et al., 2010; Solé et al., 2012; Tabarés-Seisdedos, et al., 2008; Torres et al., 2011; Wingo, Baldessarini, Holtzheimer, & Harvey, 2010; Yen et al., 2009a). Given evidence that neurocognitive deficits perpetuate psychosocial dysfunction independent of affective symptomatology, neurocognition is considered to have a significant, yet clinically separate role in the prediction of functional outcome in BD (e.g., Bowie, et al., 2010; Burdick, et al., 2010; Jaeger, et al., 2007; O'Shea et al., 2010; Tabarés-Seisdedos, et al., 2008; Torres, et al., 2011).

Nevertheless, as the variance neurocognition explains differs across studies (e.g., Martinez-Aran, et al., 2007; Martino, et al., 2009), and as BD is a complex disorder likely to have several biological, psychological and environmental aetiologies, it is likely that other core features in its phenomenological profile also contribute to its psychosocial dysfunction. For

example, documented BD patient difficulties in regulating emotion and in social-cognitive processes including emotion perception and theory of mind may be involved (e.g., Bora, et al., 2005; Getz, et al., 2003; Olley, et al., 2005; Rossell & Van Rheenen, 2013; Van Rheenen & Rossell, 2013c - Chapter 3).

Although conceptually distinct, with neurocognition describing a range of mental functions innately linked to the brain, social cognition describing a branch of processing involved in perceiving, interpreting and responding to the social world, and emotion regulation describing a range of processes involved in the evaluation and modulation of emotion, there is likely to be inherent overlap in these processes (Frith & Frith, 2007; Gratz & Roemer, 2004; Gross, 2011; Larner, 2008). Indeed, converging evidence suggests that neurocognition is influential to social cognition and emotion regulation, with the potential for good neurocognition to be a necessary precursor to good social cognitive and emotion regulatory function (Fanning, Bell, & Fiszdon, 2012; Van Rheenen & Rossell, 2013b- Chapter 3). It is theoretically possible then, that these processes contribute to psychosocial outcome in the disorder as well, particularly given their likely role in facilitating adaptive social interactions that are core to adaptive occupational and social behaviours.

Currently there is only minimal research in the BD literature explicitly investigating whether social cognition and emotion regulation are related to psychosocial function (Inoue, Tonooka, Yamada, & Kanba, 2004; Simonsen, et al., 2010; Torres, et al., 2011; Wingo, et al., 2010; Wingo, et al., 2009). As social cognition and emotion regulation have the potential to represent more proximal and complex predictors of psychosocial outcome than neurocognition itself, a better understanding of how significant these constructs may be for predicting psychosocial outcome is important for enhancing the assessment and treatment for the disorder.

This paper draws on both direct and indirect available evidence to assert a potential role for social cognition and emotion regulation in psychosocial functioning in BD. Its overarching goal is to highlight the necessary importance of considering these factors in future research examining psychosocial outcomes in the disorder. To this end the paper provides a theoretical synthesis of available evidence for an influence of i) social cognition and ii)

emotion regulation on psychosocial functioning, gives rise to important clinical questions that need addressing, and discusses what such research could offer to the treatment of psychosocial dysfunction in BD.

5.3.1 *Social cognition as a potential predictor of psychosocial dysfunction in BD*

The ability to recognise and theorise about others' emotions are important factors in social and emotional competence, and are fundamental to interpersonal relationships (e.g., Wallace, 1984). Misunderstanding facial and prosodic emotional expressions reduces the accuracy of inferences made about the emotional state of a communicator, and limits the capacity to make social hypotheses, which can lead to a range of maladaptive psychosocial consequences (Batty & Taylor, 2003). Accurate emotion perception enables empathy and pro-social behaviours, whilst misperception of emotion reduces social communication, degrades appropriate emotional responses and increases the tendency to socially withdraw (Hooker & Park, 2002; Izard et al., 2001; Schultz, Izard, Ackerman, & Youngstrom, 2001).

Accurate emotional perception has been associated with social and intercultural adjustment in healthy individuals (Leppänen, 2001; Yoo, et al., 2006). In disorders characterised by poor emotion perception and theory of mind ability there is also growing evidence to demonstrate that emotion perception is related to psychosocial functioning (e.g., Couture, Penn, & Roberts, 2006; Lee, Harkness, Sabbagh, & Jacobson, 2005; Mueser et al., 1996; Persad & Polivy, 1993). For example, in schizophrenia populations, greater ability to recognise emotions is related to better independent living and occupational skills (Kee, Green, Mintz, & Brekke, 2003), better social problem solving (Vaskinn et al., 2008), greater overall satisfaction (Sparks, McDonald, Lino, O'Donnell, & Green, 2010) and better social skills (Irani, Seligman, Kamath, Kohler, & Gur, 2012).

Schizophrenia is theoretically and phenomenologically similar to BD, and its associated deficits may also be well represented in BD samples (e.g., Bora, et al., 2009c; Tabarés-Seisdedos, et al., 2008). As in schizophrenia, patients with BD tend to have difficulty in accurately identifying or distinguishing emotional expressions and conceptualising others'

emotional and mental states (Addington & Addington, 1998; Bozikas, et al., 2007; Bozikas, et al., 2006b; Getz, et al., 2003; Hofer, et al., 2010; Lembke & Ketter, 2002; Murphy & Cutting, 1990). These difficulties are likely to detrimentally influence the formation of social networks and social relationships (Inoue, et al., 2004; Schenkel, Marlow-O'Connor, Moss, Sweeney, & Pavuluri, 2008) that are often significantly impaired in the disorder (Bauwens, Tracy, Pardoen, Vander Elst, & Mendlewicz, 1991; Blairy, et al., 2004; Calabrese et al., 2003; Elgie & Morselli, 2007; see Huxley & Baldessarini, 2007 for a review; Sanchez-Moreno, et al., 2009).

Indeed, there is some evidence to suggest that emotion perception deficits are involved in psychosocial functioning in BD. For example, in two separate studies examining samples of euthymic BD patients, facial emotion processing accuracy was found to be related to objective psychosocial functioning (Martino, et al., 2011b), lower ratings of depression, and greater subjective quality of life (Hoertnagl, et al., 2011). There were also reports of a trend level relationship between emotion perception accuracy and higher rates of employment and general functioning in the latter investigation.

Our social cognitive ability to make inferences about the mental and emotional state of others, typically referred to as theory of mind, has also been strongly related to psychosocial outcome (Couture, et al., 2006). Poor theory of mind ability has been associated with poor interpersonal skills (Pinkham & Penn, 2006), severe social behavioural problems (Brüne, 2005), worse overall community social functioning (Pollice et al., 2002) and poor pre-morbid functioning in schizophrenia (Schenkel, Spaulding, & Silverstein, 2005). In BD too, theory of mind impairments have been preliminarily linked with poor functional outcome in two euthymic BD samples (Hajnal et al., 2010; Lahera, et al., 2009). Such associations presumably occur as a result of the maladaptive emotional responses evoked on misinterpretation or misunderstanding of emotional information. Indeed, poorer ability to manage emotions is associated with poorer positive relationships and greater negative interactions with others (Lopes, et al., 2003).

5.3.2 *Emotion regulation as a potential predictor of psychosocial dysfunction in BD*

The term emotion regulation is a broad term describing abilities that involve inhibition, initiation and modulation of behaviours, acceptance, awareness, understanding and control of emotions, and the appropriate use of regulation strategies (Gratz & Roemer, 2004; Gross, 2011). Dysregulated emotional responses are common in BD (e.g., Johnson, Fulford, & Eisner, 2009; Meyer, et al., 2001); and relationships between emotion regulation and psychosocial outcome have been preliminarily demonstrated in both the disorder itself and in other clinical samples that are phenotypically related. For example, Persad and Polivy (1993) found that depressed patients reacted with avoidance and heightened negative affect to emotional cues from others. A recent study by Matthews and Barch (2010) demonstrated a positive association between emotional reactivity to affective stimuli and functional outcome in schizophrenia. Similarly, Goldstein et al. (2006) reported that social skills performance in a group of euthymic adolescent BD patients was reduced in the absence of any observable deficit in social skills knowledge. The authors argued that difficulties in emotion regulation interfere with the utilisation of appropriate social skills.

Indeed, the management of emotions has been found to be an important predictor of the ability to initiate relationships, manage conflict and provide emotional support for others (Yip & Martin, 2006). Those with greater ability to emotionally manage are also less likely to have negative interactions with others and report greater psychological wellbeing (Lopes, et al., 2003), whereas those with poorer emotion regulation have diminished self-esteem, reduced life satisfaction and depressive symptoms (Gross, 2003). Certainly, patients with BD often experience emotionally intense interpersonal situations characterised by anger or frustration, whereby emotional control is particularly dysregulated (Keenan-Miller & Miklowitz, 2011). Such explosive situations place strain on interpersonal relationships and can lead to the experience of depressive symptoms (Rowe & Morris, 2012) which impact subjective quality of life (Dias, Brissos, Frey, & Kapczinski, 2008). Accordingly, early research indicates that euthymic BD patients' experiences of emotion are more intense than that of controls and correlate with subjective psychosocial function (Hoertnagl, et al., 2011). Adolescent BD

patients reporting a diminished ability to regulate emotion in anger provoking situations have also been found to report lower self-esteem, greater feelings of hopelessness and poorer coping strategies than controls (Rucklidge, 2006).

One of several ways that poor emotion regulation may influence psychosocial functioning in BD is by influencing depressive symptoms that are strongly predictive of psychosocial impairment (see Sanchez-Moreno, et al., 2009 for a review). Indeed, problematic emotion modulation strategies including rumination for both positive and negative emotion have been associated with depressive symptoms including reduced or labile self-esteem in people with subclinical hypomania and full blown BD (Bentall et al., 2011; Gruber, et al., 2011). Depression, occurring on the basis of disturbed self-esteem in the disorder, has been reported to arise from patients' negative perceptions of others' evaluations of themselves (Johnson, Meyer, Winett, & Small, 2000a). It is certainly plausible that characteristically dysregulated and variable emotional behaviour is at the basis of these negative self-evaluations.

Fluctuations in self-esteem have been specifically associated with the disorders' trait tendency to be reactive to salient emotional stimuli, such that even minor experiences of perceived threat or reward increase emotional arousal. When ineffectively modulated this arousal affects levels of self-esteem, and confers vulnerability for the development of depressive or manic symptoms(Johnson, et al., 2000a; Klein, 1992; Shapira et al., 1999; Urosevic, et al., 2008). For example, heightened emotional reactivity is often accompanied by large changes in self-esteem in people with BD (Pavlova, Uher, Dennington, Wright, & Donaldson, 2011). These changes are reflective of ascent/descent behaviours that pre-empt the development of affective episodes; inflated self-esteem is a defining feature of mania and is prodromal to its onset. Likewise, low levels of self-esteem are prodromal to depression (Lam & Wong, 1997; Mansell & Pedley, 2008). Maladaptive emotional regulation strategies such as rumination have been found to load on the same factor as low self-esteem, suggesting that they are highly related and can be considered to form a negative cognitive syndrome that predicts BD symptoms (Van der Gucht, et al., 2009). Further evidence of this connection comes from Scott and Pope (2003), who found that hypomanic patients with negative self-esteem were significantly more likely to experience an affective relapse. Unfortunately, an increased history

of mood episodes is predictive of worse psychosocial functioning (MacQueen et al., 2000; Sierra, Livianos, & Rojo, 2005).

Trait emotional reactivity to threat or reward has been equated with neurotic temperament, which tends to be prominent in the disorder (Gray, 1981, 1987; Mitchell et al., 2007). That is, patients with BD tend to view the world as a threatening place and are highly self-conscious, insecure, low in self-esteem and tend toward worry and negative affect (Jylhä et al., 2010; Mitchell, Slade, & Andrews, 2004a). Patients with BD also demonstrate heightened levels of impulsivity, a lower order feature of neuroticism. This impulsivity is argued to arise when threat or reward inputs are made and arousal levels increase the speed of subsequently occurring responses (Wallace, Newman, & Bachorowski, 1991). There is a substantial literature that documents a relationship between facets of neuroticism and psychosocial function (Pope, Dudley, & Scott, 2007). For example in BD, neuroticism has been linked to lower subjective quality of life, increased symptom severity and frequency, and lower self-confidence (Carpenter, Clarkin, Isman, & Patten, 1999; Heerlein, Richter, Gonzalez, & Santander, 1998; Jones, Twiss, & Anderson, 2009; Lozano & Johnson, 2001; Quilty, Sellbom, Tackett, & Bagby, 2009). Family related neuroticism has also been associated with poor psychosocial outcome in children of mood disordered parents (Ellenbogen & Hodgins, 2004) and impulsivity has been related to suicide attempts, increased aggression and poorer subjective quality of life in mood disordered patients themselves (Ekinci, Albayrak, Ekinci, & Caykoylu; Perroud, Baud, Mouthon, Courtet, & Malafosse).

Neuroticism has also been found to predispose people to the experience of life events relevant to the onset or increase of BD symptoms. Poor regulation of emotions generated as a result of heightened emotional reactivity to reward or threat based environmental cues is likely to prompt these events (Magnus, Diener, Fujita, & Payot, 1993; Urošević et al., 2010). Indeed, research shows that neurotic people orient attention more readily and are attuned to or have difficulty shifting attention away from negative stimuli (Derryberry & Reed, 1994; Reed & Derryberry, 1995; Wallace & Newman, 1998). In fact, emotional reactivity is posited to be a fundamental variable in triggering BD symptoms by predisposing one to the experience of life events and emotional experiences that are subsequently poorly controlled (Johnson, 2005a).

For example, mania is associated with unrealistically high confidence following an initial success (Johnson, Ruggero, & Carver, 2005).

5.4 Discussion

Patients with BD are severely psychosocially impaired, an outcome that has been historically attributed to clinical symptomatology and more recently, neurocognitive capacity (Bonnín, et al., 2010; Brissos, et al., 2008b; Zaretsky, 2003). Importantly, there is a growing body of research in euthymic BD samples that indicates a contribution of neurocognition to psychosocial outcome; this contribution often occurs independently of the influence of subclinical depression, which supports a growing consensus amongst researchers that clinical status and psychosocial status are separable constructs (Bowie, et al., 2010; Tabarés-Seisdedos, et al., 2008; Torres, et al., 2011).

Although neurocognition has been found to have an important independent impact on psychosocial functioning, the variance it explains varies across studies (Brissos, et al., 2008b; Martinez-Aran, et al., 2007; Martino, et al., 2009). It is likely that other key trait features of the disorder's phenomenological profile are also partially accountable. In particular, it is plausible that the capacity for adaptive social cognition and emotion regulation contribute to psychosocial functioning in BD, given the roles of these processes in facilitating social interactions and modulating behaviours that are core to healthy psychosocial outcome. Indeed, there is reasonable theoretical rationale for the proposition that social cognitive impairments, like neurocognitive impairments, directly influence adaptive psychosocial function in BD. Results from initial studies partly addressing social cognitive contributions in the disorder also suggest that its influence may occur in a manner that is independent from mood (Hajnal, et al., 2010; Hoertnagl, et al., 2011; Lahera, et al., 2009; Martino, et al., 2011b). Conversely, it is likely that abnormalities in emotion regulation perpetuate psychosocial dysfunction in BD by catalysing or exacerbating clinical symptoms.

Limited research provides support for the proposition that these processes impact outcomes in BD (Hajnal, et al., 2010; Lahera, et al., 2009; Martino, et al., 2011b). That there is

reasonable theoretical justification for their association, formulated on the basis of indirect support for an association between these variables from studies of related disorders, and healthy populations (Kee, et al., 2003; Mathews & Barch, 2010; Sparks, et al., 2010), suggests that the influence of social cognition and emotion regulation on psychosocial function in BD are areas worthy of future research. Converging evidence suggesting that neurocognition is influential to social cognitive performance and emotion regulation also adds an interesting additional observation about this proposition; that neurocognition might have some impact on functional outcomes through social cognition and emotion regulation (Fanning, et al., 2012; Van Rheenen & Rossell, 2013b - Chapter 2). However, as there is little clarity with regards to how important the relative contributions of neurocognition, social cognition and emotion regulation are, or the mechanisms by which psychosocial difficulties in BD are maintained, a number of questions remain unanswered.

This is notable given that in overlapping clinical conditions such as schizophrenia, there are growing reports that the effects of neurocognition on psychosocial functioning are mediated by social cognitive processes; social cognition appears to be more proximal to psychosocial outcome and thus, a potentially better treatment target for the remediation of psychosocial difficulties (Addington, Saeedi, & Addington, 2006; Bora, Eryavuz, Kayahan, Sungu, & Veznedaroglu, 2006a; Brekke, Kay, Lee, & Green, 2005; Couture, et al., 2006; Green, Kern, Braff, & Mintz, 2000; Green & Nuechterlein, 1999; Harvey, Wingo, Burdick, & Baldessarini, 2010; Pinkham & Penn, 2006; Vaskinn, et al., 2008; Vauth, Rüsch, Wirtz, & Corrigan, 2004). Such findings are undoubtedly relevant to the study of psychosocial functioning in BD, and it is certainly possible, albeit speculative, that neurocognition effects psychosocial function indirectly via social cognition in BD as well.

Indeed, the relative influence and importance of these processes on psychosocial outcome, and the potential mechanisms of mediation they may form for the maintenance of psychosocial difficulties in BD represent important clinical questions. Future studies of psychosocial outcome would therefore do well to investigate social cognition and emotion regulation more comprehensively and concurrently with neurocognition and subclinical symptomatology. Importantly, these studies would need experimental designs that consider

the multiple interrelated variables appropriately, and thus employ robust statistical techniques including sophisticated forms of regression, path analysis or structural equation modelling to establish relationships and mechanisms of prediction. Given that it is also unclear as to whether objective psychosocial function parallels subjective psychosocial function (Goldberg & Harrow, 2005; MacQueen, et al., 2000), future studies should also endeavour to investigate whether these processes influence measures of patient rated or administrator rated psychosocial outcomes differently.

Certainly, these kinds of investigations have the potential to inform the development of psychological treatments that may be effective in improving psychosocial outcome in the disorder. Current psychological treatments for BD include Cognitive Behavioural Therapy (CBT) and Interpersonal Social Rhythm Therapy (ISRT); these techniques show small effects on the reduction of symptoms and improvement in psychosocial functioning (Costa et al., 2011; Gregory, 2010; Hlastala, Kotler, McClellan, & McCauley, 2010; Hollon & Ponniah, 2010). However, these treatments provide intervention after neurocognitive, social cognitive or emotion regulation abnormalities are established. Treatments that target abnormalities such as those associated with neurocognition and those that aim to improve emotional processing, theory of mind and emotional regulation, prior to CBT and ISRT would provide a more solid foundation to build upon, which may in turn result in better psychosocial function for BD patients.

There is growing support for the development of novel treatment approaches to reduce psychosocial dysfunction in BD (e.g., Harvey, et al., 2010; Martínez-Arán, et al., 2011; Mennin & Fresco, 2009; Tufrey & Coulston, 2010). In schizophrenia and schizoaffective disorder, programs that remediate cognitive functions have been found to be efficacious in improving psychosocial function (Anaya et al., 2012; Lewandowski, Eack, Hogarty, Greenwald, & Keshavan, 2011; McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007; Medalia & Choi, 2009). Improving cognitive function is also demonstrated to improve mood, possibly due to bolstering self-esteem and facilitating positive learning experiences (McGurk, Mueser, & Pascaris, 2005; Wykes, Reeder, Corner, William, & Everitt, 1999). Preliminary support for cognitive remediation in BD has also been recently demonstrated by Deckersbach and

colleagues (2010) who noted improvement in occupational functioning following the use of a new remediation treatment designed to improve cognition and depressive symptoms.

Improvements in the perception of facial emotions have also been demonstrated in schizophrenia with the use of a specialised intervention program aimed at remediating facial emotion perception difficulties (Frommann, Streit, & Wölwer, 2003; Wölwer et al., 2005). Such remediation has also lead to improvements in social relationships (Sachs, et al., 2012). To our knowledge, studies examining the efficacy of such a program, or of recently developed emotion regulation therapies, are yet to appear in a BD sample.

5.5 Conclusions

There are reasonable theoretical grounds formulated from indirect and preliminary evidence to suggest that social cognition and emotion regulation may be important in the prediction of psychosocial outcome in BD. However, the paucity of research directly investigating these factors leaves many questions unanswered regarding their relative contribution in the context of neurocognition and clinical symptomatology. Clearly, future research acknowledging their potential contribution is necessary.

CHAPTER 6: GENERAL AIMS AND OBJECTIVES

6.1 Chapter guide

The preceding chapters provided an overview of literature concerning neurocognition, social cognition and emotion regulation in the context of their genetic aetiology, inter-relationships and potential influence on psychosocial outcomes in bipolar disorder (BD). They identified particular gaps in the literature and specified future directions of empirical interest, many of which are addressed in this thesis and presented in the following empirical chapters. Importantly, whilst the above chapters highlighted that neurocognition, social cognition and emotion regulation are impaired in BD, they also aimed to both explicitly *and* discreetly alert the reader to the following key points;

1) BD appears to share some phenomenological and genetic overlap with schizophrenia and thus, some hypotheses about impairments in BD can be made on the basis of findings in these literatures.
2) A number of measures have been used to estimate neurocognition in BD, and deficits in neurocognition represent a consistent finding.
3) Facial emotion processing is impaired in BD, although questions remain about its underpinnings and the influence of different methodologies in estimating group differences.
4) Although research on prosodic emotion processing and theory of mind in BD is limited, there is preliminary evidence of patient-related impairments in these social cognitive functions.
5) Emotion regulation is a broad construct encompassing many different abilities. Difficulties in emotion regulation are apparent in BD and may be causally involved in perpetuating poor clinical outcomes. However, a better characterisation of the range of these deficits is necessary.
6) Neurocognitive, social cognitive and emotion regulation processes in BD may be genetically influenced by dopamine and/or serotonin genes.
7) Neurocognitive deficits may underpin deficits in social cognition and emotion regulation in BD, but poor social cognition may also directly predict difficulties in emotion regulation,

and thus, may act as a mediator of the impact of neurocognition on emotion regulation in the disorder.

8) As well as impairments in neurocognition, impairments in social cognition and emotion regulation may also impact psychosocial outcomes in BD.

The points raised above contribute heavily to the investigations presented in the following empirical chapters. Although the precise background information, aims and hypotheses pertaining to each investigation is presented within each relevant chapter below, the current chapter is provided as a short overview of the general aims and research objectives running throughout these investigations.

6.2 General aims

As specified previously, the general aim of this thesis was to further current understandings of neurocognitive, social cognitive and emotion regulation processes in bipolar disorder (BD). To address this aim, the investigations presented in the following chapters were designed to a) examine the neurocognitive, social cognitive and emotion regulation profiles of BD patients, in the context of a number of specific research objectives (see below), b) examine the underlying genetic influences on these processes, c) assess the inter-relationships between these processes, and d) examine the effects that these processes have on psychosocial functioning in the disorder.

Although not set as a hypothesis or research question, the project also generated meaningful data on the important issue of moderation of observed differences by current symptoms ([hypo]manic, mixed, depressed or euthymic), diagnosis (BD I or BD II) and medication.[5] Evidence in relation to these three potential moderators of expected effects are noted throughout.

6.2.1 *Specific research objectives*

The following specific research objectives were addressed:

i. Given that a large body of literature suggests that impairments in neurocognition are stable, trait-like features of BD, an objective of this research was to determine what the

[5] For analyses aimed at investigating the impact of mood, but where the particular valence of the mood (i.e., manic/depressed) was not of fundamental importance (i.e., in all studies but those assessing social cognition), it should be noted that (hypo)manic, mixed, and depressed subgroups were collapsed into one larger *symptomatic* group, in an attempt to conserve statistical power (i.e., smaller subgroups were compared *only* for social cognitive investigations where there was significant potential for mood valence to influence response type in the form of positive or negative biases).

neurocognitive profile of this sample looked like, using a standardised battery with established validity in a related clinical disorder.

ii. As deficits in facial emotion processing represent a core feature in BD, an objective of this research was to determine what the facial emotion processing profile of this sample looked like. In particular, it aimed to establish whether deficits in facial emotion processing were specific or generalised phenomena, and whether the consistency with which facial emotions were processed at different intensities was the same for BD patients and controls. Further, given that there has been some inconsistency in the results of previous facial emotion processing studies, this research aimed to examine whether these inconsistencies were the function of methodological problems.

iii. As there is very limited research investigating prosodic emotion processing in BD, an objective of this research was to determine whether emotional prosody processing impairments existed in this sample, and whether lower level acoustic processes contributed to this impairment.

iv. Although there is some research suggesting the theory of mind is impaired in BD, further research is needed to better establish this. An objective of this research was to determine if theory of mind impairment could be measured in this sample on a novel task.

v. As the current emotion regulation literature is very broad, and previous studies have tended to focus on only certain dimensions in its definition, an objective of this research was to characterise the emotion regulation profile of BD on the basis of performance on an integrative measure indexing many of its dimensions.

vi. As there is evidence to indicate that dopaminergic and serotonergic genes are involved in the pathophysiology of BD, an objective of this research was to determine whether neurocognitive, social cognitive and emotion regulation abnormalities in BD were partially due to the influence of specific dopaminergic and serotonergic genes.

vii. Given that converging evidence suggests that neurocognition is important to social cognition and emotion regulation, and that these processes are inherently inter-related, an objective of this research was to determine whether abnormalities in social cognition and emotion regulation were underpinned by aberrant neurocognition in the disorder.

Further, this research aimed to establish whether social-cognitive deficits mediated the relationship between neurocognition and emotion regulation in BD.

viii. Given that neurocognition, social cognition and emotion regulation may represent overlapping processes in BD, but only neurocognition has been investigated in relation to its impact on psychosocial functioning thus far, an objective of this research was to determine whether social cognition and emotion regulation concurrently explain variance in psychosocial outcome alongside neurocognition in the disorder.

CHAPTER 7: METHODS

7.1 Chapter guide

As many of the following empirical chapters have been written for publication in scientific journals that often preclude detailed methodological sections due to word limitations, this chapter is provided to ensure the reader has access to further detail about the study design, ethical procedures, recruitment methods, measures used, and the study procedure.

7.2 Experimental design

A cross sectional design was considered most appropriate, given the study aims. The design enabled the collection of data from an entire population of interest, and was relatively low in cost. Its quantitative nature was both an objective and efficient means of testing the research objectives, where results could be generalised widely.

7.3 Recruitment procedures

7.3.1 *Source of participants*

The BD group was recruited via community support groups, the Monash Alfred Psychiatry Research Centre (MAPrc) participant database and general advertisements. This group comprised only out-patients. Healthy controls were recruited for comparison purposes by general advertisement and contacts of the author.

7.3.2 *Subject selection procedures (inclusion/exclusion criteria)*

Participants were excluded if they had any of the following conditions: (i) hearing or visual, neurological, (e.g., epilepsy) or known neurodegenerative (e.g., Huntington's disease) illness/impairment; (ii) severe head injury or metal implants (iii) engaged in significant drug/alcohol use in the previous 3 months, (iv) difficulties with spoken English and (v) were pregnant. The age range for participation was between 18 and 70 years of age. To ensure no participant had an intellectual disability and was able to understand instructions, all participants included in the study had an IQ>75 (as assessed by the Wechsler Test of Adult Reading; WTAR). The sole additional inclusion criterion for the clinical group was a DSM-IV TR BD I or BD II (as confirmed by clinical interview). Inclusion criteria for the control group were: (i) no history of mood or psychiatric disorder, (ii) no first degree relatives with a history of mood or psychiatric disorder, (iii) not currently receiving psychiatric care and (iv) not currently taking mood or psychotropic medication.

7.3.3 *Participant identification and contact (method and setting)*

The author contacted potential participants identified through the Alfred Hospital outpatient clinics, or MAPrc participant database by telephone, post, email or in-person. Potential participants also contacted the author by telephone or email as a result of seeing advertising material. On first contact, interested persons received a brief verbal overview of the study. To ascertain eligibility, the person was asked a series of questions relating to the aforementioned inclusion and exclusion criteria. This screen took place entirely over the phone prior to the first visit. Eligible participants were sent copies of the participant information form by post or email. In most cases the author followed up the contact after approximately four days to arrange a time to answer any questions. If the person was still interested in participating, a time was arranged for testing. Section 7.6 provides details on the subsequent procedure for testing.

7.4 Participants

A total of 51 BD patients and 55 healthy controls met inclusion/exclusion criteria and consented to participate.[6] All of the empirical investigations described below were based on data from this sample. In some cases, certain participants did not complete all measures, and were thus not included in all investigations. The method sections of each of the following empirical chapters should be consulted for specific sample details. No further information on the participant sample is provided here.

7.5 Materials

Table 4 presents a summary of the measures used in this project. A description of each of these measures follows.

[6] The suitability to consent was determined by the author on the basis of the following criteria;: i) the person was over 18 years of age, ii) the person was able to read and understand English, iii) the person was able to understand the purpose of and the procedures required for the study, and iv) the person was willing to participate.

Table 4. *Summary of measures*

Type	Sub category	Test	Abbreviation	Notes
General	Demographics	Series Of Questions	-	-
	Premorbid IQ	Wechsler Test Of Adult Reading	WTAR	-
Clinical	Diagnosis	Mini International Neuropsychiatric Battery	MINI	-
	Depressive symptomatology/severity	Montgomery Asberg Depression Rating Scale	MADRS	-
	Manic symptomatology/severity	Young Mania Rating Scale	YMRS	-
Genetics	SNP genotyping	Whole Blood	-	-
Neurocognition	Speed of processing	Symbol Coding	BACS-SC	MCCB subtest
		Category Fluency: Animal Naming	Fluency	MCCB subtest
		Trail Making Test-Part A	TMT-A	MCCB subtest
	Attention/vigilance	Continuous Performance Task-Identical Pairs	CPT-IP	MCCB subtest
	Working memory	Wechsler Memory Scale-Spatial Span	WM-SS	MCCB subtest
		Letter Number Span	LNS	MCCB subtest
	Verbal learning	Hopkins Verbal Learning Test-Revised	HVLT-R	MCCB subtest
	Visuospatial memory	Brief Visuospatial Memory Test-Revised	BVMT-R	MCCB subtest
	Reasoning and problem solving	Neuropsychological Assessment Battery-Mazes	Mazes	MCCB subtest
	Social cognition	Mayor-Salovey-Caruso Emotional Intelligence Test	MSCIET	MCCB subtest
	Executive function	Trail Making Test-Part B	TMT-B	ISBD recommended
		Colour-Word Stroop	Stroop	ISBD recommended
Social cognition	Facial emotion processing	Static Facial Emotion Labelling		Neutral, happy, sad, angry, fear; latter stimuli presented at high, medium and low intensity
	Facial emotion processing	Dynamic Facial Emotion Labelling		Happy, sad, angry, fear
	Facial emotion processing	Static Facial Emotion Discrimination		Neutral, happy, sad, angry, fear; latter stimuli presented at high, medium and low

Type	Sub category	Test	Abbreviation	Notes
				intensity
	Facial emotion processing	Identity Discrimination		Control task
	Prosodic emotion processing	Emotional Prosody Labelling		Neutral, happy, sad, fear
		Linguistic Prosody Labelling		Control task
	Prosodic emotion processing	Amplitude Discrimination		Control task
	Prosodic emotion processing	Duration Discrimination		Control task
	Prosodic emotion processing	Frequency Discrimination		Control task
	Theory of mind	Picture Sequencing Task		
Emotion regulation	Emotional evaluation/modulation	Difficulties in Emotion Regulation Scale	DERS	Multiple dimensions of emotion regulation
Psychosocial functioning	Objective functioning	Global Assessment of Function	GAF	-
	Subjective functioning	Quality of Life in Bipolar Disorder Scale	QOL.BD	-

Note: IQ=Intelligence Quotient; SNP = Single Nucleotide Polymorphism; MCCB= MATRICS Consensus Cognitive Battery; ISBD=International Society for Bipolar Disorders

7.5.1 *General assessment measures*

7.5.1.1 Demographic

Participants were asked a series of self-report questions designed to ascertain general demographic information: age, gender, ethnicity, education, employment, marital status, living arrangements and accommodation, current medication and if relevant, psychiatric information (age of onset, age of diagnosis, immediate family history of psychiatric illness).

7.5.1.2 Premorbid IQ

The Wechsler Test of Adult Reading (WTAR: Holdnack, 2001) was used as a measure of premorbid IQ. The test, originally developed in combination with the Wechsler Adult Intelligence Test-III, requires participants to read aloud a list of 50 irregularly pronounced words whilst an administrator assigns a score of one for accuracy (or zero for inaccuracy) in pronunciation. The test is designed to minimise participants' current ability to apply standard pronunciation rules and assess previous learning of the word. It is highly correlated with

verbal and full scale IQ indices from the Wechsler Adult Intelligence Test-III (*r*=.75 and *r*= .73 respectively) and shows good stability and inter-rater reliability (r=.90 - r=.94; Dykiert & Deary, 2013; Holdnack, 2001). The total raw score is taken as the number of correctly pronounced words (Theoretical Range: 0-50). An age corrected scaled score is also produced.

7.5.2 *Clinical battery*

7.5.2.1 Diagnosis confirmation and co-morbidities

The following clinical measures were all administered by the author, a trained administrator.

The MINI International Neuropsychiatric Interview for bipolar disorder studies (MINI: Sheehan et al., 1998) was used as a brief clinical interview for major ICD-10 and DSM-IV Axis-I psychiatric disorders. The MINI is well accepted by patients and demonstrates good inter-rater reliability (*κ*=.75 for mania and depression) and validity in relation to the Structured Clinical Interview for Diagnosis and the Composite International Diagnostic Interview (Amorim, Lecrubier, Weiller, Hergueta, & Sheehan, 1998; Pinninti, Madison, Musser, & Rissmiller, 2003; Sheehan, et al.). It is divided into modules that are identified by letters. Each letter corresponds to a diagnostic category of which there are screening questions (that either permit or rule out further questioning based on core diagnostic criteria), main criteria based questions and diagnostic boxes in which the administrator must indicate whether diagnostic criteria is met.

7.5.2.2 Severity of depressive symptoms

The Montgomery Asberg Depression Rating Scale (MADRS: Montgomery & Asberg, 1979) was used to measure current severity of depressive symptoms. The MADRS is widely used 10 item scale comprising questions leading to a rating of the core symptoms of clinical depression (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts). Symptoms over the past one week period are rated on a scale of 0-6 (with defined anchor points of 0, 2, 4, 6) leading to a total score between 0 and 60. The MADRS is well validated (it is highly correlated [*r*=.89] with the HAMD) and demonstrates good inter-rater reliability

(r=.89; Montgomery & Asberg, 1979). Scores of greater than eight were taken as indicating the presence of clinically important depressive symptoms.

7.5.2.3 Severity of manic symptoms

The Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) was used to measure the severity of manic symptoms. The 11 item YMRS is a gold standard mania rating measure comprising questions leading to a rating of the core symptoms of clinical mania over the past week (elevated mood, increased motor activity/energy, sexual interest, sleep, irritability, speech, language/thought disorder, content, disruptive-aggressive behaviour, appearance, insight). Items 1, 2, 3, 4, 7, 10 and 11 are rated on a scale of defined anchor points (0-4), whilst items 5, 6, 8 and 9 are permitted ratings 0-8. The YMRS has good inter-rater reliability (r_s=.66=.95 for individual items; r_s=.93 for global rating) and is well validated (Young, et al., 1978). Scores of greater than eight were taken as indicating the presence of clinically important hypo (mania) symptoms.

7.5.3 *Genotyping*

Whole blood (30ml) was collected by a trained nurse for each consenting participant. The blood was stored in a low temperature freezer (-80°C) at the Baker IDI Genomics and Systems Laboratory at the Alfred Hospital, Melbourne, Australia. Trained staff at the Laboratory extracted the DNA using the QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany) according to manufacturer's instructions. It was sent by courier to the Brisbane Node of the Australian Genome Research Facility for genotyping. Single nucleotide polymorphism (SNP) assays were designed using the Sequenom Assay Design Suite 1.0 software (Sequenom, San Diego CA). Each assay design produces a set of DNA oligos or primer sequences: two primers for PCR amplification and a third for the primer extension reaction to detect the specific sequence variation or mutation site. Genotyping was carried out using the MassARRAY system (Sequenom, San Diego CA) as per the manufacturer's standard protocols. The MassARRAY platform relies on a primer extension reaction in combination with a mix of mass-tagged dideoxy-nucleotides (iPlex Gold chemistry) to generate a pool of

oligo products that are analysed by chip-based matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF).

Genotyping results were received by the author in electronic form. To ensure their validity, adherence to Hardy-Weinberg equilibrium and allele frequency was assessed prior to conducting any further statistical analyses. For each of the genes analysed, SNPs were selected based on association studies in the literature. Further information regarding specific SNP selection can be found in Chapter 13.

7.5.4 *Neurocognitive battery*

The MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein & Green, 2006) was used as a brief assessment of cognitive functioning across several key domains. The MCCB was developed by the National Institute of Mental Health (NIMH) Initiative, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) to act as a cognitive reference point for both clinical trials and non-intervention studies of cognition in schizophrenia and related disorders. It comprises ten co-normed, consensus based subtests of cognitive functioning in domains prone to impairment in schizophrenia. The battery of tests measures speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving and social cognition. It takes approximately 60-90 minutes to administer. The MCCB shows good test-retest reliability (scores ranging from $r = .69$ to $r = .85$), practicality, tolerability and relationship to functional outcome (Nuechterlein et al., 2008).

Cognitive domains and corresponding individual subtests of the MCCB are described below.

7.5.4.1 Speed of processing

Speed of processing is a measure of cognitive efficiency and refers to the capacity to process information automatically. The speed of processing domain on the MCCB is measured by three brief tests of visuomotor speed, verbal processing speed and visual scanning to ensure the domain is reliably and validly represented.

7.5.4.1.1 BACS symbol coding

Participants are required to write numbers that correspond to nonsense symbols as quickly as possible within a 90 second period. The total score reflects the number of correctly written number/letter matches, where higher scores represent faster visuomotor speed (Theoretical Range: 0-110).

7.5.4.1.2 Category fluency: Animal naming

Participants are required to spontaneously name as many animals as possible within a 60 second period. The total score reflects the number of animals named, where higher scores represent faster verbal processing speed.

7.5.4.1.3 Trail Making Test Part A (TMT A)

Participants are required to connect consecutive numbers arranged in irregular locations on a sheet of paper whilst being timed to a maximum of 300 seconds. The total score reflects the number of seconds required to complete the task, where higher scores represent better visual scanning (Theoretical Range: 0-300).

7.5.4.2 Attention/Vigilance

Attention refers to the selection and allocation of processing resources for the purpose of concentration on an aspect of the environment. The attention/vigilance domain of the MCCB is measured on the Continuous Performance Test - Identical Pairs (CPT-IP).

7.5.4.2.1 Continuous Performance Test-Identical Pairs (CPT-IP)

Participants are required to monitor a series of digit sequences on a computer screen and respond with a button press each time a sequence is presented that is identical to the one shown just prior (the target), in three trials; two digit sequences, three digit sequences and four digit sequences. Twenty per cent of the trials contain identical target stimuli. Scores that represent the number of hits (correct responses to identical pairs) and two types of commission errors; false alarms (responses to digits that are almost identical) and random

errors; number of responses to other digits) are generated. Signal detection analyses combine hit and false alarm information into *d* prime (*d'*) scores that represent the ability to discriminate identical pairs from nearly identical pairs, for each of the three conditions. These scores are averaged to create a total summary score. Higher scores represent better attention/vigilance.

7.5.4.3 Working memory

Working memory refers to the temporary maintenance and manipulation of information required for complex visual and verbal tasks. The working memory domain of the MCCB comprises two brief tests of verbal and visual memory to ensure the domain is reliably and validly represented.

7.5.4.3.1 Wechsler Memory Scale-Third Edition (WMS III); Spatial Span forwards and backwards

Participants are required to remember the locations of a series of irregularly spaced blocks to which the administrator points. Participants must recall the locations in the same order (forward scale) in which they were presented, or in reverse order (backwards scale). Scores for correctly remembered sequences are summed to create subscale scores (subscale score Theoretical Ranges: 0-16) which are then summed to form a total score (total score Theoretical Range: 0-32). Higher scores represent better non-verbal working memory.

7.5.4.3.2 Letter Number Sequencing(LNS)

Participants are required to mentally re-order a series of orally presented lists of intermixed letters and numbers before repeating it back to the administrator. Scores for each correctly repeated list are summed to create a total score (Theoretical Range: 0-24), where higher scores represent better verbal working memory.

7.5.4.4 Verbal Learning

Verbal learning refers to the ability to learn from information presented verbally. The verbal learning domain of the MCCB is measured on the Hopkins Verbal Learning Test - Revised (HVLT-R).

7.5.4.4.1 Hopkins Verbal Learning Test-Revised (HVLT-R)

A list of twelve target words representing three semantic categories (four words per category) is read aloud by an administrator, after which participants are asked to recall as many words as possible in any order. This is repeated for three list learning trials. The number of correctly recalled target words on each learning trial are summed to form trial scores (trial score Theoretical Ranges: 0-12) that are combined to form a total list learning score (total recall score Theoretical Range: 0-36). Higher scores represent better verbal learning.

7.5.4.5 Visual Learning

Visual learning refers to the ability to learn from information presented visually. The visual learning domain of the MCCB is measured on the Brief Visuospatial Memory Test-Revised (BVMT-R).

7.5.4.5.1 Brief Visuospatial Memory Test-Revised (BVMT-R)

On three separate trials, participants are required to reproduce the same six visually presented geometric designs on a blank sheet of paper after they have been presented for ten seconds. Scores are assigned as following; accurately drawn and correctly placed = 2, accurately drawn and incorrectly placed = 1, inaccurately drawn but recognisable as target figure and correctly placed=1, absent or not recognisable and incorrectly placed =0. Scores for each geometric design are summed to form a total score for each trial (trial total score Theoretical Range: 0-12). Scores for each trial are summed to form a total score (total score Theoretical Range: 0-36), where higher scores represent better visual learning.

7.5.4.6 Reasoning and Problem Solving

Reasoning and problem solving are executive functions that encompass foresight, planning and impulsive control. The reasoning and problem solving domain of the MCCB was measured on the Neuropsychological Assessment Battery (NAB) Mazes.

7.5.4.6.1 Neuropsychological Assessment Battery (NAB) Mazes

Participants are required to complete a series of seven timed mazes, where higher scores are given for faster time to completion on each maze. Scores for each maze are summed to form a total score (total score Theoretical Range: 0-26), with higher scores representing better executive ability.

7.5.4.7 Social Cognition

In the MCCB battery, social cognition is defined as the ability to solve emotional problems and perform tasks involving emotions. The social cognition domain comprises the Mayor-Salovey-Caruso Emotional Intelligence Test (MSCIET): Managing Emotions test.

7.5.4.7.1 Mayor-Salovey-Caruso Emotional Intelligence Test (MSCIET): Managing Emotions

Participants are required to fill in a multiple choice emotional intelligence based questionnaire in which eight scenarios are provided, each followed by a series of related questions, that assess the participant's ability to perform tasks using emotions and solve emotional problems. The questionnaire is scored on a five point Likert scale (1 = very ineffective, 5 = very effective). The eight scenarios form two subscales; *Emotion Management,* comprising five scenarios (score range 20-100) that measure participants' ability to incorporate his or her own emotions into decision making and *Social Management* (score range 9- 45), comprising three scenarios measuring participants' ability to incorporate emotions into decision making about other people. Scores on both subscales are averaged to form a total *Managing Emotions* branch score. For the purposes of this study, the scores were corrected for age and gender. The managing emotions branch is standardised to a mean of 100 and a standard deviation of 15.

7.5.4.8 Executive function

As recommended by the International Society for Bipolar Disorders (ISBD) cognition committee (Yatham et al., 2010), we included two additional measures of executive function (a set of mental processes that integrate and control other cognitive abilities and facilitate

planning, problem solving and self-regulation). They were included to improve the utility of the MCCB cognitive battery to detect deficits in cognitive functioning typically seen in BD.

7.5.4.8.1 Trail Making Test Part B (TMT-B)

Participants are required to alternately and consecutively connect numbers and letters in irregular locations on a sheet of paper whilst being timed to a maximum of 300 seconds. The total score reflects the number of seconds required to complete the task, where lower scores represent better working memory and cognitive switching (Theoretical Range: 0-300)

7.5.4.8.2 The Delis-Kaplan Executive Function System (D-KEFS) Stroop Colour and Word Interference Task

We used the D-KEFS stroop inhibition task in which participants are required to name the ink colour of a word denoting a conflicting colour (i.e., Red, Green, Blue; inhibition condition). The number of seconds to complete the task is taken as the raw condition score. Lower scores represent better interference control (i.e., better inhibition of a pre potent response).

7.5.4.9 Neurocognitive battery scoring

Further details of scoring procedures for each different analysis are presented in Chapters 8, 13, 14 and 15.

7.5.5 *Social cognition battery*

An assessment of theory of mind and a series of facial emotion processing and auditory prosodic emotion processing tasks were used to measure social cognition.

7.5.5.1 Facial emotion processing

Four computerised tasks designed by the author were used to measure facial emotion processing. The face stimuli were taken from the widely used and well validated Ekman and Friesen series known as the Pictures of Facial Affect (POFA: Ekman & Friesen, 1976). The

stimuli comprised black and white photographs of faces free of jewellery, spectacles, make up and facial hair (five female and five male) and expressing the emotions happy, sad, angry, fear and neutral (Figure 2). The faces were cropped to an oval shape spanning the top of the forehead to the bottom of the chin and excluding any hair and the ears on either side of the face. The expressions of each face in the Ekman and Friesen series exhibit emotion at 100% intensity.

Figure 2. Happy, sad, angry, fear and neutral expressions

A morphing program called Fantamorph (Abrosoft, 2012) was used to reduce the intensity of the POFA stimuli's emotional expression by 25% decrements to create static intensity varied stimuli. This resulted in static stimulus expressions at 100%, 75%, 50% and 25% intensity. Pilot testing revealed that emotions presented at 25% intensity elicited floor effects in controls, and they were therefore excluded from the task. The final stimulus set for the latter two tasks comprised static faces displaying 100%, 75% and 50% (high, medium and low) emotional intensity only. The dynamic stimuli were created by morphing the low, medium and high intensity static faces through quick successive frames from a neutral expression (0%) to the final emotional expression (100%), such that they appeared as a moving image (Figure 3).

Figure 3. Low, medium and high intensity angry expression

All tasks were presented on a 14" Lenovo laptop computer and were run through Presentation (Neurobehavioral Systems Inc, 2012), a neurobehavioural program designed to run controlled stimulus delivery experiments for the neurosciences and related fields. Analyses using these tasks are presented in Chapters 9, 13, 14 and 15. They tasks are described in detail below.

7.5.5.1.1 Static facial emotion labelling task

The static facial emotion labelling task was designed to assess participants' ability to identify emotional expressions from static facial stimuli (i.e., a photograph). It required participants to view an image of a male or female face, and identify the emotional expression exhibited by that face. The faces were presented one at a time on a black background for 2000ms followed by an inter-stimulus interval of 1500ms. The task involved 130 randomised trials in total, including ten presentations (i.e., five male, five female) for each of the emotions happy, sad, angry and fear at each of the three levels of emotional intensity (high, medium and low) and ten presentations of neutral. Participants were instructed to press a labelled keyboard button corresponding to the emotion that he/she believed the face was expressing as soon as he/she recognised it. The averaged accuracy percentage and response time for each emotion at each level of intensity was taken as the primary dependent variable. Written instructions, an example and a set of practice trials were provided to participants prior to commencement of the task (Figure 4). The task (including instructions) took approximately nine minutes to complete.

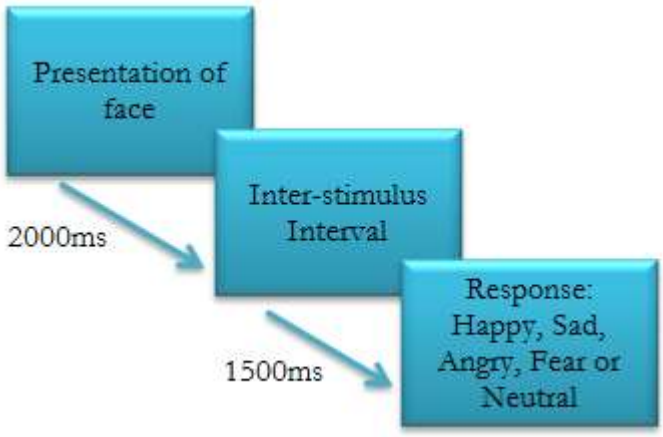

Figure 4. Diagrammatic representation of the static facial emotion labelling task

7.5.5.1.2 Static facial emotion discrimination task

The static facial emotion discrimination task was designed to assess participants' ability to differentiate between static facial emotional expressions at different levels of intensity. It required participants to view two simultaneously presented images of human faces and identify whether the emotion that the two faces were showing were congruent or incongruent. The task represents the emotions happy, sad, angry, fear, and neutral over 135 randomised paired stimulus trials at the three different intensities. Emotional expressions were paired only with those expressing the same level of intensity (i.e., high intensity expressions paired together) or a neutral expression, but never with an emotion of a different expressive intensity. There were 31 incongruent paired trials (representing pairings across the emotions happy, sad, angry, fear and neutral) and 11 congruent paired trials (representing pairings across happy, sad, angry and fear) for each level of intensity, with nine additional trials representing paired neutral expressions that were used as fillers. One face in each pair was presented to the left visual field, and the other was presented to the right visual field on a black background for 2000ms followed by an inter-stimulus interval of 1500ms. Participants were instructed to respond via two button keyboard press (same or different) as soon as he/she could discriminate the emotional expressions. Responses made from 200ms onwards were recorded. The averaged

accuracy percentage and response times across congruent and incongruent trials at each level of intensity was taken as the primary dependent variable for this task. Written instructions, an example and a set of practice trials were provided to participants prior to commencement of the task (Figure 5). The task (including instructions) took approximately nine minutes to complete.

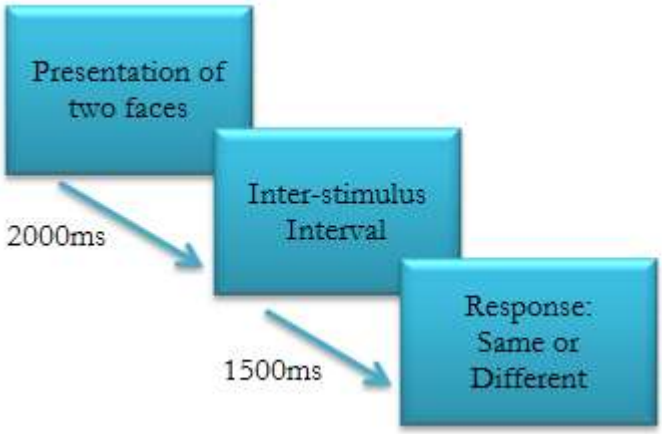

Figure 5. Diagrammatic representation of the static emotion discrimination task

7.5.5.1.3 Dynamic facial emotion labelling task

The dynamic facial emotion labelling task required participants to view dynamic facial images (i.e., morphs) and identify the emotion being expressed. Forty randomised dynamic display trials comprising ten presentations (i.e., five male, five female) each for happy, sad, fear and angry expressions were presented one at a time for 1500ms[7] followed by an inter-stimulus interval of 1500ms. Participants were instructed to press a labelled keyboard button corresponding to the emotion that he/she believed the face was expressing as soon as he/she recognised it. The averaged accuracy percentage for each emotion was taken as the primary dependent variable. Written instructions, an example and a set of practice trials were provided to participants prior to commencement of the task (Figure 6). The task (including

[7] Emotional morphs were trialled at different presentation durations. It was decided that 1500ms was the most realistic timeframe representation of a developing emotional expression and this time frame was used to maintain ecological validity.

instructions) took approximately nine minutes to complete.

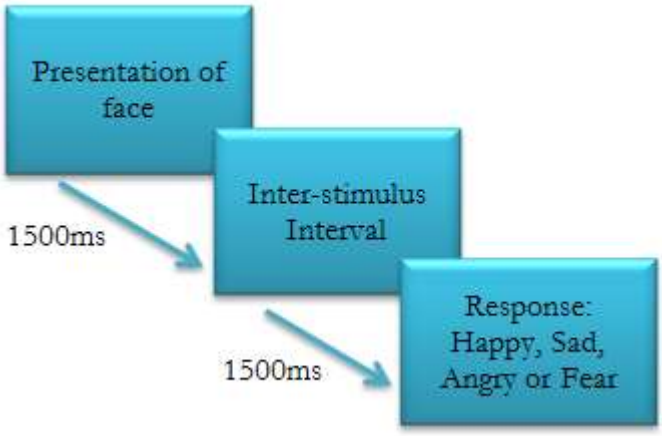

Figure 6. Diagrammatic representation of the dynamic emotion labelling task

7.5.5.1.4 Static identity discrimination task

The static identity discrimination task was used as a control measure to separate out deficits in higher order emotion processing ability from lower order face processing. The task assessed participant's ability to differentiate between two simultaneously presented static facial stimuli to identify whether the two faces had the same identity. The task comprised 55 (45 incongruent and 10 congruent) randomised trials made up of couplings between six male and six female faces displaying neutral expressions only. One face in each pair was presented to the left visual field and the other was presented to the right visual field on a black background for 2000ms followed by an inter-stimulus interval of 1500ms. The task involved 65 randomised trials with the congruent pairs being presented twice. Participants were instructed to respond via two button keyboard press (same or different) as soon as he/she could discriminate the faces. Responses made from 200ms onwards were recorded with the averaged accuracy percentage and response times across congruent and incongruent pairs taken as the dependent variables. Written instructions, an example and a set of practice trials were provided to participants prior to commencement of the task (Figure 7). The task (including instructions) took approximately five minutes to complete.

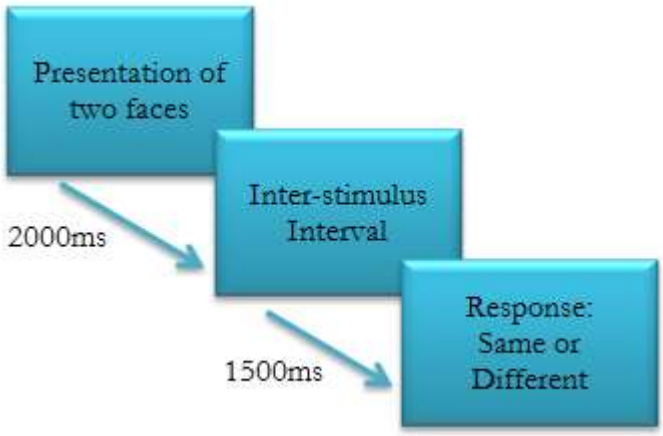

Figure 7. Diagrammatic representation of identity discrimination control task

7.5.5.2 Auditory processing: early acoustic processing and emotional prosody perception

Five computerised tasks originally designed by Groot and Rossell (2008) were used to measure auditory processing. The original tasks were modified by the author to fit with the requirements of the current sample. The auditory-emotion prosodic battery comprised an emotional prosody labelling task, three simple tone discrimination tasks and a linguistic prosody task to assess prosodic emotional processing as well as early acoustic and stress comprehension. The four latter tasks were used as controls for the emotional prosody labelling task. All tasks were presented binaurally via noise reduction headphones on a 14" Lenovo laptop computer and were run through Presentation (Neurobehavioral Systems Inc, 2012). Analyses using these tasks are presented in Chapter 10. They are described in detail below.

7.5.5.2.1 Amplitude discrimination

The amplitude discrimination task was designed to assess participants' ability to differentiate between tone amplitudes (volume). It required participants to listen to a series of paired, sequentially presented tones and decide whether the amplitude of each of the tones was the same or different to each other. The task stimuli comprised 11 tone pairs. In each pair the first tone was always set at 70dB with a base frequency of 1500Hz lasting 150ms in duration.

The second tone followed after a 500ms delay; its amplitude either remain constant or varied in a higher *or* lower direction in increments of 1dB, 2dB, 3dB, 5dB or 10dB (Figure 8). Thus the duration of each pair lasted for 800ms and was followed by an inter-stimulus interval of 3000ms. The stimuli set comprised 144 paired tone trials (120 varying in amplitude and 24 remaining constant) with 24 presentations of the unvarying paired tones and 12 presentations of the varying tones for each incremental dB increase or decrease. Participants were instructed to respond via two button keyboard press (same or different) as soon as he/she could discriminate the tone's amplitude. Responses made from 200ms onwards were recorded. Written instructions, an example and a set of practice trials were provided to participants prior to commencement of the task. The task (including instructions) took approximately 11 minutes to complete.

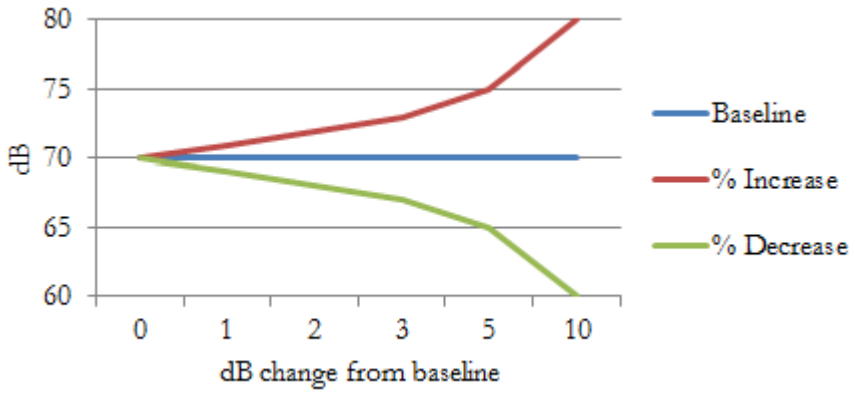

Figure 8. Decibel (dB) stimuli ranges on the amplitude discrimination task

7.5.5.2.2 Duration discrimination

The duration discrimination task was designed to assess participants' ability to differentiate between tone durations (length). It required participants to listen to a series of paired, sequentially presented tones and decide whether the duration of each of the tones was the same or different to each other. The task stimuli comprised 11 tone pairs. In each pair the first tone was always set at 70dB with a base frequency of 1500Hz lasting 150ms in duration. The second tone followed after a 500ms delay; its duration either remained constant or varied

incrementally in increases or decreases of 2%, 5%, 10%, 25%, or 50% (Figure 9). Each tone pair was followed by an inter-stimulus interval of 3000ms. The stimuli set comprised 144 paired tone trials (120 varying in duration and 24 remaining constant) with 24 presentations of the unvarying paired tones and 12 presentations of the varying tones for each incremental % increase or decrease in duration. Participants were instructed to respond via a two button keyboard press (same or different) as soon as he/she could discriminate the tone's duration. Responses made from 200ms onwards were recorded. Written instructions, an example and a set of practice trials were provided to participants prior to commencement of the task. The task (including instructions) took approximately 13 minutes to complete.

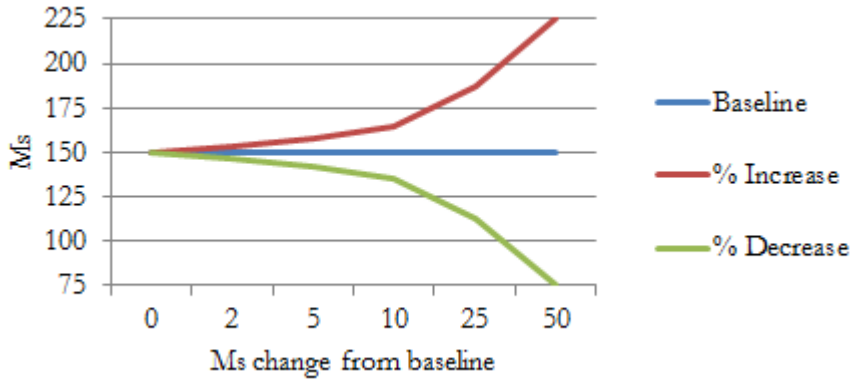

Figure 9. Millisecond (Ms) stimuli range on the duration discrimination task

7.5.5.2.3 Frequency discrimination

The frequency discrimination task was designed to assess one's ability to differentiate between pitch. It required participants to listen to a series of paired, sequentially presented tones and decide whether the frequency of each of the tones was the same or different to each other. The task stimuli comprised 11 tone pairs. In each pair the first tone was always set at 70dB with a base frequency of 1500Hz lasting 150ms in duration. The second tone followed after a 500ms delay; its frequency either remained constant or varied incrementally in increases or decreases of 2%, 5%, 10%, 25%, or 50% (Figure 10). Each tone pair was followed by an inter-stimulus interval of 3000ms. The stimuli set comprised 144 paired tone trials (120

varying in frequency and 24 remaining constant) with 24 presentations of the unvarying paired tones and 12 presentations of the varying tones for each incremental % increase or decrease in frequency. Participants were instructed to respond via a two button keyboard press (same or different) as soon as he/she could discriminate the tone's frequency. Responses made from 200ms onwards were recorded. Written instructions, an example and a set of practice trials were provided to participants prior to commencement of the task. The task (including instructions) took approximately 11 minutes to complete.

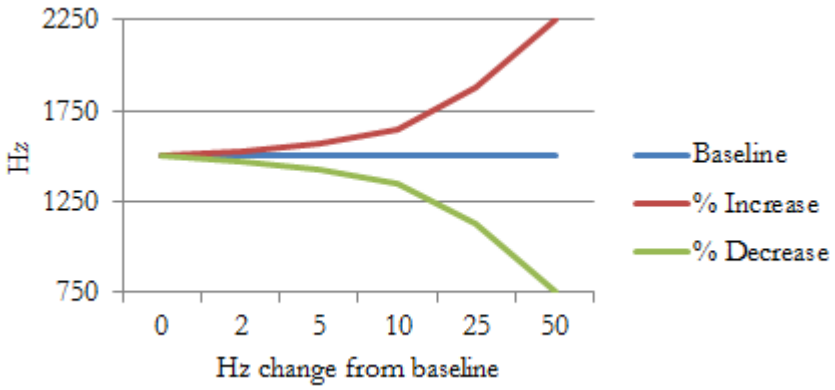

Figure 10. Hertz (Hz) stimuli range on the frequency discrimination task

A diagrammatic representation of the amplitude, duration and frequency discrimination tasks is presented in Figure 11.

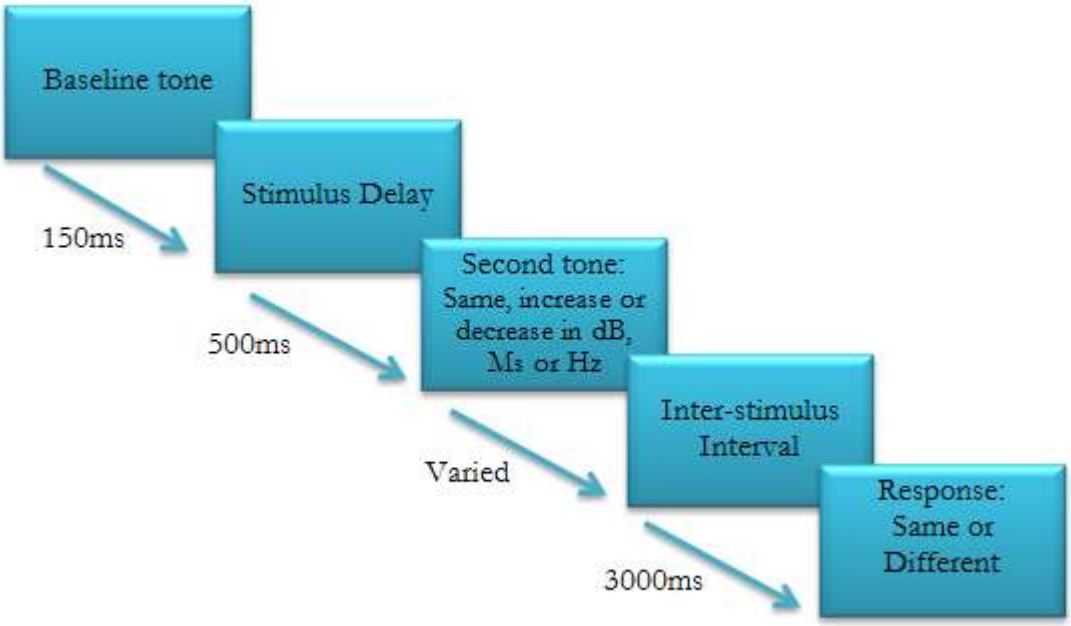

Figure 11. Diagrammatic representation of amplitude, duration and frequency discrimination tasks

7.5.5.2.4 Linguistic prosody task

The linguistic prosody task was designed to assess participants' ability to comprehend non-emotional propositional stress used to alter semantic meaning. It required participants to listen to semantically neutral sentences and identify whether each sentence was inquisitive or declarative in nature (i.e., question or statement "I've finished my lunch? *or* I've finished my lunch!"). The task comprised 48 trials involving 24 presentations of inquisitive and 24 presentations of declarative sentences. Each trial lasted 4500ms (sentence length was approximately 3000ms on average, followed by an inter-stimulus interval of 1500ms). Participants were instructed to respond via two button keyboard press (*question* or *statement*) as soon as he/she could discriminate the sentence stress (Figure 12). Responses made from 200ms onwards were recorded. Written instructions, an example and a set of practice trials were provided to participants prior to commencement of the task. The task (including instructions) took approximately five minutes to complete.

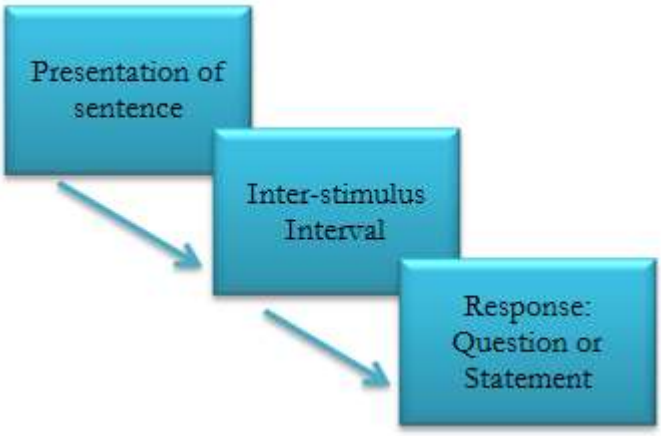

Figure 12. Diagrammatic representation of linguistic prosody labelling task

7.5.5.2.5 Emotional prosody labelling task

The emotional prosody labelling task was designed to assess participants' ability to recognise emotions from prosodic expressions. It required participants to listen to emotionally neutral sentences ("the windows are made of glass") and identify the emotional tone with which each sentence was spoken. The sentences were spoken by four actors (two males and two females) who were directed to express each of four emotional tones (happy, sad, fear and neutral). The sentences were matched for length.

The task comprised 88 trials involving 22 presentations each for happy, sad, fear and neutral emotions. Each trial lasted 4500ms. Participants were instructed to press a labelled keyboard button corresponding to the emotion that he/she believed was being expressed as soon as he/she recognised it. Responses made from 200ms onwards were recorded. Written instructions, an example and a set of practice trials were provided to participants prior to commencement of the task (Figure 13). The task (including instructions) took approximately eight minutes to complete.

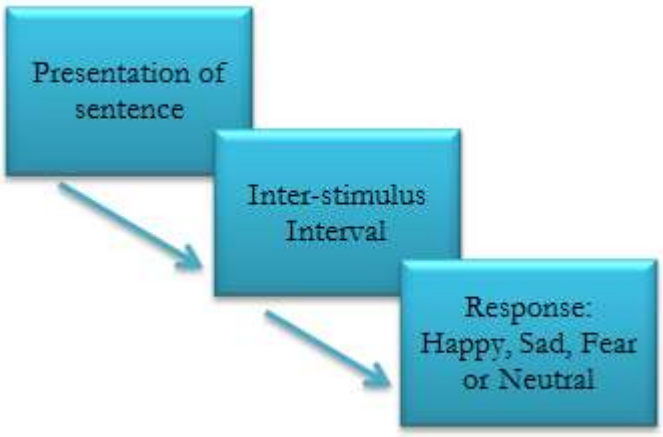

Figure 13. Diagrammatic representation of emotional prosody labelling task

7.5.5.3 Auditory and emotional prosody processing scoring

Measures of response accuracy were recorded by the computer and the averaged accuracy percentage was taken as the dependent variable for the emotional prosody labelling task. Signal detection theory was employed to calculate *d'* prime scores for each level of amplitude, duration or pitch change on the tone discrimination tasks, and for each utterance type (inquisitive or declarative) on the linguistic task. *d'* prime is an estimate of perceptual sensitivity that takes into account information bearing response patterns (signals) in light of random responses (noise) on tasks with a two choice response format. Higher *d'* prime scores indicate greater signal receptivity, with scores of zero to three generally accepted as measures of increasing task difficulty (Stanislaw & Todorov, 1999).[8]

7.5.5.4 Theory of mind

The ability to mentalise about another's thoughts and feelings was measured using the *Picture Sequencing Task* (Langdon & Coltheart, 1999). The task requires participants to logically sequence a series of 16 stories that have different primary contentions. Four of the stories are classed as *Mechanical*; stories depicting cause and effect and requiring participants to reason

[8] To avoid the problem of infinite values or division by zero when calculating *d'* prime, we used the formula 1/ (2N).

about causal relationships, four are classed as *Social Script*: stories depicting everyday social situations and requiring participants to reason logically using social script knowledge, four are classed as *Capture*; stories containing a decoy cue intentionally designed to mislead participants and requiring them to inhibit salient inappropriate information to determine a logical sequence, and four are classed as *False Belief*; stories depicting the misinformed actions of a story character that is entirely unaware of an occurrence in the story. This type of story requires participants to infer false beliefs. As the mechanical, social script and capture tasks do not require participants to make mental inferences about another's thoughts and feelings, they are considered to be control tasks. Participants begin with two practice stories and then arrange the four story card stimuli for each story in each story type. Each of the story cards depict a different black and white scene from the story. They are initially placed face down on a table in a prearranged order to maintain consistency, after which participants are prompted to flip them over and arrange them as quickly as possible, into a logical story sequence. Participants are timed whilst sequencing each story and points are given for the correct location of a story card. The first (card 1) and last (card 4) correct card in a sequence receives a score of two, whilst the correct location of each of the interim (card 2 and 3) cards receive a score of one. These scores are averaged to form a total for each sequence (Theoretical Range: 0-6). The scores in each sequence within a story type are averaged to form a total story type score (Theoretical Range: 0-24). Higher scores represent better ability to carry out a given tasks demands. Analyses using this task are presented in Chapters 11, 14 and 15.

7.5.6 *Emotion regulation*

The self-report measure used to assess emotion regulation is described below. Analyses using this measure presented in Chapters 12, 13, 14 and 15.

7.5.6.1 Multiple dimensions of emotion regulation

Emotion regulation was measured with the 36 item *Difficulties in Emotion Regulation Scale* (DERS: Gratz & Roemer, 2004) that assesses ways that emotions are experienced, approached and processed. The DERS is scored on a five point Likert scale ranging from Almost Never (1) to Almost Always (5). It comprises six subscales made up of items reflecting non-

acceptance of emotional responses (Theoretical Range: 6-30); difficulties engaging in goal directed behaviours when experiencing negative emotions (Theoretical Range: 5-25); difficulties in impulse control (Theoretical Range: 6-30); lack of emotional awareness (Theoretical Range: 6-30); limited access to emotion regulation strategies (Theoretical Range: 8-40) and lack of emotional clarity (Theoretical Range: 5- 25). Scores on each subscale are summed to form an aggregate total score (Theoretical Range: 36-180) with higher scores representing greater difficulties in each dimension of emotion regulation or overall. The DERS shows good validity, internal consistency (Cronbach's $\alpha = .93$) and test- retest reliability ($\varrho = .88$).

7.5.7 *Psychosocial functioning battery*

7.5.7.1 Objective global functioning

Objective global psychosocial functioning was measured with the Global Assessment of Functioning Scale (GAF). The GAF is an administrator rated scale that takes into account one's current occupational, psychological and social circumstances on the basis of a clinical interview. It forms Axis V of the multi-axial system of DSM-IV-TR (American Psychiatric Association, 2000). A score is generated based upon judgement of symptom severity or level of functioning, whichever is worse. The GAF is rated on a scale ranging between 0-100, with higher scores representing better functioning. The GAF was scored by the author, a trained administrator.

7.5.7.2 Subjective quality of life

Subjective psychosocial functioning was assessed with the disorder specific *Quality of Life in Bipolar Disorder* questionnaire (Qol.BD: Michalak, Murray, & Crest.Bd, 2010). The Qol.BD is a 48-item self-report questionnaire that requires participants to rate the range of experiences, behaviours and feelings related to quality of life that he/she has experienced over the past seven days. The scale is rated on a five point Likert scale ranging from Strongly Disagree (1) to Strongly Agree (5) with items making up subscales reflective of core quality of life domains including physical, sleep, mood, cognition, leisure, social, spirituality, finances,

self-esteem, independence and identity. There are four items per subscale that include items such as "had plenty of energy" - physical scale and "felt emotionally balanced" - mood scale. Two additional and optional subscales, comprising four items each and reflecting work and educational activities are included. The authors of the questionnaire present data suggesting that the QOL.BD is a sensitive measure of quality of life impairments that can be used across BD subtypes and phases to provide assessment over and above symptom scores. The QoL.BD demonstrates good relationships with other measures of quality of life and is highly reliable (Cronbach α's ranging from .79-.93 for all scales). Individual subscale scores are formed by summing individual item scores in each subscale. A total Qol.BD score is generated by summing responses on the first 48 items of the scale (Theoretical Range: 48-240) where higher scores represent better quality of life.

7.6 Procedure

Persons expressing interest in the study were contacted by telephone and briefly explained the details of the study. Those that met criteria and agreed to participate were sent an information pack containing the study information and consent form. The person received this at least 48 hours prior to attending their first testing session to ensure they had enough time to carefully consider the provided information and withdraw if necessary. A questionnaire was sent out to them in the information pack. They were instructed to complete and return the questionnaire at the start of the first testing session, and that their return of the completed questionnaire would be taken as consent for that aspect of the study. The questionnaire comprised a serious of demographic questions, including those related to; education, employment, marital status, living arrangements, accommodation, alcohol consumption, substance use, medical information and medication, psychiatric information and family history in addition to the QoL.BD.

On the day of the first session, participants were met at the reception of MAPrc and escorted to a small, private testing room. The room was quiet and held only a desk, two chairs and the materials needed for the testing session. A complete description of the study was provided to participants and they were given the opportunity to ask any questions. Written

consent was then obtained and participants were instructed that they were free to withdraw their consent at any time. They were also instructed to alert the researcher at any time if they needed a break. To ensure confidentiality, participants were assigned a unique code that was used to label all subsequent hard and softcopy data. This data was kept in a locked cabinet or password protected computer file, accessible only to those directly associated with the project. The administration of all tests was completed by the author.

The first session involved the completion of a behavioural task battery of cognitive and emotion processing tests, followed by a small donation of blood. This session took approximately 3.5 – 4 hours to complete. Some of the tests were paper and pencil in nature and generated written or oral answers, whereas others were computer based and generated softcopy data. These tasks were presented on a 14" Lenovo laptop computer screen, with participants seated directly in front at a distance of approximately 60cm. Participants used a labelled keyboard or mouse button to respond during these tasks.

Participants undertook tasks in the following order; amplitude discrimination, linguistic prosody labelling, static facial emotion labelling, static face emotion discrimination, dynamic face emotion labelling, identity matching, MSCIET, WTAR, the Stroop task, TMT-A, TMT-B, BACS symbol coding, HVLT-R, WMS-III spatial span, LNS, Mazes, BVMT-R, HVLT-R delayed recall, HVLT-R delayed recognition, Category fluency-animal naming, duration discrimination, prosodic emotion labelling, blood sample donation.

In general, participants returned for the second session no more than three days after the first. Upon their return participants were again met at the reception of MAPrc and escorted to the same or similar small, private testing room. The second session involved the completion of the remaining behavioural task battery of cognitive and emotion processing tests, as well as the completion of a clinical interview. The second session took approximately 3.5 – 4 hours to complete. Again, some of the tests were paper and pencil in nature and generated written or oral answers, whereas others were computer based and generated softcopy data. These tests used the same 14" Lenovo laptop computer screen, seating and responding conventions as used in the first session. Participants undertook tasks in the following order; pitch discrimination task, Picture Sequencing Task, the CPT and the DERS. Participants then completed the clinical interview comprising the MINI, MADRS, YMRS and

were asked questions in related to their general level of functioning for the author to complete a GAF score for them.

CHAPTER 8: NEUROCOGNITION IN BIPOLAR DISORDER

8.1 Chapter guide

Van Rheenen, T. E., & Rossell, S. L. (online, 2013). An empirical evaluation of the MATRICS Consensus Cognitive Battery in Bipolar Disorder. *Bipolar Disorders,* DOI: 10.1111/bdi.12134.

Chapter 2 provided an overview of neurocognitive deficits in bipolar disorder (BD), and indicated that many different measures have been used to assess these deficits in the past. Certainly, a standardised battery would assist in the integration of neurocognitive findings across samples and disorders, and thus the aim of the investigation described in this chapter was to establish the neurocognitive profile of the sample of BD patients recruited as part of this research, using in part, a consensus based cognitive battery that was initially developed to assess neurocognition in schizophrenia. This chapter is the first of the empirical chapters of this thesis and comprises the aforementioned article that can be found in its published form in Appendix G.

8.2 Abstract

Objectives: There is a large body of evidence to indicate that neurocognitive impairments in bipolar disorder (BD) may represent viable endophenotypes; however, a standard consensus based battery of cognitive tests used to measure them is yet to appear. There is potential for a neurocognitive battery developed for use in related disorder schizophrenia, called the MATRICS Consensus Cognitive Battery (MCCB: Nuechterlein, et al., 2008), to provide a consistent measurement tool with a standard to which the cognitive capacity of BD can be compared to other disorders. However, its suitability for capturing neurocognitive impairment in BD cohorts is not well established. Moreover, neurocognitive tests recently recommended by the International Society for Bipolar Disorder (ISBD) for inclusion in a consensus neurocognitive battery for BD have not been evaluated in the context of the MCCB. An evaluation of i) the clinical efficacy of the MCCB and ii) the tests recommended by the ISBD in a BD cohort were the aims of the current study.

*Methods:*50 BD patients (Age M = 38) and 52 healthy controls (Age M =34) completed all of the MCCB subtests, in addition to the well-recognised Trail Making Test-Part B and the Colour-Word Stroop.

Results: Multivariate analyses of variance of the MCCB domains revealed a significant group effect for overall cognition, and significantly reduced patient performance on speed of processing, working memory, visual learning and verbal learning. A second multivariate analysis of variance using a newly created composite score called 'executive function', comprising scores on an existing MCCB subtest in addition to TMT-B and Colour-Word Stroop, revealed significant differences on this domain as well. Subgroup analysis indicated that there were no differences in any domain score performance between symptomatic and euthymic patients, or BD I and BD II patients groups.

Conclusions: Our findings suggest that the MCCB and two additionally recommended ISBD executive function measures form a promising consensus based research tool for examining neurocognition in BD.

8.3 Introduction

Neurocognitive impairment is a stable phenomenological feature of bipolar disorder (BD). Despite a large body of research indicating deficits across several core cognitive domains including learning, memory and executive functions, there is no unanimous cognitive battery for use in clinical BD research (e.g., Bora, et al., 2009a; Ferrier, et al., 1999; Gogos, Joshua, & Rossell, 2010; Robinson, et al., 2006). The disorder has a strong genetic component, and there is a growing research interest in examining cognition as an endophenotypic marker for clarifying links between its genetic and phenotypic variability. This indicates the importance of such a battery in facilitating consistent comparison across samples, time and genetically related disorders (i.e., schizophrenia).

Over recent years, a Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) taskforce has developed a valid and reliable consensus based neurocognitive measurement tool called the MATRICS Consensus Cognitive Battery (MCCB). This battery has proven utility as a sensitive measure of neurocognitive impairment in schizophrenia samples, but despite its potential for providing a standard to which the cognitive capacity of other disorders can be compared, its suitability for capturing neurocognitive impairment in BD cohorts is not well established(August, Kiwanuka, McMahon, & Gold, 2012; Kern et al., 2011).

Recently, a newly formed cognition taskforce commissioned by the International Society for Bipolar Disorders (ISBD) conducted an extensive literature review to determine the most sensitive and relevant cognitive measures for use in BD research. Following review, the committee endorsed the applicability of the majority of MCCB subtests for use in BD, with further recommendations made for the inclusion of additional executive function tests (core: Colour-Word Stroop and the Trail Making Test-Part B [TMT-B]; optional: the Wisconsin Card Sorting Task), and the substitution of verbal learning measures (the California Verbal Learning Test [CVLT] in place of the Hopkins Verbal Learning Test-Revised [HVLT]) that form the ISBD-Battery for the Assessment of Neurocognition (ISBD-BANC). The two core executive measures have particular utility for indexing executive impairment in the disorder and may also reference genetic liability (Arts, et al., 2008; Bora, et al., 2009a; Zalla, et al., 2004)

To our knowledge, there is only one study that has systematically evaluated the MCCB in a BD sample; Burdick and colleagues (2011) examined its utility for detecting impairments in patients with BD I. The authors reported impaired patient/control performance for processing speed, attention/vigilance, working memory, verbal learning and visual learning domains, in addition to the composite score. A limitation however, concerned the lack of task based analysis on the MCCB domains comprised of more than one measure, making it impossible to infer the primary driver of group differences on these domains. Hence, sufficient justification for the use of certain measures in a BD specific battery cannot be made on the basis of these findings alone. Moreover, the absence of significant group effects for the domain of reasoning and problem solving indicates that the subtest used to assess it (Neuropsychological Assessment Battery: Mazes) may be an insufficient means of accurately representing the executive impairments present in BD. This fits with the ISBD cognition committee's directions to include additional executive measures with proven utility for indexing impairment in the disorder into the battery.

With this in mind the objectives for this study were twofold; first, we aimed to expand on Burdick et al.'s research by examining the clinical efficacy of the MCCB in a BD cohort. Second, we aimed to evaluate the tests recommended by the ISBD by examining performance on subtests from the MCCB that are part of the ISBD-BANC, as well as on two additional ISBD recommended core measures of executive function that were not used by Burdick et al. Therefore, we administered the MCCB in addition to the ISBD recommended Colour-Word Stroop and the TMT-B, to a sample of BD I and II patients. However, to remain consistent with Burdick et al we chose not to substitute the HVLT-R for the ISBD recommended CVLT as a measure of verbal learning. Further, in the interests of time and to reduce patient load, we also did not include the ISBD recommended but optional Wisconsin Card Sorting Task. Given that both of the additional measures of executive function included in this study assess overlapping inhibitory and switching behaviours, we calculated a new domain score including these executive measures with the current reasoning and problem solving subtest. In keeping with results reported by these authors, we predicted that the BD group would show impairments on all MCCB domains but social cognition and reasoning and problem solving.

We also predicted the BD group would show impairment on the new measure of executive function.

8.4 Methods

This study was approved by the Alfred Hospital and Swinburne University Human Ethics Review Boards and abided by the Declaration of Helsinki. Written informed consent was obtained from each participant before the study began.

8.4.1 *Participants*

The clinical sample comprised 50 patients (16 male, 34 female) diagnosed as having DSM-IV-TR BD using the Mini International Neuropsychiatric Interview (MINI: Sheehan, et al., 1998). Patients were recruited via community support groups and general advertisements and were all out-patients. Current mood symptomology was assessed (by the author) using the Young Mania Rating Scale (YMRS: Young, et al., 1978) and the Montgomery Asberg Depression Rating Scale (MADRS: Montgomery & Asberg, 1979). Patients with significant visual or verbal impairments, neurological disorder and/or a history of substance/alcohol abuse or dependence during the past six months were excluded.

A control sample of 52 healthy participants (20 male, 32 female) were recruited for comparison purposes by general advertisement and contacts of the authors. Using the MINI screen, no control participant had a current diagnosis or previous history of psychiatric illness (Axis I). An immediate family history of mood and psychiatric disorder in addition to a personal history of neurological disorder, current or previous alcohol/substance dependence or abuse, visual impairments and current psychiatric medication use was exclusion criteria for all controls.

All participants were fluent in English, were between the ages of 18 and 65 years and had an estimated pre-morbid IQ as scored by the Wechsler Test Of Adult Reading (WTAR) of >90. Demographic and clinical characteristics are presented in Table 5.

8.4.2 *Measures*

The MATRICS Consensus Cognitive Battery (MCCB; see Nuechterlein & Green, 2006 for task instructions and methods) was used as a brief assessment of cognitive functioning across the domains of speed of processing (Trail Making Test Part A: TMT-A, Brief Assessment of Cognition in Schizophrenia; Symbol Coding: BACS-SC, Category Fluency: Animal naming), attention/vigilance (Continuous Performance Test-Identical Pairs: CPT), working memory (Wechsler Memory Scale; Spatial Span: WMS-SS, Letter Number Span: LNS), verbal learning (Hopkins Verbal Learning Test Revised: HVLT-R), visual learning (Brief Visuospatial Memory Test-Revised: BVMT-R), reasoning and problem solving (Neuropsychological Assessment Battery: Mazes: NAB Mazes) and social cognition (Mayer-Salovey-Caruso Emotional Intelligence Test; Managing Emotions: MSCIET). The MCCB shows good test-retest reliability (scores ranging from $r = .69$ to $r = .85$), practicality and tolerability (Nuechterlein, et al., 2008). To fit with ISBD recommendations, the Trail Making Test-Part B and the Colour-Word Stroop were also included (see Delis, Kaplan, & Kramer, 2001; Reitan & Wolfson, 1985 for task instructions and methods). These, coupled with the NAB Mazes, formed an executive function domain score. The collective battery took approximately 60-90 minutes to administer.

Table 5. *Demographic and clinical characteristics of the sample*

Group	Control		BD		Group comparisons^		Symptomatic		Euthymic		Group comparisons^	
	M	***SD***	***M***	***SD***	***F***	***p***	***M***	***SD***	***M***	***SD***	***F***	***p***
N	52		50				33		17			
Gender (M/F)	20/32		16/34		χ^2=.47	.50	11/22		5/12		χ^2=.08	.78
Age	34.00	14.27	38.44	13.02	2.71	.10	36.48	11.88	42.24	14.63	2.24	.14
WTAR	111.64	7.24	109.40	12.06	1.30	.40	108.76	12.79	110.64	10.75	.27	.60
Age of onset (years)	-	-	21.36	10.07	-	-	21.41	9.65	21.14	11.54	.01	.94
Age of diagnosis (years)	-	-	28.00	10.75	-	-	27.5	9.22	29.31	13.80	0.29	.59
Illness duration (years)	-	-	14.00	9.61	-	-	13.29	9.81	15.13	9.71	0.37	.55
YMRS	-	-	6.22	5.47	-	-	8.51	5.35	1.76	1.56	25.64	.001
MADRS	-	-	11.82	10.02	-	-	16.42	9.28	2.88	2.54	34.53	.001

Note: ^ Group comparisons all one-way ANOVA except gender which was Chi square; M/F = Male / Female, WTAR = Wechsler Test of Adult Intelligence, YMRS = Young Mania Rating Scale (Theoretical Range: 0-60), MADRS = Montgomery Asberg Depression Rating Scale (Theoretical Range: 0-60)

8.4.3 *Statistical Analysis*

Given that that we included two additional measures to the MCCB battery and that our sample was Australian and well matched on key demographic variables (i.e., gender and premorbid IQ), we chose not to use the published norms from the MCCB reference group. Instead we calculated Z scores based on our own healthy control sample's means and standard deviations. This was in keeping with the methods of Burdick et al. On domains that comprised more than one measure, we created composites from the raw test scores and standardised them; scores with inconsistent metrics were reversed to ensure that all scores represented the same metric (i.e., higher scores reflected better performance).[9] We used the same method to create an additional domain score, standardised using the composite of the two newly included measures and the NAB Mazes subtest. Although we chose to use our own healthy control sample as a comparison, we have reported the age and gender corrected T scores based on the MCCB normative group for comparison purposes with other studies that do choose to use this data (see Table 6). We used our own healthy control data for all other analyses. Demographic and clinical group differences were assessed via one-way between-groups analysis of variance. Due to a subsequently observed trend level difference in age between groups, we incorporated age as a covariate into our primary, secondary analyses and subgroup analysis; multivariate analyses of co-variance were run to investigate group differences on the MCCB itself (aim one), on the MCCB and the additional executive function tests (aim two), and to follow up task performance on significant multi-test domain scores. A conservative α of .01 was always set to correct for multiple testing. Subgroup analyses comparing symptomatic (n=33) and euthymic patients (n=17, defined as those that met strict criteria for YMRS and MADRS scores $\leq$ 8) and diagnostic subtypes (BD I n=38 versus BD II n=12) were run using the same method. Multivariate analyses of variance were also conducted to examine the influence of current medications on performance for patients on and off

[9] The speed of processing comprised a standardised composite of the TMT-A, BACS-SC and Category Fluency subtests. The working memory domain comprised a standardised composite of the WMS-SS and the LNS. The executive function domain comprised a standardised composite of the Stroop, the TMT-B and the NAB-Mazes.

medications. Bivariate correlations with correction for multiple testing set at an α of .01 were conducted to examine the relationship between performance and symptom severity on the YMRS and MADRS.

Table 6. *Control and BD patient MCCB performance using the age and gender corrected MCCB normative data (M = 50, SD = 10)**

	Control		BD		Group Comparisons	
	M	***SD***	***M***	***SD***	***F***	***p***
Speed of processing	53.87	12.11	49.56	9.91	3.85	.05
Attention/Vigilance	44.94	9.94	45.81	9.49	.20	.65
Working Memory	52.78	10.87	48.35	11.86	3.82	.05
Verbal Learning	49.81	11.96	46.27	9.59	2.67	.11
Visual Learning	53.51	11.98	49.37	10.97	3.24	.08
Social Cognition	42.06	13.95	43.78	11.29	.46	.50
Reasoning and Problem Solving	44.34	15.49	44.59	14.46	.01	.93
Overall Composite	49.13	10.79	44.92	11.08	3.67	.06

*This data is presented for descriptive purposes and as a means of comparison with other studies that choose to use age and gender corrected MCCB normative scores. It has not been used in the analyses presented in the current paper

8.5 Results

There was no significant difference in gender, education level completed or pre-morbid IQ (as scored by the WTAR) between the two groups.

8.5.1 *MCCB domain and task analysis*

Multivariate analyses of co-variance with the MCCB domain scores revealed a significant group effect for cognitive domain performance overall (F (7, 90) = 2.47 p<.05, *Wilk's Λ* = .84) and significantly reduced patient performance on the speed of processing, working memory, verbal learning and visual learning domains. After correction for multiple testing only differences in speed of processing (F (1, 96) = 7.33, p<.01), working memory (F (1, 96) = 9.78, p<.01) and visual learning (F (1, 96) = 8.19, p<.01) remained significant. Post hoc analysis of the non-corrected significant multi-test domains using multivariate analysis of

covariance revealed a significant overall effect (F (5, 93) = .3.68, p<.01, *Wilk's Λ* = .83) and significant patient/control differences in performance on the BACS-SC (F(1,97) = 14.57, p<.01), WMS-SS tasks (F(1,97) = 11.70, p<.01) and the LNS (F(1,97)=4.01, p=.05). The LNS did not survive correction for multiple testing.

8.5.2 *Domain and task analysis of the ISBD recommended tests*

A second multivariate analysis of co-variance was conducted to examine performance on the ISBD recommended tests from the MCCB and two additional measures of executive function; we included the newly created executive functioning domain score, comprised of performance on the TMT-B, the Colour-Word Stroop and the NAB Mazes subtests. This MANCOVA revealed a trend for a group effect for cognitive domain performance overall (F (7,87) = 1.86, p<.09) and significantly reduced patient performance on the speed of processing, working memory, visual learning and executive function domains with a trend for verbal learning (Figure 14). Only working memory and visual learning survived correction for multiple testing. Post hoc multivariate analysis of co-variance for the executive function domain revealed a trend for reduced overall performance across the three subtests (F (3,92)=2.10, p=.11) and significantly worse patient group performance on the TMT-B (F(1,94)= 5.40, p<.05) although this did not survive correction. Figure 15 presents the Z scores for all tasks used in the battery.

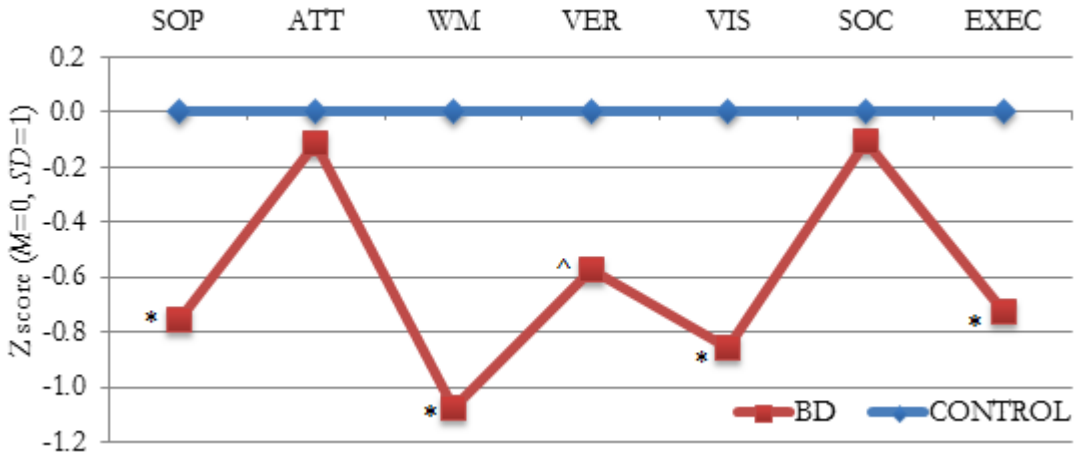

Figure 14. Domain performance in BD patients relative to controls on the ISBD recommended tests

Note: * $p<.05$; ^indicates a trend at $p<.06$; SOP = Speed of processing, ATT = Attention/vigilance, WM = Working memory, VER = Verbal learning, VIS = Visual learning, SOC = Social cognition, EXEC = Executive function

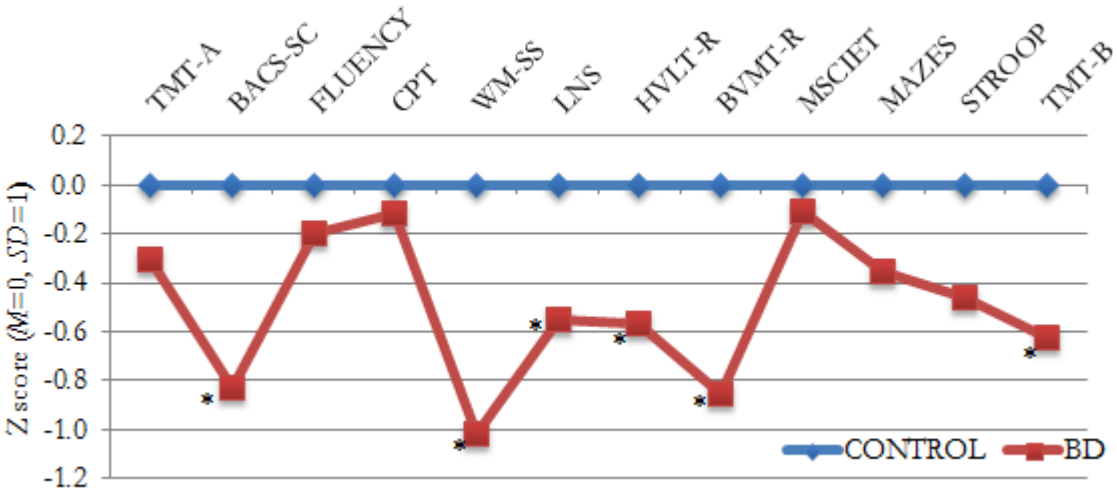

Figure 15. Subtest performance in BD patients relative to controls on the ISBD recommended tests

Note: * p<.05; TMT-A=Trail Making Test-Part A, BACS-SC=Brief Assessment of Cognition in Schizophrenia-Symbol Coding, Fluency=Category Fluency: Animal Naming, CPT=Continuous Performance Task Identical Pairs, WMS-SS= Working memory Spatial Span, LNS= Letter Number Span, HVLT-R = Hopkins Verbal Learning Test - Revised, BVMT-R=Brief Visuospatial Memory Test-Revised, MSCIET=Mayor-Salovey-Caruso Emotional Intelligence Test, Stroop=Colour-Word Stroop, TMT-B=Trail Making Test-Part B

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8.5.3 *Subgroup analyses – ISBD recommended tests*

To better understand the effects of mood on cognition in our patient sample, we conducted subgroup analyses comparing euthymic patients to symptomatic patients in two multivariate analyses of covariance controlling for age. Results indicated that symptomatic and euthymic patients did not differ from each other on any of the domains or tasks (all p's >.05). Further bivariate correlations supported this, indicating no associations between any of the domains and scores on the MADRS and YMRS in the entire patient group (all p's >.05). We also sought to better understand potential differences between diagnostic subtypes using the same method to compare patients with a diagnosis of BD I compared to BD II. When age was controlled, the results revealed no significant differences between diagnostic groups on

any of the domains or tasks (all *p*'s >.05). Multivariate analyses using medication (dichotomously coded to yes/no) as the between subjects factor revealed no significant difference on any of the domain scores for patients on or off antipsychotics/anticonvulsants (F (7, 36) = 1.03, p = .43), antidepressants (F (7, 36) = .81, p = .59), lithium (F (7, 36) = 1.91, p =.10) and benzodiazepines (F (7, 36) = 1.71, p=1.39).

8.6 Discussion

The current study was designed to evaluate the MCCB for use in BD, and to evaluate cognitive tests recommended by the ISBD from the MCCB in the context of an additional two measures of executive function, in a cohort of BD I and II patients. Two well matched demographic groups were compared. Statistically significant patient/control differences were evident on three domains of the MCCB battery, with the BD group demonstrating impaired working memory, visual learning and processing speed (effect sizes ranging from just under 0.8 to just over one standard deviation below the control mean). Further examination of the significant MCCB multi task domains indicated that the primary drivers of group effects on speed of processing and working memory domains were performance differences on the BACS-SC (SOP) and WMS-SS (WM) subtests only, although a trend was evident on the LNS (WM).

When we re-ran the domain analysis with the inclusion of the two executive measures recommended by the ISBD, we found a trend for executive functioning to be impaired in the patient group. This was primarily driven by performance on the TMT-B, suggesting that it added sufficient data to overcome the normal performance on the MCCB reasoning and problem solving domain.

Interestingly, although most effect sizes for these impairments were within similar range to those reported by Burdick et al.(2011), we failed to find a significant difference on the attention domain as they did. This is unlikely to be attributable to sample differences for demographic or mood variables given that age, gender, and the mean severity ratings for both mania and depression were fairly consistent across the two studies. We also observed only a

trend level reduction in patient performance for verbal learning. Although the size of our effect was consistent with that reported by Burdick et al, their sample was substantially larger than ours and it is certainly possible that the difference in results is partially attributable to power restrictions in our study. Nevertheless, given that there is consistent evidence of verbal learning impairment in persons with BD, and that the effect size observed in both ours and Burdick's studies are somewhat smaller than those evidenced in large scale meta-analyses of cognitive functioning in the disorder, it seems likely that that the HVLT-R subtest is insufficient for identifying subtle verbal learning impairment in persons with the disorder (Arts, et al., 2008; Bora, et al., 2009a; Martinez-Aran, et al., 2004b; Torrent, et al., 2006; Zubieta, et al., 2001). We therefore recommend the inclusion of the slightly more challenging and well-studied California Verbal Learning Test to the battery, which is a flexible measure of verbal learning originally recommended as a substitute for the HVLT-R by the ISBD cognition committee(Yatham, et al., 2010).

The absence of significant patient impairment on the reasoning/problem solving and social cognition domains in the current study, coupled with Burdick et al.'s reports of only trend level patient impairment on these domains suggests that subtests, the NAB Mazes and the MSCIET, are insufficient for detecting executive and social cognitive impairment in BD. Both tasks have not been well researched in the disorder, thus there is insufficient evidence for their utility in this cohort. Instead, the TMT-B appears to demonstrate greater sensitivity to executive impairment (Bora, et al., 2009a). Measures of facial emotion processing and/or theory of mind ability may also be more suitable for the examination of social cognition in BD, given that there is growing evidence for their sensitivity to BD impairment (Addington & Addington, 1998; Bora, et al., 2005; Getz, et al., 2003; Lembke & Ketter, 2002; Montag et al., 2010; Rossell & Van Rheenen, 2013; Summers, et al., 2006). We recommend that these be included in future studies using this battery.

Importantly, neither symptomatic status, nor diagnostic subtype appeared to have any influence on the results. This supports a large body of research indicating that cognitive impairment in BD is a relatively stable and enduring trait evidenced across both diagnostic subtypes (Bora, Yücel, Pantelis, & Berk, 2011; Goswami, et al., 2006; Torrent, et al., 2006;

Zubieta, et al., 2001). Unfortunately as the size of our euthymic and BD II subgroups were relatively small, these results should be interpreted with caution. Moreover, although dichotomously coded medication effects were not evident when comparing patients on and off classes of psychotropic medication, it was not possible to partial out all effects of medication, and this may have had a confounding effect on our results. Future studies will do well to explicitly recruit larger groups of patients across the major mood phases and who meet distinct criteria for BD I and II, both on and off psychotropic medication, in the interests of a more powerful and controlled examination of this battery.

The current study has demonstrated the efficacy of the MCCB for cognition research in BD, although the ISBD recommended additional measures of executive function may represent tests of necessary incorporation into the battery. Importantly, a uniform battery can facilitate the search for cognitive endophenotypes by permitting more accurate comparison and synthesis of cognitive findings across study samples. Our findings suggest that the BACS-SC, WMS-SS and BVMT-R from the MCCB processing speed, working memory and visual learning domains adequately measure impairments in BD. The inclusion of the TMT-B is also efficacious, given its sensitivity to executive impairments in our sample. Notably, there is evidence to indicate that this task is genetically influenced (Bora, et al., 2009a; Glahn et al., 2010) and further use of it in BD studies may establish it as cognitive endophenotype.

In sum, our findings suggest that the MCCB and the additionally recommended ISBD executive function measures form a promising consensus based research tool; however, further study is needed to assess utility for assessing attention/vigilance, reasoning and problem solving, verbal learning and cognition in larger and more defined samples.

CHAPTER 9: FACIAL EMOTION PROCESSING IN BIPOLAR DISORDER

9.1 Chapter guide

Van Rheenen, T. E., & Rossell, S. L. (in submission). Let's face it: facial emotion processing is impaired in bipolar disorder.[10]

This chapter is the second of the empirical chapters in this thesis. It comprises the aforementioned article that is currently in submission. As described in the background information in Chapter 3, there are currently a number of methodological limitations in the facial emotion processing literature of bipolar disorder (BD) that may impede our precise understanding of its facial emotion processing profile. The investigation described in this chapter aimed to address these limitations in order to provide greater insight into our understanding of facial emotion processing in the disorder.

[10] The article comprised in this chapter has been resubmitted to the Journal of the International Neuropsychological Society with minor changes, and its potential for acceptance looks promising.

9.2 Abstract

Patients with bipolar disorder (BD) have difficulty in recognising and discriminating facial emotions. However, beyond this broad finding, existing literature is equivocal about the specific nature of impairments, and progress toward adequately profiling facial emotion processing in BD is hampered by methodological inconsistencies. The current study aimed to advance the literature by comparing 50 BD patients and 52 controls on a series of facial emotion processing tasks. Results indicated that patients with BD had a small, yet consistent impairment in emotion processing overall. This impairment did not vary as a function of specific emotions, tasks, or intensities between groups, and was not influenced by current mood state. These results suggest that past inconsistencies in the literature are unlikely to be attributable to task related artefacts influencing the estimation of an effect. These findings add to our understanding of social cognition in BD, and have important implications for clinicians treating patients with the disorder.

9.3 Introduction

Perception of emotion from facial information is vital for effective social and relational functioning; misinterpretation of emotional expressions can lead to uncomfortable social situations and reduce appropriate social communication. There is growing evidence that impaired facial emotion processing ability is a feature of the social cognitive profile of bipolar disorder (BD) (see Van Rheenen & Rossell, 2013c- Chapter 3, for a review). This impairment is likely to be a factor in the problematic psychosocial functioning and reduced quality of life seen in BD (Hoertnagl, et al., 2011; Martino, et al., 2011b).

Studies investigating emotion processing have shown that patients with BD have an impaired capacity to recognise and discriminate facial emotions. This effect has been demonstrated in both symptomatic and euthymic samples as well as in at risk groups (e.g., Bozikas, et al., 2006b; Brotman, et al., 2008a; Getz, et al., 2003; Lembke & Ketter, 2002; Vederman, et al., 2012). Although this body of research is growing, there is still little clarity around the nature of the deficit. For example, although many studies have reported a general reduction in emotion processing accuracy (Brotman, et al., 2008b; Derntl, et al., 2009; Getz, et al., 2003; Gray, et al., 2006; Guyer, et al., 2007), there are findings suggesting that abnormalities are more heavily weighted toward the processing of fear (Lembke & Ketter, 2002; Vederman, et al., 2012), sadness (Derntl, et al., 2009; Schenkel, et al., 2007; Vederman, et al., 2012) or surprise (Summers, et al., 2006). Some studies have found no deficit (Vaskinn, et al., 2007), and some have found impairments of emotion discrimination but not labelling (Addington & Addington, 1998; Rossell, et al., In Press).

Progress toward adequately profiling facial emotion processing abilities in BD is currently hampered by a number of factors. Firstly, existing studies differ in terms of task, with some using still photographic stimuli (static tasks), and some employing morphing facial expressions (dynamic tasks). As there has been no study directly comparing performance across static and dynamic stimuli in the same BD cohort, the impact of subtle differences between task stimuli designs is not known. Dynamic tasks are arguably more ecologically

valid; in the healthy population accuracy rates for facial emotion recognition are better for dynamic task designs which suggests that motion has a facilitatory effect on facial emotion perception (Ambadar, et al., 2005). Whether this effect extends to BD however, remains to be seen.

Secondly, very few studies in BD have investigated both emotion labelling and discrimination performance. However, as these separate, albeit related abilities require different skills (Feinberg, Rifkin, Schaffer, & Walker, 1986; Walker, McGuire, & Bettes, 1984), it is uncertain as to whether facial emotion processing problems in BD reflect a specific difficulty in recognising emotions on the basis of an impairment in matching emotional facial cues (discrimination), a specific difficulty in applying linguistic labels to different expressions (labelling), or a more generalised impairment involving both processes. Thirdly, given the generally small effect sizes for facial emotion processing differences between patients and controls (Samamé, et al., 2012; Vaskinn, et al., 2007), it is likely that emotion processing impairments in BD are subtle. Therefore, slight alterations in the *intensity* of a facial expression stimulus could well influence observed group related differences in identification or discrimination of expressions. Although some studies have attempted to profile sensitivity thresholds for emotion in BD, there are few that have assessed the threshold of intensity at which emotions are most consistently identified. The former use paradigms in which respondents themselves alter the intensity of an expression until it reaches a level at which it is recognisable (Gray, et al., 2006; Schaefer, et al., 2010; Summers, et al., 2006; Venn, et al., 2004). However, these paradigms merely permit the assessment of how much intensity is required to perceive an emotion, rather than how reliably emotions are perceived at different intensities. To determine if BD is associated with reduced perceptual processing of emotional cues, research designs manipulating stimulus intensity are required. Demonstration that people with BD require higher levels of stimulus intensity to reliably label and discriminate facial emotions would constitute evidence for this hypothesised subtle but functionally important deficit.

In light of these factors, we set out to comprehensively examine facial emotion processing in a group of patients with BD compared to controls in a single experiment in which multiple variables were manipulated sequentially. Our objectives were fourfold in

nature; firstly we aimed to establish the comparability of two emotion labelling task stimuli designs (dynamic and static) by directly contrasting performance between them. Secondly, we aimed to test for group related differences in the consistency with which facial emotions are processed at different levels of intensity. Thirdly, we aimed to determine the specificity of potential emotion processing deficits as a function of task type (labelling versus discrimination). Finally, we aimed to determine whether emotion labelling performance varied as a function of emotion types between groups, to establish whether impairments generalise to a range of basic emotions, or are more weighted toward a single emotion or subset of emotions in BD. Broadly we expected that BD-related impairments in facial emotion processing would be seen in both labelling and discrimination tasks. The following specific hypotheses were made; BD-related impairments will be seen irrespective of stimulus type (dynamic versus static: Hypothesis 1), BD-related impairments will be significant across all emotions (Hypothesis 2), BD-related impairments will be seen at all levels of stimulus intensity for both emotion labelling (Hypothesis 3a) and emotion discrimination (Hypothesis 3b) , BD will not be associated with a deficiency in non-emotional identification of faces (Control task: Hypothesis 4).

9.4 Method

This study was approved by the Alfred Hospital and Swinburne University Human Ethics Review Boards and abided by the Declaration of Helsinki. Written informed consent was obtained from each participant before the study began.

9.4.1 *Participants*

The clinical sample comprised 50 patients (16 male, 34 female) diagnosed as having DSM-IV-TR BD (39 BD I, 12 BD II) using the Mini International Neuropsychiatric Interview (MINI: Sheehan, et al., 1998). Patients were recruited via community support groups and general advertisements and were all out-patients. Current symptomology was assessed using the Young Mania Rating Scale (YMRS: Young, et al., 1978) and the Montgomery Asberg

Depression Rating Scale (MADRS: Montgomery & Asberg, 1979); there were 17 depressed (defined as those that met strict criteria for MADRS scores > 8), 12 mixed (defined as those that met strict criteria for YMRS *and* MADRS scores > 8), 4 (hypo)manic (defined as those that met strict criteria for YMRS scores > 8) and 18 euthymic (defined as those that met strict criteria for YMRS and MADRS scores $\leq$ 8) patients (i.e., 33 that were symptomatic). Patients with current psychosis, co-morbid psychotic disorders, visual impairments, neurological disorder and/or a history of substance/alcohol abuse or dependence during the past six months were excluded. Thirty two patients were taking antipsychotics, 16 were taking antidepressants, 16 were taking mood stabilisers and 10 were taking benzodiazepines[11]. Demographic and clinical characteristics are presented in Table 7.

A control sample of 52 healthy participants (20 male, 32 female) were recruited for comparison purposes by general advertisement and contacts of the authors. Using the MINI screen, no control participant had a current diagnosis or previous history of psychiatric illness (Axis I). An immediate family history of mood and psychiatric disorder, in addition to a personal history of neurological disorder, current or previous alcohol/substance dependence or abuse, visual impairments and current psychiatric medication use was exclusion criteria for all controls.

All participants were fluent in English, were between the ages of 18 and 65 years and had an estimated pre-morbid IQ as scored by the Wechsler Test Of Adult Reading (WTAR) of >90.

[11] Repeated measures ANOVAs using medication (dichotomously coded to yes/no) as the between subjects factor revealed no significant difference on any of the tasks for patients on or off any of the classes of medication

Table 7. *Demographic and clinical characteristics of the sample*

Group		**Control**			**BD**		**Group comparisons**	
	N	**M**	**SD**	N	**M**	**SD**	F/χ^2	p
N	52			50				
Age		33.98	14.27		37.92	12.45	-1.48	.14
Gender (M/F)	20/32			16/34			0.47^	.50
WTAR (scaled)		111.65	7.24		109.40	11.95	.96	.34
Education standard completed							8.70^	.12
Completed secondary	12	-	-	7	-	-	-	-
Completed TAFE/diploma	3	-	-	11	-	-	-	-
Completed trade qualification	3	-	-	4	-	-	-	-
Completed tertiary degree	28	-	-	20	-	-	-	-
Other	4	-	-	8	-	-	-	-
Current mood state ([Hypo]manic/ Depressed/ Mixed/ Euthymic)		-	-	4/17/12/17	-	-	-	-
Diagnostic subtype (BD I / BD II)		-	-	38/12	-	-	-	-
Age of onset		-	-		20.49	8.45	-	-
Age of diagnosis		-	-		27.40	9.99	-	-
YMRS		-	-		6.33	5.48	-	-
MADRS		-	-		11.96	10.07	-	-

Note: ^ Group comparisons all independent samples t-tests except gender and education which was Chi square; M/F = Male / Female, WTAR = Wechsler Test of Adult Intelligence, YMRS = Young Mania Rating Scale, MADRS = Montgomery Asberg Depression Rating Scale

9.4.2 *Materials*

All participants completed three computerised tasks (designed by the author) that were used to measure (1) emotion labelling performance across stimulus type (dynamic versus static) and emotion type (happy, sad, angry, fear, neutral), (2) emotion discrimination, and (3) emotion labelling and discrimination performance across three levels of intensity. Participants also completed a control task (designed by the author) to test whether potential impairments

on the facial emotion processing tasks were reflective of a generalised performance deficit or were specific to facial emotion processing.

The face stimuli were taken from the widely used and well validated Ekman and Friesen series known as the Pictures of Facial Affect (POFA: Ekman & Friesen, 1976). The stimuli comprised black and white photographs of faces free of jewellery, spectacles, make up and facial hair (five female and five male) and expressing the emotions happy, sad, fear, angry and neutral. The faces were cropped to an oval shape spanning the top of the forehead to the bottom of the chin and excluding any hair and the ears on either side of the face. Thirteen faces were used in total. However, given that we endeavoured to have an equal presentation of emotional expressions of different genders in the labelling tasks across ten different trials for each emotion and neutral, and that some expressions were not available for all faces, the tasks presented below varied in the exact faces used.

A morphing program called Fantamorph (Abrosoft, 2012) was used to reduce the intensity of the POFA stimuli's emotional expression by 25% decrements to create static intensity varied stimuli. This resulted in static stimulus expressions at 100%, 75%, 50% and 25% intensity. Pilot testing revealed that emotions presented at 25% intensity elicited floor effects in controls, and they were therefore excluded from the task. The final stimulus set for the latter two tasks comprised static faces displaying 100%, 75% and 50% (high, medium and low) emotional intensity only. The dynamic stimuli were created by morphing the low, medium and high intensity static faces through quick successive frames from a neutral expression (0%) to the final emotional expression (100%), such that they appeared as a moving image. All tasks were presented on a 14" Lenovo laptop computer and were run through Presentation (Neurobehavioral Systems Inc, 2012). These tasks are described below.

9.4.2.1 The dynamic facial emotion labelling task

The dynamic facial emotion labelling task required participants to view dynamic facial images (i.e., morphs) and identify the emotion being expressed. Forty randomised dynamic display trials comprising ten presentations (five male and five female faces) each for happy, sad, fear

and angry expressions were presented one at a time for 1500ms[12] followed by an inter-stimulus interval of 1500ms. Participants were instructed to press a labelled keyboard button corresponding to the emotion that they believed the face was expressing as soon as they recognised it. The averaged accuracy percentage for each emotion was taken as the primary dependent variable. This task was used in the analysis testing Hypothesis 1 and 2.

9.4.2.2 The static facial emotion labelling task

The static facial emotion labelling task was designed to assess participants' ability to identify emotional expressions from static facial stimuli (i.e., a photograph). It required participants to view an image of a male or female face, and identify the emotional expression exhibited by that face. The faces were presented one at a time on a black background for 2000ms followed by an inter-stimulus interval of 1500ms. The task involves 130 randomised trials in total, including ten presentations (five male and five female faces) for each of the emotions happy, sad, angry and fear at each of the three levels of emotional intensity (high, medium and low) and ten presentations of neutral. Participants were instructed to press a labelled keyboard button corresponding to the emotion that they believed the face was expressing as soon as they recognised it. The averaged accuracy percentage and response time for each emotion at each level of intensity was taken as the primary dependent variable. This task was used in analyses testing Hypotheses 1and 3a.

9.4.2.3 The static facial emotion discrimination task

The static facial emotion discrimination task was designed to assess participants' ability to differentiate between static facial emotional expressions at different levels of intensity. It required participants to view two simultaneously presented images of human faces and identify whether the emotion that the two faces were showing was the same or different. The task represents the emotions happy, sad, angry, fear, and neutral over 135 randomised paired

[12] Emotional morphs were trialled at different presentation durations. It was decided that 1500ms was the most realistic timeframe representation of a developing emotional expression and this time frame was used to maintain ecological validity.

stimulus trials at the three different intensities.[13] Emotional expressions were paired only with those expressing the same level of intensity (i.e., high intensity expressions paired together) or a neutral expression, but never with an emotion of a different expressive intensity. There were 31 incongruent paired trials (representing pairings across the emotions happy, sad, angry, fear and neutral) and 11 congruent paired trials (representing pairings across happy, sad, angry and fear) for each level of intensity, with nine additional trials representing paired neutral expressions that were used as fillers. One face in each pair was presented to the left visual field, and the other was presented to the right visual field on a black background for 2000ms followed by an inter-stimulus interval of 1500ms. Participants were instructed to respond via two button keyboard press (same or different) as soon as they could discriminate the emotional expressions. Responses made from 200ms onwards were recorded. Written instructions, an example and a set of practice trials were provided to participants prior to commencing the task. The averaged accuracy percentage and response times across congruent and incongruent trials at each level of intensity was taken as the primary dependent variable for this task. This task was used in analyses testing Hypothesis 3b.

9.4.2.4 Control task

To rule out the possibility that BD is associated with a more fundamental deficit in facial processing (i.e., not specific to higher order facial emotion processing), a *static identity discrimination task* was designed. The tasks assessed participant's ability to determine whether two simultaneously presented static facial stimuli were identical or not. The task comprised 55 (45 incongruent and 10 congruent) randomised trials made up of couplings between six male and six female faces displaying neutral expressions only. One face in each pair was presented to the left visual field and the other was presented to the right visual field on a black background for 2000ms followed by an inter-stimulus interval of 1500ms. The task involved

[13] It should be noted that the number of stimuli in each set differed depending on the nature of the task. For the two labelling tasks there were ten presentations of each emotional expression. In the static task this occurred per intensity in addition to ten presentations of neutral. As neutral morphs and different intensities were not available in the dynamic task, the number of trials in that task was reduced (in comparison to the static task).

65 randomised trials with the congruent pairs being presented twice. Participants were instructed to respond via two button keyboard press (same or different) as soon as they could discriminate the faces. Responses made from 200ms onwards were recorded with the averaged accuracy percentage and response times across same/different pairs taken as the dependent variables. This task was used in the analysis testing Hypothesis 4.

9.4.3 *Statistical analysis*

Demographic and clinical group differences were assessed via independent samples t-tests or Chi square tests. We conducted a series of analyses to address our hypotheses: we employed a four (emotion: happy, sad, angry, fear) *two (stimuli type static, dynamic) *two (group: control, BD) repeated measures analysis of variance (ANOVA) of the accuracy data to address Hypothesis 1 and 2. Significant main effects of group, emotion, and of stimuli type were expected to show support for this hypothesis. Only responses to high intensity conditions were used as the static emotion labelling variables in this analysis. Due to the response time windows differing between dynamic and static stimuli tasks, we were unable to analyse response time differences across these tasks.[14]

Two repeated measures ANOVAs using a four (emotion: happy, sad, angry, fear) *three (intensity: high, medium, low) *two (group: control, BD) design with the accuracy and response time data of the static emotion labelling task were used to address Hypothesis 3a. To address Hypothesis 3b we also completed two, three (intensity: high, medium, low) *two (group: control, BD) repeated measures ANOVAs on the static emotion discrimination task,

[14] Accuracy performance for the labelling of happy emotions was found to be at ceiling for both groups, so we re-ran the analysis excluding happy. Results remained largely unchanged, so only the analyses including happy are reported here. To determine whether having neutral anchoring expressions as a point of comparison impacted static facial emotion labelling effects, we re-ran the repeated measures ANOVA including neutral expressions *and* the four emotions used in the previous analysis in a five (emotions: happy, sad, angry, fear and neutral) *two (group: controls, BD) design with only the static emotion labelling data. This analysis obviously did not include the static/ dynamic within group contrast. However, as this analysis made no difference to the participant*group interaction or between group effects, again for brevity it is not presented

separately for the accuracy and response time data. Support for these hypotheses was expected to be shown through main effects of group and intensity. Two one way ANOVAs were used to compare accuracy and response time performance between groups on the control task (i.e., the static identity discrimination task), and thus to address Hypothesis 4. The absence of a significant group effects would demonstrate support for this hypothesis.

To better understand the effects of mood and diagnostic status on facial emotion processing performance, all analyses were re-run in the patient group: in the first series of analyses, diagnosis (BD I; *n*=38 or BD II; *n*=12) was entered as the between groups factor for all tasks. For the second series of analyses current mood state was entered as the between groups factor, however given that the sample size of some of the mood state subgroups was too small for meaningful analysis, we collapsed the mixed (*n* = 12) and manic (n = 4) groups into one (resulting *n*=16) and compared this to patients meeting criteria for euthymia (*n*=17) or depression (*n*=17). Bivariate correlations were also conducted to examine the relationship between emotion labelling and discrimination performance and symptom severity on the YMRS and MADRS. All analyses were corrected for multiple testing using a conservative α set at .01.

9.5 Results

No significant differences in age, gender, education level completed or pre-morbid IQ were found between the two groups (see Table 7).

9.5.1 *Emotion labelling accuracy as a function of task type (Hypothesis 1 and 2)*

Investigation of the determinants of emotion labelling accuracy found main effects of emotion (Greenhouse Geisser corrected F (2.715, 271.538) =71.51, p<.001, *partial* η^2=.42), stimuli type: static versus dynamic (F (1,100) =8.21, p<.01, *partial* η^2=.08) and group (F (1,100) =7.04, p<.01, *partial* η^2=.07), but no two or three way interactions reached significance. Accuracy across emotions occurred in the descending order of happy (M=98.43, SD=2.90), fear (M=86.32, SD=12.60), angry (M=81.76, SD=13.67) and sad (M=79.59, SD=13.93), with

performance being slightly better for the dynamic stimuli task relative to the static stimuli task (dynamic: *M*=87.60, *SD*=8.02; static *M*=85.44, *SD*=9.20; *d*=-0.25) and BD patients performing less accurately than controls overall (Control: *M*=88.43, *SD*=6.73; BD: *M*=84.50, *SD*=8.30; *d*=-0.52). Figure 16 presents emotion labelling accuracy performance for dynamic and static stimuli tasks as a function of emotion across groups.

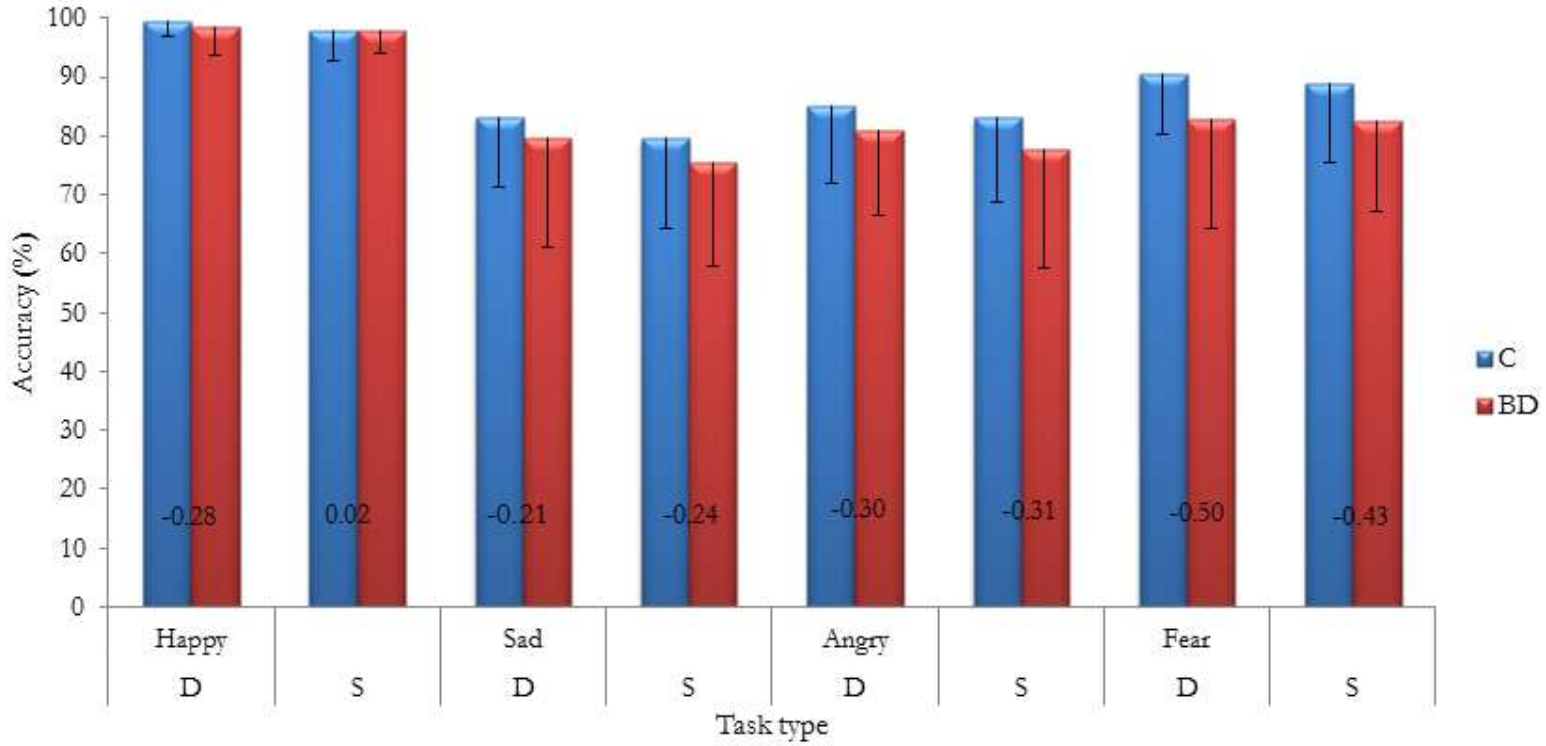

Figure 16. Emotion labelling accuracy performance for dynamic and static tasks as a function of emotion across groups

Note: D=Dynamic; S=Static; numbers in bars represent effect sizes (Cohen's d) between groups; error bars represent standard deviations

9.5.2 *Static emotion labelling as a function of emotion and intensity (Hypothesis 3a)*

Table 8 presents the accuracy and response time means and standard deviations for static emotion labelling as a function of intensity across groups.

9.5.2.1 Accuracy:

There was a main effect of emotion (F (3,297) =152.37, p<.001, *partial* η^2=.61) and intensity (Greenhouse Geisser corrected F (1.86, 184.22) =621.83, p<.001, *partial* η^2=.86), but no group effect or two or three way interactions. Accuracy across emotions occurred in the descending order of happy (M=91.74, SD=6.57), fear (M=75.52, SD=13.82), sad (M=69.51, SD=14.94) and angry (M=60.98, SD=14.05), with performance best in high intensity (M=85.44, SD=9.20), followed by medium intensity (M=80.02, SD=9.52) and low intensity (M=57.72, SD=11.62) conditions. Although not significant, BD patients performed less accurately than controls and the effect size difference was in the medium range (Control: M=76.01, SD=8.18; BD: M=72.73, SD=9.56; d=-0.37).

9.5.2.2 Response time:

There was a main effect of emotion (Greenhouse Geisser corrected F (2.65, 265.30) =190.03, p<.001, *partial* η^2=.66), intensity (Greenhouse Geisser corrected F (1.62, 161.94) =98.901, p<.001, *partial* η^2=.50) and group (F (1,100) =5.61, p<.05, *partial* η^2=.05), although the latter did not survive statistical correction. There were no two or three way interactions. Response latencies across emotions occurred in the ascending order of happy (M=1233.55, SD=224.86), sad (M=1471.30, SD=238.63), angry (M=1522.61, SD=245.00) and fear (M=1617.83, SD=235.61), with performance best in high intensity (M=1385.78, SD=229.36), followed by medium intensity (M=1436.21, SD=221.60) and low intensity (M=1562.30, SD=224.10) conditions. Although not significant, BD patients had longer latencies than controls and the effect size difference was in the medium range (Control: M=1413.72, SD=209.27; BD: M=1511.05, SD=205.63; d=0.47).

Table 8. *Accuracy and response time means and standard deviations for static emotion labelling as a function of intensity*

		Control		BD			Control		BD			Control		BD		
Intensity		**High**					**Medium**					**Low**				
		M	***SD***	***M***	***SD***	***d***	***M***	***SD***	***M***	***SD***	***d***	***M***	***SD***	***M***	***SD***	***d***
Accuracy	**(%)**															
	Happy	97.88	4.98	98.00	4.040	-0.02	96.47	6.88	95.40	8.38	0.14	82.50	14.26	79.00	14.18	-0.25
	Sad	79.62	15.34	75.60	17.63	-0.24	73.65	15.09	74.40	19.18	-0.04	58.85	16.65	54.80	21.78	-0.21
	Angry	83.08	14.35	77.60	20.16	-0.31	69.81	19.56	64.20	19.07	0.29	37.12	18.61	33.80	15.50	-0.19
	Fear	88.85	13.23	82.60	15.50	-0.43	86.54	12.35	79.40	16.59	0.49	57.50	18.77	58.00	23.82	0.02
	Overall	87.36	8.55	83.45	9.51	-0.43	81.65	7.91	78.35	10.75	0.35	58.99	10.87	56.40	12.32	-0.22
Response time	**(ms)**															
	Happy	1069.73	207.25	1207.77	226.04	0.64	1111.25	207.65	1251.83	247.80	-0.61	1322.59	249.86	1448.59	253.11	0.50
	Sad	1364.69	257.57	1493.44	261.81	0.50	1404.48	238.00	1520.97	271.97	-0.46	1500.48	281.90	1549.53	265.83	0.18
	Angry	1424.85	345.78	1486.64	259.48	0.20	1483.81	323.56	1537.65	259.34	-0.18	1530.10	465.50	1677.75	298.19	0.38
	Fear	1480.36	268.08	1566.87	242.83	0.34	1553.42	274.06	1633.97	257.58	-0.30	1718.86	282.62	1757.55	261.55	0.14
	Overall	1334.91	231.18	1438.68	217.26	0.46	1388.24	218.44	1486.10	215.80	-0.45	1518.01	224.56	1608.36	216.30	0.41

Note: BD=bipolar disorder; d=Cohen's d; static labelling group accuracy effect p=.07; static labelling group response time effect p<.05

9.5.3 *Static emotion discrimination as a function of intensity (Hypothesis 3b)*

Table 9 presents the accuracy and response time means and standard deviations for static emotion discrimination as a function of intensity across groups. Analyses were conducted separately for the two dependent variables.

9.5.3.1 Accuracy:

There was a main effect of intensity (F (2,200) =97.78, p<.001, *partial* η^2=.49) and group (F (1,100) =9.04, p<.01, *partial* η^2=.08), but no two way interaction. Performance accuracy was best in high intensity (M=78.85, SD=8.89) followed by medium intensity (M=69.40, SD=10.88) and low intensity (M=65.59, SD=9.55) conditions, with overall performance being worse in patients than controls (BD: M=68.94, SD=7.94; Controls M=73.52, SD=7.43, d=-0.60).

9.5.3.2 Response time:

There was a main effect of intensity (F (2,200) =69.33, p<.001, *partial* η^2=.41) but no effect of group and no two way interaction. Response latencies were shortest in medium intensity (M=1544.58, SD=198.71) followed by high intensity (M=1598.50, SD=281.22) and low intensity (M=1700.73, SD=286.84) conditions.

Table 9. *Accuracy and response time means and standard deviations for static emotion discrimination as a function of intensity*

		Control		BD			Control		BD			Control		BD		
Intensity		**High**					**Medium**					**Low**				
		M	***SD***	***M***	***SD***	***d***	***M***	***SD***	***M***	***SD***	***d***	***M***	***SD***	***M***	***SD***	***d***
Accuracy	**(%)**	80.52	8.27	77.11	9.26	-0.39	72.18	10.39	66.50	10.71	0.54	67.87	8.95	63.22	9.65	-0.50
Response time	**(ms)**	1578.45	286.88	1619.26	276.56	0.14	1535.68	198.03	1553.85	201.42	-0.09	1706.64	289.67	1694.59	286.68	0.04

Note: BD= bipolar disorder; RT = response time; d= Cohen's d; static discrimination group accuracy effect $p<.01$; static labelling group response time effect $p=.75$

9.5.4 *Control task performance (Hypothesis 4)*

There were no significant accuracy or response time differences between groups on the identity labelling control task (both *p*'s >.05).

9.5.5 *Subgroup analyses*

There were no between group main effects or interactions on any of the tasks for patients diagnosed as having BD I versus BD II (all *p*'s >.05), nor were there any between group main effects or interactions on any of the tasks for patients classified as euthymic, depressed or mixed/manic (all *p*'s >.05). Furthermore, bivariate correlation analyses found no significant associations between accuracy or response time performance (where applicable) on any measure and severity of current depression (MADRS score) or mania (YMRS score).

9.6 Discussion

The current study examined facial emotion processing in a cohort of BD patients compared to controls in a complex experiment whereby multiple variables were manipulated. In addition to examining whether emotion labelling performance varied as a function of specific emotions between groups, we aimed to establish the comparability of two commonly used emotion labelling task stimuli designs, determine the existence of differences in facial emotion processing at varying levels of intensity, *and* establish the specificity of emotion processing deficits as a function of task types; labelling versus discrimination. These aims were formulated to further understandings of the emotion processing profile of BD.

Our results indicated that emotion labelling performance was better for the dynamic task stimuli relative to the static task stimuli, with patients performing worse overall (supporting Hypothesis 1). This is consistent with previous research in the healthy population indicating that emotion processing performance is more accurately assessed using tasks that enable the facilitatory effect of motion to guide emotion recognition (Ambadar, et al., 2005). Further, given the significant group and emotion effects in the absence of interactions between

them, there was no evidence that BD-related impairments were more heavily weighted toward a particular emotion. Rather BD patients appear to be globally compromised in processing a range of emotional expressions (supporting Hypothesis 2). We also found that the accuracy with which facial emotions were labelled and discriminated diminished in line with the degradation of stimulus intensity across groups. However, BD patients did exhibit overall deficits in discriminating emotions across these intensities compared to their control counterparts (supporting Hypothesis 3b). Contrary to expectations, this group effect was not evident for intensity labelling performance (i.e., there was no support for Hypothesis 3a), although the effect size difference between groups was still in the medium range. Finally, as no group difference was observed on the control task, it appears that the general processing of facial information was not compromised in this cohort (supporting Hypothesis 4).

Taken together, this pattern of findings suggests that BD patients have a relatively generalised impairment for the labelling of facially conveyed emotional expressions, which cannot be attributed to a pervasive impairment in the general processing of faces. These results accord with several studies in which emotion labelling (Derntl, et al., 2009; Getz, et al., 2003; Vederman, et al., 2012) but not face processing itself (e.g., Bozikas, et al., 2006b; Getz, et al., 2003) has been shown to be impaired in BD. Thus it appears that BD related facial emotion processing difficulties reflect inabilities in both adequately matching facial cues of emotion to recognise expressions *and* adequately applying or understanding the linguistic labels used to identify them. Moreover, as diagnostic subtype and current mood state did not have any influence on the present findings, the generalised facial emotion processing impairment we have observed here is likely to be reflective of a trait-like feature of the disorder, which is consistent with past research (Bozikas, et al., 2006b; Vederman, et al., 2012).

Importantly, it appears that whilst variability between tasks designs and intensities may subtly influence the *strength* at which emotion processing abilities are apparent (i.e., performance accuracy is better at higher compared to lower levels of intensity, and in tasks employing dynamic instead of static stimuli), these procedural factors are unlikely to significantly impact the detection of a facial emotion processing effect in BD (as evidenced by the main effects of group, but not interactions across analyses). Thus, it is improbable that

inconsistencies evident in the current BD literature are by-products of emotion processing impairments being masked by task related artefacts (as BD performance on all emotion processing tasks was impaired here). Rather, they may be a function of other factors such as differences amongst study cohorts with regards to clinical history, or the use and dosage of medications. Alternatively, the null effects of past research may represent a result of poor statistical power (see Vaskinn, et al., 2007 who's BD sample comprised only 21 patients).

The present results should be interpreted within the confines of a number of limitations. Firstly, as emotion processing under time pressure relies on general processing speed which is known to be compromised in BD (see Van Rheenen & Rossell, 2013b - Chapter 2), it is possible that the effects we have observed here are confounded by generic BD-related cognitive impairments. Secondly, given that there was overlap in the stimuli used across the different tasks, it is possible that our results are partly attributable to cross-contamination effects whereby responses on earlier trials affected responses on later trials using the same face and facial expression. Thirdly, as abnormalities of disgust and surprised expressions have been demonstrated in some studies (Gray, et al., 2006; Harmer, et al., 2002), our omission of these emotions from the battery limited our understanding of how accurately and quickly patients in this cohort were able to process these emotions. Fourth, as we did not explicitly counterbalance the presentation of faces and emotions across visual fields, we cannot account for hemisphere specific laterality effects. Finally, we were unable to directly compare mood subgroups to controls due to the restricted power after stratification into mixed/manic, depressed and euthymic subgroups. Although within group analyses failed to differentiate performance across patients in these current states for all tasks, it is still possible that mood may have had an effect on performance. Thus, given the rather heterogeneous nature of our BD sample, our results should be interpreted with caution.

Nevertheless, as this study is the first of its kind to provide insight into the nature of emotion processing impairments in BD while paying attention to a range of potential confounds including task stimuli designs, intensity, and emotion specific factors in a single experiment, these findings do add substantially to the existing literature on facial emotion processing in BD. Future studies would certainly do well to address the present limitations

however, with a view to providing greater clarity with regards to the impact of pre-existing cognitive impairments, cross-contamination effects and mood state related factors on facial emotion processing.

In sum, this study is the first of its kind to comprehensively examine emotion processing performance on a battery that controlled for subtle differences in task stimuli, and investigated the specificity of impairments across task types, emotions, and intensities in persons with BD. Our primary finding of a generalised patient impairment in the ability to label facial expressions and to make use of available emotional facial cues to differentiate them, suggests that facial emotion processing is considerably more challenging for people with the disorder than for those without. This may have direct impact on the significant psychosocial burden carried by patients, although this remains to be seen.

CHAPTER 10: PROSODIC EMOTION PROCESSING IN BIPOLAR DISORDER

10.1 Chapter guide

Van Rheenen, T. E., & Rossell, S. L. (2013). Auditory-prosodic processing in bipolar disorder; from sensory perception to emotion. *Journal of Affective Disorders,* 151, 1102-1107.

This chapter is the third of the empirical chapters of this thesis. It comprises the aforementioned article that can be found in its published form in Appendix H. The aim of this chapter was to establish the capacity for prosodic emotion processing in the sample of participants recruited for this project. Specifically, given the very limited research investigating auditory and prosodic emotion processing in bipolar disorder (BD: as described in Chapter 3), the investigation described in this chapter was designed to overcome this paucity of research by examining i) whether prosodic emotion processing deficits exist in BD and ii) factors that may contribute to these deficits.

10.2 Abstract

Objectives: Accurate emotion processing is critical to understanding the social world. Despite growing evidence of facial emotion processing impairments in patients with bipolar disorder (BD), comprehensive investigations of emotional prosodic processing is limited. The existing (albeit sparse) literature is inconsistent at best, and confounded by failures to control for the effects of gender or low level sensory-perceptual impairments. The present study sought to address this paucity of research by utilising a novel behavioural battery to comprehensively investigate the auditory-prosodic profile of BD.

*Methods***:** 50 BD patients and 52 healthy controls completed tasks assessing emotional and linguistic prosody, and sensitivity for discriminating tones that deviate in amplitude, duration and pitch.

Results: BD patients were less sensitive than their control counterparts in discriminating amplitude and durational cues but not pitch cues or linguistic prosody. They also demonstrated impaired ability to recognise happy intonations; although this was specific to male's with the disorder. The recognition of happy in the patient group was correlated with pitch sensitivity in female patients only.

*Limitations***:** The small sample size of patients after stratification by current mood state prevented us from conducting subgroup comparisons between symptomatic, euthymic and control participants to explicitly examine the effects of mood.

*Conclusions***:** Our findings indicate the existence of a female advantage for the processing of emotional prosody in BD, specifically for the processing of happy. Although male BD patients were impaired in their ability to recognise happy prosody, this was unrelated to reduced tone discrimination sensitivity. This study indicates the importance of examining both gender and low order sensory perceptual capacity when examining emotional prosody.

10.3 Introduction

Accurate emotion processing from facial expressions and nonverbal variations of intonation in speech patterns, called prosody, are critical to understanding the social world. There is growing evidence to indicate that persons with bipolar disorder (BD) are impaired in their ability to process facial expressions (Getz, et al., 2003; Lembke & Ketter, 2002; Vederman, et al., 2012). However, available research with regards to the prosodic emotion processing profile of BD is narrow and inconsistent at best; there are findings of impaired emotional prosody processing in some studies of euthymic *and* symptomatic BD groups (Bozikas, et al., 2007; Hofer, et al., 2010; Murphy & Cutting, 1990; Rossell, et al., In Press) but not others (Edwards, et al., 2001; Mitchell, Elliott, Barry, Cruttenden, & Woodruff, 2004b; Vederman, et al., 2012), with little explanation for the disparity.

It is possible that failure to consistently detect such impairments may be accounted for, at least in part, by various confounds or omissions in previous research. For example, much of the emotional prosody recognition research in BD has 1) used patients as psychiatric controls, or grouped them with patients diagnosed as having another affective or psychotic disorder (Edwards, et al., 2001; Hofer, et al., 2010; Murphy & Cutting, 1990; Rossell, et al., In Press), 2) given little attention to the impact of mood state or diagnostic subtype, 3) failed to conduct well powered investigations of gender effects despite growing evidence of a female advantage for cognitive functions including emotional prosody recognition in both healthy (Donges, Kersting, & Suslow, 2012; Kret & De Gelder, 2012; Schirmer, Kotz, & Friederici, 2002; Szymanowski, Kotz, Schröder, Rotte, & Dengler, 2007) and other psychiatric populations (Barrett, Kelly, Bell, & King, 2008; Bozikas, et al., 2006a; Carrus et al., 2010; Gogos, et al., 2010), and 4) failed to examine linguistic processing, or control for potential deficits in the processing of auditory information which could provide insight into whether reported patient difficulties reflect an emotion specific deficit or a generalised auditory problem (see Van Rheenen & Rossell, 2013c - Chapter 3, for a review).

Further, despite it being well recognised that prosody comprises both affective (emotional) and linguistic (semantic) components formed on the basis of phonemic inputs

from early acoustic properties (e.g., Lancker & Sidtis, 1992; Pihan, 2006; Shipley-Brown, Dingwall, Berlin, Yeni-Komshian, & Gordon-Salant, 1988; Wildgruber et al., 2004), there has been limited investigation of early sensory abilities and their relationship to the perception of emotional prosody recognition in BD. Prosody affects the meaning of the speech signal through subtle alterations in fundamental frequency (pitch), acoustic intensity (amplitude) and phoneme or syllable length ([duration]; e.g., Lieberman & Michaels, 1962; Murray & Arnott, 1993; Quam & Swingley, 2012; Thompson, Schellenberg, & Husain, 2003). For example, rising or falling pitch inflections convey declarative or interrogative intonation contours and are important to linguistic prosody processing (Raithel & Hielscher-Fastabend, 2004). In addition, tone duration and amplitude are important for conveying emotional signals and provide cues by which persons can distinguish emotional intonations(Scherer, 1996 ; i.e., anger and happy comprise short durations and heightened intensities whilst sad comprises a long duration and weak intensity).

To date, preliminary evidence indicates that pitch perception and semantic/linguistic understanding is unimpaired in BD (Force, et al., 2008; Rossell, et al., In Press). There is however, some indirect psychophysiological data to suggest reduced auditory receptiveness to changes in duration (elicited in mismatch negativity paradigms; Andersson, Barder, Hellvin, Løvdahl, & Malt, 2008; Jahshan et al., 2012; Takei et al., 2010) and amplitude (elicited in loudness dependence auditory evoked potential and prepulse inhibition paradigms; Gogos, et al., 2009; Lee, Park, & Lee, 2012; Park, Lee, Kim, & Bae, 2010) in patients with the disorder. Impairments in the bottom up processing of these acoustic cues may critically impact prosodic emotion perception in patients with BD; however this remains to be seen. That is, there has been no behavioural examination of acoustic speech parameters in the disorder despite the possibility that potential deficits in the perception of lower order sensory information may contribute to deficits in higher-order emotional prosodic processing, as is the case for schizophrenia (Leitman, et al., 2005; Leitman, et al., 2010).

The present study sought to address this paucity of research by utilising a novel behavioural battery to comprehensively investigate the auditory-prosodic profile of BD. To our knowledge this is the first study to investigate prosody in its entirety in BD, by comparing the performance of an explicitly DSM-IV-TR diagnosed BD sample to a well matched control

group on assessments of emotional and linguistic prosody and the fundamental acoustic properties that they encompass. We predicted that the patient group would show impaired emotional prosody recognition relative to controls, and that female BD patients would show an advantage relative to their male counterparts. We also predicted that duration and amplitude discrimination would be impaired in the BD group but that pitch perception and linguistic prosody would not. Two further research questions pertained to a) whether there were relationships between potential higher order auditory emotion and /or linguistic prosody impairments *and* lower order acoustic properties and b) whether current mood symptoms influenced performance on auditory-prosodic processing tasks.

10.4 Method

This study was approved by the Alfred Hospital and Swinburne University Human Ethics Review Boards and abided by the Declaration of Helsinki. Written informed consent was obtained from each participant before the study began.

10.4.1 *Participants*

The clinical sample comprised 50 patients (16 male, 34 female) diagnosed as having DSM-IV-TR BD ([Hypo]manic = 4[2 male]), Depressed=17[7 male], Mixed=12[2 male], Euthymic=17[5 male]) using the Mini International Neuropsychiatric Interview (MINI: Sheehan, et al., 1998). Patients were recruited via community support groups and general advertisements and were all out-patients. Current symptomology was assessed using the Young Mania Rating Scale (YMRS: Young, et al., 1978) and the Montgomery Asberg Depression Rating Scale (MADRS: Montgomery & Asberg, 1979). Patients with current psychosis, co-morbid psychotic disorders, visual impairments, neurological disorder and/or a history of substance/alcohol abuse or dependence during the past six months were excluded.

Thirty one patients were taking antipsychotics, 16 were taking antidepressants, 16 were taking mood stabilisers and 9 were taking benzodiazepines[15].

A control sample of 52 healthy participants (20 male, 32 female) were recruited for comparison purposes by general advertisement and contacts of the authors. Using the MINI screen, no control participant had a current diagnosis or previous history of psychiatric illness (Axis I). An immediate family history of mood and psychiatric disorder, in addition to a personal history of neurological disorder, current or previous alcohol/substance dependence or abuse, visual impairments and current psychiatric medication use was exclusion criteria for all controls.

All participants were fluent in English, were between the ages of 18 and 65 years and had an estimated pre-morbid IQ as scored by the Wechsler Test Of Adult Reading *(WTAR)* of >90.

10.4.2 *Measures*

A battery of computerised tasks, originally designed by Groot and Rossell (2008) and modified by the author to fit the requirements of the current study, were used to comprehensively assess auditory processing in BD. The battery comprised three simple tone discrimination tasks (amplitude, duration and pitch), a linguistic prosody discrimination task and an emotional prosody labelling task. All tasks were presented binaurally via noise reduction headphones and were run on a 14" Lenovo laptop computer using Presentation (Neurobehavioral Systems Inc, 2012). These tasks are described in detail below.

10.4.2.1 Emotional prosody labelling task.

The emotional prosody labelling task required participants to listen to nonsense sentences ("the windows are made of glass") and identify the emotional tone with which each sentence was spoken. The sentences were matched for length and were spoken by four actors (two males and two females) who were directed to express each of four emotional tones

[15] Multivariate analyses using medication (dichotomously coded to yes/no) as the between subjects factor revealed no significant difference on any of the tasks for patients on or off any of the classes of medication.

(happy, sad, fear and neutral). The task comprised 88 trials involving 22 presentations each for happy, sad, fear and neutral emotions. Each trial lasted 4500ms. Participants were instructed to press a labelled keyboard button corresponding to the emotion that he/she believed was being expressed as soon as he/she recognised it.

10.4.2.2 Linguistic prosody labelling

The linguistic prosody task required participants identify whether a nonsense utterance was inquisitive (question) or declarative (statement) in nature (i.e., "I finished my lunch?" *or* "I finished my lunch!"). The task comprised 48 trials involving 24 presentations of inquisitive and 24 presentations of declarative sentences. Each trial lasted 4500ms. Participants were instructed to respond via two button keyboard press (*question* or *statement*) as soon as he/she could discriminate the sentence stress.

10.4.2.3 Tone discrimination tasks

The amplitude, duration and pitch discrimination tasks required participants to listen to a series of paired, sequentially presented tones and decide whether the tone pairs were the same or different to each other. For each task there were 11 tone pairs varied on amplitude, duration or pitch. For each pair in the three tasks, the first tone was always set at 70dB with a base frequency of 1500Hz lasting 150ms. The second tone always followed after a 500ms delay. For the amplitude task, the second tone either remained constant or its amplitude varied in a higher *or* lower direction in increments of 1dB, 2dB, 3dB, 5dB or 10dB (tones ranging from 71dB to 80dB). For the duration task, the second tone either remained constant or its duration varied incrementally in length increases or decreases of 2%, 5%, 10%, 25%, or 50%. For the pitch task, the second tone either remained constant or varied incrementally in frequency increases or decreases of 2%, 5%, 10%, 25%, or 50%. The duration of each pair in the amplitude and pitch tasks lasted 800ms. All pairs in all tasks were followed by an inter-stimulus interval of 3000ms. The stimuli set comprised 144 paired tone trials (120 varied and 24 remaining constant) with 24 presentations of the unvaried paired tones and 12 presentations of the varied paired tones for each incremental amplitude, duration or pitch increase or decrease. On every tone discrimination task participants were instructed to

respond via two button keyboard press (same or different) as soon as he/she could discriminate the tone pairs.

10.4.3 *Statistical analysis*

Statistical analyses were conducted using IBM SPSS statistics version 20. Demographic and clinical group differences were assessed via independent samples t-tests or Chi square tests where applicable. To investigate overall group and gender related differences in performance, emotional prosody labelling accuracy scores were entered into a four (emotional tone)*two (group)*two (gender) repeated measures analysis of variance (ANOVA). Significant results were followed up with appropriate post-hoc tests; the emotional prosody labelling scores were split by gender and entered into two separate repeated measures ANOVAs with planned one way ANOVA follow ups to compare male and female patients to controls.

Signal detection theory was employed to calculate *d'* prime scores for each level of amplitude, duration or pitch change on the tone discrimination tasks and for each utterance type(inquisitive or declarative) on the linguistic task. *d'* prime is an estimate of perceptual sensitivity that takes into account information bearing response patterns (signals) in light of random responses (noise) on tasks with a two choice response format. Higher *d'* prime scores indicate greater signal receptivity, with scores of zero to three generally accepted as measures of increasing task difficulty (Stanislaw & Todorov, 1999)[16]. *d'* prime scores for the linguistic task were entered into a two (utterance type)*two (group)*two (gender) repeated measures ANOVA. *d'* prime scores for each tone discrimination level deviation were entered into three separate five (level)*two (group)*two (gender) repeated measures ANOVAs. Both linguistic and tone discrimination analyses were followed up with appropriate post hoc tests.

To better understand the effects of mood and diagnostic status on auditory-prosodic performance, a series of post-hoc repeated measures ANOVAs were run in the patient group. In the first series of analyses, patient diagnosis (BD I; n=38 or BD II; n=12) was entered as the between subjects factors for all tasks. For the second series of analyses current mood status

[16] To avoid the problem of infinite values or division by zero when calculating *d'* prime, we used the formula 1/ (2*N*).

was considered. Given that the sample size of some of the mood phase subgroups were too small for meaningful analysis, we collapsed the mixed and manic groups into one (resulting n=16) and compared this to patients meeting criteria for euthymia (n=17) or depression on all tasks (n=17). Neither set of these analyses occurred with gender as a between subjects factor. This is because after stratification by mood episode/diagnostic subtype and gender, some groups contained less than 10 participants which would limit statistical power.

Bivariate correlations split by gender and group were conducted to examine the relationship between significantly different emotional prosody recognition scores and composite measures of tone sensitivity. These scores were also correlated with YMRS and MADRS scores to assess the impact of symptom severity in the patient group as a whole, and per gender.

Given the novelty of our study and the reduced statistical power of our smaller gender/diagnostic subtype/mood phase subgroups, we chose not to Bonferroni correct the post hoc tests or correlations as the correction is too statistically stringent and has been associated with an increase in type II error (Nakagawa, 2004; Perneger, 1998; Rothman, 1990).

10.5 Results

10.5.1 *Demographic variables*

The patient group as a whole did not differ from controls in age ($t(100)=-1.48$, $p>.05$), gender ($\chi^2(1)=.50$, $p>.05$) or premorbid IQ ($t(77.91)=1.23$, $p>.05$); nor did male and female BD subgroups differ from their control counterparts in this regard (Age male/female: $t(34)= -1.95$, $p>.05$ and $t(64)=-.34$, $p>.05$; Premorbid IQ male/female: $t(17.41)=1.52$, $p>.05$ and $t(63)=.41$, $p>.05$). In the BD group there were no significant differences in the mood state (depressed, mixed, manic and euthymic) distribution between male and female patients (χ^2 (3) =2.60 $p>.05$), nor were there differences in current manic and depressive symptom severity between male and female patients (see Table 10.)

Table 10. *Demographic and clinical characteristics of the sample*

Group	**Control (N=52)**			**BD (N=50)**		**Control males (n=20)**		**Control females (n=32)**			**BD males (n=16)**			**BD Females (n=34)**		**Male BD–female BD group comparisons**	
	M	***SD***	***n***	***M***	***SD***	***M***	***SD***	***M***	***SD***	***n***	***M***	***SD***	***n***	***M***	***SD***	***t***	***p***
Diagnostic subtype (BD I/ BD II)			38/12							13/3			25/9				
Age	34.22	14.31		37.90	12.57	32.55	15.54	34.88	13.61		42.19	13.64		35.91	11.51	1.70	.10
WTAR (scaled)	111.65	7.24		109.40	12.10	112.55	5.05	111.06	8.39		107.33	12.57		110.00	12.00	-.71	.48
Age of onset	-	-		18.42	15.90	-	-	-	-		25.07	12.76		15.10	16.46	2.05	.05
Age of diagnosis	-	-		27.26	11.86	-	-	-	-		26.88	16.32		27.44	9.7	.54	.59
YMRS	-	-		6.33	5.48	-	-	-	-		6.400	5.91		6.29	5.37	-.17	.86
MADRS	-	-		11.92	10.10	-	-	-	-		10.47	9.18		12.56	10.54	-.89	.38

Note: WTAR = Wechsler Test of Adult Intelligence, YMRS = Young Mania Rating Scale, MADRS = Montgomery Asberg depression Rating Scale

10.5.2 *Emotional and linguistic prosody labelling*

Table 11 shows the emotional prosody data. There was a trend for a main effect of group, with accuracy performance being worse for patients (M=77.94, SD=12.39) compared to controls (M=81.34, SD=8.91; F (1, 93) = 2.81, p=.10, d = .32). A main effect of gender (F (1, 93) =4.94, p<.05) indicated that females were more accurate than males overall (Female M = 81.36, SD= 8.21; Male M = 76.60, SD = 14.09), whilst a main effect of emotional tone (F (3,279) =163.96, p<.001) suggested that overall performance varied across emotions (recognition accuracy occurred in the descending order of neutral, sad, happy, fear). There was no significant interaction between emotional tone and group, and no group by gender interaction. However, a significant three way interaction between group, gender and emotional tone (F (3,279) = 3.13, p<.05) indicated that the effect of emotional tone on accuracy performance across groups varied according to gender. In males, patient/control performance differed according to emotional tone (F (3, 96) =3.63, p<.05), with male BD patients (M=66.36, SD=12.79) being significantly less accurate at labelling happy sentences than their control counterparts (M=78.95, SD=12.79; F (1, 32) =4.71, p<.05, d=.73), but exhibiting no differences for the labelling of other emotions (fear, sad, neutral). For females there were no group or interaction effects evident. No main effect of group and no interactions between group and utterance type or group, utterance type and gender were evident for the linguistic prosody task.

Table 11. *Mean accuracy scores and group comparisons for the emotional prosody task.*

Task		**Control**		**BD**		***Whole group comparisons***		**Control Male**		**BD Male**		***Male group comparisons***		**Control Female**		**BD Female**		***Female group comparisons***	
		M	**SD**	**M**	**SD**	***F***	***p***	**M**	**SD**	**M**	**SD**	***F***	***p***	**M**	**SD**	**M**	**SD**	***F***	***p***
Emotional prosody labelling	Happy	81.63	11.02	75.42	17.11	4.57	.04	78.95	12.79	66.36	20.82	4.71	.04	83.28	9.63	79.67	13.42	1.50	.23
	Sad	83.78	15.11	80.26	14.76	1.35	.25	81.34	17.60	80.30	16.36	.03	.86	85.22	13.51	80.24	14.22	2.07	.16
	Fear	63.10	15.68	62.19	15.08	.09	.77	57.89	13.71	60.00	19.45	.14	.71	66.19	16.16	63.21	12.77	.67	.42
	Neutral	95.72	7.01	93.84	10.19	.84	.36	95.45	8.30	90.62	20.49	.89	.35	95.88	6.26	95.45	5.89	.08	.78

10.5.3 *Tone discrimination*

Table 12 displays the mean sensitivity scores for each group on the three tone discrimination tasks. There was no significant group effect, or two and three way interactions for the pitch discrimination task. For amplitude discrimination, there was no significant main effect of group, but there was a significant two way interaction between group and amplitude deviation level sensitivity (F (2.71, 241.07) =5.60, p<.01); this was not influenced by gender. Follow up one way ANOVAs revealed that patients were significantly less sensitive than controls at discriminating 2dB (F (1, 96) =4.80, p<.05) and 3dB amplitude deviations (F (1, 96) =3.82, $p\leq$.05). For the duration discrimination task there was no significant variation in group related sensitivity as a result of the deviation level, and no interaction between group and gender. However, we observed a significant group effect with patients (M=.38, SD=.10) being less sensitive to duration differences than controls (M=.44, SD=.10) overall (F (1, 94) =8.56, p<.01). Follow up one way ANOVAs revealed that patients were significantly less sensitive than controls at discriminating duration deviations of 5% (F(1,96)=5.46, p<.05), 10% (F(1,97)=4.97, p<.05) and 50% (F(1,97)=3.98, p<.05).

Table 12. *Mean sensitivity scores for the tone discrimination and linguistic prosody tasks*

Task	Deviation difference or utterance type	Control		BD		Group comparisons		
		M	***SD***	***M***	***SD***	***Cohen's d***	***F***	***p***
Amplitude dB	**One**	.10	.41	.02	.67	0.14	1.02	.32
	Two	.71	.47	.48	.56	0.44	4.80	.03
	Three	1.25	.61	1.0	.72	0.37	3.82	.05
	Five	.24	.44	.18	.53	0.12	.45	.51
	Ten	2.28	.56	2.20	.32	0.18	.42	.52
	Overall	.92	.45	.81	.38	0.26	1.95	.17
Duration %	**Two**	.07	.07	.05	.22	0.12	1.33	.25
	Five	.16	.17	.09	.09	0.51	5.50	.02
	Ten	.28	.18	.20	.15	0.48	5.00	.03
	Twenty-five	.74	.17	.67	.06	0.55	3.51	.06
	Fifty	.94	.04	.90	.19	0.29	3.98	.05
	Overall	.44	.10	.38	.10	0.6	8.56	.00
Frequency %	**Two**	.47	.04	.49	.19	-0.15	.07	.80
	Five	.66	.32	.71	.32	-0.16	.54	.46
	Ten	.83	.20	.84	.27	-0.04	.05	.82
	Twenty-five	.94	.35	.89	.21	0.17	3.40	.07
	Fifty	.94	.07	.9 3	.14	0.09	.76	.39
	Overall	.77	.16	.77	.19	0	.01	.94
Linguistic	**Inquisitive**	1.73	.88	1.17	1.60	0.43	1.67	.21
	Declarative	1.17	.41	2.45	.86	-1.90	1.84	.18
	Overall	2.24	.60	1.81	1.09	0.49	2.06	.16

10.5.4 *Subgroup analyses*

There were no between group main effects or interactions on any of the tasks for patients diagnosed as having BD I versus BD II (all *p*'s >.05), nor were there any between group main effects or interactions on any of the tasks for patients classified as euthymic, depressed or mixed/manic (all *p*'s >.05). Further bivariate correlations supported this, indicating no associations between composite tone sensitivity/happy prosody recognition and scores on the MADRS and YMRS in the patient group as a whole, or in the male BD subgroup (all *p's* >.05). However, a significant correlation between YMRS scores and composite amplitude sensitivity was evident in females patients only (r=.45, p<.05; all other *p's*>.05).

10.5.5 *Correlations*

To investigate whether auditory processing sensitivity is related to emotional prosody performance, we examined correlations between the labelling of happy sentences (given the significant group differences on this variable) and composite tone discrimination scores, separately per gender. There were no correlations amongst emotional prosody labelling accuracy for happy intonations and composite performance on any of the tone discrimination tasks in either male or female control groups or the male patient group. In female BD patients we observed a significant relationship between accuracy labelling performance for happy intonations and composite tone discrimination performance for pitch (r=.52, p<.01) and amplitude (r=.39, p<.05) deviations.

10.6 Discussion

This study sought to investigate the prosodic emotion processing profile of BD. We were interested in understanding whether patients with the disorder were impaired in their ability to process emotional prosody, and specifically, whether this was modulated by gender. Two secondary aims were to address the impact of current mood state on performance in BD, and to examine whether any impairment in emotional prosody recognition was specific to its emotional nature, or whether it was an outcome of an inability to process early sensory-perceptual acoustic information in general. These questions were formulated to address limitations in the emergent emotional prosody literature in BD and to examine the applicability of recent work from schizophrenia populations in which elementary sensory deficits have been found to contribute significantly to emotional prosody disturbances (Leitman, et al., 2005; Leitman, et al., 2010).

In support of our hypothesis, we found no group differences in linguistic prosody discrimination and observed a trend towards an overall BD group deficit in emotional prosody labelling. That is, we found that emotional prosody accuracy for the labelling of happy intonations was impaired in the patient group, although this was specific to males. These findings are congruent with existing research demonstrating enhanced emotional prosody

recognition for women relative to men in both healthy and psychiatric populations (Bozikas, et al., 2006a; Schirmer, et al., 2002; Szymanowski, et al., 2007).

These findings cannot be explained by mood symptom severity or differences in the gender distribution of patients in different mood states. Rather, such an emotion specific gender effect in the absence of a significant group by gender interaction suggests that impairment for the recognition of happy prosody in males is reflective of differences in cognitive assessment rather than sensory-perception (Ross & Monnot, 2011). That is, given that overall emotional prosody performance deficits were not modulated by gender, the deficient processing of happy intonations is likely to be related to the way it is attended and responded to in males versus females with BD. Indeed, BD patients have demonstrated impairments on higher order cognitive tasks sensitive to frontal brain activity (Sweeney, Kmiec, & Kupfer, 2000). Dysfunction in this region has also been associated with impaired processing of happy prosody (Rymarczyk & Grabowska, 2007). Our results suggest this may be more pronounced in males with the disorder, although replication of this gender specific finding is needed.

As expected, we found significantly reduced sensitivity in the patient group for the discrimination of duration deviations, but not for the discrimination of deviations in pitch. We also found that amplitude sensitivity for lower level (2dB and 3dB) deviations was modulated by BD diagnosis. Patient performances on these tasks were between a quarter and half a standard deviation lower than controls. These findings are consistent with some previous, yet indirect psychophysiological studies in which BD patients have demonstrated impaired durational mismatch negativity and altered receptivity to amplitude deviances (e.g., Gogos, et al., 2009; Jahshan, et al., 2012; Lee, et al., 2012). Interestingly, we did not observe any relationships between the recognition of happy and duration sensitivity for either male or female patients, although the recognition of happy intonations was correlated with the capacity to discriminate pitch and amplitude cues; this was specific to female patients only. It thus appears that the lower order perception of amplitude, duration and pitch properties do not sit at the core of difficulties in emotional prosody perception in male's with BD.

When taken together, our findings indicate the existence of a female advantage for the processing of prosody in BD, which does not accord with the only prior study to have

investigated gender effects on emotional prosody recognition in the disorder (Bozikas, et al., 2007). However, given that our sample size was substantially more powerful and possibly better matched with regards to age and IQ across genders, it is arguable that our results offer a more precise reflection of the status of prosodic processing in BD. More generally, these findings sit well in the context of evidence demonstrating gender biases in cognitive performance in both psychiatric and healthy populations (Bozikas, et al., 2006a; Gogos, et al., 2010; Schirmer, et al., 2002).

As with previous studies, ours was not without its limitations. For example, the small sample subgroup sizes of male and female patients after stratification into mixed/manic, depressed and euthymic states prevented us from conducting subgroup analyses by gender. We were also unable to directly compare these mood subgroups to controls due to the restricted subgroup power. Although within group analyses failed to differentiate performance across mixed/manic, euthymic or depressed BD patients on any of the tasks, it is still possible that mood may have had an effect on performance. Thus, given the rather heterogeneous nature of our BD sample, our results should certainly be interpreted with caution. Moreover, although we found no evidence of medication effects on auditory-prosodic processing when comparing patients on and off medication, we were unable to completely partial out their effects. However, medications have not had an effect on emotional prosody recognition in the past (Hoekert, 2007; Mitchell, et al., 2004b). Future studies should aim to recruit larger samples across all major mood states as well as to explicitly examine the effects of medication on these samples.

Despite these limitations, our study was the first of its kind to examine the auditory-prosodic emotion processing profile of a sample of patients explicitly diagnosed as having BD. Importantly, we found that male BD patients were impaired in their ability to recognise happy emotional prosody but this was not underpinned by lower level impairments in the detection of acoustic information, current mood status or diagnostic subtype. However, the combination of lower order sensory-perceptual patient impairments in amplitude and duration sensitivity *and* higher-order patient impairments for the labelling of happy prosody may be reflective of a top-down, cognitive problem, although this remains to be seen.

As there is some evidence indicating that males are at increased risk of unfavourable psychosocial outcome in BD (Tohen, Waternaux C. M, & Tsuang M. T, 1990; Yen et al., 2009b), it is possible that gender related differences in emotion recognition contribute to psychosocial impairments in males with the disorder. Indeed, there is growing support for the notion that intact social cognition plays a vital role in healthy psychosocial function (Hoertnagl, et al., 2011; Martino, et al., 2011b). Future studies would do well to examine the relationship shared between emotional prosody recognition and quality of life or social and interpersonal functioning in BD

CHAPTER 11: THEORY OF MIND IN BIPOLAR DISORDER

11.1 Chapter guide

Van Rheenen, T. E., & Rossell, S. L. (2013). Picture Sequencing Task Performance Indicates Theory of Mind Deficit in Bipolar Disorder. *Journal of Affective Disorders,* 151, 1132-1134

The background chapters indicated that theory of mind is impaired in bipolar disorder (BD); however research on this topic is in its infancy. The aim of the investigation described in this chapter was to establish the capacity for theory of mind in the sample of BD patients recruited as part of this research, using a well-recognised measure commonly employed in the schizophrenia literature, which has not yet been validated for use in BD. This chapter comprises the aforementioned article that can be found in Appendix I in its published form.

This paper attracted the attention of Medwire News, leading to a news article titled "Theory of mind deficit found in bipolar disorder" (See Appendix J for a copy).

11.2 Abstract

Background: This paper reports the performance of DSM-IV-TR diagnosed bipolar disorder (BD) patients on a well-recognised measure of theory of mind (ToM) that commonly elicits group-related differences in schizophrenia research.

Methods: Forty-nine BD patients and 49 controls completed Langdon and Coltheart's (1999) Picture Sequencing Task.

Results: Relative to controls, patients with BD performed significantly worse on the ToM relevant false-belief stories of the picture sequencing task, but not on the control stories requiring social script knowledge, executive control or an understanding of causal connections. There were no differences in the ToM performance of symptomatic versus euthymic patients or those categorised as having BD I or BD II.

Limitations: As sub group sizes were small, data suggesting a trait-like deficit in ToM should be interpreted with caution.

Conclusions: The results support previous evidence of ToM impairment in BD and indicate a potential endophenotypic overlap in the features of both schizophrenia and BD.

11.3 Introduction

Theory of Mind (ToM) describes the ability to make inferences about other's emotional and mental states (Premack & Woodruff, 1978). It enables empathy and perspective taking and is critical to adaptive social communication and interaction. There is limited research on ToM in bipolar disorder (BD), but the emergent literature from both behavioural and imaging paradigms does appear to indicate patient (relative to control) abnormalities that occur regardless of mood state (Bora, et al., 2005; Cusi, et al., 2012; Donohoe et al., 2012; Kerr, et al., 2003; McKinnon, Cusi, & MacQueen, 2010; Olley, et al., 2005; Rossell & Van Rheenen, 2013). Indeed, a recent meta-analysis estimated impairments in the disorder to be of moderate effect size for both basic and complex forms of ToM (Samamé, et al., 2012). These impairments have been evidenced across a variety of measures, including those that index patients' capacity to understand false beliefs or interpret complex social cues (Bora, et al., 2005; Inoue, et al., 2004), although no studies have investigated ToM performance on the *Picture Sequencing Task* in BD. This is important, given that the picture sequencing task a) has multiple internal controls that examine different aspects of functioning with the same type of stimuli, and b) is a commonly used measure of ToM in schizophrenia research that consistently elicits patient deficits in comparison to healthy controls (e.g., Gavilán & García-Albea, 2011; Langdon, Coltheart, & Ward, 2006; Langdon, Coltheart, Ward, & Catts, 2002; Langdon, Davies, & Coltheart, 2002). Importantly, the task permits the parcelling out of different aspects of cognitive reasoning to enable the relatively pure investigation of basic ToM skills.

As it is becoming increasingly recognised that schizophrenia and BD share genetic and phenotypic overlap, the use of common measures to assess and compare ToM across these disorders is necessary to enable greater understanding of possible endophenotypic features common to the two. Moreover, examination of tasks that incorporate control conditions as an integral aspect, are necessary for understanding the precise nature of any potential deficit in BD. In light of this, we aimed to examine ToM performance on the picture sequencing task in a well characterised sample of BD patients to determine whether impairments commonly elicited by it in schizophrenia, extend to BD as well.

11.4 Methods

This study was approved by the Alfred Hospital and Swinburne University Human Ethics Review Boards and abided by the Declaration of Helsinki. Written informed consent was obtained from each participant before the study began.

11.4.1 *Participants*

The clinical sample comprised 49 patients diagnosed as having DSM-IV-TR BD using the Mini International Neuropsychiatric Interview (MINI: Sheehan, et al., 1998). Patients were recruited via community support groups and general advertisements and were all out-patients. The Young Mania Rating Scale (YMRS: Young, et al., 1978) and the Montgomery Asberg Depression Rating Scale (MADRS: Montgomery & Asberg, 1979) were used to assess current symptomatology. Patients with visual impairments, neurological disorder and/or a history of substance/alcohol abuse or dependence during the past six months were excluded. Thirty one patients were taking antipsychotics, 15 were taking antidepressants, 16 were taking mood stabilisers and 10 were taking benzodiazepines.

A control sample of 49 healthy participants was recruited for comparison purposes by general advertisement and contacts of the authors. Using the MINI screen, no control participant had a current diagnosis or previous history of psychiatric illness (Axis I). An immediate family history of mood and psychiatric disorder, in addition to a personal history of neurological disorder, current or previous alcohol/substance dependence or abuse, visual impairments and current psychiatric medication use was exclusion criteria for all controls.

All participants were fluent in English, were between the ages of 18 and 65 years and had an estimated pre-morbid IQ as scored by the Wechsler Test Of Adult Reading (WTAR) of >90. Clinical and demographic data for the sample are presented in Table 13.

Table 13. *Demographic and clinical characteristics of the sample*

	Control	BD	Group comparisons	
	M(SD)	***M (SD)***	t / χ^2	***p***
N	49	49		
Gender (#M/F)	18/31	16/33	.18	.67
Age	34.65 (14.43)	38.45 (13.20)	-1.36	.17
WTAR	111.692 (7.28)	109.20 (12.11)	1.34	.18
Diagnostic subtype (#BD I /BD II)		37/12		
Age of onset (years)	-	20.37 (10.72)	-	-
Age of diagnosis (years)	-	28.00 (10.93)	-	-
MADRS	-	11.86 (10.12)	-	-
YMRS	-	6.31 (5.50)	-	-
#Depressed (MADRS>8)		16	-	-
#(hypo)Manic (YMRS>8)		4	-	-
#Mixed (MADRS>8 & YMRS>8)		12	-	-
#Euthymic(MADRS≤8 & YMRS≤8)		17	-	-

Note: M/F = Male / Female, WTAR = Wechsler Test of Adult Intelligence, YMRS = Young Mania Rating Scale (Theoretical Range: 0-60), MADRS = Montgomery Asberg Depression Rating Scale (Theoretical Range: 0-60)

11.4.2 *Materials*

ToM was assessed with the *Picture Sequencing Task* (described in detail by Langdon & Coltheart, 1999) which requires the logical sequencing of a series of stories with different primary contentions. *False Belief* stories reflecting ToM ability and requiring inferences of false beliefs were the primary story type of interest. *Mechanical* stories requiring reasoning about causal relationships, *Social Script* stories requiring reasoning using social script knowledge and *Capture* stories requiring inhibition of salient inappropriate information to determine a logical sequence were considered control stories. Higher scores represented better ability to carry out the given tasks demands.

11.5 Results

Independent sample t-tests and Chi square tests revealed no significant differences in age, gender or pre-morbid IQ between the two groups.

A two (group) by four (story type) repeated measures ANOVA revealed a significant main effect for story type (F [3,288] =83.82, p<.05; errors increasing in the order of social script, mechanical, false-belief and capture stories for both patients and controls), a significant main effect of group (F[1,96]=4.31, p<.05; patients performed worse than controls) as well as a significant two way interaction of story type and group (F [3,288]=3.09, p<.05; accuracy performance varied according to story type). Follow up independent samples t-tests failed to reveal group related differences in performance on the picture sequencing mechanical, social script and capture control stories. Patients did however, perform significantly worse on the false-belief task than controls, in the order of an 11.86% decrement in accuracy (Table 14).

Table 14. *Mean accuracy scores and group comparisons for the picture sequencing task*

Story type	**Control**			**BD**			**Group comparisons**		
	n	*M*	*SD*	*n*	*M*	*SD*	*t*	*p*	*d*
Social Script*	49	22.59	2.24	49	22.12	2.60	1.00	.34	.02
Mechanical*	49	21.24	3.32	49	21.00	3.82	.34	.74	.06
Capture*	49	15.96	3.83	49	14.98	4.32	1.19	.24	.24
False Belief*	49	19.78	3.72	49	16.94	6.31	2.71	.01	.55

Note: * Theoretical Range 0-24

To better understand the effects of medication, diagnostic subtype and mood on false belief performance in the patient group, a series of post-hoc analyses were run; four post hoc independent samples t-tests using medication class (dichotomously coded to yes/no) as the grouping variable revealed no significant difference on the false-belief task for patients on or off antipsychotics (t[44]=-1.58, p=.12), antidepressants (t[44]=-1.00, p=.32), mood stabilisers (t[44]=-.11, p=.92) or benzodiazepines (t[44]=-51, p=.61). Similarly, an independent samples t-

test using diagnostic subtype as the grouping variable revealed no significant differences on the task between patients classified as BD I and BD II (t[47], =-1.71, p=.10).

As the sample size of some of the mood phase subgroups were too small for meaningful subgroup analysis, we collapsed the mixed and manic groups into one (resulting n=16) and compared this to patients meeting criteria for euthymia or depression in a one way ANOVA. Although there was a trend for differences between the groups (F [2, 46] =2.95, p=.06), follow up planned contrasts revealed no significant differences between any of the groups (all p's>.09). This state independent effect was supported by bivariate correlations that indicated no significant relationships between YMRS (r=.20, p=.16) or MADRS (r=.08, p= 60) scores and performance on the task.

11.6 Discussion

The present study examined ToM performance on a picture sequencing task in patients with BD, with a view to assessing the use of this task as a common and sufficient measure of ToM across both schizophrenia and bipolar disorder. This study specifically aimed to enable greater understanding of possible endophenotypic features common to the two disorders, and to advance the BD ToM literature by examining performance on a never before tested task in BD research that is capable of parcelling out the effects of different types of non-ToM cognitive reasoning.

Our results indicated that there were no group related differences on the mechanical, social script and capture control stories, but patients did perform significantly worse than controls when sequencing false-belief stories. With an effects size difference in the medium range, this finding supports previous evidence of ToM impairments in BD, and particularly on similar measures referencing a false-belief component (Inoue, et al., 2004; Kerr, et al., 2003). Importantly, this data is also supportive of recent meta-analytic findings in the disorder (Samamé, et al., 2012).

The pattern of findings presented here are unlikely to be a result of sensitivity to increased task difficulty, given that no group differences were evident on the most difficult story type (i.e., capture stories). Moreover, as we found no differences in ToM performance

between patients on and off different classes of medications, false-belief story task performance is also unlikely to be attributed to patients' medication status. Thus, the results suggest that patients with BD demonstrate a selective ToM deficit that cannot be accounted for by poor social script knowledge, executive control or an inability to understand causal connections.

This significant difference was consistently demonstrated when examined across both diagnostic subtypes (BDI and BDII) and mood phases (mixed, depressed and euthymic), although sub sample sizes within these groups were small, and these results should be interpreted with caution. Nevertheless, they do appear to suggest that patient impairment for false belief inferences may represent a stable, trait-like feature in BD. The results of the present study also mirror some prior evidence of selective false-belief impairments on the picture sequencing task in schizophrenia patients (Langdon, et al., 2006), and are supportive of past studies indicating trait-like ToM deficits in BD itself (Bora, et al., 2005; Olley, et al., 2005). Thus, impairment on the task may represent potential overlap in the features and possibly genetic aetiology of schizophrenia and BD. Use of the task in endophenotype studies that aim to examine social-cognition on the bipolar-schizophrenia spectrum could therefore be valuable.

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CHAPTER 12: EMOTION REGULATION IN BIPOLAR DISORDER

12.1 Chapter guide

Van Rheenen, T. E., Murray, G. & Rossell, S. L. (in submission). An examination of the emotion regulation profile of bipolar disorder.

This chapter is the fifth of the empirical chapters and the last focussing on a specific process in bipolar disorder (BD). It comprises the aforementioned article that is currently in submission. The aim of the investigation reported here was to characterise the emotion regulation profile of the sample of BD patients recruited as part of this project, using a multi-dimensional measure of emotion regulation

12.2 Abstract

Background: The aetiology of bipolar disorder (BD) is unclear, although impairments in emotion regulation have been implicated as a potential contributor. While increasing research tends to focus on the extent to which patients regulate their emotions and moods using positive or negative strategies, surprisingly, few studies have comprehensively investigated emotion regulation across the full range of its different dimensions, including that concerning the capacity to be aware of and accepting of emotions, and to appropriately differentiate between the full range of emotions and their associated somatic sensations. This investigation was designed to overcome this paucity of research by utilising a multi-dimensional measure of difficulties in emotion regulation, to characterise the emotion regulation profile of BD.

Methods: 50 BD patients and 52 healthy controls completed the Difficulties in Emotion Regulation Scale (DERS), which assesses emotion regulation across multiple dimensions concerning the awareness, acceptance and understanding of emotion as well as the modulation of emotional intensity and arousal.

Results: Examination of the DERS revealed that in addition to problems in the modulation of emotions (impulse control, access to appropriate strategies), patients with BD had considerably less emotional clarity and were avoidant/unaccepting their emotional responses when compared to controls.

Conclusions: The current study suggests that emotion regulation is compromised across a range of dimensions in BD. These findings represent an important step toward informing the development of treatment strategies to remediate these difficulties. However, further study is needed to see if these findings hold in other BD cohorts.

12.3 Introduction

Bipolar disorder (BD) is a complex emotional disorder characterised by extreme fluctuations between markedly irritable, euphoric or depressive mood states (American Psychiatric Association, 2000). The aetiology of BD is unclear, although difficulties in emotion regulation are becoming increasingly recognised in models of BD pathogenesis (e.g., Green, et al., 2007; Gruber, et al., 2012; Meyer, et al., 2001; Stange et al., 2013; Townsend & Altshuler, 2012). Typically emotion regulation in BD is operationalised as the modulation of overt and covert emotional behaviours and cognitions for the purpose of altering their intensity (Phillips, et al., 2008). Current research has thus tended to focus on the extent to which patients use cognitive strategies such as rumination or re-appraisal for this purpose (Green, et al., 2011; Rowland, et al., 2013b). It is becoming clear that in comparison to healthy individuals, patients with BD tend to rely more heavily on negative coping strategies, including rumination and catastrophising, to regulate mood (Green, et al., 2011; Gruber, et al., 2011; Rowland et al., 2013a; Van der Gucht, et al., 2009).

However, whilst control over emotions is certainly important in regulating emotional experience, emotion regulation also broadly involves the capacity to be aware of and accepting of emotions, and to appropriately differentiate between the full range of emotions and their associated somatic sensations (Gratz & Roemer, 2004). Indeed, the ability to acknowledge, accept, monitor, and evaluate negative and positive emotions may be equally important in maintaining healthy emotional equilibrium, given that deficits in these abilities have been implicated in reduced resilience for coping with stress, heightened vulnerability to depressive symptoms, neuroticism, rumination and anxiety disorders, all of which are associated with BD (Flynn & Rudolph, 2010; Gohm & Clore, 2002; Salovey, et al., 1995; Tull & Roemer, 2007).

Few studies have comprehensively investigated emotion regulation across the range of these different dimensions in BD, which is surprising given the significance that deficits in one or all of them may have for clinical and psychosocial outcomes in the disorder. Indeed, a better characterisation of all emotion regulation difficulties experienced by patients with BD

may afford insight into the underlying processes at play in the disorder, and may thus provide potential targets for the development of new interventions for its treatment.

With this in mind, the purpose of the present study was to provide an investigation of emotion regulation in BD, using a clinically-relevant measure designed to provide an integrative assessment of its multiple dimensions. Specifically, this study sought to characterise the emotion regulation profile of BD patients by comparing them to controls on a multifaceted measure of emotion regulation called the *Difficulties in Emotion Regulation Scale* (DERS; Gratz & Roemer, 2004). The DERS offers an assessment tool with the capacity to capture the full range of emotion regulation difficulties in a single measure. It defines emotion regulation as involving six core dimensions; 1) the tendency to be aware and acknowledging of one's emotions (Awareness dimension), 2) the tendency to be accepting of one's distressing emotional states (Non-acceptance dimension), 3) the ability to control impulses (Impulse dimension), 4) the ability to access appropriate and adaptive emotion regulation strategies (Strategies dimension), 5) the ability to maintain goal focussed behaviours when experiencing negative affect (Goals dimension) and 6) the ability to distinguish among emotion states and be clear of one's emotions (Clarity dimension).

We are aware of one recent study that has examined the DERS in a BD population (Becerra, et al., 2013). The authors of this study reported omnibus group differences across the six dimensions, such that in comparison to controls, euthymic patients with BD reported greater difficulties in regulating emotion overall. This effect was largely driven by the increased patient related endorsement of items on all but the Awareness dimension of the DERS. Importantly, this work made a first step toward characterising emotion regulation difficulties in BD. It is nonetheless preliminary, and further research is needed to establish whether the results replicate. Hence the focus of the current investigation was to establish whether this pattern of findings holds across different BD cohorts.

On the basis of these recent findings, we hypothesised that patients with BD would report higher scores on the DERS, and thus, demonstrate greater difficulties in regulating emotions. These difficulties were expected to be driven by greater patient endorsement of items on the following dimensions; Non-acceptance, Impulse, Strategies, Goals and Clarity. A

further research question pertained to whether DERS scores would be modulated by current mood state or diagnostic subtype status.

12.4 Methods

This study was approved by the Alfred Hospital and Swinburne University Human Ethics Review Boards and abided by the Declaration of Helsinki. Written informed consent was obtained from each participant before the study began.

12.4.1 *Participants*

The clinical sample comprised 50 patients diagnosed as having DSM-IV-TR BD using the Mini International Neuropsychiatric Interview (MINI: Sheehan et al., 1998). Patients were recruited via community support groups and general advertisements and were all out-patients. Current symptomology was assessed using the Young Mania Rating Scale (YMRS: Young, Biggs, Ziegler, & Meyer, 1978) and the Montgomery Asberg Depression Rating Scale (MADRS: Montgomery & Asberg, 1979). Patients with visual impairments, neurological disorder and/or a history of substance/alcohol abuse or dependence during the past six months were excluded. Thirty three patients were taking antipsychotics, 16 were taking antidepressants, 16 were taking mood stabilisers and 10 were taking benzodiazepines. Demographic and clinical characteristics are presented in Table 15.

A control sample of 52 healthy participants was recruited for comparison purposes by general advertisement and contacts of the authors. The MINI screen indicated that no control participant had a current diagnosis or previous history of psychiatric illness (Axis I). Participants were excluded from the control group based on an immediate family history of mood and psychiatric disorder, in addition to a personal history of neurological disorder, current or previous alcohol/substance dependence or abuse, visual impairments and/or current psychiatric medication.

All participants were fluent in English, were between the ages of 18 and 65 years and had an estimated pre-morbid IQ of >90, as scored by the Wechsler Test of Adult Reading (WTAR).

12.4.2 *Materials*

Emotion regulation was measured with the *Difficulties in Emotion Regulation Scale* (DERS: described in detail by Gratz & Roemer, 2004). The DERS is a 36 item measure of the approach, understanding and modulation of emotions, that is scored on a five point Likert scale ranging from "almost never" (1) to "almost always" (5). It consists of six subscales made up of items reflecting 1) non-acceptance of emotional responses (Non-acceptance), ii) difficulties engaging in goal directed behaviours when experiencing negative emotions (Goals), iii) difficulties in impulse control (Impulse), iv) lack of emotional awareness (Awareness), v) limited access to emotion regulation strategies (Strategies) and vi) lack of emotional clarity (Clarity). Items are summed to form a total score for each subscale. An aggregate score comprising total scores from each subscale is also calculated, with higher scores representing greater difficulties in emotion regulation. The DERS shows good validity, internal consistency (Cronbach's $\alpha = .93$) and test- retest reliability ($\varrho = .88$).

12.4.3 *Statistical analysis*

Demographic and clinical group differences were assessed using one-way between-groups analysis of variance (ANOVA) or Chi square tests where relevant. A multivariate analysis of variance (MANOVA) was employed to investigate group differences in scores on the DERS. To better understand the effects of mood and diagnostic status on emotion regulation, this analysis was re-run in the patient group: in the first analysis patient diagnosis (BD I; n=38 or BD II; n=12) was entered as the between group's factor. For the second analysis we compared symptomatic (n=33) and euthymic patients (n=17, defined as those that met strict criteria for YMRS and MADRS scores ≤ 8) by entering current mood status as the between groups factor. Post hoc bivariate correlations were conducted across the whole patient sample to further examine relationships between emotion regulation measures and symptom severity on the YMRS and MADRS. MANOVAs were also used to examine the influence of current medications on performance for patients on and off medications. To correct for multiple testing, the α was set at .01 for all analyses.

12.5 Results

There were no significant differences in age, gender or pre-morbid IQ between the two groups (Table 15).

Table 15. *Demographic and clinical characteristics of the sample*

	Control	BD	Group comparisons	
	M(SD)	***M (SD)***	***F/ χ^2***	***p***
N	52	50		
Gender (M/F)	20/32	16/34	.47	.50
Age	33.98 (14.28)	38.44 (13.02)	2.71	.10
WTAR	111.64 (7.24)	109.40 (12.06)	1.29	.26
Age of onset (years)	-	20.25 (10.63)	-	-
Age of diagnosis (years)	-	28.10 (10.84)	-	-
MADRS	-	11.82 (10.02)	-	-
YMRS	-	6.22 (5.47)	-	-

Note: M/F = Male / Female, WTAR = Wechsler Test of Adult Intelligence, YMRS = Young Mania Rating Scale (Theoretical Range: 0-60), MADRS = Montgomery Asberg Depression Rating Scale (Theoretical Range: 0-60)

12.5.1 *Emotion regulation on the DERS*

Figure 17 presents the means, standard deviations of DERS scores in the patient and control groups. There was a significant group difference in DERS scores overall (*F*(6,93)=7.05, p<.01, *Wilks Λ*=.69). Further analysis indicated that patients endorsed more items than controls on the Clarity(*F*(1,98)=16.07, *p*<.001, *d*=0.80), Impulse (*F*(1,98)=32.76, *p*<.001, *d*=1.13), Non-acceptance (*F*(1,98)=26.86, *p*<.001, *d*= 1.02), Goals (*F*(1,98)=26.13, *p*<.001, *d*=1.02) and Strategies subscales (*F*(1,98)=35.57, *p*<.001, *d*=1.02) but not on the Awareness subscale (*F*(1,98)=.03, *p*=.86, *d*=1.18).

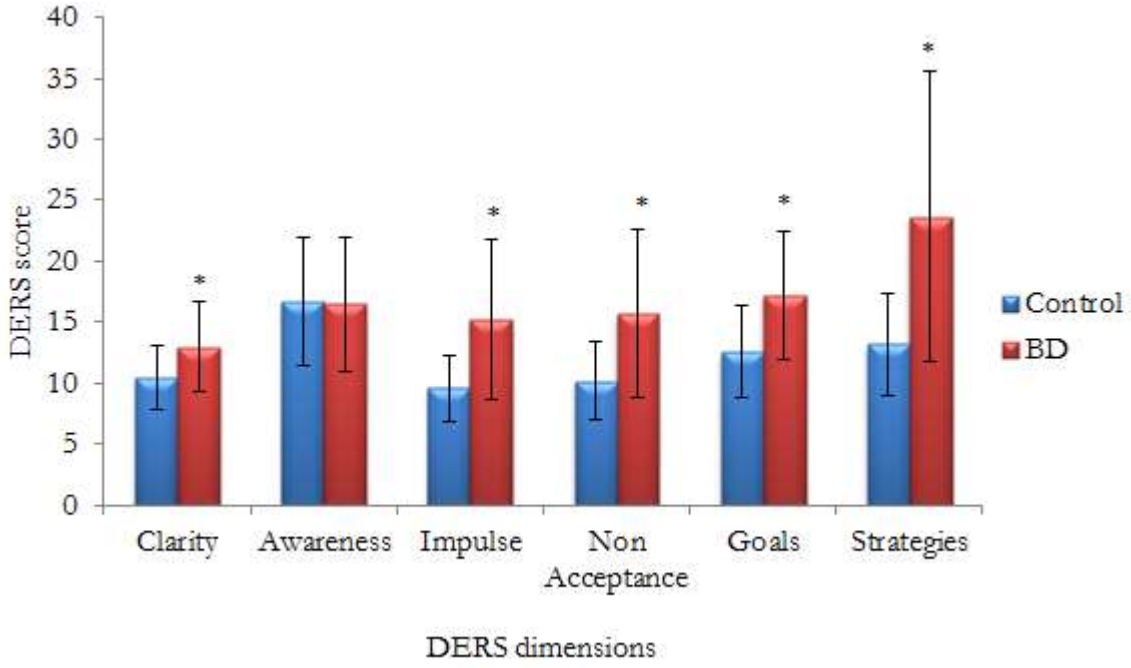

Figure 17. Means and standard deviations on the DERS across BD and control groups

Note: * p<.001; DERS=Difficulties in Emotion Regulation Scale; Higher scores indicates greater difficulties in emotion regulation; Theoretical ranges: DERS Clarity 5-25; DERS Awareness 6-30; DERS Impulse 6-30; DERS Non Acceptance 6-30; DERS Goals 5-25; DERS Strategies 8-40

12.5.2 *Subgroup analyses*

There were no significant differences between euthymic and symptomatic groups on any key demographic variables, nor were there differences between patients with BD I and BD II (all *p*'s >.05). There were also no significant omnibus effects of emotion regulation between these groups (euthymic versus symptomatic: F (6, 40) =1.27, p=.29; BD versus BD II: F (6, 41) =.67, p=.68). However, bivariate correlations indicated that increased manic symptomatology (according to the YMRS) was related to higher scores on the Non-acceptance (r=.40, p<.01), and Strategies (r=.35, p<.01) subscales of the DERS in all patients. Similarly, greater

depression symptomatology (according to the MADRS) was also related to higher scores on the Clarity (r=.42, p<.01), Impulse (r=.48, p<.01) and Strategies (r=.52, p<.01) subscales of the DERS.

MANOVAs using medication (dichotomously coded to yes/no) as the between subjects factor revealed no significant omnibus differences on the DERS for patients on or off antipsychotics/anticonvulsants (F (6,38) = 2.03, p = .08), antidepressants (F(6,38) = 1.60, p = .17), lithium (F(6,38) = .64, p =.69) and benzodiazepines (*Wilks Λ*=.69, F(6,38) =1.87, p=.11).

12.6 Discussion

This study utilised the DERS, a multi-dimensional measure of difficulties in emotion regulation, to characterise the emotion regulation profile of BD. The DERS reflects an integrative conceptualisation of emotion regulation and provides a single, reliable assessment of its various dimensions. As expected, patients with BD reported greater difficulties in regulating emotions overall. This was largely driven by higher patient-related scores on the Clarity, Non-Acceptance, Strategies, Impulse and Goals dimensions of the DERS. There were no significant group differences on the Awareness subscale however; suggesting that patients had no difficulty in acknowledging and attending to their emotions. This finding is consistent with recent reports using the DERS in another BD cohort (Becerra, et al., 2013), and might be explained as a function of the heightened frequency with which emotions such as depression and euphoria are experienced in BD. Indeed, the positive impact of the greater occurrence of these emotions in patients might be to increase their attention to them. Regardless, in the present data this finding suggests that the dysregulation of emotion in BD cannot be explained by an influence of an inability to be aware of it.

Further analysis revealed that difficulties in emotion regulation did not differ between symptomatic versus euthymic patients or those diagnosed with BD I versus BD II. Although this speaks to some evidence suggesting that emotion regulation difficulties in BD have a trait-like quality, correlational analyses still indicated that some of the DERS dimensions were associated with the presence of manic and depressive symptoms in patients (Becerra, et al., 2013; Chang, et al., 2000; Cichon, et al., 2011; Green, et al., 2011; Grigoroiu-Serbănescu, et al.,

1989; Gruber, et al., 2011; Hayden, et al., 2008; Jones, et al., 2006; Salavert, et al., 2007). These findings appear to indicate that regardless of current mood episode, greater symptom severity is associated with worse emotion regulation.

Taken together, the current results suggest that emotion regulation in BD is characterised by poor acceptance and differentiation of emotion, as well as difficulties in inhibiting impulsive actions, using appropriate regulation strategies to modulate emotions, and engaging in adaptive behaviours to achieve a desired goal when experiencing negative mood. These results are consistent with broader research findings using other measures, in which some of these dimensions have been demonstrated as being impaired in BD (Green, et al., 2007; Green, et al., 2011; Gruber, et al., 2011; Gruber, et al., 2012; Rowland, et al., 2013a; Townsend & Altshuler, 2012).

Notably, the findings that patients with BD have considerably less emotional clarity and are avoidant/unaccepting of responses to negative emotions have considerable clinical implications; poor emotional clarity has been postulated to place greater emphasis on resources needed to understand emotional experiences, in turn decreasing the allocation of resources necessary for the formulation of adaptive behaviours (Salovey, et al., 1995). Moreover, increased use of suppression or emotional avoidance is predictive of negative coping strategies (Gohm & Clore, 2000). The intact capacity for these emotion regulation processes is thus important for adaptive goal directed behaviours as well as positive reinterpretation of emotional experiences (Gohm & Clore, 2002; Hayes, Wilson, Gifford, Follette, & Strosahl, 1996). Routine inclusion of therapeutic strategies focusing on improving the clarity and increasing the acceptance of emotions might therefore be of benefit to clinical interventions in BD, particularly as these dimensions appear to be quite amendable to change (Gratz & Gunderson, 2006; Gratz & Tull, 2010).

Readers are cautioned to interpret the current findings in light of a number of limitations. Firstly, as the DERS is a self-report measure, its use requires a degree of insight for accurate reporting. It is as such, inherently susceptible to personal bias (Atkinson, Zibin, & Chuang, 1997). Secondly, the relatively small sample of BD mania and depression subgroups was a limitation to explicitly comparing the effects of different mood phenotypes on emotion

regulation measures in our sample. Finally, although medication effects were not evident when comparing patients on and off classes of psychotropic medication, it was not possible to partial out all of its effects and this may have had a confounding effect on the current findings.

Despite these limitations, the current study does add considerably to the literature by characterising the emotion regulation profile of BD using the DERS. Importantly, a better understanding of the emotion regulation difficulties experienced by patients with BD can guide the development of new treatment strategies that may ultimately improve outcomes in the disorder. As the profile of emotion regulation deficits evidenced here supports previous preliminary research using the DERS in BD, it is possible that the measure may be efficacious as a diagnostic tool to assess emotion regulation in patients with the disorder (Becerra, et al., 2013). Importantly, as there is evidence that the DERS is sensitive to change over time, it may also represent a clinically valuable outcome measure by which treatment progress may be assessed (Gratz & Gunderson, 2006; Gratz & Tull, 2010). Additional research is needed to explore these possibilities further.

CHAPTER 13: GENETIC INFLUENCES ON FEATURES OF BIPOLAR DISORDER

13.1 Chapter guide

Van Rheenen, T.E., Bozaoglu, K., and Rossell, S.L. (in submission). The influence of Catechol-*O*-methyltransferase on cognition is modulated by bipolar disorder diagnosis.

The previous empirical chapters focussed specifically on defining the neurocognitive, social cognitive and emotion regulation profiles of bipolar disorder (BD). This chapter is broader in scope, and builds on propositions specified in Chapter 2, that neurocognition, social cognition and emotion regulation represent candidate BD endophenotypes that may be influenced by genes linked to the dopamine and serotonin neurotransmitter systems. Here we present investigations in which an endophenotype strategy has been employed to investigate the influence of two specific genes on these processes.

This chapter comprises three sections; the first section (see 13.2 - 13.6) consists of the aforementioned article that is currently under review. The submitted article focuses specifically on the role that Catechol-*O*-methyltransferase (COMT) plays in neurocognition in BD. The second and third sections of this chapter comprise additional brief reports describing i) analyses investigating the influence of COMT on aspects of social cognition and emotion regulation, and ii) analyses investigating the influence of Tryptophan Hydroxylase 2 (TPH2) on neurocognition, social cognition and emotion regulation in the disorder. The latter two reports have not been submitted as scientific articles, but have been provided to ensure appropriate follow through in the context of arguments concerning the role of *both* of these genes in neurocognition, *and* social cognition and emotion regulation made in Chapter 2. These accompanying reports can be found in sections 13.7 and 13.12 respectively.

Given that genetic association studies require substantial power that can be reduced by the use of a large number of assessments, the analyses described in this chapter use measures of only the most well validated or theoretically viable candidate endophenotypes. Thus, only some of the measures that have been described in previous chapters have been used here. For example, while all sections describe analyses using a full neurocognitive battery (given that neurocognition is one of the most widely researched candidate endophenotypes in BD), the accompanying sections utilise only facial emotion processing or emotion regulation measures,

but not emotional prosody processing or theory of mind measures (given that the former have large heritability estimates, have been more widely studied and are found to be more consistently impaired in BD than the latter ; see Chapters 2, 3 and 4 and Anokhin, Golosheykin, & Heath, 2010 and ; Canli, Ferri, & Duman, 2009). Similarly, as the number of single nucleotide polymorphisms (SNPs) examined also reduces the power to detect an effect, the accompanying analyses utilise only specific SNPs that have received wide support for their involvement in these candidate endophenotypes. These SNPs are described in more detail in the accompanying sections

13.2 Abstract

Background: Catechol-O-Methyltransferase (COMT) variations have been implicated in the genetic predisposition to bipolar disorder (BD) and may modulate candidate endophenotypes related to neurocognition. Given the sparse empirical data examining this proposition, the aim of the current study was to determine the relationship of three single nucleotide polymorphisms (SNPs) within the COMT gene (rs165599, rs4680 and rs4818) and performance on standardised cognitive battery in a well characterised sample of BD patients compared to controls.

Methods: Fifty BD patients and 52 healthy controls were genotyped across rs165599, rs4680 and rs4818, and their association with performance on a battery of cognitive measures tested in a case-control design.

Results: Significant interaction effects were evident for executive functioning across all three SNPs, and for visuospatial learning on the rs4680. On these tasks, G allelotype carrier performance was associated with better performance in the control group, but worse performance in the patient group.

Conclusions: These novel findings suggest that aberrations of executive function and visuospatial memory in BD are, at least partially, the result of a significant influence of COMT on these particular domains. Thus, COMT may be involved in the pathophysiology of the disorder by influencing the capacity for certain cognitive processes.

13.3 Introduction

Bipolar disorder (BD) is a complex mental illness likely to represent the outcome of several interacting biological and environmental processes. It is now well established that BD is highly transmissible, with family, twin and adoption studies indicating a genetic basis to familial aggregation and heritability estimated at approximately 85% (e.g., Gershon et al., 1982; Kieseppä, Partonen, Haukka, Kaprio, & Jouko Lönnqvist, 2004; Lichtenstein, et al., 2009; McGuffin et al., 2003; Rice et al., 1987; Smoller & Finn, 2003; Strober et al., 1988; Weissman et al., 1984; Winokur, Coryell, Keller, Endicott, & Leon, 1995). Nevertheless, the specific genes involved in the disorder are unclear, owing in part to frequently unsuccessful replications across studies, the likely polygenic interaction between multiple genes of small effect, and the heterogeneity of BD's nosological description. Attempts to identify genetic determinants of the disorder have included genome-wide association studies. Whilst these are informative, they tend to require much power to return consistent results. Recent and growing consensus in BD research circles however, supports an endophenotype approach for exploring BD's genetic aetiology (Arts, et al., 2008; Bora, et al., 2009a; Frangou, 2013; Frantom, et al., 2008; Hasler, Drevets, Gould, Gottesman, & Manji, 2006). The approach affords a promising opportunity to examine transitional variables that mediate between genotype and phenotype (Gottesman & Gould, 2003). Indeed, endophenotypes are likely to have stronger links to the underlying genetic makeup of BD than that of its phenotypic description. As genes are selected on the basis of psychopathologies presumed to confer vulnerability for the disorder, the endophenotype approach is fast becoming a feasible mechanism for facilitating progress toward uncovering BD's genetic basis (Glahn, et al., 2010).

Neuropsychological impairments including deficits in prefrontal neurocognition represent consistent findings in BD research, and have been proposed as candidate endophenotypes for the disorder (e.g., Arts, et al., 2008; Balanzá-Martínez, et al., 2005; Bora, et al., 2011; Burdick, Goldberg, Harrow, Faull, & Malhotra, 2006; Burdick, et al., 2011; Van Rheenen & Rossell, In press - Chapter 8). In particular, meta analytic effects sizes for executive and memory/learning impairments in euthymic samples are large, and impairments

on these domains have been evidenced in healthy first degree relatives of BD probands (Balanzá-Martínez, et al., 2008; Bora, et al., 2009a; Frantom, et al., 2008). These deficits are linked to underlying neural abnormalities that are modulated in part, by the dopaminergic neurotransmitter system (Floresco & Magyar, 2006; Jay, 2003).

Dopamine is certainly a critical component of the functioning of the prefrontal cortex (Cools, Barker, Sahakian, & Robbins, 2001; Lange et al., 1992; Mattay et al., 2002), serving to both enhance processing in some cases and retard it in others. As the influence of dopamine on cognition has been proposed to follow an "inverted U" function, whereby performance is impaired by sub or supra-optimal dopamine activity, the rate of dopamine transmission is important for optimal cognitive performance (Cools & Robbins, 2004). The density of dopamine transporters that remove extracellular dopamine is less profuse in the prefrontal cortex than elsewhere in the brain, and the catabolism of dopamine is therefore a critical process in this region. Its degradation is mediated by Catechol-O-Methyltransferase (COMT), a predominantly brain expressed protein encoded by a BD candidate gene located on chromosome 22q11.21 (Craddock, et al., 2005). The COMT gene comprises a number of single nucleotide polymorphisms (SNP) that are implicated in severe psychiatric disorders (Craddock, et al., 2006; Funke et al., 2005; Massat et al., 2011; Ohara, et al., 1998; Shifman et al., 2002).

These specific variations in COMT's nucleotide sequence are posited to influence cognition by modulating dopamine signalling pathways in the frontal cortex (Bilder et al., 2002; Egan, et al., 2001). For example, a SNP occurring at codon $Val^{158}Met$ (rs Id: 4680; G/A) of the COMT gene results in a functional nucleotide variation that encodes an enzyme involved in altering the rate of synaptic dopamine degradation. Other SNPs such as the synonymous $lLeu^{136}Leu$ (rs Id: 4818; G/C) and one occurring at the 3 prime untranslated region of COMT (rs Id: 165599; G/A) impacts enzymatic activity by affecting mRNA expression, although the mechanisms of action are not clear (Bray et al., 2003; Nackley et al., 2006).

Individual differences in these SNPs may impact cognition by influencing the concentration of dopamine in the prefrontal cortex. For example, the G allele's of rs4680 and rs4818 are high activity alleles that either directly (due to reduced thermo-stability) or indirectly

(by affecting mRNA translation efficiency) result in substantial increases in the rate of dopaminergic catabolism compared to their low activity allelotype counterparts (Bray, et al., 2003; Diatchenko et al., 2005; Nackley, et al., 2006; Roussos, Giakoumaki, Pavlakis, & Bitsios, 2008). Consequently, and depending on the basal dopaminergic background in which COMT exerts its effect, variation in enzymatic action may impair or facilitate cognitive performance by increasing or decreasing dopaminergic load (Tunbridge, et al., 2006).

Indeed, fluctuating dopaminergic activity has been critically implicated in the pathophysiology of BD (Berk et al., 2007; Cousins, et al., 2009), and there is early support from association studies that implicate rs4818 (Massat, et al., 2011), rs165599 (Ancín et al., 2011; Funke, et al., 2005) and rs4680 in the disorder (Lachman, et al., 1996a; Papolos, et al., 1998). Nevertheless, there has been no research directly examining rs4818 in relation to cognition in patients with BD, despite some evidence of differential allelotype effects on planning and problem solving in healthy people (Roussos, et al., 2008).

There is also only very limited research specifically investigating the effect of rs165599 and rs4680 on cognition in well-defined BD samples, and the findings of existing studies are mixed. For example, one group reported worse overall cognitive (as referenced by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score) and delayed memory (as referenced by the delayed memory index score on the RBANS) performance in homozygous G allele carriers (Dickerson et al., 2006), while three others failed to find associations between COMT and cognition at all (Szöke et al., 2006; Wirgenes, et al., 2010). Another group failed to find an association between rs4680 and BD, but reported worse verbal memory performance (as referenced by the California Verbal Learning Task) in homozygous BD carriers of the rs165599 G allele (Burdick, et al., 2007). Another group still, reported the opposite effect, with better performance evident in allele G patient carriers on a number of measures of executive function in both rs4680 (as referenced by the Wisconsin Card Sorting Task and Digit Span backwards) and rs165599 (as referenced by Matrix Reasoning and the Stroop task) . Better verbal fluency (as referenced by the Controlled Oral Word Association Test; FAS-F) and estimated IQ were however, specific to G allele patient carriers of rs4680, whilst better visuo-spatial memory (as referenced by the Rey-Osterrieth

Figure Copy Task) and execution IQ was specific to rs165599 G allele patient carriers in this sample (Soeiro-de-Souza, Machado-Vieira, Soares Bio, Do Prado, & Moreno, 2012b).

It is not clear how to explain these inconsistencies in the literature, but it is possible that they are due to differences in sample characteristics and methodologies. Indeed, a failure to consistently use standardised cognitive batteries coupled with potential differences in patient mood symptomatology and the varied use of statistical correction between these past studies may certainly account for mixed findings. To this end, the aim of the current study was to examine relationships between three COMT SNPs and candidate cognitive endophenotypes in a well characterised sample of BD patients compared to controls, on a standardised battery with established validity in both schizophrenia and BD populations, using a conservative statistical correction for multiple testing.

We genotyped 51 BD patients and 52 healthy controls across rs165599, rs4680 and rs4818, and tested their association with performance on a series of standardised cognitive tasks in a case-control design. We hypothesised that COMT variation would influence cognitive function in both BD and healthy control groups. A further research question pertained to whether the effect of any or all of these SNPs varied across cognitive tasks.

13.4 Methods and Materials

This study was approved by the Alfred Hospital and Swinburne University Human Ethics Review Boards and abided by the Declaration of Helsinki. Written informed consent was obtained from each participant before the study began.

13.4.1 *Participants*

The clinical sample comprised 50 patients diagnosed as having DSM-IV-TR BD (BD I n=38 and BD II n=12) using the Mini International Neuropsychiatric Interview (MINI; Sheehan, et al., 1998). Patients were recruited via community support groups and general advertisements and were all out-patients. The mean Young Mania Rating Scale (YMRS; Young, et al., 1978) and Montgomery Asberg Depression Rating Scale (MADRS; Montgomery

& Asberg, 1979) scores indicated the presence of subclinical manic but slightly elevated depression symptomatology in the sample. Patients with visual impairments, neurological disorder and/or a history of substance/alcohol abuse or dependence during the past six months were excluded.

A control sample of 52 healthy participants was recruited for comparison purposes. The MINI screen indicated that no control participant had a current diagnosis or previous history of psychiatric illness (Axis I). Participants were excluded from the control group based on an immediate family history of mood and psychiatric disorder, in addition to a personal history of neurological disorder, current or previous alcohol/substance dependence or abuse, visual impairments and/or current psychiatric medication.

All participants were fluent in English, were between the ages of 18 and 65 years and had an estimated pre-morbid IQ of >90, as scored by the Wechsler Test of Adult Reading (WTAR).

13.4.2 *Materials*

13.4.2.1 Neurocognition.

All subtests from the MATRICS Consensus Cognitive Battery (MCCB; see Nuechterlein & Green, 2006 for task instructions), in addition to the Trail Making Test-Part B (TMT-B) and the Colour-Word Stroop (see Delis, et al., 2001; Reitan & Wolfson, 1985 for task instructions) were included as a brief assessment of cognitive functioning across the domains of speed of processing (Trail Making Test Part A: TMT-A, Brief Assessment of Cognition in Schizophrenia; Symbol Coding: BACS-SC, Category Fluency: Animal naming), attention/vigilance (Continuous Performance Test-Identical Pairs: CPT), working memory (Wechsler Memory Scale; Spatial Span: WMS-SS, Letter Number Span: LNS), verbal learning (Hopkins Verbal Learning Test Revised: HVLT-R), visuospatial learning (Brief Visuospatial Memory Test-Revised: BVMT-R), executive function (Neuropsychological Assessment Battery: Mazes: NAB Mazes; TMT-B; Stroop), and social cognition (Mayer-Salovey-Caruso Emotional Intelligence Test; Managing Emotions: MSCIET).

13.4.2.2 Genotyping

DNA was extracted from whole blood using QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany) according to manufacturer's instructions and was genotyped for COMT rs165599 (allele's A/G), rs4680 (allele's A/G) and rs4818 (allele's G/C). Following variant identification, SNP assays were designed using the Sequenom Assay Design Suite 1.0 software (Sequenom, San Diego CA). Each assay design produces a set of DNA oligos or primer sequences: two primers for PCR amplification and a third for the primer extension reaction to detect the specific sequence variation or mutation site. Genotyping was carried out using the MassARRAY system (Sequenom, San Diego CA) as per the manufacturer's standard protocols. The MassArray platform relies on a primer extension reaction in combination with a mix of mass-tagged dideoxy-nucleotides (iPlex Gold chemistry) to generate a pool of oligo products that are analysed by chip-based matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF). Adherence to Hardy-Weinberg equilibrium (HWE) and allele frequency were assessed to ensure validity of the results.

13.4.3 *Statistical analysis*

Participants were stratified according to G allele presence (G+ allelotype; GG or GA/GC) or absence (G- allelotype; AA, CC). Groups were not analysed by genotype because of the small number of homozygous G allele carriers relative to their homozygous and heterozygous allelotype counterparts. All analyses were carried out using the allele G because it has been reported as the risk allele for BD, schizophrenia and cognition (Burdick, et al., 2007; Egan, et al., 2001; Malhotra, et al., 2002; Shifman, et al., 2004; Tsai et al., 2003). One way analysis of variance (ANOVA) and Chi square tests were employed to compare groups and allelotypes on demographic measures. Multivariate analyses of variance (MANOVA) or covariance (MANCOVA; to control for demographic differences as presented below) with group and allelotype as between subject's factors and the 12 cognitive tasks as within subjects factors were used to examine potential omnibus effects on cognition for each of the SNPs. As we were interested in examining allelotype effects and interactions with participant group

performance on specific cognitive measures a priori, between subject effects were also examined. We applied a conservative alpha level of .01 to these effects to account for multiple testing, and followed up significant results with post hoc univariate analyses comparing either group (split by allelotype) or allelotype (split by group).

13.5 Results

13.5.1 *Descriptive analyses*

The COMT genotype distributions for all SNPs were in Hardy-Weinberg equilibrium (rs165599 χ^2=0.04; rs4680 χ^2=2.26; rs4818 χ^2=0.29). Table 16 presents the frequencies of G allelotypes for rs165599, rs4680 and rs4818 in BD and control groups. There were no significant differences in age or gender between groups or allelotypes overall (data not shown). There were also no differences in age or gender for the allelotypes of SNPs rs4680 and rs4818 within either participant group. However, in the BD group there were significantly more female relative to male carriers of the G- type of rs165599, while in the control group there was a trend for G- allele carriers to be older than G+ allele carriers. As a result we controlled for both age and gender in subsequent analyses of this SNP. There were no differences between the SNP allelotypes for age of illness onset, YMRS or MADRS scores in the BD group. Table 17 presents the demographic characteristics and group comparisons for the three SNP allelotypes in the BD and control groups.

Table 16. *Allelotype distribution for rs165599, rs4680 and rs4818 in BD and control groups*

SNP	**Allele**	**Control** (*N*=52: Caucasian n=41, Asian n=9, Eurasian n=1, African n=1)	**BD** (*N*=50; all Caucasian)
		n	*n*
Rs165599	G+	34	20
	G-	18	31
Rs4680	G+	43	35
	G-	9	13
Rs4818	G+	36	29
	G-	16	21

Table 17. *Descriptive characteristics and comparisons of G+ and G- allelotypes for BD and control participants*

		Control							BD						
		G+			G-				G+			G-			
SNP	**Demographic variable**	***N***	***M***	***SD***	***N***	***M***	***SD***	**Group comparisons**	***N***	***M***	***SD***	***N***	***M***	***SD***	**Group comparisons**
Rs165599															
	Age		31.15	13.48		38.89	15.13	$F(1,50)=3.57$, $p=.07$		39.70	12.71		37.77	13.36	$F(1,48)=.26$, $p=.61$
	Gender (M/F)	14/20			8/10			$\chi^2(1)=.05$, $p=.82$	10/10			7/23			$\chi^2(1)=3.80$, $p=.05$
	MADRS		-	-		-	-			10.55	10.64		12.52	9.81	$F(1,48)=.44$, $p=51$
	YMRS		-	-		-	-			6.20	5.85		6.17	5.39	$F(1,47)=.26$, $p=.61$
	Age of illness onset		-	-		-	-			22.00	12.60		16.26	17.64	$F(1,47)=.00$, $p=.99$
Rs4680															
	Age		32.72	14.12		39.11	15.47	$F(1,50)=1.48$, $p=.23$		38.86	12.79		36.00	13.17	$F(1,45)=.44$, $p=.51$
	Gender(M/F)*	19/24			3/6			$\chi^2(1)=.36$, $p=.55$	13/22			2/10			$\chi^2(1)=1.72$, $p=.19$
	MADRS		-	-		-	-			10.47	9.74		14.92	10.16	$F(1,44)=.18$, $p=.68$
	YMRS		-	-		-	-			6.12	5.57		6.92	5.90	$F(1,44)=.26$, $p=.61$
	Age of illness onset		-	-		-	-			17.79	18.20		20.80	7.05	$F(1,41)=.26$, $p=.61$
Rs4818															
	Age		34.44	14.57		32.44	14.42	$F(1,50)=.21$,		39.62	13.42		37.05	12.91	$F(1,47)=.49$,

		Control							BD						
		G+			G-				G+			G-			
SNP	**Demographic variable**	***N***	***M***	***SD***	***N***	***M***	***SD***	**Group comparisons**	***N***	***M***	***SD***	***N***	***M***	***SD***	**Group comparisons**
	Gender(M/F)^	13/23			9/7			p=.65 $\chi^2(1)$=1.84, p=.18	10/19			6/14			p=.51 $\chi^2(1)$=.12, p=.74
	MADRS		-	-		-	-			12.14	10.87		11.60	9.18	$F(1,46)$=.03, p=.86
	YMRS		-	-		-	-			6.21	5.02		6.35	6.35	$F(1,46)$=.01, p=.93
	Age of illness onset		-	-		-	-			17.85	19.87		19.88	7.31	$F(1,42)$=.16, p=.69

Note: MADRS=Montgomery Asberg Depression Rating Scale; YMRS=Young Mania Rating Scale; * genotype analysis failure for one male and one female patient; ^ genotype analysis failure for one male participant

13.5.2 *Allelotype*group analyses*

Omnibus, task specific effects, interactions and follow up within group analyses for rs165599, rs4680 and rs4818 allelotypes are specified below.

13.5.2.1 Rs165599

A 2(allelotype)*2(group) MANCOVA controlling for age and gender indicated a significant main effect of group (*Wilks Λ*=.75, *F*(12,81)= 2.20, *p*=.02) and allelotype (*Wilks Λ*=.76, *F*(12,81)= 2.20, *p*=.02) as well as a trend level two way interaction (*Wilks Λ*=.81, *F*(12,81)=1.60, *p*=.12). There were no task specific effects of rs165599 but there were task specific interactions on the Stroop (*F* (1, 92) =11.09, *p*=.01) and the BVMT-R (*F* (1, 92) =5.38, *p*=.02). The latter did not survive correction for multiple testing however. Further post hoc analyses (split by group) controlling for age and gender, revealed that Stroop performance was better for G+ relative to G- allele carriers in the control group (*F*(1,48)=9.37, *p*=.004, *d*=-1.06). Conversely, Stroop performance was significantly worse for G+ relative to G- allele carriers in the BD group (*F*(1,46)=5.15, *p*=.03, *d*=0.67).

13.5.2.2 Rs4680

A 2(allelotype)*2(group) MANOVA indicated no group (*Wilks Λ*=.84, *F*(12,80=1.20, *p*=.30) or allelotype effect (*Wilks Λ*=.82, *F*(12,80)=1.44.*p*=.17) and no overall interaction (*Wilks Λ*=.18, *F*(12,80)=1.47, *p*=.15). However, significant task specific allelotype*group interactions were evident for performance on the BVMT-R (*F* (1, 91) =6.63, *p*=.01) and the Stroop (*F* (1, 91) =7.27, *p*=.01). Further post hoc analyses (split by group) revealed that in the control group, G+ allele carrier performance was significantly better than G- allele carrier performance on the Stroop (*F*(1,50)=.14.86, *p*=.01, *d*=-1.28) but not the BVMT-R (*F*(1,49)=.36, *p*=.55, *d*=0.20), whilst in the BD group G+ allele carrier performance was significantly worse relative to G- allele carrier performance on the BVMT-R task (*F*(1,43)=6.48, *p*=.02, *d*=-1.00) but not the Stroop (*F*(1,44)=.83, *p*=.37, *d*=0.34).

13.5.2.3 Rs4818

A 2(allelotype)*2(group) MANOVA for rs4818 indicated a main effect of participant type (*Wilks Λ*=.79, *F*(12,82)=1.84, *p*=.05), but no effect for allelotype (*Wilks Λ*=.86, *F*(12,82)=106, *p*=.41) and no overall interaction (*Wilks Λ*=.84, *F*(12,82)=1.27, *p*=.25). However, a task specific allelotype*group interaction was evident for performance on the Stroop (*F* (1, 93) =6.35, *p*=.01). Further post hoc analyses (split by group) revealed that G+ allele performance was significantly better than G- carriers on the Stroop in the control group (*F*(1,50)=8.52, *p*=.01, *d*=-0.85) but allelotype performance differences were not significant in the BD group (*F*(1,46)=1.48, *p*=.23, *d*=0.37).

13.5.3 *Between groups allelotypes comparison*

Figure 18 and Figure 19 present the results of significant task specific allelotype*group interactions. On all of these tasks, BD G+ carriers had significantly worse performance than control G+ carriers, while there was no difference in performance for G- allelotypes across groups (see Table 18).

Table 18. *Simple effects comparisons between BD and controls for G+ and G- allelotype performance*

SNP		***G+***						***G-***					
		C		**BD**				**C**		**BD**			
		M	***SD***	***M***	***SD***	***d***	***Between group effect***	***M***	***SD***	***M***	***SD***	***d***	***Between group effect***
Rs165599													
	Stroop	43.68	8.70	61.20	22.93	-1.01	$F(1,50)=9.891$, $p=.003$	54.00	10.75	48.83	12.72	0.44	$F(1.44)=2.32$, $p=.14$
Rs4680													
	BVMT-R	30.14	4.81	23.97	7.82	0.95	$F(1,73)=17.71$, $p=.000$	29.00	6.82	30.00	3.91	-0.17	$F(1,19)=.18$, $p=.68$
	Stroop	44.95	8.91	55.50	20.73	-0.66	$F(1,75)=9.05$, $p=.004$	58.22	11.60	49.67	12.58	0.71	$F(1,19)=2.54$, $p=.13$
Rs4818													
	Stroop	44.58	9.35	56.79	21.78	-0.73	$F(1,62)=9.16$, $p=.004$	53.25	11.04	50.20	12.47	0.26	$F(1,62)=.59$, $p=.45$

Note: BVMT-R= Brief Visual Memory Test-Revised; note that higher scores on BVMT-R represent better performance whilst higher scores on the Stroop represent worse performance.

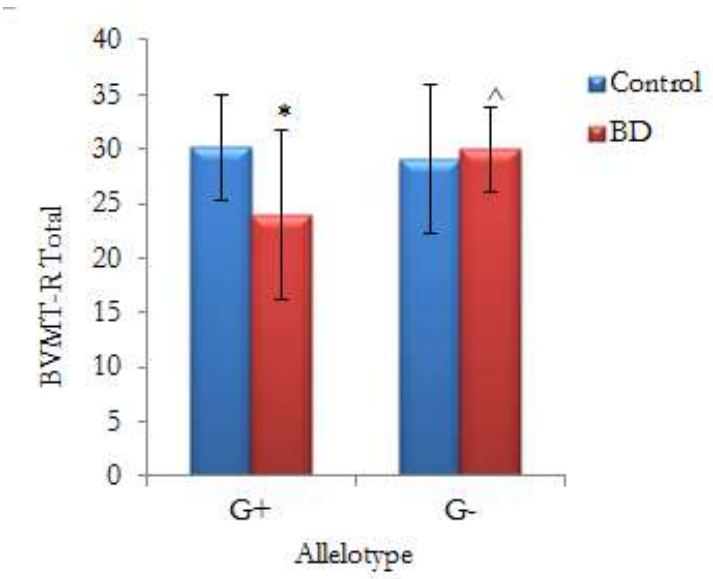

Figure 18. Performance on BVMT-R by rs4680 allelotypes in BD and healthy control groups

Note: BVMT-R-Brief Visual Memory Task-Revised; *p<.01 G+ allelotype difference between groups; ^ p<.02 BD group difference between allelotypes

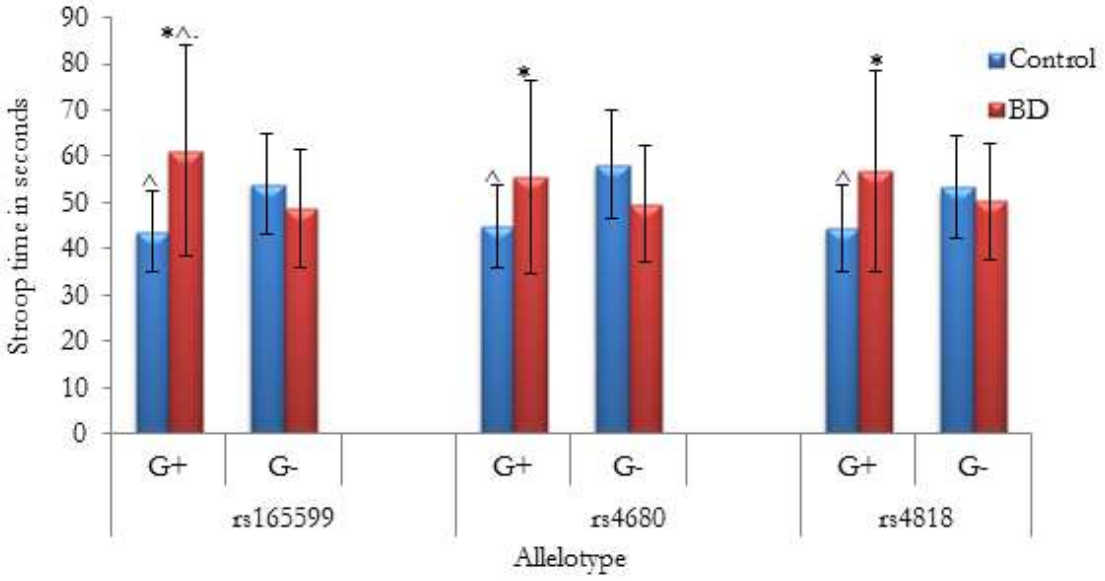

Figure 19. Performance on the Stroop task by rs165599, rs4680 and rs4818 allelotypes in BD and healthy control groups

Note: *p<.01 G+ allelotype difference between groups; ^ p<.05 within group difference between allelotypes

13.6 Discussion

In this study we tested associations between neurocognition and three SNPs within the COMT gene in BD and healthy control groups. To the best of our knowledge this is one of only a small number of published studies that have explicitly examined cognitive associations with SNPs' rs4680 or rs165599 in BD, and the first to examine them for rs4818. This is also the first study to report diagnostic*allelotype interactions on specific cognitive markers for rs165599, rs4680 and rs4818 across BD and control groups. Our data showed that the presence of the G allele across all three SNPs was associated with better performance on a measure of executive function in controls, but worse performance on the same measure in patients. The same pattern was evident for a measure of visuospatial learning for rs4680.

Control G allele carriers in this study far outperformed BD G allele carriers on these measures, whereas the performance of those with an absence of G allele loading was similar for both groups. In addition, the presence of some significant differences between alleloypes

in both groups (controls: Stroop performance on all SNPs, BD: rs165599 Stroop and rs4680 BVMT-R) suggests that the COMT SNPs examined here modulate visuospatial memory and executive function differently for controls and patients. Our data indicates that the G alleles of these SNP confer cognitive risk in the disorder.

These results are consistent with studies that have observed poorer G allele performance for rs165599 (Burdick, et al., 2007) and rs4680 (Dickerson, et al., 2006) on measures of verbal and delayed memory in BD. However, we observed the opposite cognitive pattern in the control group which contradicts control findings in these previous studies. This inverse pattern may be explained by differences in the dopaminergic background of the groups on which COMT was exerting its effect. Indeed, the influence of COMT on cognition is likely to depend on the level of local dopaminergic input that determines one's position on the inverted U curve in any given environmental or genetic context (Prata et al., 2009; Tunbridge, et al., 2006). Although the precise influence the different allele's of rs165599 have for enzymatic activity are not clear, the G alleles of rs4680 and rs4818 are becoming increasingly recognised as high activity enzymatic catabolism codons for dopamine. Given the presence of relatively low level manic, yet slightly elevated depressive symptomatology in our patient sample, it is certainly possible that our results of sub-optimal G+ allele performance between groups, represents the outcome of an exacerbated catabolic rate on a background of pre-existing hypo-dopaminergic activity. Conversely, optimal cognitive function in healthy patients with the absence of G allele loading was likely exceeded due to the presence of a supra-optimal dopaminergic load as catalysed by lower enzymatic allele activity. As this pattern was present for executive functioning across all three SNPs, these findings further support evidence suggesting that rs165599 is of functional significance regardless of its non-coding status (Bray, et al., 2003; Burdick, et al., 2007; Shifman, et al., 2002).

The inverted U theory may also explain the divergence between our results and a recent study where the authors found better executive performance for rs165599 in manic and mixed BD G allele carriers (Soeiro-de-Souza, et al., 2012b). It is certainly possible that the reduction in basal dopaminergic levels resulting from G allele loading in the context of mania related hyper-dopaminergic activity in these patients facilitated performance. Conversely,

heightened dopamine load in low activity allele carriers was likely to have exceeded that required for optimal executive function.

Our findings are in agreement with a large body of evidence suggesting a role for COMT in cognition in the healthy population (Blasi et al., 2005; Caldú et al., 2007; de Frias et al., 2005; Mitaki et al., 2013). The significant differences we observed in executive performance between allele G carriers in controls and BD patients across all COMT SNPs also concurs with reports that executive functioning is one of the most severely impaired neurocognitive domains in BD. Similarly, visuospatial deficits may also represent a core cognitive feature of the disorder (Rubinsztein, et al., 2000; Sweeney, et al., 2000). That these deficits occur independently of mood state, and are also present in persons at genetically high risk for the disorder at a higher rate than that of the normal population, is certainly consistent with endophenotypic criteria (Bora, et al., 2009a). Thus, in light of the present findings it is possible that aberrations of executive function and visuospatial memory are, at least partially, the result of a significant influence of COMT on these particular domains. In particular, the SNP specific effect of rs4680 on visuospatial memory may be a consequence of its direct influence on enzymatic dopamine activity, given that rs165599 and rs4818 are thought to contribute to the degradation of dopamine indirectly by affecting mRNA translation instead.

These results should be interpreted with caution however, as there were a number of limitations in the current study. Firstly, given variability in cognitive performance across allele types in the patient group, and that the overall size of our sample was small, it is possible that effects or interactions for other cognitive tasks were not apparent. Secondly, the small sample precluded analysis of genotype specific effects and thus, precise differences between genotypic distributions across the three SNPs remain unclear. Finally, the restricted power prevented the co-analysis of other dopaminergic genes that may play a role in cognition in BD. As such, we were unable to examine additive genetic interaction effects in this study. Future research aiming to replicate these results in larger sample sizes is warranted.

Nevertheless, this study adds considerably to the growing body of research implicating COMT in cognition and BD, and suggests that the effects of certain SNPs on executive cognition is modulated by BD diagnosis. Indeed, it appears that COMT may be involved in

the pathophysiology of the disorder, at least in part, by influencing the capacity for certain cognitive processes

13.7 Accompanying analysis one: The influence of the Catechol-*O*-methyltransferase Val^{158}Met polymorphism on emotion processing and emotion regulation performance

This section comprises a brief report on the analyses that were conducted to investigate the influence of the Catechol-*O*-methyltransferase (COMT) Val^{158}Met single nucleotide polymorphism (SNP) on facial emotion processing and emotion regulation performance in BD patients and healthy controls. The Val^{158}Met SNP was specifically chosen for examination here because it has received the most support (in comparison to other COMT SNPs) with regards to its role in these processes (see Chapter 2, section 2.3.3.1). The sample used in these analyses is the same as that referred to in section 13.4.1. Therefore, sample characteristics are not reported again here. This section has not been written as a scientific article at this stage.

13.8 Introduction

There is growing evidence that patients with bipolar disorder (BD) are impaired in their ability to recognise emotion from facial expressions, and have difficulty in regulating emotions in an adaptive manner (Getz, et al., 2003; Green, et al., 2007; Marchand, et al., 2011; Townsend & Altshuler, 2012; Van Rheenen & Rossell, in submission-a- Chapter 12; in submission-b- Chapter 9; Wessa & Linke, 2009). As these may be dopamine dependent processes, COMT has been implicated as a mechanism of action in the prefrontal cortical-limbic system networks responsible for emotion-related functioning (Mier, et al., 2010). Indeed, COMT has been proposed to have pleiotropic effects; in addition to exerting a favourable influence on neurocognition, the Methionine (Met) encoding allele (A) of the COMT Val^{158}Met Single nucleotide polymorphism (SNP; reference Id: rs4680) in particular, is evidenced as conferring susceptibility for emotion-related impairment (Mier, et al., 2010; Swart et al., 2011), while the Valine (Val) encoding allele (G) appears to confer emotion-related advantage (Bishop, et al., 2006). Some studies have shown that negatively valenced emotion recognition abilities are associated with Met homozygosity (Weiss, et al., 2007) and that Met allele density in the limbic system is correlated with limbic reactivity to negative emotional stimuli that may contribute to emotional dysregulation (Drabant, et al., 2006; Smolka, et al., 2007; Smolka, et al., 2005; Williams, et al., 2010). Thus, it is possible that the genetic influence of COMT's Val^{158}Met SNP on cognitive function might affect emotion relevant processes as well, particularly given that cognition and emotion are inherently interacting processes (Lelli-Chiesa, et al., 2010).

Despite COMT (particularly the Val^{158}Met SNP) being widely implicated in emotion processing and emotion regulation, research examining the gene in relation to these processes in BD is rare (e.g., Canli, et al., 2009). Recently however, the Val^{158}Met SNP has been implicated in behavioural measures of facial emotion recognition in patients with the disorder; BD Met allele carriers were reported to be less accurate at correctly categorizing facial expressions than Val carriers, although this is in need of replication (Soeiro-de-Souza, et al., 2012a). Given the sparse available data directly investigating the effect of COMT on performance in emotional paradigms in BD, we were interested in examining the effect of the

Val[158]Met SNP on measures of facial emotion processing and emotion regulation. In particular, we aimed to determine if carriers of the Met allele would demonstrate less favourable emotion processing performance and fewer difficulties in regulating emotions relative to those not carrying the Met allele.

13.9 Methods

13.9.1 *Measures*

We used a *static facial emotion labelling task* as a measure of facial emotion processing. The task was designed by the author and required participants to identify emotional expressions exhibited by a series of faces. Fifty randomised trials including ten presentations for each of the five emotions happy, sad, angry, fear and neutral were presented one at a time on a black background for 2000ms followed by an inter-stimulus interval of 1500ms. Participants were instructed to press a labelled keyboard button corresponding to the emotion that he/she believed the face was expressing as soon as he/she recognised it. Percentage correct scores were taken as the dependent variable.

We used the aggregate score of the *Difficulties in Emotion Regulation Scale* (DERS: described in detail by Gratz & Roemer, 2004) as a measure of emotion regulation. The DERS is a 36 item measure of the approach, understanding and modulation of emotions that is scored on a five point Likert scale ranging from "almost never" (1) to "almost always" (5). Higher scores represented greater difficulties in regulation emotions.

13.9.2 *Statistical Analysis*

Again, given the small sample size groups were not analysed by genotype. Instead, as we were interested in the effects of the Met allele on emotion relevant performance, all analyses were carried out according to Met allele presence, with participants stratified according to Met allele loading (Met+ allelotype; AA or GA) or Met allele absence (Met- allelotype; GG). However, given the size of the Met absence group was very small, all subsequent findings should be interpreted with caution.

One way ANOVAs and Chi square tests were employed to compare groups and allelotypes on demographic measures. Univariate analysis of the DERS total score and multivariate analyses of variance of the emotion labelling task, both with group and allele presence as between subject's factors, were used to examine the effects of rs4680 on emotion regulation and emotion labelling across groups.

13.10 Results

13.10.1 *Descriptive analysis*

The COMT genotype distributions for rs4680 were in Hardy-Weinberg equilibrium (χ^2=2.26). The allelotype frequency for rs4680 in our sample was 78.6% (*n*=81) for Met+ and 19.4% (*n*=20) for Met-. There were no significant differences in age or gender between groups or allelotypes overall (data not shown). There were also no differences in age or gender for allelotype for controls, or in age, gender, MADRS or YMRS score and age of illness onset in the BD group (Table 19).

Table 19. *Descriptive characteristics and comparisons of Met+ and Met- rs4680 allelotype groups for BD and control participants*

	Control							BD						
	Met+			Met-				Met+			Met-			
Demographic variable	***N***	***M***	***SD***	***N***	***M***	***SD***	**Group comparisons**	***N***	***M***	***SD***	***N***	***M***	***SD***	**Group comparisons**
Age		34.00	14.51		33.31	14.65	$F(1,50)=.02$, $p=.88$		38.29	13.31		41.00	13.69	$F(1,46)=.25$, $p=.62$
Gender (M/F)	17/22			5/8			$\chi^2(1)=.11$, $p=.75$	14/27			2/5			$\chi^2(1)=.08$, $p=.77$
MADRS									11.67	9.88		10.71	10.36	$F(1,45)=.06$, $p=.82$
YMRS									6.48	5.79		4.71	4.31	$F(1,45)=.59$, $p=.45$
Age of illness onset									17.92	16.56		23.17	13.18	$F(1,42)=.54$, $p=.47$

Note: MADRS=Montgomery Asberg Depression Rating Scale; YMRS=Young Mania Rating Scale

13.10.2 *Allelotype*group analyses for rs4680*

Table 20 presents the means and SDs of Met+ and Met - allele performance for the emotion processing and emotion regulation tasks in the control and BD groups.

Table 20. *Means and SDs of Met+ and Met - allele performance for the emotion processing and emotion regulation tasks in the control and BD groups*

		Control				BD			
		Met+		Met-		Met+		Met-	
Emotion processing (% correct)		***M***	***SD***	***M***	***SD***	***M***	***SD***	***M***	***SD***
	Happy	97.69	4.85	97.69	5.99	97.56	4.89	97.14	4.88
	Sad	79.49	15.55	80.77	15.53	72.44	21.88	80.00	12.91
	Angry	84.87	13.35	77.69	16.41	77.00	22.21	87.14	9.51
	Fear	89.49	10.50	86.92	19.32	81.46	18.51	82.86	12.54
	Neutral	85.64	11.42	83.08	16.01	79.27	12.53	82.86	7.56
Emotion regulation									
	DERS[1]	73.50	14.20	70.58	14.93	103.29	28.50	91.00	27.01

Note: [1] Higher scores represent greater difficulties in emotion regulation; DERS=Difficulties in Emotion Regulation Scale (Theoretical Range 36-180)

13.10.2.1 Emotion processing

A 2 (allelotype)*2 (group) MANOVA revealed no significant main effect of group (*Wilks Λ*=.04, *F*(5,91)= .66, *p*=.66) or allelotype (*Wilks Λ*=.02, *F*(5,91)= .30, *p*=.91) and no interaction effect (*Wilks Λ*=.06, *F*(5,91)=1.13, *p*=.35).[17]

13.10.2.2 Emotion regulation

A 2(allelotype)*2(group) univariate ANOVA revealed a significant main effect of group (control *M*=72.80, *SD*=14.30; BD *M*=101.38, *SD*=28.33; *F*(5,91)=18.55, *p*=.001), but no effect of allelotype (*F*(5,91)=1.70, *p*=.20), and no interaction effect (*F*(5,91)=.65, *p*=.42).

[17] The absence of a group effect here differs from the findings described in Chapter 9. Not all participants in the sample used in Chapter 9 provided blood for genetic analysis; therefore some additional participants were recruited for the genetic analyses described here. It is possible that the absence of an effect in this analysis is due to sample differences between these studies.

13.11 Discussion

The aim of this analysis was to examine potential associations between the COMT Val^{158}Met SNP and measures of emotion processing and emotion regulation in BD and healthy control groups. Although our data indicate that COMT has no effect on the emotion-related processes measured here, they must be interpreted with extreme caution due to the small sample of Val allele carriers in the patient group. This is likely to have significantly restricted the power of our analyses, and thus reduced the sensitivity of observing an effect that actually exists.

Indeed, our results do not accord with previous evidence indicating that the Met allele of the Val^{158}Met SNP modulates emotion processing performance by degrading the capacity for adaptive emotional functioning in the healthy population or in those diagnosed with BD (Drabant, et al., 2006; Lelli-Chiesa, et al., 2010; Smolka, et al., 2005). Further testing will reveal whether this pattern of results holds in a larger sample.

13.12 Accompanying analysis two: The influence of the Tryptophan Hydroxylase 2 G703T polymorphism on neurocognition, emotion processing and emotion regulation

This section comprises a brief report on the analyses that were conducted to investigate the influence of the Tryptophan Hydroxylase 2 (TPH2) G730T single nucleotide polymorphism (SNP) on neurocognition, facial emotion processing and emotion regulation performance in BD patients and healthy controls. The G703T SNP was specifically chosen for examination here because it has the most support (direct and indirect) of the TPH2 SNPs for involvement in these processes (see Chapter 2, section 2.3.3.1). The sample used in these analyses is the same as that referred to in section 13.4.1. Similarly, we used the same measures as that reported in section 13.4.2 and section 13.9.1. Therefore, sample characteristics and information on measures are not reported again here. This section has not been written as a scientific article at this stage.

13.13 Introduction

Serotonin (also called 5-hydroxytryptamine or 5-HT) is an important monoamine neurotransmitter involved in the regulation of mood. Several studies have implicated it as a significant component in the pathogenesis of severe psychiatric disorders including major depression and bipolar disorder (BD: see Mahmood & Silverstone, 2001 for a review). Consequently, genes involved in the synthesis, transmission and catabolism of 5-HT have been widely studied in these neuropsychiatric fields. Among these is a gene located in a BD candidate region on chromosome 12q21 that encodes Tryptophan Hydroxylase 2 (TPH2), the first and rate limiting enzyme involved in the biosynthesis of 5-HT.

Significant associations between TPH2 and affective disorders have been reported in several studies (Harvey, et al., 2004; Lin, et al., 2007; Van Den Bogaert, et al., 2006; Zhou, et al., 2005; Zill, et al., 2004a), although the mechanisms of action are unclear. It is possible that TPH2 may influence the disorder by modulating cognitive and emotional processes in these disorders (Reuter, et al., 2007a; Waider, et al., 2011). Indeed variants of TPH2 have been implicated in working memory and executive control impairments (Reuter, et al., 2008; Reuter, et al., 2007b) as well as in personality traits characterised by heightened emotionality (Gutknecht, et al., 2007). In particular, the T allele of a single nucleotide polymorphism (SNP) occurring in the promoter region at position 703 (reference Id: 4570625) has been associated with increased amygdala responsivity to emotional faces (Canli, et al., 2005; Furmark, et al., 2009) and heightened neural activity in response to emotionally arousing pictures (Herrmann, et al., 2007). The T allele has also been associated with an increased error rate and slowed performance on tasks of cognitive control (Osinsky, et al., 2009; Reuter, et al., 2007b; Strobel, 2007).

Despite the fact that BD is characterised by difficulties in emotion regulation and impairments in neurocognitive functioning, few studies have investigated the effects of the G703T SNP on cognitive and emotion relevant tasks in BD. Given this paucity of research, we were interested in examining the effect of TPH2 on measures of neurocognition, facial emotion processing and emotion regulation in BD. In particular, we aimed to determine if carriers of the T allele of the G703T SNP would demonstrate less favourable performance

relative to those without the allele on tasks of neurocognition, emotion processing and regulation. A further research question pertained to whether the effect of this SNP would vary across cognitive tasks.

13.14 Methods

13.14.1 *Statistical analysis*

The sample was stratified according to T allele presence (T+ allelotype: TT or TG) or absence (T- allelotype: GG). Groups were not analysed by genotype because of the small number of homozygous T allele carriers relative to their homozygous and heterozygous allelotype counterparts. We carried out all analysis by allele T because it has been reported as conferring risk for cognitive/emotion relevant impairment. We used the same statistical tests as that specified in section 13.4.3 (neurocognition) and section 13.9.2 (emotion processing and regulation).

13.15 Results

13.15.1 *Descriptive analysis*

The TPH2 genotype distributions for rs4570625 were in Hardy-Weinberg equilibrium (χ^2=0.34). The allelotype frequency in our sample was 52.4% (n=54) for T+ and 46.6% (n=48) for T-. There were no significant differences in age or gender for allelotype for controls, or in age, gender, MADRS or YMRS score and age of illness onset in the BD group (Table 21).

Table 21. *Descriptive characteristics and comparisons of T+ and T- rs4570625 allelotype groups for BD and control participants*

	Control							BD						
	T+			T-				T+			T-			
Demographic variable	***N***	***M***	***SD***	***N***	***M***	***SD***	**Group comparisons**	***N***	***M***	***SD***	***N***	***M***	***SD***	**Group comparisons**
Age		34.00	15.43		32.85	13.54	$F(1,50)=.24$, $p=.63$		39.46	14.69		36.81	10.65	$F(1,46)=.25$, $p=.49$
Gender(M/F)	8/18			14/12			$\chi^2(1)=2.84$, $p=.09$	8/20			9/12			$\chi^2(1)=1.08$, $p=.30$
MADRS									12.32	9.53		11.45	10.97	$F(1,46)=.09$, $p=.77$
YMRS									6.64	5.50		5.80	5.70	$F(1,46)=.27$, $p=.60$
Age of illness onset									18.38	20.30		19.25	9.17	$F(1,42)=.03$, $p=.86$

Note: MADRS=Montgomery Asberg Depression Rating Scale; YMRS=Young Mania Rating Scale

13.15.2 *Allelotype*group analyses for rs4570625*

Table 22 presents the means and SDs of T+ and T - allele performance for the neurocognition, emotion processing and emotion regulation tasks in the control and BD groups.

Table 22. *Means and standard deviations of T+ and T - allele performance for the neurocognition, emotion processing and emotion regulation tasks in the control and BD groups*

	Task	Control				BD			
		T+		T-		T+		T-	
		M	***SD***	***M***	***SD***	***M***	***SD***	***M***	***SD***
Neurocognition	**TMTA[1]**	25.69	8.57	28.15	11.06	31.11	11.67	30.05	11.91
	BACS-SC	65.46	12.00	68.19	11.52	57.43	10.53	56.20	14.02
	HVLT-R	29.19	3.78	28.46	4.536	25.93	4.77	27.40	4.67
	WMS	18.40	2.69	18.46	2.213	15.19	3.79	16.45	3.97
	LNS	16.62	2.28	17.58	2.90	15.07	3.66	16.25	4.01
	NAB	17.96	5.81	19.12	5.68	15.52	7.43	17.40	6.20
	BVMT-R	29.68	5.91	30.19	4.41	25.44	7.60	25.25	7.61
	Fluency	27.54	5.91	27.00	7.08	26.32	6.03	26.55	7.28
	MSCIET	94.54	11.57	92.58	10.58	91.15	12.70	93.65	12.39
	CPT	2.56	.52	2.97	.45	2.55	.62	2.90	.659
	TMTB[1]	43.52	15.11	47.04	22.30	59.64	27.39	63.65	49.29
	Stroop[1]	48.54	11.29	45.96	9.88	55.00	20.33	51.10	15.22
Emotion Processing (%)	**Happy**	98.46	3.68	96.92	6.18	97.50	5.18	97.62	4.36
	Sad	82.31	14.51	77.31	16.14	70.71	24.33	78.10	14.01
	Angry	85.77	10.65	80.38	17.08	77.40	23.63	76.19	20.37
	Fear	88.46	10.08	89.23	15.73	77.50	20.48	84.76	12.09
	Neutral	84.62	12.40	85.38	13.03	79.64	12.01	79.52	12.03
Emotion Regulation	**DERS[1]**	71.50	12.98	74.00	15.54	102.42	27.39	100.81	31.38

Note: [1] Higher scores represent poorer performance/emotion regulation; DERS=Difficulties in Emotion Regulation Scale; TMTA=Trail Making Test Part A, BACS-SC=Brief Assessment of Cognition in Schizophrenia-Symbol Coding, Fluency=Category Fluency: Animal Naming, CPT=Continuous Performance Task Identical Pairs, WMS-SS= Working memory Spatial Span, LNS= Letter Number Span, HVLT-R = Hopkins Verbal Learning Test - Revised, BVMT-R=Brief Visuospatial Memory Test-Revised, MSCIET=Mayor-Salovey-Caruso Emotional Intelligence Test, Stroop=Colour-Word Stroop, TMTB=Trail Making Test Part B

13.15.2.1 Neurocognition

A 2 (allelotype)*2 (group) MANOVA revealed a significant main effect of group (*Wilks Λ*=.76, *F*(12,82)= 2.12, *p*=.02), a trend for an effect of allelotype (*Wilks Λ*=.81, *F*(12,82)= 1.66, *p*=.09) and no interaction effect (*Wilks Λ*=.91, *F*(12,82)=.71, *p*=.74). However, a task specific effect of TPH2 was evident for the CPT (*F* (1, 93) =10.75, *p*=.001), with T+ carriers showing worse performance than those absent of the T allele.

13.15.2.2 Emotion processing

A 2(allelotype)*2(group) MANOVA revealed a trend for a significant main effect of group (*Wilks Λ*=.90, *F*(5,92)= 2.14, *p*=.07) but no effect of allelotype (*Wilks Λ*=.95, *F*(5,92)= 1.02, *p*=.41) and no interaction effect (*Wilks Λ*=.96, *F*(5,92)=.79, *p*=.63). Further inspection of between subject's effects also revealed no emotion specific effects or interactions (all *p*'s>.05).

13.15.2.3 Emotion regulation

A 2(allelotype)*2(group) univariate ANOVA revealed a significant main effect of group (*F*(1,93)= 38.56, *p*=.000), but no effect of allelotype (*F*(1,93)= .01, *p*=.92) ,and no interaction effect (*F*(1,93)=.20, *p*=.66).

13.16 Discussion

The aim of this analysis was to examine potential associations between the TPH2 G703T SNP and measures of neurocognition, emotion processing and emotion regulation in BD and healthy control groups. Although our data suggest that TPH2 has no effect on the emotion-related processes measured here, we did find that T allele carriers of the G703T SNP had worse performance on a measure of sustained attention. This is consistent with past findings indicating an association between the T allele and reduced attentional performance on another version of the same measure (Strobel, 2007), and fits well in the context of evidence pointing to a relationship between the T allele and poor executive control (Osinsky, et al., 2009). That we did not find an interaction effect however, suggests that the influence of

TPH2 on attentional processing is not modulated by BD diagnosis. However, these results should be interpreted with caution given that the restricted power as a result of the small sample. Further testing will reveal whether this pattern of results holds in a larger sample.

CHAPTER 14: INTER-RELATIONSHIPS BETWEEN FEATURES OF BIPOLAR DISORDER

14.1 Chapter guide

The first five empirical chapters of this thesis described focussed studies investigating neurocognition, social cognition and emotion regulation in bipolar disorder (BD), whilst the previous chapter branched out to explore aetiological genetic influences *on* these processes. This chapter investigates relationships *between* these processes in BD. Specifically, this chapter estimates the nature of associations between neurocognition, social cognition and emotion regulation in BD by testing a series of hypothesised directional relationships that were asserted in Chapters 2, 3 and 4. As we were interested in estimating the associations between these variables in BD patients specifically, they were not tested in the control group. This chapter has not been submitted to a scientific journal at this stage.

14.2 Abstract

Objectives: Converging evidence suggests that in bipolar disorder (BD), social cognition and emotion regulation are affected by the capacity for effective neurocognitive function. Adaptive emotion regulation may also rely on intact social cognition however, and it is possible that social cognition acts as a mediator in its relationship with neurocognition, although this has not been systematically investigated. We aimed to address this hypothesis by explicitly examining inter-relationships among neurocognition, social cognition and emotion regulation in an outpatient sample meeting criteria for a DSM-IV-TR diagnosis of BD.

Methods: 50 BD patients completed a battery of tests assessing neurocognition, social cognition (emotion perception and theory of mind) and emotion regulation.

Results: Path analysis revealed that neurocognition was associated with social cognition (both emotion perception and theory of mind), but social cognition was not associated with emotion regulation as expected. Thus, there was no evidence that social cognition mediated the impact of neurocognition on emotion regulation in this cohort. This pattern of relationships was consistent regardless of symptomatic status or diagnostic subtype.

Conclusion: Our findings indicate that neurocognitive capacity is important for social cognition, but that these functions are dissociated from emotion regulation in BD. These results may represent inherent overlap in brain mechanisms underlying these processes in the disorder. Results are discussed in terms of treatment advances for BD.

14.3 Introduction

Bipolar disorder (BD) is a complex mood disorder characterised by abnormalities in emotion regulation; patients with the disorder demonstrate reduced modulatory control over emotions, and tend not to employ productive coping strategies, such that the capacity for overt and covert cognitive, physiological and motivational emotional behaviours is compromised (Green, et al., 2011; Gruber, et al., 2011; Meyer, et al., 2001; Rowland, et al., 2013b). Recent interest in the disorders social cognitive profile has also facilitated understandings of patients' capacity to perceive emotional expressions from faces and prosody (emotion perception), and make inferences about others' emotional and mental states (theory of mind). Growing evidence of mood independent impairments in these important social cognitive processes suggests a trait-like dysfunction that may have substantial implications for psychosocial outcome in the disorder (Lembke & Ketter, 2002; Martino, et al., 2011b; Samamé, et al., 2012; Van Rheenen & Rossell, 2013d- Chapter 11). Importantly, abnormalities in both emotion regulation and social cognition may represent modifiable domains of dysfunction (Lahera et al., 2013).

Converging evidence suggests that social cognition and the regulation of emotion in BD may be affected by the capacity for effective neurocognitive function, although this has not been comprehensively investigated (see Van Rheenen & Rossell, 2013b -Chapter 2, for a review). Concurrent neurocognitive, social cognitive and emotion regulatory impairments are evident in the disorder (e.g., Addington & Addington, 1998; Summers, et al., 2006), and consistently poor performance on emotionally relevant cognitive tasks (e.g., Gopin, et al., 2011) indicates that patients' aptitude for self-regulatory behaviours including inhibition and flexibility is reduced (e.g., Kerr, et al., 2005; Larson, et al., 2005; Mitchell et al., 1992)

Indeed, cognitive processes are responsible for enacting flexible responses to changing environmental conditions, inhibiting impulsive actions, and configuring a range of sensory inputs necessary for the organisation, monitoring, evaluation and modulation of emotions and behaviours. They also enable the perception, storage and access of emotional information

(necessary for emotion perception), and permit its integration with other contextual material to infer behaviour (necessary for theory of mind).

Aberrations of neurocognition could therefore independently impede the capacity for adaptive social cognition and/or emotion regulation. On the other hand, as the regulation of emotional responses is likely to rely on both neurocognitive *and* social cognitive inputs from observable (emotion expressions) and inferential (theory of mind) information sources, emotion regulation may also be impacted directly by social cognition itself. It is certainly plausible that impaired neurocognition affects emotion perception and theory of mind in BD, with impairments in either or both of these social cognitive processes likely to have implications for the regulation of emotion (Arts, et al., 2008; Bora, et al., 2011; Kurtz & Gerraty, 2009).

In other psychiatric illnesses, poor cognitive function has been associated with deficits in social cognitive abilities, suggesting that cognitive inefficiency confers a liability for poor social cognition (Fanning, et al., 2012; Kee, Kern, & Green, 1998; Sergi et al., 2007; Shur, Shamay-Tsoory, & Levkovitz, 2008). Aspects of social cognition have also been related to difficulties in emotional regulation (Harrison, et al., 2009). However, there is limited previous research directly and explicitly examining these likely inter-relationships in BD (Bora, et al., 2005; Olley, et al., 2005). This is important given that understanding pathways and connections between features of the disorder is critical to understanding the mechanisms that contribute to episodic relapse and maintenance, and for developing necessary psychosocial interventions to remediate cognitive or regulatory deficits.

To this end we aimed to examine the relationships between neurocognition, social cognition (emotion perception and theory of mind) and emotion regulation by testing an integrated predictive model in an outpatient sample meeting criteria for a DSM-IV-TR diagnosis of BD. We hypothesised that neurocognition would influence emotion regulation (Hypothesis 1) as well as emotion perception and theory of mind relevant aspects of social cognition (Hypothesis 2). A further hypothesis was that social cognition would influence the regulation of emotion and thereby mediate its predicted relationship with neurocognition (Hypothesis 3). Figure 20 presents a pictorial diagram of these hypothesised relationships.

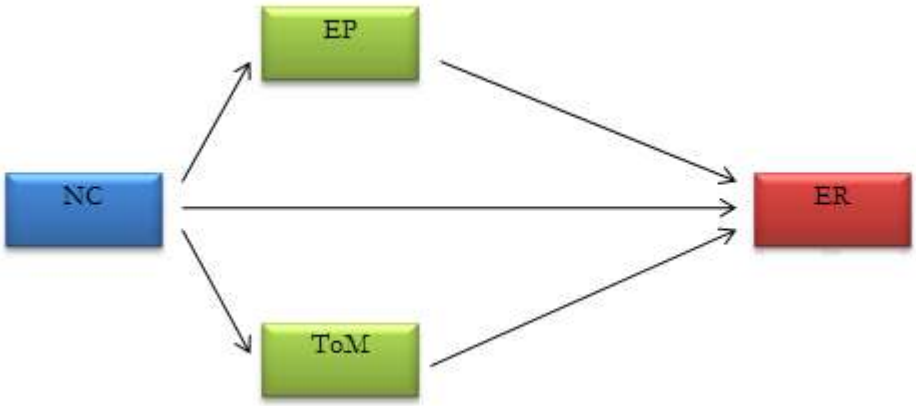

Figure 20. Hypothesised directional relationships between neurocognition, social cognition (EP and ToM) and emotion regulation variables

Note: NC=neurocognition; EP=emotion perception; ToM=theory of mind; ER= emotional regulation

14.4 Methods

This study was approved by the Alfred Hospital and Swinburne University Human Ethics Review Boards and abided by the Declaration of Helsinki. Written informed consent was obtained from each participant before the study began.

14.4.1 *Participants*

The clinical sample comprised 50 patients diagnosed as having DSM-IV-TR BD using the Mini International Neuropsychiatric Interview (MINI: Sheehan, et al., 1998). Patients were recruited via community support groups and general advertisements and were all out-patients. Current symptomology was assessed using the Young Mania Rating Scale (YMRS: Young, et al., 1978) and the Montgomery Asberg Depression Rating Scale (MADRS: Montgomery & Asberg, 1979). Patients with visual impairments, neurological disorder and/or a history of substance/alcohol abuse or dependence during the past six months were excluded. All participants were fluent in English, were between the ages of 18 and 65 years and had an

estimated pre-morbid IQ as scored by the Wechsler Test Of Adult Reading (WTAR) of >90. At the time of assessment, 33 patients were taking antipsychotics, 16 were taking antidepressants, 16 were taking mood stabilisers and 10 were taking benzodiazepines. Demographic and clinical characteristics are presented in Table 23.

Table 23. *Demographic and clinical characteristics of the sample*

	N	***M***	***SD***
	50		
Age		38.44	13.02
Gender (M/F)	16/34		
Premorbid IQ		109.40	12.06
Age of illness onset		18.47	15.92
Age of diagnosis		25.92	13.72
MADRS		11.82	10.08
YMRS		6.22	5.47

Note: M/F = Male / Female, Premorbid IQ as measured by the WTAR = Wechsler Test of Adult Intelligence, YMRS = Young Mania Rating Scale, MADRS = Montgomery Asberg depression Rating Scale

14.4.2 *Materials*

14.4.2.1 Neurocognition

A standardised composite reflecting cognitive functioning across the domains of speed of processing, attention/vigilance, working memory, verbal learning, visual learning and executive function performance was used as the *neurocognitive* measure.[18] It was derived from the summation of the Trail Making Test-Part B (Reitan & Wolfson, 1985), the Colour-Word Stroop (Delis, et al., 2001) and all subtests (except the Mayor Salovey Caruso Emotional Intelligence Test) from the MATRICS consensus cognitive battery (MCCB: described elsewhere by Nuechterlein & Green, 2006).[19] Higher scores reflect better neurocognitive ability.

[18] A composite score was formed in an attempt to conserve statistical power and improve parsimony in the path model. This was deemed appropriate given that the individual neurocognitive tests are theoretically related and that BD patients scores on each fell within one standard deviation of each other (see Chapter 8).

[19] Although the Mayor Salovey Caruso Emotional Intelligence Test is an important aspect of the MCCB, it is designed to measure social cognition. Thus, in the interests of maintaining a pure neurocognitive measure, it was excluded from the neurocognitive Z score in this study.

14.4.2.2 Social-cognition

14.4.2.2.1 Emotion perception

A standardised composite reflecting facial emotion perception was used as the *emotion perception* measure.[20] The score was derived from the summation of percentage correct responses on a static facial emotion labelling task. This task required participants to accurately identify a series of high intensity facial emotional expressions (depicting happy, sad, angry, fear, neutral) presented sequentially (Van Rheenen & Rossell, in submission-b- Chapter 9), with higher scores representing better emotion perception ability.

14.4.2.2.2 Theory of mind

A score reflecting performance on the False Belief stories from the Picture Sequencing Task (Langdon & Coltheart, 1999) was used to assess *Theory of mind*. The task required participants to make false belief inferences to logically sequence a series of stories. Higher scores on the task represent better theory of mind ability.

14.4.2.3 Emotion regulation

The aggregate score of the Difficulties in Emotion Regulation Scale (DERS: Gratz & Roemer, 2004) was used as the *emotion regulation* measure. The DERS is a 36 item self-report scale for the assessment of non-acceptance of emotional responses, difficulties engaging in goal directed behaviours when experiencing negative emotions, difficulties in impulse control, lack of emotional awareness, limited access to emotion regulation strategies and lack of emotional clarity across six subscales. Scores on each item were summed to form subscale scores, the aggregate of which formed a total score. Higher scores represent greater difficulties in emotion regulation.

[20] We chose to use a measure of facial emotion processing, as opposed to a measure of prosodic emotion processing, as it showed the strongest impairment in the BD group in earlier chapters.

14.4.3 *Statistical Analysis*

Bivariate correlations between variables of interest and mood symptomatology were estimated using Pearson's r. Path analysis was used to estimate the relationships between variables of interest in this study. Path analysis is a statistical technique used to model the magnitude and strength of theoretical associations between constructs. It can facilitate understanding about which causal structure best fits correlational patterns in the data and is advantageous over regression because it accounts for measurement error and allows for the specification of any number of dependent, independent and mediating variables of which both indirect and direct effects can be captured. It also allows for the concurrent estimation of pathways between distinct groups and permits the examination of path moderation based on group membership (Jupp, 2006; Lleras, 2005). We used SPSS Amos version 20 (Arbuckle, 2011) to test our hypotheses and employed the Chi square test, and the following well recognised fit indices to test the overall model fit; The Normed Fit index, the Relative Fit Index, The Incremental Fit Index, the Tucker-Lewis coefficient and the Comparative Fit Index (a score above .9 on all fit indices indicates a good fit).[21] We ran an initial predictor model simultaneously testing all of our hypotheses, and trimmed insignificant pathways one at a time until we reached an appropriate model fit where all paths were statistically significant. A multi-group analysis strategy was used to test for symptomatic status (symptomatic n=33, euthymic n=18, defined as those that met strict criteria for YMRS and MADRS scores $\leq$ 8) and diagnostic subtype (BD I n=39, BD II n=12) moderation of pathways in the final predictor model.

[21] Bentler and Chou (1987) proposed that a ratio of 5 cases (participants) to each free parameter (i.e., measured variables and paths) is necessary for appropriate statistical power using path analysis. As our model comprised 4 measured variables and 5 pathways, the sample of 50 BD participants is sufficient.

14.5 Results

14.5.1 *Initial correlational analyses*

Bivariate correlations between mood severity and standardised neurocognition, social cognition and emotion regulation scores are presented in Table 24. Depressive and manic symptomatology was related only to emotion regulation (the dependent variable) and not to any of the other independent variables (neurocognition) or mediators (emotion perception and theory of mind).[22]

Table 24. *Correlations between predictor variables, dependent variables and current mood symptomatology*

	NC	**EP**	**ToM**	**ER[1]**	**Depression**	**Mania**
NC	1.00	.47**	.57**	.09	-.09	.11
EP		1.00	.47**	.00	.02	.09
ToM			1.00	.09	.09	.21
ER[1]				1.00	.53**	.41**
Depression					1.00	.41**
Mania						1.00

Note: **p<.01 [1]Higher scores represent poorer emotion regulation; NC= Neurocognition; EP=emotion perception; ToM = theory of mind; ER-emotion regulation

[22] There is a fundamental link between variability in mood and emotion regulation (that is, as emotion regulation decreases mood symptoms may become worse), thus co-varying out current depression and mania symptoms was not possible. Variables can only be used as covariates if they are related to both independent and dependent variables (not clearly only to the dependent variable as shown in Table 24). Thus we chose not to control for mood symptomatology in the path analysis.[22]

14.5.2 *Hypothesis testing*

Table 25 summarizes the process of model development when testing our hypotheses. As the proposed separate paths from neurocognition, emotion perception, or theory of mind to emotion regulation were not statistically significant, there was no support for Hypothesis 1 or 3, and these direct paths were eliminated from the model. Significant direct pathways from neurocognition to emotion perception and from neurocognition to theory of mind however, did indicate full support for Hypothesis 2. Neurocognition explained 22% of the variance in emotion perception and 33% of the variance in theory of mind. The final predictor model reflecting the supported hypotheses is shown in Figure 21.

Table 25. *Process of model development during hypothesis testing*

χ^2 statistics	Fit indices					Steps taken
	NFI	**RFI**	**IFI**	**TLI**	**CFI**	
$\chi^2(1)=2.07$, $p=.15$	.94	.65	.97	.78	.96	Remove non-significant path from EP→ ER
$\chi^2(2)=2.30$, $p=.32$	.94	.81	.99	.97	.99	Remove non-significant path from ToM→ER
χ^2 (3) $=2.52$, $p=.47$	.93	.86	1.02	1.03	1.00	Remove non-significant path from NC→ER
$\chi^2(4)=6.050$, $p=.418$	.92	.88	1.00	1.05	1.00	All paths significant→No further action required

Note: Non-significant χ^2 and all fit indices above .9 indicates a good model fit; NFI=Normed Fit Index: RFI=Relative Fit Index; IFI=Incremental Fit Index; TLI=Tucker-Lewis Index; CFI=Comparative Fit Index; EP=emotion perception; ER=emotional regulation; NC=neurocognition; ToM=theory of mind

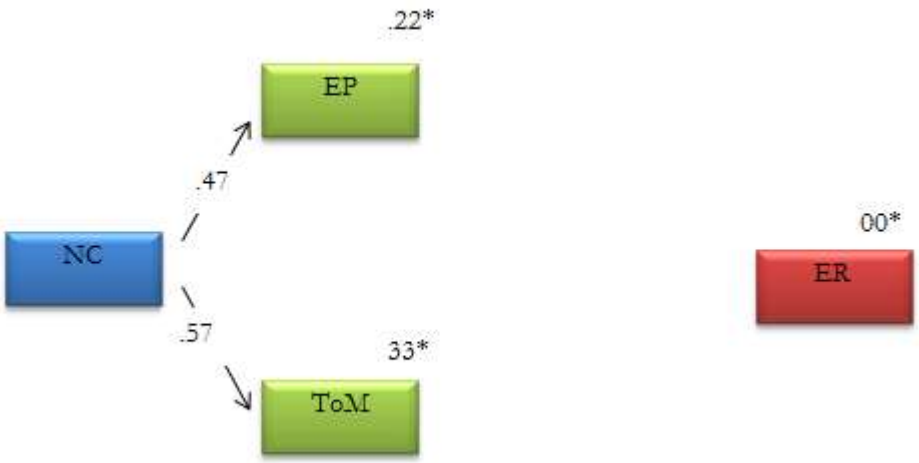

Figure 21. Final predictor model representing directional relationships between neurocognition, social cognition (EP and ToM) and emotion regulation variables

Note: NC=neurocognition; EP=emotion perception; ToM=theory of mind; ER= emotional regulation

14.5.3 *Symptomatic status and diagnostic subtype moderation testing*

The final predictor model was a good fit of the data for the symptomatic (χ^2 (4) =4.56, p=.37), euthymic (χ^2 (4) =4.96, p=.29) and BD I (χ^2 (4) =2.02, p=.73) subgroups. It was less adequate for the data of patients with BD II (χ^2 (4) =7.97, p=.09). Nevertheless, there was no significant moderation of regression weights as a function of symptom status (χ^2 (2) =4.01, p=.14) nor diagnostic group (χ^2 (2) =1.20, p=.55).

14.6 Discussion

Given disturbed emotional regulation is proposed to be a contributor to negative clinical/emotional outcomes in BD, understanding the connections it has with other features of the disorder is important. Likewise, as growing evidence indicates that both neurocognitive and social cognitive impairments are stable features of the disorder, establishing the

relationship between them is fundamental for the development of psychosocial and cognitive remediation programs. The aim of this study was to examine inter-relationships between neurocognition, social cognition and emotion regulation in a sample of DSM-IV-TR diagnosed BD patients.

Our initial examination of correlations demonstrated relationships between neurocognitive and social cognitive variables, but not between neurocognitive/social cognitive and emotion regulation variables. This pattern of associations was largely replicated when we tested a model including neurocognition and social cognition as direct and indirect predictors of emotion regulation in a path analysis. Specifically, we found support for the notion that neurocognition directly predicts variance in both emotion perception and theory of mind in BD (Hypothesis 2). However, the pathways from social cognition (both emotion perception and theory of mind) to emotion regulation were not significant, and thus we did not obtain support for the prediction that social cognition influences emotion regulation and thereby mediates its predicted relationship with neurocognition (Hypothesis 3). The lack of association between social cognition and emotion regulation could not be explained as a result of emotion regulatory function relying directly on neurocognitive as opposed to social cognitive skills, given that a statistically significant path directly from neurocognition to emotion regulation was also absent (Hypothesis 1). Thus, the notion the emotion regulation is underpinned by neurocognition was also not supported.

In the present data, these results appear to indicate that neurocognitive and social cognitive abilities generally operate in isolation from emotion regulation in BD. These findings complement those of a recent behavioural study in which links between social cognition and the use of emotion regulation strategies were missing in a BD cohort compared to controls (Rowland, et al., 2013b). However, given reasonable evidence to suggest that emotion regulation, social cognition and neurocognition *should* be related (see Green, et al., 2007; Van Rheenen & Rossell, 2013b - Chapter 2), it is possible that the absence of associations in the present findings represent limitations inherent in the current study's methodology. Indeed, the use of a *self-report* measure to assess emotion regulation, and estimate its associations with *objective performance based* neurocognitive and social cognitive measures may have restricted the observation of significant associations between these processes. It is possible that the use of

all performance based measures would have been a fairer test of the hypotheses and future studies investigating these associations in BD should take this possibility into account.

Regardless, our findings did indicate that neurocognition and social cognition are related. Specifically, neurocognition predicted substantial variance in social cognition even after accounting for measurement error; a one point decrease in neurocognitive capacity was reflective of a decrease in both emotion perception and theory of mind to the order of half a standard deviation each, indicating that intact neurocognition is a necessary precursor to good social cognition in BD. These findings are consistent with research indicating that dysfunction in the same brain networks involved in neurocognition mediate dysfunctions in social cognition as well (see Green, et al., 2007 for a review). Given that there were no overall differences between euthymic and symptomatic patients or those meeting criteria for BD I or BD II in the final path model, this pattern of relationships appears to be independent of mood symptoms and clinical subtype.

These findings should be interpreted with caution however, as they are limited by at least two factors. Firstly, we were unable to explicitly investigate the influence of current mood state on these variables. The comparison of euthymic versus symptomatic patients revealed no significant differences in the pattern of relationships, but future studies would do well to compare the pattern of inter-relationships between neurocognition, social cognition and emotion regulation in explicitly defined manic, depressed and euthymic mood phases of the illness. Further, an inability to partial out the effects of medication may represent a potential confound. Therefore future studies should aim to explicitly compare inter-relationships between these variables in patients on and off different classes of medications.

In sum, this study was among the first of its kind to explicitly examine inter-relationships between neurocognition, social cognition and emotion regulation in a sample of BD patients. Our results reveal that in BD, neurocognitive ability is predictive of social cognition, yet associations between neurocognition and emotion regulation appear to be absent. The finding that neurocognition predicts social cognition has substantial implications for psychosocial therapies for the disorder. Specifically, they suggest that the remediation of neurocognitive deficits may at least partially remediate social cognitive deficits in BD too. On the basis of these results it would be wise for researchers and clinicians developing treatments

that target psychosocial dysfunctions plausibly linked to poor social cognitive function, to consider the impact of neurocognitive deficits on social perception, and to adjust current treatments to reduce cognitive load.

CHAPTER 15: PSYCHOSOCIAL CONSEQUENCES OF NEUROCOGNITION, SOCIAL COGNITION AND EMOTION REGULATION IN BIPOLAR DISORDER

15.1 Chapter guide

In the introductory chapters we proposed a potential pathway in which deficits in neurocognition might impede social cognition, which in turn might contribute to difficulties in emotion regulation in bipolar disorder (BD). One of the potential endpoints of this pathway was its impact on clinical and psychosocial outcomes. However, the investigation described in the previous chapter indicated that the hypothetical pathway between neurocognition>social cognition >emotion regulation in BD was not entirely supported by the data. Thus, further examination of the psychosocial outcomes associated with this pathway was not possible (i.e., the pathway that goes neurocognition>social cognition >emotion regulation>psychosocial functioning was not able to be tested). Nevertheless, given that impairments in each of these processes are core characteristics of the disorder, it remains likely that psychosocial functioning is impacted by each of them, albeit in a manner that is somewhat independent of each other. Here we describe an investigation testing this possibility, by investigating the relative importance of each of these processes for predicting objective and subjective psychosocial outcomes in BD.[23] This chapter is the final of the empirical chapters and has not been submitted to a scientific journal at this stage.

[23] This chapter presents BD-control group comparisons for the purpose of demonstrating to the reader that this BD cohort was experiencing psychosocial difficulties. We felt that this was necessary to qualify subsequent analyses in which the influence of neurocognitive, social cognitive, emotion regulation and mood related processes were tested in relation to these psychosocial outcomes in the patient group only.

15.2 Abstract

Objectives: Despite propositions that impairments in neurocognition, social cognition and emotion regulation are involved in psychosocial dysfunction in bipolar disorder (BD), the influence of these factors has not been concurrently examined in studies of psychosocial functioning thus far. Moreover, whether these constructs contribute to subjective *and* objective evaluations of psychosocial capacity (or both) in the same way has not yet been explored. This study aimed to address these limitations by conducting a comprehensive investigation of psychosocial functioning in a well characterised group of DSM-IV-TR diagnosed BD patients.

Methods: Fifty one BD patients were compared to 52 healthy controls on objectively (using the Global Assessment of Functioning; GAF) and subjectively assessed psychosocial outcomes (using the Quality Of Life in Bipolar Disorder Scale; QoL.BD). Relationships between psychosocial function and neurocognitive, social cognitive and emotion regulation measures were also examined in the patient group.

Results: Patients has significantly worse global objective and subjective functioning relative to controls. In the patient group, although these scores were correlated, regression analyses showed that variance in each of the measures was explained by different variables. Depressive symptomatology was the most important predictor of the global QoL.BD score (subjective psychosocial function) and neurocognition had a concurrent and important influence on the GAF score (objective psychosocial function), as did depressive symptoms. Emotion regulation also had an indirect effect on QOL.BD and GAF scores via its influence on depressive symptomatology.

Conclusions: These results suggest that patients' own evaluations of their subjective functioning represent important indicators of the extent to which their observable function is impaired. They also highlight the importance of incorporating cognitive and emotion regulation assessments into clinical practice when working with patients diagnosed with BD.

15.3 Introduction

Bipolar disorder (BD) is a complex affective disorder characterised by cognitive and emotional abnormalities, and impairments in subjective and objective psychosocial functioning (Brissos, et al., 2008a; Martinez-Aran, et al., 2007; Simonsen, et al., 2010). The debilitating nature of the disorder is highlighted by research indicating that occupational, interpersonal and psychological adjustment is significantly reduced in BD (Australian Bureau of Statistics, 2007; Judd, et al., 2008). Such impairment has detrimental clinical effects, reducing time to relapse and subsequently increasing suicide risk (Finseth, Morken, Andreassen, Malt, & Vaaler, 2012; Gitlin, et al., 1995; Gonda et al., 2012). As such, the development of effective treatments that may remediate impairments and improve both functional and subjective evaluations of quality of life is vitally important.

Given that BD is a multifaceted disorder likely to be underpinned by a combination of genetic and environmental components, research examining the factors involved in functional outcomes and quality of life need to look beyond traditionally recognised predictors of psychosocial function in BD. That is, despite a considerable body of research indicating that clinical symptoms including depression play a substantial part in reducing psychosocial adjustment and perpetuating relapse in the disorder (Coryell, et al., 1998; Judd, et al., 2005; MacQueen, et al., 2001), it is becoming clear that psychosocial dysfunctions persist during clinical remission and that other factors may be contributing to the disorders' psychosocial profile (Mur, et al., 2009; Torres, et al., 2011).

For example, difficulties in emotional regulation may be indirectly involved given they catalyse and perpetuate mood symptomatology by ineffectively modulating transient depressed or elevated states. Indeed, emotion regulation deficits may have trait-like qualities that predict the course of symptoms over time (Becerra, et al., 2013; Johnson, 2005b; Phillips & Vieta, 2007; Urošević, et al., 2010; Van Rheenen, Murray, & Rossell, in submission- Chapter 12). Some evidence indicates that intense experiences of emotion and poor regulation of anger in BD patients are associated with increased feelings of hopelessness, poorer self-esteem and reduced quality of life (Hoertnagl, et al., 2011; Johnson, 2005b; Rucklidge, 2006). Despite this,

there are only limited studies empirically examining the functional and quality of life implications of emotion regulation difficulties in the disorder.

Likewise, only recently has there been interest in the psychosocial implications of mood independent neurocognitive dysfunctions that are consistently reported in BD (Torres, Boudreau, & Yatham, 2007; Yatham, et al., 2010). Arising from this interest are studies revealing that executive function (Bonnín, et al., 2010; Mur, et al., 2009; Solé, et al., 2012), learning and memory (Bonnín, et al., 2010; Martinez-Aran, et al., 2007) and processing speed (Dickerson, et al., 2010) predict psychosocial outcome independently of mood symptoms. Although this highlights the importance of neurocognition in investigations of psychosocial outcome in BD, heterogeneity in the variance it explains across studies suggests that other factors still, may be involved. For example, as social cognition may partially reflect neurocognitive operations in social contexts, it may also predict psychosocial outcome (Van Rheenen & Rossell, 2013b - Chapter 2)

Indeed, impaired social cognition is becoming increasingly recognised in descriptions of the neuropsychological profile of BD, with patients evidencing deficits in the recognition of facial and prosodic emotions as well as in their ability to understand the thoughts and intentions of others (Bora, et al., 2009c; Van Rheenen & Rossell, 2013c- Chapter 3; 2013d - Chapter 11). These impairments are important factors to consider in psychosocial studies given that intact emotion perception and theory of mind ability would seem to be necessary for adaptive social interaction. Preliminary research indicates that better social cognition is related to lower depression severity, quality of life and functional outcome in BD (Hajnal, et al., 2010; Hoertnagl, et al., 2011), but further research is certainly needed to ascertain whether social cognition independently predicts psychosocial function in the disorder or whether it may be mediating the influence of neurocognition.

Given that neurocognition, social cognition and emotion regulation have not been regularly and concurrently examined in studies of psychosocial functioning in BD thus far, this study was designed to overcome this paucity of research to investigate the relative contributions of these variables in the prediction of psychosocial outcome. A further research question pertained to whether potential mediations amongst these processes could more effectively explain the mechanisms involved in reducing psychosocial function than the

independent prediction of each. Thus, we aimed to investigate whether social cognition mediated the relationship between neurocognition and psychosocial function, and whether mood symptomatology mediated the relationship between emotion regulation and psychosocial function.

As current evidence is mixed with regards to whether subjective psychosocial evaluations (i.e., quality of life) are parallel to objective accounts (i.e., occupational, physical and interpersonal functioning) of psychosocial functioning in BD (Goldberg & Harrow, 2005; MacQueen, et al., 2000), we were particularly interested in investigating whether these processes contributed to subjective and objective evaluations of psychosocial capacity in the same way. Further, we aimed to understand the relationship between these two different, yet important facets of psychosocial functioning in order to establish the extent to which subjective reports of poor life satisfaction should be valued as an indicator of objective dysfunction and vice versa. This paper reports the results of a comprehensive investigation of these research questions in a cross sectional group of well characterised BD patients.

15.4 Methods

This study was approved by the Alfred Hospital and Swinburne University Human Ethics Review Boards and abided by the Declaration of Helsinki. Written informed consent was obtained from each participant before the study began.

15.4.1 *Participants*

The clinical sample comprised 51 patients diagnosed as having DSM-IV-TR BD using the Mini International Neuropsychiatric Interview (MINI: Sheehan, et al., 1998). Patients were recruited via community support groups and general advertisements and were all out-patients. Current symptomology was assessed using the Young Mania Rating Scale (YMRS: Young, et al., 1978) and the Montgomery Asberg Depression Rating Scale (MADRS: Montgomery & Asberg, 1979). Patients with visual impairments, neurological disorder and/or a history of substance/alcohol abuse or dependence during the past six months were excluded.

A control sample of 52 healthy participants was recruited for comparison purposes by general advertisement and contacts of the authors. Using the MINI screen, no control participant had a current diagnosis or previous history of psychiatric illness (Axis I). An immediate family history of mood and psychiatric disorder, in addition to a personal history of neurological disorder, current or previous alcohol/substance dependence or abuse, visual impairments and current psychiatric medication use was exclusion criteria for all controls.

All participants were fluent in English, were between the ages of 18 and 65 years and had an estimated pre-morbid IQ as scored by the Wechsler Test Of Adult Reading (WTAR) of >90.

15.4.2 *Materials*

15.4.2.1 Neurocognition

A composite score (standardised based on the means and standard deviations of our control group) reflecting cognitive functioning across the domains of speed of processing, attention/vigilance, working memory, verbal learning, visual learning and executive function performance was used as the neurocognitive measure.[24] It was derived from the summation of the Trail Making Test-Part B (Reitan & Wolfson, 1985), the Colour-Word Stroop (Delis, et al., 2001) and all subtests (bar the Mayor Salovey Caruso Emotional Intelligence Test) from the MATRICS consensus cognitive battery (MCCB: described elsewhere by Nuechterlein & Green, 2006).[25] Higher scores reflect better neurocognitive ability.

[24] A composite score was formed in an attempt to conserve statistical power and improve parsimony. This was deemed appropriate given that the individual neurocognitive tests are theoretically related, and BD patients' scores on each fell within one standard deviation of each other (see Chapter 8).

[25] Although the Mayor Salovey Caruso Emotional Intelligence Test is an important aspect of the MCCB, it is designed to measure social cognition. Thus, in the interests of maintaining a pure neurocognitive measure, it was excluded from the neurocognitive Z score in this study.

15.4.2.2 Social-cognition

A composite score reflecting facial emotion perception and ToM ability was used as the social-cognitive measure. The score was derived from the summation (and subsequent standardisation based on our healthy control groups data) of correct responses on the False Belief stories from Langdon and Coltheart's (1999) Picture Sequencing Task (requiring participants to make false belief inferences to logically sequence a series of stories) and an emotion processing task (see Van Rheenen & Rossell, in submission-b - Chapter 9)that required participants to label a series of sequentially presented facial emotional expressions (happy, sad, angry, fear, neutral).[26] Higher scores represent better social-cognitive ability.

15.4.2.3 Emotion regulation

The aggregate score of the Difficulties in Emotion Regulation Scale (DERS: Gratz & Roemer, 2004) was used as the emotion regulation measure. The DERS is a 36 item self-report scale for the assessment of non-acceptance of emotional responses, difficulties engaging in goal directed behaviours when experiencing negative emotions, difficulties in impulse control, lack of emotional awareness, limited access to emotion regulation strategies and lack of emotional clarity across six subscales. Scores on each item were summed to form subscale scores, the aggregate of which formed a total score. Higher scores represent greater difficulties in emotion regulation.

15.4.2.4 Psychosocial function

Subjective and objective psychosocial functioning were assessed with the *Quality of Life in Bipolar Disorder* questionnaire (Qol.BD: Michalak, et al., 2010) and the *Global Assessment of Functioning* (GAF) scale. The QoL.BD is a *subjective*, disorder specific 48 item self-report scale that required participants to rate the range of experiences, behaviours and feelings related to quality of life that they have experienced over the past seven days. It is rated on a five point Likert scale ranging from Strongly Disagree (1) to Strongly Agree (5) with items making up

[26] The facial emotion processing and ToM measures were combined in an attempt to conserve statistical power. This was deemed appropriate as these measures are theoretically related, and were moderately correlated in the previous investigation (see Chapter 14).

subscales reflective of core quality of life domains including physical, sleep, mood, cognition, leisure, social, spirituality, finances, self-esteem, independence and identity. Two additional and optional subscales reflecting work and educational activities were also included. Subscale scores were formed by summing individual item scores in each subscale and then standardising them with data from our control group. A global Qol.BD score was generated by summing and then standardising responses on the first 48 items of the scale, where higher scores represent better quality of life.

The GAF is an *objective* administrator rated scale that takes into account the current occupational, psychological and social circumstances of each participant. A score was generated based on the judgement of a trained administrator (the author) regarding symptom severity and level of functioning. It was rated on a scale ranging from between 0-100, with higher scores representing better functioning.

15.4.3 *Statistical analysis*

In order to compare with the other standardised measures, Z scores based on our healthy control sample's data were created for the emotion regulation and subjective and objective psychosocial function measures. Group differences in demographic, clinical and core predictor variables were assessed via one-way between-groups analysis of variance or Chi square tests with correction for multiple testing set at α=.01. Subgroup analyses comparing objective and subjective psychosocial functioning for symptomatic (n=33) and euthymic patients (n=18, defined as those that met strict criteria for YMRS and MADRS scores $\leq$ 8), diagnostic subtypes (BD I n=39 versus BD II n=12) and patients dichotomously coded as on or off antipsychotics, antidepressants, mood stabilisers and benzodiazepines were run using the same method. In the patient group, bivariate correlations using a conservative α=.01 to account for multiple testing were used to examine relationships between clinical and outcome variables. Stepwise regressions were also run to determine the most valuable predictors of subjective and objective psychosocial function in the BD group. These were followed up by appropriate tests regarding mediation as necessary.

15.5 Results

The demographic and clinical characteristics of the sample are presented in Table 26. There were no significant group differences in age, gender, pre-morbid IQ, marital status and living arrangements. However, a significant difference in employment status was evident; significantly fewer patients were engaged in employment (full-time=6, part-time=10, causal employment=7, unemployed =, home duties = 2, student = 3, unemployed = 4, home duties=2, disability pension = 17) relative to controls (full-time=15, part-time=11, casual = 8, unemployed= 3, disability pension = 1) when those who were retired or were students were not counted ($\chi^2(1)=14.87$, $p<.001$). Thirty-three patients were taking antipsychotics, 16 were taking antidepressants, 16 were taking mood stabilisers and 10 were taking benzodiazepines.

Table 26. *Demographic and clinical characteristics of the sample*

		Controls			BD			Group comparisons	
Demographic variable		***N***	***M***	***SD***	***N***	***M***	***SD***	***F/χ²***	***p***
		52			51				
Age			33.98	14.28		38.44	12.89	2.79	.10
Gender (M/F)		20/32			17/34			2.94	.59
WTAR			111.64	7.24		109.40	12.06	1.29	.26
Age of illness onset			-	-		20.31	10.91		
Age of diagnosis			-	-		28.10	10.84		
MADRS			-	-		11.82	10.08		
YMRS			-	-		6.22	5.47		
Employment status								30.64	.00
	Employed	34			24				
	Not employed	4			23				
	Retired/student	14			4				
Marital status								2.29	.68
	Never Married	29			25				
	Legally Married	10			10				
	De-facto/Co-Habiting	7			5				
	Divorced/Separated	5			10				
	Spouse Deceased	1			1				
Living arrangements								3.44	.33
	Alone	6			12				
	Living With Parents/Relatives	16			10				
	With Partner/Dependants	22			21				
	With Others (Not Family)	8			8				

Note: ^ Group comparisons all one-way ANOVA except gender, employment status, marital status and living arrangements which were Chi square; M/F = Male / Female, WTAR = Wechsler Test of Adult Intelligence, YMRS = Young Mania Rating Scale, MADRS = Montgomery Asberg depression Rating Scale

15.5.1 *Descriptive and correlational analyses*

Table 27 presents the raw score means and standard deviations of scores on the QOL.BD and GAF, as well as on the Z score composites of performance on these measures and on measures of neurocognition, social cognition and emotion regulation for BD and control groups. Raw scores and/or interactions on the latter three variables are discussed in further detail elsewhere (Van Rheenen & Rossell, 2013a - Chapter 11; 2013d - Chapter 12; In press - Chapter 8; in submission-a - Chapter 9; in submission-b - Chapter 10). Patients had *objectively* worse psychosocial functioning on the GAF and *subjectively* worse psychosocial functioning on all domains of the QoL.BD (except "work" and "spirituality"). There were no differences between diagnostic subtypes for either objective or subjective psychosocial functioning in the patient group. However, patients that were symptomatic had significantly worse mood related subjective psychosocial function (F (1, 48) =7.09, p<.01) and worse global objective function (F (1, 48) =5.43, p<.05) relative to those who were euthymic. Patients on antidepressants also had significantly worse work related subjective psychosocial function relative to those not on antidepressants (F (2, 29) =7.67, p<.01). There were no significant differences between patients on/off antipsychotics, mood stabilisers and benzodiazepines.

Table 27. *Raw and Z scores descriptive statistics of relevant variables for BD and control groups*

Scale	Subscale		Control		BD					
			Raw		*Raw*		*Z score*		*Group comparisons*	
		TR	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*
QOL.BD (subjective)										
	Physical	4-20	13.37	3.01	11.56	2.73	-0.60	0.91	10.06	.01
	Sleep	4-20	13.45	3.21	10.60	3.93	-0.89	1.22	15.94	.01
	Mood	4-20	16.27	2.26	13.24	3.61	-1.34	1.60	24.59	.01
	Cognition	4-20	15.61	2.69	12.55	4.04	-1.14	1.50	19.96	.01
	Leisure	4-20	16.14	2.52	13.84	3.64	-0.91	1.44	13.49	.01
	Social	4-20	16.51	3.20	14.14	4.05	-0.74	1.27	10.68	.01
	Spirituality	4-20	13.98	3.39	12.91	4.10	-0.31	1.21	2.00	.16
	Finances	4-20	14.55	3.73	12.18	4.70	-0.64	1.26	7.90	.01
	Household	4-20	15.23	3.13	12.70	3.45	-0.81	1.10	14.96	.01
	Self-esteem	4-20	16.02	2.27	12.88	3.73	-1.38	1.64	26.26	.01
	Independence	4-20	17.47	2.033	15.40	2.93	-1.01	1.44	16.50	.01
	Identity	4-20	16.63	2.38	13.98	3.81	-1.11	1.60	18.27	.01
	Total	48-240	184.90	21.17	153.92	35.18	-1.46	1.66	28.89	.01
QOL.BD optional[2]	**Work**	4-20	17.15	2.62	15.28	3.06	-0.71	1.17	7.79	.01
	Education	4-20	15.16	3.40	13.33	5.89	-0.54	1.73	1.56	.22
GAF (objective)		0-100	91.69	5.06	63.54	13.62	-5.57	2.69	194.37	.01
NC		-	-	-	-	-	-0.81	1.36	11.00	.01
SC							-0.82	1.49	10.17	.01
ER[1]							2.02	2.03	40.56	.01

Note: [1]Higher scores indicate greater difficulties in regulating emotion; TR=Theoretical Range, [2] Work (Control *n*=40, BD *n*=32) and education (Control *n*=25, BD n=15) subscales of the QoL.BD has smaller *n's* as these were optional scales.

Correlations among psychosocial outcome and clinical symptoms are presented in Table 28, while correlations among GAF (objective) and QoL.BD (subjective) psychosocial functioning scales in the patient group are presented in Table 29. Neither GAF nor QoL.BD global scores correlated significantly with age, gender, age at illness onset or diagnosis, employment status or psychosis history. However, manic symptomatology was significantly associated with QoL.BD spiritual functioning and GAF score. Depressive symptomatology was associated with subjective QoL.BD across the domains of mood, cognitive, leisure, social, spirituality, self-esteem, independence, identity, work and global score, as well as with GAF score. The GAF score correlated significantly with the QoL.BD global score and mood, cognition, leisure, social function, independence and identity subscale scores. The global Qol.BD and GAF scores were also significantly related.

Table 28. *Correlations among clinical variables and global psychosocial outcome measures in BD patients*

Clinical variables	**Subjective psychosocial function**	**Objective psychosocial function**
	QoL.BD Global	GAF
Age	.01	.16
Gender (1=male, 2=female)	-.23	-.29^
Employment status (1=employed, 2=not employed)	-.20	-.12
Age at illness onset	-.28	-.07
Age at diagnosis	-.15	.20
Psychosis history (1=no, 2=yes)	-.03	-.01
MADRS	-.59**	-.56**
YMRS	-.17	-.35^

Note: ^p<.05, **p<.001; all correlations with dichotomous variables were Spearman's ϱ, all others were Pearson's r; Qol.BD Global=Global Quality Of Life in BD Scale Score; GAF=Global Assessment of Function; MADRS=Montgomery Asberg Depression Rating Scale; YMRS=Young Mania Rating Scale

Table 29. *Inter-correlations between objective and subjective psychosocial functioning global and subscale scores in BD patients*

	Subjective subscales														Subjective	Objective
QoL.BD	**QoL Phys**	**QoL Sleep**	**QoL Mood**	**QoL Cog**	**QoL Leis**	**QoL Soc**	**QoL Spirit**	**QoL Fin**	**QoL House**	**QoL S-E**	**QoL Indep**	**QoL Iden**	**QoL Work**	**QoL Edu**	**QoL Global**	**GAF**
Phys	1.00	.23	.46**	.35**	.26	.53**	.57**	.36**	.21	.24	.30^	.49**	.28	.42	.48**	.26
Sleep		1.00	.42**	.35**	.35**	.29^	.28^	.30^	.33^	.38^	.35**	.35**	.04	.18	.60**	.30^
Mood			1.00	.77**	.63**	.61**	.47**	.39**	.20	.50**	.70**	.76**	.37^	.62^	.84**	.44**
Cog				1.00	.57**	.44**	.55**	.41**	.24	.49**	.68**	.75**	.47**	.57^	.80**	.42**
Leis					1.00	.58**	.35**	.26^	.18	.49	.65**	.60**	.03	.34	.73**	.40**
Soc						1.00	.43**	.19	.19	.53**	.62**	.67**	.44**	.73**	.73**	.41**
Spirit							1.00	.31^	.37**	.29^	.40**	.48**	.34	.31	.67**	.33^
Fin								1.00	.22	.20	.42**	.35**	.21	.59^	.43**	.33^
House									1.00	.14	.21	.32^	.42	.47	.36**	.36**
S-E										1.00	.57**	.59**	.02	.45	.71**	.36**
Indep											1.00	.75**	.36^	.63**	.80**	.53**
Iden												1.00	.56**	.65**	.86**	.50**
Work													1.00	.81**	. 22	.43^
Edu														1.00	72**	.45
Global															1.00	.46**
GAF																1.00

Note: ^p<.05, **p<.001; Qol.BD Global=Global Quality Of Life in BD Scale Score; Phys=Physical; Cog=Cognition; Leis=Leisure; Soc=Social; Spirit=Spirituality; Fin=Finance; Household=Household; S-E=Self-Esteem; Indep=Independence; Iden=Identity; Edu=Education; GAF=Global Assessment of Function

15.5.2 *Regression analyses*

To examine whether neurocognition, social cognition and emotion regulation were predictors of psychosocial outcome in BD, two stepwise regressions using these processes as independent predictors were carried out in the patient group. The GAF (objective psychosocial functioning) or QOL.BD (subjective psychosocial functioning) scores were used as the dependent variables. The first regressions revealed that 8% of the variance in *subjective psychosocial functioning* was explained by emotion regulation (Adjusted R^2=.08, F (1, 41) =4.77, p<.05). Similarly, 16% of the variance in *objective psychosocial function* was predicted by emotion regulation (Adjusted R^2=.16, F (1, 42) =9.10, p<.01) and 11% was predicted by neurocognition (ΔR^2 =.11, ΔF (1, 41) =6.26, p<.05), with the combination explaining 25% of the available variance (Adjusted R^2=.25, F (2, 41) = 8.23, p<.01).

Given that we were interested in understanding whether cognitive and emotion regulatory variables could explain unique variance in the context of mood symptomatology, two additional stepwise regressions were carried out in the patient group. Manic and depressive symptomatology were thus specified as additional independent predictors in the models, and regressed on objective and subjective psychosocial function. When these additional variables were included, only depression explained 34% of the variance in *subjective psychosocial functioning* (Adjusted R^2=.34, F (1, 41) =22.31, p<.001). Depression also explained 26% of the variance in *objective psychosocial functioning* (Adjusted R^2=.26, F (1, 42) =16.43, p<.01), with neurocognition explaining an additional 8% (ΔR^2 =.08, ΔF (1, 41) =5.24, p<.05) and the two together explaining 33% of the available variance (Adjusted R^2=.33, F (2, 41) =11.66, p<.001).

In both regressions, emotion regulation disappeared from the models when manic and depressive symptomatology scores were added as predictors. Therefore, to determine whether mood symptomatology was mediating the relationship between emotion regulation and objective or subjective psychosocial functioning, we regressed emotion regulation and mood symptomatology on the GAF (objective) and QOL.BD (subjective) scores separately, in a hierarchical fashion (see Table 30).

When *objective psychosocial function* was entered as the dependent variable, emotion regulation significantly predicted 18% of its variance at step one (Adjusted R^2=.18, p<.01). When manic and depressive symptomatology were entered at step two, only depressive symptomatology significantly explained additional variance (ΔR^2 =.15, ΔF (2, 43) =5.01, p<.01) and the relationship between emotion regulation and objective psychosocial function became redundant. This indicated a mediation effect of depression symptomatology for emotion regulation and objective psychosocial functioning in BD. Similarly, when *subjective psychosocial function* was entered as the dependent variable, emotion regulation again significantly predicted 10% of its variance at step one (Adjusted R^2=.10, p<.05). When manic and depressive symptomatology were entered at step two, only depressive symptomatology significantly explained additional variance (ΔR^2 =.25, ΔF (2, 42) =8.29, p<.01), and the relationship between emotion regulation and subjective psychosocial function became redundant. Again, this indicated a mediation effect of depression symptomatology for emotion regulation and objective psychosocial functioning in BD.

As there were no significant and concurrent predictions of psychosocial function by social cognition *and* neurocognition, the potential mediation of the relationship between neurocognition and psychosocial outcome by social cognition was not tested.

Table 30. *Summary of hierarchical regression predicting objective and subjective psychosocial functioning in BD patients*

DV: Objective	***F***	***B***	***SE B***	***β***
Block one	$F(1,45)=11.20^{**}$			
Emotion regulation		-.59	.18	-.47**
Block two	$F(3,43)=7.74^{**}$			
Emotion regulation		-.25	.19	-.19
MADRS		-.11	.04	-.41**
YMRS		-.06	.07	-.12
DV: Subjective	***F***	***B***	***SE B***	***β***
Block one	$F(1,44)=5.67^{**}$			
Emotion regulation		-.28	.12	-.34*
Block two	$F(3,42)=8.04^{**}$			
Emotion regulation		-.06	.12	-.06
MADRS		-.11	.03	-.63**
YMRS		.06	.05	.17

Note: $^{**}p<.01$; MADRS=Montgomery Asberg Depression Rating Scale; YMRS=Young Mania Rating Scale

15.6 Discussion

This study was designed to investigate objective and subjective psychosocial functioning in BD, by exploring measures of neurocognition, social cognition and emotion regulation as predictors. When compared with controls, we observed significant reductions in both objectively and subjectively rated psychosocial functioning in our patient sample, which is consistent with a myriad of empirical and anecdotal evidence (e.g., Dittmann, et al., 2007; Malhi, et al., 2007a; Sanchez-Moreno, et al., 2009; Simonsen, et al., 2010). Higher objectively rated global functioning in this group was associated with better subjective evaluations of mood, sleep, autonomy, cognitive functions, involvement in leisure and social activities, consistency in the self-concept, spiritual functioning, self-esteem and capacity to manage household duties, but not with subjective ratings of functioning related to physical ability.

Nevertheless in patients, objective psychosocial functioning was moderately related to total subjective ratings of functioning, and the relationships between objective or subjective function *and* clinical symptoms did not vary. Thus, global subjective psychosocial functioning

appeared to be reasonably reflective of global objective psychosocial functioning in BD. As this finding suggests that patients' own evaluations of their quality of life represent important indicators of the extent to which their observable function is impaired, it has important implications for the clinical setting. Specifically, it suggests that clinicians should place greater weight on patients' self-rated life dissatisfactions, which may serve to improve patient-clinician engagement and thereby enhance treatment outcomes (Murray & Michalak, 2012).

Despite the parallel relationship between objective and subjective outcomes, our regression analyses indicated that these outcomes are generated via slightly different pathways. Specifically, we found that objectively measured psychosocial functioning was significantly predicted by neurocognition and emotion regulation (although the latter effect appeared to be masked by the impact of depressive symptomatology). That neurocognition explained variance in objective psychosocial functioning separately from mood symptomatology is consistent with existing research indicating the predictive value of neurocognitive ability (Bonnín, et al., 2010; Jabben, et al., 2010; Martinez-Aran, et al., 2004a). It also accords with growing evidence that clinical remission is not necessarily indicative of healthy psychosocial outcomes (Malhi, et al., 2007a; Mur, et al., 2009).

Of the three phenomenological variables examined, emotion regulation was found to be the strongest predictor of objective functioning in BD. However, when we accounted for the effect of mood related variables this relationship became redundant; it appears the emotion regulation had an indirect effect on objective global functioning via its influence on mood symptomatology. With regards to subjective functioning (quality of life), we found that neither neurocognition, nor social cognition were significant predictors. However, some of the variance in subjective psychosocial function was explained by emotion regulation. As with objective functioning, when depressive symptomatology was included in the model predicting subjective psychosocial functioning, the effect of emotion regulation on subjective functioning was significantly reduced. Further analysis indicated that depression was actually mediating the effect of emotion regulation on subjective psychosocial functioning.

When taken together, these results highlight the somewhat different pathways to dysfunctional psychosocial outcome in the disorder; it appears that depressive symptomatology, as perpetuated by difficulties in emotion regulation, is most important when

patients rate their overall life satisfaction. In contrast, both neurocognition and depression appear to have an important influence on objective estimates of psychosocial functioning in BD. Thus the possibility that emotion regulation affects psychosocial function through its effect on mood appears to be supported. This finding is consistent with the conceptualisation of emotion regulation as a bio-behavioural process involved in the experience and modulation of mood related arousal (Gross & Muñoz, 1995). In BD, impairments in emotional regulation presumably perpetuate transient negative affect to predict the course of symptoms (Alloy, et al., 2009a; Gruber, et al., 2011; Johnson, et al., 2008; Thomas & Bentall, 2002). Our results suggest that emotion regulation indirectly influences psychosocial outcome by proliferating depression symptomatology.

A number of limitations in the current investigation should be noted. Firstly, our objective functioning measure was not matched to the subjective measure of psychosocial function across domains, making it difficult to ascertain specific parallels between objective and subjective domains of function. Secondly, because we used aggregate measures of neurocognition and social cognition, it is possible that some relationships between specific processes within these domains of neuropsychological function and psychosocial outcome were attenuated. Given that a variety of neurocognitive functions have been implicated in psychosocial outcome in BD, it is less likely that this was the case for neurocognitive predictions of functioning. However, as emotion processing and ToM performance have not been systematically investigated in relation to psychosocial functioning in the disorder, future studies would do well to explicitly investigate the relationship between these variables. Thirdly, due to the fundamental differences in the method of measuring the processes in this study, it is possible the relationships between them were reduced. As we have provided evidence that subjective and objective psychosocial functioning are reasonably reflective of each other, future studies might aim to use *all performance* based measures to better investigate the impact of neurocognition, social cognition and emotion regulation on functioning. Finally, because this study was cross-sectional in nature, we are unable to draw precise conclusions regarding contributing pathways involved in psychosocial functioning in BD. Future longitudinal studies investigating these neuropsychological variables of interest would certainly assist in our understanding of causal mechanisms related to outcome in BD.

Nevertheless, this study supports an association between neurocognition, emotion regulation and psychosocial outcome in BD, and highlights the importance of incorporating cognitive and emotion regulation assessments into clinical practice when working with patients diagnosed with BD. In particular, our results emphasise the role that difficulties in emotion regulation play in perpetuating depressive symptoms that are critical predictors of psychosocial functioning in the disorder. Future psychosocial intervention studies should aim to include cognitive and emotion regulation remediation techniques in adjunct to pharmacological treatment to improve symptomatology and reduce psychosocial dysfunction.

CHAPTER 16: GENERAL DISCUSSION

The general aim of this project was to further current understandings of neurocognitive, social cognitive and emotion regulation processes in bipolar disorder (BD). To address this aim, investigations were conducted to a) examine the neurocognitive, social cognitive and emotion regulation profiles of BD patients while taking into account potential confounds and using new measures of assessment, b) examine the underlying genetic influences on these processes, c) assess the inter-relationships between these processes, and d) examine the effects that these processes have on psychosocial functioning in the disorder.

The following general discussion provides an overview and synthesis of the main findings of these empirical investigations. Specific hypotheses have been addressed in the relevant chapters and are not reiterated here. This chapter begins with a summary organised in accordance with the major goals that correspond to the empirical focus of each of the preceding chapters, namely focussed studies aimed at understanding the (i) neurocognitive (Chapter 8), (ii) social cognitive (comprising facial and auditory emotion processing and theory of mind (ToM) in Chapters 9, 10, 11) and (iii) emotion regulation (Chapter 12) profiles of BD, and broader approaches to understanding (iv) aetiological genetic influences on these features (Chapter 13) (v), inter-relationships between them (Chapter 14) and (vi) the impact they have on psychosocial outcome (Chapter 15) in BD. This is followed by a discussion of the implications of these findings and suggestions for future research.

16.1 Summary of important findings

16.1.1 *Neurocognition in BD*

Chapter 8 described the first study of its kind to establish the neurocognitive profile of BD using the MATRICS Consensus Cognitive Battery (MCCB) and two additional tests recommended by the International Society for Bipolar Disorders (ISBD). Patients with BD exhibited significant overall impairments in neurocognitive performance relative to controls. This was particularly pronounced for the domains of working memory, visual learning, and processing speed; although there were also trend level deficits for executive function, and verbal learning. At the subtest level, patients had significantly worse performance on the Brief Assessment of Cognition in Schizophrenia: Symbol Coding and the Wechsler Memory Scale;

Spatial Span. Again, trend level deficits were evident for performance on the Letter Number Sequencing task and the Trail Making Test B. Importantly, there were no differences in cognitive performance between patients with BD I versus BD II, nor were there differences between symptomatic and euthymic patients or patients on and off different classes of medication. These results are in agreement with past studies investigating neurocognition in BD, and suggest that neurocognitive impairment in the disorder is a relatively stable and enduring trait evidenced across diagnostic subtypes (Bora, et al., 2011; Burdick, et al., 2011; Goswami, et al., 2006; Torrent, et al., 2006; Zubieta, et al., 2001). It was concluded that the MCCB, together with the additional ISBD recommended tests of executive function form a promising consensus based research tool for establishing the neurocognitive profile of BD, and permits a more accurate comparison and synthesis of cognitive findings across study samples.

16.1.2 *Social cognition in BD*

The overarching aim of the studies described in chapters 9, 10 and 11 was to establish the social cognitive profile of BD, using novel assessments and taking into account potential methodological confounds (as reviewed in Chapter 3). This is an essential area of research because despite social cognitive functions being arguably more complex than neurocognitive functions, social cognition has received far less empirical attention than neurocognition. In the spirit of extending understandings of its complex nature, three of its components; facial emotion processing, prosodic emotion processing and theory of mind were examined.

16.1.2.1 Facial emotion processing

Chapter 9 described the first study that aimed to establish the facial emotion processing profile of BD by addressing a number of past methodological limitations that had potential for confounding estimations of true effects. The results of this study indicated that emotion labelling performance was better on a task using a dynamic stimuli design relative to a static stimuli design, with patients performing worse than controls on these tasks overall. This poor performance was generalised across a range of emotional expressions, suggesting a globally compromised facial emotion processing impairment in BD. Further, although the

accuracy with which facial emotions were labelled and discriminated diminished in line with the degradation of stimulus intensity in both groups, BD patients still performed more poorly on the discrimination task than controls. No group difference was observed on a control task measuring the non-emotional identification of faces, and this pattern of findings did not differ between diagnostic subtypes or patients classified as euthymic, depressed or mixed/manic.

These findings of facial emotion processing impairment are broadly consistent with past research investigating facial emotion processing in BD (Derntl, et al., 2009; Lembke & Ketter, 2002; Venn, et al., 2004). Importantly, the small, yet consistent pattern of deficits across different task designs and facial emotions, suggests that past inconsistencies in the literature may not be attributable to emotion processing impairments being masked by task-related artefacts in different studies. In other words, as different task procedures resulted in the same general finding in the present data, it is unlikely that past inconsistencies in the literature are related to procedural factors. Instead, these differences may be better accounted for by other cohort-related factors. It was concluded that BD patients exhibit a generalised impairment in the ability to label facial expressions and to make use of available emotional facial cues to differentiate them.

16.1.2.2 Prosodic emotion processing

Chapter 10 described the first study to examine prosodic emotion processing performance *and* assess the influence of a number of potential confounds including gender and early acoustic sensitivity in BD. Patients with the disorder were less sensitive than their control counterparts in discriminating amplitude and durational cues, but not pitch cues or linguistic prosody. They also demonstrated impaired ability to recognise happy intonations; although this was specific to males with BD. The recognition of happy in the patient group was correlated with pitch and amplitude sensitivity in female patients only, and did not appear to impact the recognition of happy prosody in males. There were no differences between diagnostic subtypes or patients classified as euthymic, depressed or mixed/manic.

These findings are not consistent with the only prior study to have investigated gender effects on emotional prosody recognition in the disorder (Bozikas, et al., 2007). Nevertheless, they do indicate the existence of a female advantage for the processing of emotional prosody

in BD. That happy prosody recognition was not impacted by lower order sensory-perceptual patient impairments in males suggests that this prosodic emotion processing deficit is reflective of a top-down, cognitive problem.

16.1.2.3 Theory of mind

Chapter 11 described the first study to examine BD patient performance on a well-recognised measure of ToM that commonly elicits group-related differences in schizophrenia research. Patients with BD performed significantly worse on the ToM relevant false-belief stories of the task, but not on the control stories requiring social script knowledge, executive control or an understanding of causal connections. There were no differences in the ToM performance of symptomatic versus euthymic patients or between those with BD I versus BD II. These results support previous evidence of ToM impairment in BD (as noted by Inoue, et al., 2004; Kerr, et al., 2003; Samamé, et al., 2012), validate the use of the Picture Sequencing Task in BD, and indicate a potential endophenotypic overlap in schizophrenia and BD.

16.1.3 *Emotion regulation in BD*

Chapter 12 described an investigation assessing multiple dimensions of emotion regulation on the Difficulties in Emotion Regulation Scale (DERS) in BD. We were able to demonstrate that relative to controls, patients with the disorder had significantly worse emotion regulation in terms of their clarity and acceptance of emotion, impulse control, goal-directed behaviours and access to adaptive regulation strategies. Whilst this profile did not differ between patients classified as symptomatic and patients classified as euthymic, those with greater manic or depressive symptom severity did tend to have greater difficulties in accessing adaptive coping strategies, controlling impulses, and being accepting and valuing of inherent emotional reactions to distress.

These findings accord with the broader literature indicating emotion regulation deficits in BD (Becerra, et al., 2013; Green, et al., 2007; Green, et al., 2011; Gruber, et al., 2011; Gruber, et al., 2012; Rowland, et al., 2013a; Townsend & Altshuler, 2012). The findings that patients with BD have considerably less emotional clarity and tend to be unaccepting of their

distressing emotion states have particularly important clinical implications, because these factors may reduce the allocation of resources necessary for the formulation of adaptive behaviours, and increase the use of negative coping strategies (Gohm & Clore, 2002; Hayes, et al., 1996; Salovey, et al., 1995).

16.1.4 *Genetic influences on neurocognition, social cognition and emotion regulation in BD*

The first section of Chapter 13 described one of only a few studies to have examined relationships between cognitive tasks and Catechol-*O*-methyltransferase (COMT) SNPs rs165599, rs4680 and rs4818 in a well characterised sample of BD patients compared to controls. Similarly, the novel accompanying analyses included in the chapter examined relationships between aspects of social cognition (namely facial emotion processing) and emotion regulation (namely total score performance on the DERS) and a) the rs4680 ($Val^{158}Met$) COMT SNP and b) the rs4570625 (G703T) Tryptophan Hydroxylase 2 (TPH2) SNP. Potential relationships between the latter SNP and neurocognition were also assessed.

This investigation was conducted in an attempt to link candidate endophenotypes to underlying vulnerability genes that have roles in cognition and emotional processes and have been implicated in BD. Results revealed significant interaction effects for executive functioning across all three COMT SNPs and for visuospatial learning on rs4680. These interactions are the first to be reported in the BD literature. On these tasks, G allelotype carrier performance was associated with better performance in the control group, but worse performance in the patient group. A task specific effect of TPH2 rs4570625 was also evident for a measure of sustained attention, with T allelotype carriers showing worse performance than those absent of the T allele. There were no significant effects of COMT rs4680, or TPH2 rs4570625 on emotion recognition or emotion regulation in either patients or controls.

This set of findings suggests that aberrations of executive function and visuospatial memory in BD are, at least partially, the result of a significant influence of COMT on these particular domains, whilst TPH2 appears to have an effect on attention regardless of the presence or absence of a clinical diagnosis of BD. Although these genes may play a role in the

pathophysiology of the disorder by influencing the capacity for certain cognitive processes, they do not appear to have any influence on facial emotion processing or emotion regulation.

16.1.5 *Inter-relationships between neurocognition, social cognition and emotion regulation in BD*

Chapter 14 described a study that aimed to explicitly examine inter-relationships among neurocognition, social cognition and emotion regulation in a BD cohort. The rationale for this aim was converging evidence suggesting that social cognition and emotion regulation are affected by the capacity for effective neurocognitive function (as reviewed in Chapter 2) in BD, and the novel hypothesis that aberrations in social cognition could also impede adaptive emotion regulation (as specified in Chapter 4).

A robust path analysis statistical design was employed to examine these relationships, with results indicating that neurocognition was associated with social cognition (both emotion perception and theory of mind), but neither neurocognition nor social cognition was associated with emotion regulation. This pattern of relationships was consistent regardless of symptomatic status or diagnostic subtype and indicates a dissociation of cognition from emotion regulation in BD at the trait level. Although these results support a recent behavioural study also reporting that links between social cognition and emotion regulation strategies are absent in BD (Rowland, et al., 2013b), it is possible that relationships between neurocognition/social cognition and emotion regulation in the present data were attenuated due to limitations inherent in the different methodologies employed to assess these processes (i.e., performance based versus self-report). Nevertheless our findings did suggest that neurocognition and social cognition are related in BD, which is consistent with research indicating that dysfunction in the same brain networks involved in neurocognition in BD mediate dysfunctions in social cognition as well (Green, et al., 2007). This latter finding may have important implications for psychosocial therapies for the disorder as they indicate that the remediation of neurocognitive deficits may at least partially remediate social cognitive deficits in BD too.

16.1.6 *Psychosocial consequences of neurocognition, social cognition and emotion regulation in BD*

Chapter 15 described a study examining the relative influence of clinical symptomatology, neurocognition, social cognition and emotion regulation on psychosocial function in BD, with a sub-aim to determine whether these constructs contributed to subjective and objective evaluations of psychosocial capacity in the same way. The study was designed in the context of limited empirical evidence, but a defensible theoretical rationale to suggest that the latter variables are important in the prediction of psychosocial function in BD (as reviewed in Chapter 5).

Global objective and subjective functioning was significantly impaired in BD patients relative to controls. In the patient group, objective psychosocial functioning appeared to be reasonably reflective of subjective psychosocial functioning, suggesting that patients' own evaluations of their quality of life are important indicators of the extent to which their observable function is impaired. Although these two facets of psychosocial functioning were related, the predictors of each differed; stepwise regression analyses showed that depressive symptomatology was the most important predictor of the global subjective psychosocial function score, whilst both depressive symptomatology *and* neurocognition had a concurrent and important influence on the objective psychosocial function score. Emotion regulation also had an indirect effect on global objective and subjective functioning via its influence on depressive symptomatology.

These results support an association between neurocognition and psychosocial outcome in BD, and emphasise the role that poor emotion regulation plays in perpetuating depressive symptoms that impact psychosocial outcomes in the disorder. When taken together, these results highlight different pathways to dysfunctional psychosocial outcome and emphasise the importance of incorporating neurocognitive and emotion regulation assessments into clinical practice when working with patients diagnosed with BD.

16.2 Significant contributions and implications

The following section provides a discussion of the project's contribution to the literature and the implications it has for the description, explanation and treatment of BD.

16.2.1 *Implications for diagnosis*

There have been a number of recommendations for including neuropsychological markers into diagnostic classification systems, so as to improve diagnostic precision, provide complementary information for clinicians, and to work as a source facilitating the stimulation of further research (Cuthbert & Insel, 2010b; Hyman, 2007; National Institute of Mental Health, 2008; Phillips & Kupfer, 2013; Vieta & Phillips, 2007). The findings of this project add weight to these recommendations, as they indicate neurocognitive impairment across a number of domains in BD patients compared to controls. They also indicate a genetic influence on neurocognition in BD, which contributes to the ongoing discussion concerning whether an emphasis on research enabling better understandings of aetiological foundations is necessary in the formulation of revised taxonomies for diagnosis (Cuthbert & Insel, 2010a; Cuthbert & Insel, 2010b; Kupfer & Regier, 2011; Phillips & Vieta, 2007).

Furthermore, the findings of the present project suggest that neurocognitive impairments can be demonstrated on a brief battery that doubles as a source of comparison with related disorders (see Chapter 8). As the majority of neurocognitive work before the MCCB (and its predecessor Repeatable Battery for the Assessment of Neuropsychological Status; RBANS) was with large and lengthy batteries, the use of the MCCB in clinical populations has shown that an overall cognitive profile can be obtained on a short battery without subjecting individuals to 4-5 hours of testing. This is important for reducing the effect of stress and fatigue on participants, and thus improving the likelihood of capturing an accurate neurocognitive profile. Moreover, the use of this facile battery in baseline neurocognitive assessments is important for improving the feasibility of clinical trials that aim to enhance cognitive function. Importantly, the MCCB results here may also facilitate research examining the generalisability of neurocognitive endophenotypes for BD, and may in turn

contribute to the debate regarding the validity of the schizophrenia-BD spectrum (see Craddock, et al., 2006; Craddock & Owen, 2010).

The results of this project also highlight the potential for considering social cognition (especially facial emotion processing and theory of mind) and emotion regulation in diagnostic assessments of BD. Although social cognition, emotion regulation or neurocognition are not adequate for providing clear diagnostic precision alone, their assessment in combination with existing criteria might provide useful information that improves the reliability and validity of diagnosis. Indeed, the current diagnostic system enables the same diagnosis of BD to be made with a multitude of criteria sets (Lieberman, Peele, & Razavi, 2008). This hampers the precision of our understanding of the disorder because it impedes the identification of homogenous populations for research. A valid diagnosis should transcend mere description and afford ancillary information concerning aetiological foundations and outcome (Joyce, 2008). To facilitate research progress that may eventually enable greater ecological validity in diagnosis and improvements in prognostic value, it is thus certainly important to consider these phenomenological impairments in future revisions of the diagnosis of BD (Kupfer & Regier, 2011). It would be hoped that more valid diagnosis would in turn permit better targeted treatment to improve outcomes (National Institute of Mental Health, 2008).

16.2.2 *Implications for endophenotype research*

As the current psychiatric diagnostic system is optimised for clinicians and not researchers, the lack of importance placed on biological foundations in such systems has partially contributed to the limited success in establishing the neurobiological and genetic aetiological mechanisms of BD diagnosis (Gottesman & Gould, 2003). Instead, recent adoption of an endophenotype approach to understanding BD serves to improve understandings regarding its underlying psychopathology and perhaps eventually improve diagnostic specificity (Frangou, 2013; Glahn & Blangero, 2011; Glahn, et al., 2010; Hasler, et al., 2006).

The results of this project certainly contribute to the ongoing search for reliable candidate endophenotypes for BD; in the context of previous results, the demonstrated

neurocognitive, facial emotion processing and theory of mind impairments in patients with BD reported here, appear to represent consistently measureable features that are indistinguishable in patients on the basis of symptomatic or diagnostic subtype status. These results support growing evidence specifying that these phenomenological impairments are stable, trait-like characteristics of the disorder (e.g., Bearden & Freimer, 2006; Bora, et al., 2009a; Samamé, et al., 2012), and qualify at least two components of the criteria for an endophenotype: (i) the endophenotype is associated with illness in the population; and (ii) the endophenotype is primarily state-independent (Gottesman & Gould, 2003).

Indeed, this work fits well in the context of current research indicating that certain neurocognitive abilities represent robust, objectively measurable vulnerability markers for BD. In particular, there appears to exist a genetic influence on neurocognition in the disorder, stemming in part, from within the dopaminergic neurotransmitter system (see Chapter 13). Findings from this project specifically demonstrating evidence of interaction effects and between group differences in carriers of different allelotypes of the COMT gene in sample groups with relative sizes of $n \leq 52$, suggests that the effect of COMT on cognition may be fairly pronounced. This is consistent with the hypothesised role of dopaminergic mechanisms in the aetiology of BD, and encourages further research examining the influence of COMT in its psychopathology.

16.2.3 *Implications for the understanding and treatment of BD*

One of the primary contributions of this project was to emphasise the importance of considering neurocognition, social cognition and emotion regulation in both aetiological formulations in the disorder and in clinical practice. As such, the results presented in this thesis have a number of specific implications for our understanding of BD. The main contributions of this project are:

i. This thesis gives to the ongoing search for a better understanding of the relationship between brain pathology and behavioural outcomes in BD, as it is possible that the finding that neurocognition partially underpins social cognition (both emotion

perception and theory of mind) reflects an overlap in at least some of the brain regions involved in these processes in the disorder.

ii. Findings from this thesis reinforce past observations of consistent state independent impairments in neurocognitive function in BD, and highlight the importance of routinely considering neurocognitive ability in clinical settings. As neurocognition appears to be an important predictor in the functional outcome of BD, it may represent an important treatment target (Kumar & Frangou, 2010).

iii. The findings of this thesis may be used to inform clinicians about difficulties in neurocognitive, social cognitive and emotion regulation function in patients with BD. This would educate them to consider these difficulties when setting tasks, examining cognitive biases, and in interacting with patients. In particular, the potential for misinterpretation of emotional feedback by patients should be taken into account in treatment, because it could impede progression by leading to confusion in therapy or even premature treatment termination. On the basis of this work it is suggested that clinicians need be particularly aware of the clarity of their communications given that patients may not interpret them in the manner in which they were intended.

iv. This work could also be used to inform patients about the potential impairments they may experience. This would promote awareness and potentially reduce medication non-compliance given that patients tend to view medication as the primary source of their cognitive difficulties (Goodwin, Martinez-Aran, Glahn, & Vieta, 2008). Further, given the findings that neurocognition and emotion regulation to a lesser degree are of functional significance, this work suggests that traditional pharmacotherapy interventions for BD may be complemented with novel psychological treatments directly targeting these abnormalities. For example, findings of this work suggest that targeted neurocognitive skills training in early problem areas such as memory and visual learning may improve cognitive performance and facilitate an improvement in psychosocial functioning (see Chapter 15). Novel emotion regulation therapies that have been tested in other clinical populations might also be usefully applied to patients with BD to remediate emotion regulation difficulties and subsequently improve depressive symptomatology. Further, evidence that there is a directional relationship

between social cognition and neurocognition in BD may influence the development of social cognitive remediation strategies because both neurocognition *and* social cognition appear to be appropriate targets for remediation of deficits in the latter.

v. Finally, this work reiterates that low level depressive symptomatology is an important predictor of psychosocial functioning. These symptoms should thus be judiciously monitored, and appropriately treated to improve psychosocial outcome and reduce the recurrence of episodes that may result in further neuropsychological decline.

16.3 Limitations

Although specific limitations were reported within each of the previous empirical chapters, there are several that warrant further discussion because they are i) of the most importance, ii) are present in many of the aforementioned investigations or iii) have only emerged on synthesis of this work. These generally relate to sample characteristics and methodological issues.

Firstly, despite the reasonably sized sample of BD patients and control participants in all empirical investigations presented here, the project was still constrained in the type of analyses that could be used to investigate the data. For example, the sample size limited detailed exploration regarding inter-relationships between neurocognition, social cognition, emotion regulation and psychosocial functioning (Chapter 14 and 15), because to maintain power, the number of parameters needed to be reduced to global composite scores. Thus, the studies had to forego the use of robust statistical methods like structural equation modelling. Further, the stratified subgroups of manic, depressed and euthymic patients (stratified into symptomatic and euthymic in Chapters 8, 12 and 15 to provide more power) or BD I and BD II diagnostic subtype groups were small. Unfortunately, it is very difficult to recruit BD patients in any state or diagnostic category and retain their co-operation in a study that requires considerable concentration. Further, as the author was the sole person involved in the recruitment and testing of participants on the large battery of measures in this project, time constraints were also a factor in the small subgroup numbers. Ultimately, recruitment aims for this study had to remain feasible and due to practicality, inpatients were not targeted for

recruitment for this project. Nevertheless, as current mood states and diagnoses of participants are of great importance in BD research due to their potential for blurring estimations of true effects, we attempted to provide insight into the influence of these characteristics throughout the thesis by comparing symptomatic versus euthymic patients and those meeting criteria for BD I or BD II. Although these factors did not confound the results, the restricted power after stratification and the subsequent inability to sufficiently explore other potential confounding issues within these groups suggests that inferences based on the results of analyses using them should be viewed with caution. Researchers conducting further research in the area should certainly aim to recruit actively manic or depressed patients to provide greater insight into the effects of mood, particularly if using smaller batteries than that used here. Although this has a level of difficulty, it is not impossible (see Rossell & Van Rheenen, 2013 , who obtained 30 manic patients using a smaller more focussed battery of tasks).

Secondly, the project did not account for the number of previous psychotic or manic and depressed episodes of each patient, nor did it explicitly examine the influence of diagnostic co-morbidities including DSM-IV-TR Axis II disorders. Certainly, this work could have benefited from more detailed analyses pertaining to these sample characteristics. For example, analyses examining relationships between performance and number of past episodes would have provided greater insight into the influence of a chronic course of illness on the variables at hand. Further, despite performance comparisons between patients on and off different classes of psychopharmacological medications in all between groups studies, it was not possible to fully partial out their effects. It is therefore still possible that medication may have influenced the results.

Thirdly, the reliance on a self-report assessment of emotion regulation represents a noteworthy methodological confound given that self-report measures may be inherently subjectively biased (Atkinson, et al., 1997). This limitation however, should not minimise the gains that have been made by including this kind of data in this work, particularly as it provides information that can used to target treatment to areas most likely to be of importance to patients (Becerra, et al., 2013). For example, the substantial patient-control differences in the ability to access appropriate regulation strategies, control impulses, participate in goal directed

activities and be clear about and accepting of emotions observed in the investigation in Chapter 12 could certainly provide a focus for future emotion regulation therapies.

Finally, one major limitation to this work relates to differences in the construct validity and state of knowledge between the conceptually distinct phenomenological features of focus in this thesis. Certainly, based on the authors review of the literature it has become clear that understandings of neurocognitive, and to a lesser degree social cognitive processes, emerge from a fundamentally stronger, and more methodologically sound empirical research base than those of emotion regulation processes. That is, as definitions of emotion regulation vary widely, the ensuing conceptual heterogeneity of the construct substantially impedes the consistent application of well-defined, objective, standardised measurements for its assessment (Becerra, et al., 2013; Gratz & Roemer, 2004; Gruber, et al., 2012). Thus, there is potential that differences in the relative standing of the literatures from which these processes are borne represent a significant limitation to the exposition of accurate, valid and reliable understandings of interactions between them.

16.4 Important recommendations for future research

The current thesis has bettered current descriptions of the phenomenological profile of BD, and furthered understandings of its mechanisms and indirect aetiological underpinnings. However, given the limitations specified above, the findings of this work are not conclusive and further research is certainly warranted. Although specific recommendations for research are presented within each of the previous empirical chapters, an inclusive outline of the key areas recommended as a focus for prospective investigations is presented below.

The studies described in Chapter 8 and 11 offered some of the first attempts to examine the efficacy of using measures (neurocognitive and theory of mind relevant) that are well established in the schizophrenia literature, in a BD sample. The results of these studies are promising, and provide further evidence of the potential for shared endophenotypes for psychosis (Lin & Mitchell, 2008). However, substantial replication across different mood phases of BD, in first degree relatives of BD patients, and in comparison to schizophrenia patients is necessary to establishing the reliability of these measures for appropriately

characterising candidate endophenotypes that can be employed in genetic studies of the disorders aetiology.

Replication of the auditory-prosodic study presented in Chapter 10 is also prudent. This is needed to further current knowledge with regards to the involvement of early sensory deficits in prosody recognition in BD (Leitman, et al., 2005; Leitman, et al., 2010). In particular, such research, using large and well matched samples of male and female BD patients, would facilitate greater insight into the impact of gender on prosodic emotion processing performance. Similarly, better powered and more homogenous BD samples are required to replicate the novel genetic findings presented in Chapter 13. It is therefore recommended, that future studies aim to recruit and compare large samples of BD I and BD II diagnosed individuals across manic, depressed and euthymic mood state on the measures used in this work. Investigation of the relationships shared between the measures and psychosis history in these groups would also be useful.

Many questions also remain regarding the specific foundations of the facial emotion processing deficits presented in Chapter 9. Certainly additional study using modern neuroscience technologies such as eye tracking and neuroimaging would complement the current research and provide a better understanding of neurobiological mechanisms involved in facial emotion perception, with directly translatable therapeutic outcomes such as training to direct eyes to important features of the face during emotion perception (Calvo & Nummenmaa, 2009; Fossella & Casey, 2006).

Future work should also endeavour to clarify associations between emotion regulation and manic and depressive symptomatology, to facilitate the better identification of trait factors in BD and provide better insight into the clinical consequences of emotion regulation difficulties. There are also grounds for future efforts to be made to better define emotion regulation, and subsequently develop more objectively measured and standardised emotion regulation assessments for consistency, and comparison purposes. This would certainly go some way in improving the power of future attempts to examine relationships between neurocognition, social cognition and emotion regulation.

Further, prospective studies should aim to conduct more detailed investigations assessing the impact of individual domains of neurocognition, social cognition and emotion

regulation on psychosocial outcome in longitudinal designs, to better inform understandings of their contribution to outcome over time. Moreover, both researchers and clinical practitioners alike would benefit from a better understanding of patient response and receptiveness to neurocognitive remediation programs and psychosocial interventions. Forthcoming studies could thus utilise randomised control trial designs examining the efficacy of such treatments as adjuncts to traditional pharmacotherapy compared to pharmacotherapy alone.

Finally, researchers should aim to build on the findings of this work to facilitate the development of protocols for personalised medicine (Ozomaro, Wahlestedt, & Nemeroff, 2013; Phillips & Kupfer, 2013). Indeed, the results generated from this thesis suggest that it may be possible to identify a personalised and comprehensive endophenotypic profile for individuals with BD. That is, if each individual is examined on a range of neurocognitive, social cognitive and emotion regulation measures, it may be possible to ascertain which alternative treatments would be most pertinent on an individual basis (i.e., if neurocognition is impaired then a combination of cognitive remediation and pharmacological medication designed to improve cognition may be required; if facial emotion processing is impaired then eye movement training may be needed). A personalised approach would certainly go a long way in improving the current trial and error method of treatment.

16.5 Summary

In sum, BD is a complex mood disorder with a range of detrimental psychosocial outcomes affecting a significant number of individuals worldwide. Reviews of the literature indicated abnormalities in processes related to neurocognition, emotion regulation, and social cognition in patients with BD. In light of the potential for advancements to be made with regards to our current understandings of the phenomenological profile of BD, and the way in which features within it interact, this thesis was formulated to comprehensively assess neurocognitive, social cognitive and emotion regulation abnormalities in BD. It adopted a view toward developing a better understanding of the intricate processes within each domain of functioning, their genetic aetiology and relationships shared between them, as well as their psychosocial consequences.

By using an approach that characterised the profile of these processes in the disorder, as well as examined broader inter-relationships between them, this thesis provided substantial empirical data permitting important insights about neurocognition, social cognition and emotion regulation that addressed gaps in the current research literature. Specifically, the findings of this work further supported assertions that patients with BD experience trait-like neurocognitive and social cognitive deficits, and provided a step toward characterising the emotion regulation profile of the disorder across a variety of dimensions. They also suggested that there may be inherent overlap in brain processes underlying neurocognition and social cognition in BD. These findings offered significant methodological and clinical implications, particularly given that neurocognition and emotion regulation were found to be important predictors of psychosocial dysfunction (the latter albeit indirectly).

It is hoped that this research will advance the overall understanding of BD, and ultimately result in better outcomes for BD patients by increasing scientific knowledge in the field.

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Appendix A: Certificates of ethical approval

TheAlfred

ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project No: 304/10

Project Title: Understanding Emotion Abnormalities in Bipolar Disorder

Principal Researcher: Professor Susan Rossell

Protocol No: Version 2 **dated:** 13-Oct-2010

Participant Information and Consent Form version 2 **dated:** 13-Oct-2010
Psychiatric Disorder Biobank Participant Information Sheet version 2 **dated:** 15-Jan-2010
Psychiatric Disorder Biobank Consent Form version 2 **dated:** 15-Jan-2010

was considered by the Ethics Committee on ***21-Oct-2010*** *and* ***APPROVED*** *on* **22-Oct-2010**

It is the Principal Researcher's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Principal Researcher is required to notify the Secretary of the Ethics Committee, via amendment or progress report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project;
- Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Principal Researcher is required to submit

- A Progress Report on the anniversary of approval and on completion of the project *(forms to be provided)*;

The Ethics Committee may conduct an audit at any time.

All research subject to the Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Hospital Ethics Committee is a properly constituted Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Human Research (2007).

SPECIAL CONDITIONS

None

SIGNED: _____
Chair, Ethics Committee (or delegate)

R. FREW
SECRETARY
ETHICS COMMITTEE

Please quote Project No and Title in all correspondence

SWINBURNE UNIVERSITY OF TECHNOLOGY

Swinburne University of Technology
Human Research Ethics Committee (SUHREC)
Certificate of Ethics Clearance

SUHREC Project 2010/310
Understanding Emotion Abnormalities in Bipolar Disorder

Chief Investigator/Supervisor:	Prof Susan Rossell
Co-Investigator(s):	Assoc Prof Greg Murray Dr Jeremy Jowett (Baker Inst)
Duration Approved:	13/12/2010 To 13/11/2013

This is to certify that the above project has been given ethics clearance in accordance with the current *National Statement on Ethical Conduct in Human Research*. The standard conditions and any special conditions for on-going ethics clearance are here printed.

All human research activity undertaken under Swinburne auspices must conform to Swinburne and external regulatory standards, including the above-mentioned *National Statement* and with respect to secure data use, retention and disposal.

The named Swinburne Chief Investigator/Supervisor remains responsible for any personnel appointed to or associated with the project being made aware of ethics clearance conditions, including research and consent procedures or instruments approved. Any change in chief investigator/supervisor requires timely notification and SUHREC endorsement.

The above project has been approved as submitted to date for ethical review by or on behalf of SUHREC. Amendments to approved procedures or instruments ordinarily require prior ethical appraisal/ clearance. SUHREC must be notified immediately or as soon as possible thereafter of (a) any serious or unexpected adverse effects on participants and any redress measures; (b) proposed changes in protocols; and (c) unforeseen events which might affect continued ethical acceptability of the project.

At a minimum, an annual report on the progress of the project is required as well as at the conclusion (or abandonment) of the project.

A duly authorised external or internal audit of the project may be undertaken at any time.

Additional Note:
Project approved by and subject to monitoring by The Alfred HREC (Alfred Proj 301/210)
Approval includes:
- PICF version 2 dated 13 October 2010
- Psychiatric Disorder Biobank PI Sheet version 2 dated 15 Jan 2010
- Psychiatric Disorder Biobank CF version 2 dated 15 Jan 2010

The SUHREC project number and title should be cited in any communication.

Keith Wilkins
Secretary, SUHREC and Research Ethics Officer
16/02/2011

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Appendix B: Van Rheenen, T. E., & Rossell, S. L. (2013). Genetic and neurocognitive foundations of emotion abnormalities in bipolar disorder, *Cognitive Neuropsychiatry,* 18:168-207

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Appendix C: Glossary of genetic terminology

Allele: One of two alternate forms of the same gene that are found at the same location on a chromosome

Allelotype: The frequency distribution of a given set of alleles at a single locus on a chromosome

DNA: Deoxyribonucleic acid (DNA) is a molecule coding the genetic information for all living organisms. It comprises nucleotide bases Adenine (A), Thymine (T), Guanine (G) and Cytosine (C). The former bases always pair together and the latter bases always pair together.

Endophenotype: A measureable biological, behavioural or cognitive phenotypic marker with clear genetic connection that is found more often in individuals with a disorder than in the general population.

Genome Wide Association Study: A study investigating associations between many common genetic variants and phenotypic traits like psychiatric disorders.

Genotype: The allele constitution of an organism/ the allelotype makeup inherited for a particular gene

Heterozygote: A dissimilar genotype occurring at a single locus on a chromosome

Homozygote: An identical genotype occurring at a single locus on a chromosome

Methionine: An amino acid with codons AUG

mRNA: Messenger ribonucleic acid is a molecule that carries genetic codes from the nucleus to the cytoplasm of a cell

Single nucleotide polymorphism: A variation in the DNA sequence occurring when one single nucleotide base is substituted for another

Synonymous: a substitution of one nucleotide base for another in an exon of a gene encoding a protein that does not result in a change to the amino acid sequence.

Valine: An amino acid with codons GUU GUC GUA GUG

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Appendix D: Van Rheenen, T. E., & Rossell, S. L. (2013). Is the non-verbal behavioural emotion-processing profile of bipolar disorder impaired? A critical review. *Acta Psychiatrica Scandinavica*, 128,163-178

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Appendix E: Van Rheenen, T. E., & Rossell, S. L. (in press, September 2013). Phenomenological predictors of psychosocial function in bipolar disorder: is there evidence that social cognitive and emotion regulation abnormalities contribute? ***Australian and New Zealand Journal Of Psychiatry.*** **Doi: 10.1177/0004867413508452**

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Appendix F: Supplementary table for Chapter 5

Table 31. *Neurocognitive and socio-emotional predictors of psychosocial outcome in BD*

Reference	Study type	Participants	Psychosocial measure	Psychosocial measure type	Cognitive &/or socio-emotional domains measured	Relevant Key Results	Relevant comments
(Altshuler, et al., 2008)	Cross-sectional	N= 14 BD (7 well-functioning and 7 poor functioning) Mood state: Euthymic N= 22 HC	GAF	Objective	Neurocognitive: verbal declarative memory, executive functioning. Social cognitive: NI Emotion regulation: NI	The poor functioning group had significantly worse verbal memory and executive functions in comparison to well-functioning BD patients and healthy controls.	The authors suggest that poor functioning may be restricted to a subgroup of BD patients with poor cognitive functioning
(Atre-Vaidya, et al., 1998)	Cross-sectional	N= 36 BD Mood state: Euthymic	IRS SSAIM	Objective	Neurocognitive: General intelligence, verbal fluency, verbal memory, visuospatial ability Social cognitive: NI Emotion regulation: NI	Poor memory and verbal fluency was associated with poor psychosocial functioning.	-
(Bonnín, et al., 2010)	Longitudinal follow up over 4 years	N= 32 BD Mood state: Euthymic	GAF & FAST	Objective	Neurocognitive: Estimated IQ, attention & executive functions. Social cognitive: NI Emotion regulation: NI	Verbal memory & subclinical depressive symptomatology best predictors of overall psychosocial function. Executive function & depressive symptomatology best predictors of occupational outcome.	The author's suggest that psycho-education programs & neurocognitive remediation might play an important protective role in enhancing functional outcome.

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Reference	Study type	Participants	Psychosocial measure	Psychosocial measure type	Cognitive &/or socio-emotional domains measured	Relevant Key Results	Relevant comments
(Bowie, et al., 2010)	Cross sectional	N= 130 BD N= 161 SCZ Mood state: Not clear	SLFS	Objective	Neurocognitive: Composite score based on a neurocognitive battery including measures of verbal declarative memory, attention, verbal working memory, executive functioning, processing speed, verbal fluency Social cognitive: NI Emotion regulation: Social Skills Performance Assessment	Depressive symptoms independently predicted poor work skills in the BD group. Neurocognition indirectly contributed to work skills and interpersonal relationships through its influence on adaptive and social competence in BD.	The authors suggest that the results indicate that persistent functional deficits in BD may persist even after they cross traditional thresholds for treatment success
(Brissos, et al., 2008b)	Cross sectional	N= 55 BD N= 50 HC Mood state: Euthymic	WHOQOL-BREF	Subjective	Neurocognitive: Attention & mental control, perceptual-motor skills, executive functions, verbal abstraction, visuospatial attention & memory. Social cognitive: NI Emotion regulation: NI	Poorer self-reported QOL correlated significantly with worse cognitive performance. All QOL domains significantly predicted by cognitive variables in a regression model. The best models were one's that included both subclinical depressive symptoms and cognitive variables.	The authors conclude results lend in favour of a cognitive rehabilitation approach for restoring QOL to baseline levels in BD

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Reference	Study type	Participants	Psychosocial measure	Psychosocial measure type	Cognitive &/or socio-emotional domains measured	Relevant Key Results	Relevant comments
(Brissos, et al., 2008a)	Cross sectional	N= 30 BD 23 SCZ 23 HC Mood state: Euthymic	WHOQOL-BREF	Subjective	Neurocognitive: Attention & mental control, perceptual-motor skill, executive functions, Neurocognitive: verbal fluency, verbal abstraction, visuospatial attention & memory. Social cognitive: NI Emotion regulation: NI	More symptomatic BD patients reported worse QoL, especially for physical & environmental domains. These domains were also associated with worse neurocognitive performance.	The author's suggest that there is need for psychological interventions aimed at remediating cognitive deficits as an important component of functional recovery in BD.
(Burdick, et al., 2010)	Longitudinal follow up over 6 months	N= 33 BD Mood state: Not clear	Global function$. Work disability & social adjustment%	Objective	Neurocognitive: Verbal learning & memory, processing speed executive function & accessing of general knowledge. Social cognitive: NI Emotion regulation: NI	Processing speed significantly associated with global functional impairment & work disability associated with verbal learning deficits & recent depression	The authors remark that studies assessing functional outcome also need to assess cognitive status.
(Dickerson, et al., 2010)	Longitudinal follow up over 6 months	N= 52 BD Mood state: At follow up: n=24 full depression/ manic syndrome n=7 partial remission n=21 full remission	SAS & MVI	Objective	Neurocognitive: Verbal memory, executive functioning, visual memory, verbal fluency, processing speed, visuospatial abilities & premorbid IQ. Social cognitive: NI Emotion regulation: NI	Occupational status at follow up was not associated with cognition, or mania or depression severity score. Depressive or manic symptomatology also did not predict social adjustment, while processing speed & symptom remission did. There was also a trend	-

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Reference	Study type	Participants	Psychosocial measure	Psychosocial measure type	Cognitive &/or socio-emotional domains measured	Relevant Key Results	Relevant comments
						for a trend for processing speed to be associated with the work adjustment score.	
(Dickerson, et al., 2004)	Cross sectional	N= 117 BD Mood state: Not clear	Employment status	Objective	Neurocognitive: Immediate memory, visuospatial & constructional, language, Attention, delayed memory. Social cognitive: NI Emotion regulation: NI	Greater cognitive functioning & lower severity of symptoms independently associated with better employment status.	The author's suggest that BD vocational programs would benefit from the inclusion of a formal cognitive assessment to better assess employment potential.
(Dittmann, et al., 2007)	Cross-sectional	N= 55 BD N=17 HC Mood state: Euthymic	SAS	Objective	Neurocognitive: Immediate memory, visuospatial/constructional abilities, language, attention, and delayed memory Social cognitive: NI Emotion regulation: NI	Psychosocial function correlated with working memory but not with mood symptomatology	-
(Fujii, et al., 2004)	Prospective follow up 15 years post testing	N= 30 patients with severe & persistent mental illness, 6 of which had BD Mood state: Not clear	BQOLI	Subjective	Neurocognitive: Executive functioning, working memory, short-term memory, psychomotor functioning . Social cognitive: NI Emotion regulation: NI	Family & financial support predicted by executive function, satisfaction with family contact predicted by motor skills & satisfaction with social contacts predicted by memory.	The author's remark that neurocognitive status provides long-term prediction of functional outcome in persons with severe and persistent mental illness.
(Hajnal, et	Cross	N= 23 BD	GAF &	Subjective	Neurocognitive:	ToM was the best	Note that only the

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Reference	Study type	Participants	Psychosocial measure	Psychosocial measure type	Cognitive &/or socio-emotional domains measured	Relevant Key Results	Relevant comments
al., 2010)	sectional	N= 31 HC Mood state: Euthymic	employment status		Neurocognitive battery (domains not stated). Social cognitive: Theory of mind Emotion regulation: NI	predictor of functional outcome.	published abstract for this study was available
(Hoertnagl, et al., 2011)	Cross sectional	N= 47 BD N= 45 HC Mood state: Euthymic	GAF, WHOQOL-BREF & employment status	Objective & subjective	Social cognitive: Facial emotion processing, Emotion regulation: Emotional experience & emotion regulation.	The experience of shame, guilt, sadness, fear, lifelessness, loneliness, & fear were more intense in patients than controls. Recognition of happy expressions & experienced emotion correlated with most QoL domains. There was also a trend for employment status & global functioning score to be positively correlated with facial emotion processing accuracy. Mood symptomatology was not correlated with functioning.	The author's remark that their findings support evidence that clinical remission & psychosocial status are separable constructs.
(Jabben, et al., 2010)	Cross-sectional	N= 76 BD Mood state: Euthymic	GAF	Objective	Neurocognitive: Verbal memory, sustained attention Social cognitive: NI Emotion regulation: NI	Better attentional reaction time was associated with a higher GAF score.	The authors state that the findings indicate that clinical state is an important variable in

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Reference	Study type	Participants	Psychosocial measure	Psychosocial measure type	Cognitive &/or socio-emotional domains measured	Relevant Key Results	Relevant comments
						Associations were reduced but did not disappear after additionally entering subclinical depression scores into the equation. Subclinical depressive symptomatology was a stronger predictor of psychosocial functioning than neurocognition in BD	predicting outcome in bipolar disorder and may be more predictive of psychosocial outcome than cognition
(Jaeger, et al., 2007)	Longitudinal follow up over 12 months	N= 78 BD Mood state: At follow up: n=29 euthymic n=8 depressed n=5 manic	MSIF	Objective	Neurocognitive: Attention, working memory, learning, verbal knowledge, non-verbal functions & ideational fluency. Social cognitive: NI Emotion regulation: NI	Depressive symptomatology not significantly predictive of functioning although greater mania severity was associated with a lower likelihood for better functioning. After co-varying for symptoms, attention & ideational fluency significantly predictive of functional recovery at 12 months follow up.	The author's remark that pharmacological & rehabilitative treatment targets focusing on functional recovery can benefit from understanding that neurocognitive test performance can predict long-term functional recovery.
(Laes &	Cross	N= 27 BD	SAS-II	Objective	Neurocognitive: IQ,	BD patients with worse	-

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Reference	Study type	Participants	Psychosocial measure	Psychosocial measure type	Cognitive &/or socio-emotional domains measured	Relevant Key Results	Relevant comments
Sponheim, 2006)	sectional	N= 39 SCZ N= 38 HC Mood state: Not clear			immediate & secondary memory, motor functioning, fluency, attention, vigilance, & executive functions. Social cognitive: NI Emotion regulation: NI	planning & problem solving tended to have worse social functioning.	
(Lahera, et al., 2009)	Cross sectional	N= 27 BD (comprising 18 high & 9 low functioning patients) Mood state: Euthymic	GAF	Objective	Neurocognitive: Sustained attention & executive functions. Social cognitive: Facial emotion processing & theory of mind Emotion regulation: NI	Low-functioning patients showed worse cognitive, ToM & facial emotional processing performance than the high functioning patients.	Note that only the published abstract for this study was available
(Malhi, et al., 2007a)	Longitudinal follow up over 30 months	N= 25 BD N= 25HC Mood state: 14 assessed in one phase only: n=7euthymic n=4depressed n=2hypomanic Of the remaining 12 patients: n=4 assessed in all three phases n=8 in two phases of BD	GAF	Objective	Neurocognitive: attention, working memory, learning and memory, executive functioning, psychomotor speed Social cognitive: NI Emotion regulation: NI	In depressed BD patients, poor psychosocial function was associated with poor selective attention / inhibition. In hypomanic BD patients, poor psychosocial function was associated with poor working memory and learning. There were no correlations between neurocognition and working memory in	The authors suggest that even when clinically 'well', patients with BD have subtle functional impairments potentially reflecting neurocognitive deficits.

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Reference	Study type	Participants	Psychosocial measure	Psychosocial measure type	Cognitive &/or socio-emotional domains measured	Relevant Key Results	Relevant comments
						euthymic patients	
(Martínez-Arán, et al., 2002)	Cross-sectional	N= 49 BD N= 49 SCZ Mood state: Euthymic	GAF	Objective	Neurocognitive: Executive function Social cognitive: NI Emotion regulation: NI	General psychopathology and verbal fluency were predictive of functional outcome (the latter at trend level).	The authors suggest that subsyndromal features have an influence on psychosocial function in BD.
(Martinez-Aran, et al., 2004a)	Cross-sectional	N= 40BD N= 30HC Mood state: Euthymic	GAF	Objective	Neurocognitive: Premorbid IQ, Executive functions, attention/concentration and mental tracking, verbal learning and memory Social cognitive: NI Emotion regulation: NI	Verbal memory, working memory and learning were related to psychosocial functioning.	Psychosocial functioning was found to correlate more with neuropsychological measures than with clinical variables.
(Martinez-Aran, et al., 2007)	Cross sectional	N= 77 BD (comprised of 46 high & 31 occupationally low functioning patients) N= 35 HC Mood state: Euthymic	Occupation-al functioning as accounted for by the GAF & occupational adaptation	Objective	Neurocognitive: Premorbid IQ, frontal executive functions, verbal learning & memory. Social cognitive: NI Emotion regulation: NI	Subclinical depression was correlated with global functioning. High-functioning patients less cognitively impaired than low functioning patients on verbal recall & executive functions. Although low level depressive symptoms predicted psychosocial functioning to a small degree, the best	The author's suggest that psychosocial interventions such as psycho-education, family intervention & cognitive rehabilitation should be incorporated into treatment for BD.

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Reference	Study type	Participants	Psychosocial measure	Psychosocial measure type	Cognitive &/or socio-emotional domains measured	Relevant Key Results	Relevant comments
						predictor was verbal memory.	
(Martino, et al., 2011b)	Cross sectional	N= 81 BD N= 34 HC Mood state: Euthymic	GAF	Objective	Neurocognitive: Attention, verbal memory & executive functions Social cognitive: Facial emotion processing & theory of mind. Emotion regulation: NI	There was a relationship between facial emotion processing & psychosocial functioning, however facial emotion processing did not contribute variance in psychosocial functioning beyond neurocognitive impairments.	-
(Martino, et al., 2009)	Longitudinal follow up over 12 months	N= 35 BD Mood state: Euthymic	GAF &FAST	Objective	Neurocognitive: Attention, verbal memory & executive functions. . Social cognitive: NI Emotion regulation: NI	Impairments in verbal memory, attention & subclinical depression explained 43% of variance in global functioning whilst impairments in attention & executive functioning explained 28% of variance in functioning & disability.	The author's suggest that further research investigating cognitive rehabilitation as a means of improving functional outcome is needed.
(Mur, et al., 2009)	Cross sectional	N= 44 BD Mood state: Euthymic	GAF & WHO-DAS	Objective	Neurocognitive: Executive function, attention, processing speed, verbal memory, visual memory.	A large proportion of patients were occupationally inactive & differed from active	The author's remark that clinical remission does not necessarily indicate functional

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Reference	Study type	Participants	Psychosocial measure	Psychosocial measure type	Cognitive &/or socio-emotional domains measured	Relevant Key Results	Relevant comments
					Social cognitive: NI Emotion regulation: NI	patients in visual memory performance & chronicity. Processing speed & subclinical depression was significantly correlated with psychosocial functioning.	recovery & that the development of cognitive & psycho-educational interventions are of great importance in improving psychosocial outcome.
(O'Shea, et al., 2010)	Cross sectional	N= 29 BD N= 29 HC Mood state: Euthymic	GAF & SOFAS	Objective	Neurocognitive: Premorbid IQ, executive function, memory & attention. Social cognitive: NI Emotion regulation: NI	Although unemployment was associated with impaired attention, no cognitive variables were associated with global functioning.	-
(Simonsen, et al., 2010)	Cross-sectional	N= 64 BD N= 60SCZ N=54affective disorders Mood state: Not clear	GAF SFS	Objective and subjective	Neurocognitive: Verbal memory, processing speed, working memory, verbal fluency, executive function Social cognitive: NI Emotion regulation: NI	Depressive symptoms and all neurocognitive variables were associated with objective and subjective psychosocial function, but current symptoms had a greater independent contribution than neurocognition to functioning in BD.	The authors suggest the findings may suggest that symptoms mediate the relationship between neurocognition and functioning
(Solé, et al.,	Cross	N= 43 BD	SOFAS	Objective	Neurocognitive: Premorbid	Psychosocial	The author's suggest

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Reference	Study type	Participants	Psychosocial measure	Psychosocial measure type	Cognitive &/or socio-emotional domains measured	Relevant Key Results	Relevant comments
2012)	sectional	N= 42 HC Mood state: Euthymic			IQ, verbal learning, memory & executive functions. Social cognitive: NI Emotion regulation: NI	functioning was best predicted by subclinical depression, followed by executive function.	that neurocognitive rehabilitation should consider differences in cognitive profiles when designing programs to improve functional outcome.
(Tabarés-Seisdedos, et al., 2008)	Longitudinal follow up over 1 year	N= 43 BD N= 47 SCZ Mood state: At baseline: n=33 euthymic n=6depressed n=4manic At follow up of the 33 euthymic at baseline, n=27 remained euthymic	GAF, WHO-DAS & employment status	Objective	Neurocognitive: Executive functions, working memory, verbal memory, visual memory, visual-motor processing, vigilance, vocabulary & motor speed. Social cognitive: NI Emotion regulation: NI	Deficits in the visual/motor processing domain, positive symptom severity & premorbid adjustment at the first assessment best predicted functioning or disability changes over follow-up period	The author's suggest that neurocognitive remediation programs would improve functional recovery.
(Torres, et al., 2011)	Longitudinal	N= 53 BD Mood state: Not clear	GAF & MSIF	Objective	Neurocognitive: Premorbid IQ, Visual-spatial/non-verbal reasoning, attention/processing speed, executive function, learning & memory. Social cognitive: NI Emotion regulation: NI	After controlling for mood symptoms, verbal learning/memory was associated with follow up functional outcome on the MSIF. Depression ratings at follow up, but not cognitive variables, were associated with global functioning	The authors remark that their findings further support the distinction between clinical & functional outcome & that verbal memory may be a potential treatment target for functional remediation in the early course of the

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Reference	Study type	Participants	Psychosocial measure	Psychosocial measure type	Cognitive &/or socio-emotional domains measured	Relevant Key Results	Relevant comments
						scores on the GAF	illness.
(Wingo, et al., 2010)	Cross-sectional	N= 65 BD (28 functionally recovered, 37 unrecovered) Mood state: n=56 euthymic n=9 mildly depressed	RSI VSI	Objective	Neurocognitive: Premorbid IQ, verbal learning and memory, attention, concentration, and mental tracking, executive functions. Social cognitive: NI Emotion regulation: NI	Unrecovered patients had significantly worse executive function than recovered patients but this difference became redundant after adjusting for residual mood symptoms and education.	-
(Yen, et al., 2009a)	Cross-sectional	N= 96BD N= 96SCZ Mood state: Euthymic	CLS	Objective	Neurocognitive: Executive function Social cognitive: NI Emotion regulation: NI	Psychosocial function was related to executive function in BD	-

Note: BD= Bipolar Disorder; BQOLI= Brief Quality Of Life Inventory; CGAS = Children's Global Assessment Scale; CLS=Community Life Scale; FAST= Functioning; Assessment Short Test; GAF= Global Assessment Of Function; HC=Healthy Control; IQ=Intelligence Quotient; IRS= Impairment Rating Scale LIFE= Longitudinal Interval Follow-Up Evaluation; MSIF= Multidimensional Scale For Independent Functioning; MVI= Modified Vocational Index; NI=Not Included; NP-BD=Narrow Phenotype Bipolar Disorder; QLS= Quality Of Life Scale; QOL=Quality of Life; SAS= Social Adjustment Scale; RSI=Modified Residential Status Index (RSI);SAS-II= Social Adjustment Scale II; SCZ=Schizophrenia; SDS= Sheehan Disability Scale; SLFS= Specific Level of Functioning Scale; SMD=Severe Mood Dysregulation; SOFAS= Social & Occupational Functioning Assessment Scale; SRS= Social Responsiveness Scale; SSAIM=Structures And Scales Interview For Maladjustment; VSI=Vocational Status Index; WHO-DAS= World Health Organization Disability Assessment Schedule; WHOQOL-BREF= World Health Organization Quality Of Life-Brief Form; $8-point scale developed by Levenstein et al. (1966); % 5-point outcome scales developed by Strauss & Carpenter (1972)

Appendix G: Van Rheenen, T.E. & Rossell, S.L., (in press, July 2013). An empirical evaluation of the MATRICS Consensus Cognitive Battery in bipolar disorder. *Bipolar Disorders,* doi: 10.1111/bdi.12134

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Appendix H: Van Rheenen, T.E. & Rossell, S.L. (2013). Auditory-prosodic processing in bipolar disorder; from sensory perception to emotion. *Journal of Affective Disorders,* 151, 1102-1107

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Appendix I: Van Rheenen, T. E. & Rossell, S. L. (2013). Picture Sequencing Task Performance Indicates Theory of Mind Deficit in Bipolar Disorder. *Journal of Affective Disorders*, 151, 1132-1134.

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Appendix J: Theory of mind news article

Theory of mind deficit found in bipolar disorder

By Joanna Lyford, Senior medwireNews Reporter

08 August 2013

J Affect Disord 2013; Advance online publication

medwireNews: People with bipolar disorder show theory of mind impairment, based on impaired performance on the Picture Sequencing Task, Australian researchers have found.

The Task is a well recognized measure of theory of mind that commonly elicits deficits in people with schizophrenia, explain the study authors, who say their results indicate that "impairment on the task may represent potential overlap in the phenomenology and possibly genetic aetiology of schizophrenia and [bipolar disorder]."

Tamsyn Van Rheenen and Susan Rossell, from Monash Alfred Psychiatry Research Centre in Melbourne, Victoria, Australia, studied 49 patients with bipolar disorder and 49 psychiatrically healthy controls matched for age and gender. All participants completed the Task, which assesses the ability to make inferences about other people's emotional and mental states.

Results, reported in the *Journal of Affective Disorders*, show that people with bipolar disorder performed significantly worse than healthy individuals on the "false belief" story part of the Task, with an average 11.9% decrement in accuracy. These stories require the inference of false beliefs and were the main focus of the study.

Patients and controls performed similarly on the mechanical, social script, and capture stories. Further analysis found that patients' performance on the Task did not differ according to diagnostic subtype, current mood state, or use of psychotropic medications.

Noting that their results should be interpreted cautiously in view of the small sample size, Van Rheenen and Rossell say the data nevertheless "appear to suggest that patient impairment for false belief inferences may represent a stable, trait-like feature in [bipolar disorder]."

The results also "mirror some prior evidence of selective false-belief impairments on the picture sequencing task in schizophrenia patients" and support previous findings which indicate "trait-like [theory of mind] deficits in [bipolar disorder] itself."