

## THEORY OF MIND AND EMPATHY IN MOOD DISORDERS

THEORY OF MIND AND EMPATHIC RESPONDING  
IN  
PATIENTS WITH MOOD DISORDERS

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A Thesis Submitted to the School of Graduate Studies

in Partial Fulfilment of the Requirements for

the Degree Doctor of Philosophy

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DOCTOR OF PHILOSOPHY (2011)  
(Neuroscience)

McMaster University  
Hamilton, Ontario

TITLE: Theory of mind and empathic responding in patients with mood disorders

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NUMBER OF PAGES: xv, 285

## **Abstract**

Theory of mind (ToM) and empathic responding are thought to rely on the joint contribution of cognitive and affective processes, and the corresponding complex neural networks involved in these diverse cognitive and affective functions. Individuals with mood disorders demonstrate deficits in many of the same cognitive and affective processes thought to mediate ToM and empathy, and demonstrate structural and functional changes in the neural regions that subservise these social cognitive domains. We examined ToM and empathic responding in patients with major depressive disorder (MDD) and bipolar disorder (BD) using standardized measures of social cognitive responding. Patients with BD and MDD with sub-syndromal depressive symptoms showed deficits on a cognitively challenging task that required them to integrate two perspectives simultaneously (second-order ToM stimuli). Sub-syndromal patients with BD also showed a trend toward poor performance on a less demanding first-order ToM task; no such deficit was observed for sub-syndromal MDD patients. Patients with BD were also impaired at discriminating mental states from pictures of eyes and in making complex social judgments. Both patient groups reported reduced levels of cognitive empathy, but differed in response on affective empathy domains. Specifically, whereas the BD group reported higher levels of distress in response to others' negative experiences, the MDD group reported less feelings of care and concern in response to another's emotional experience. Across the BD studies, impaired ToM and empathic responding were found to be associated with poor social functioning and increased depressive symptoms, but the influence of illness burden variables on performance was

variable. Across the MDD studies, the associations between social cognitive performance, illness variables, and social functioning were inconsistent. Taken together, our findings indicate that patients with mood disorders demonstrate altered ToM and empathic responding that may contribute to the difficulties in social communication observed in these patient populations.

## **Acknowledgements**

First and foremost, I would like to thank my supervisor, Dr. Margaret McKinnon, for giving me the opportunity to work under her guidance. Her patience and support over the last four years have been invaluable. I am very grateful to Dr. Glenda MacQueen for her helpful advice and invaluable contributions to my dissertation. I also extend my gratitude to Drs. Geoffrey Hall and Michael Kiang, for their time and valuable comments. I am thankful also to the Ontario Mental Health Foundation for providing me with financial support throughout my graduate training.

I would also like to thank the participants who generously donated their time to participate in this study. I am grateful to the MDP staff for their assistance in recruiting participants, data collection, and administrative support. To my labmates, thank you for your friendship, being my sounding board and my comic relief these past four years.

I would also like to thank and acknowledge my family; in particular my parents, their continued support and unwavering encouragement were integral to realizing this goal. Last, but not least, I would like to thank my husband for his unfailing support, patience, encouragement and humour.

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## List of all Abbreviations and Symbols

ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
BD	Bipolar disorder
CBT	Cognitive behavioural therapy
DLPFC	Dorsolateral prefrontal cortex
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
fMRI	Functional magnetic resonance imaging
GAF	Global Assessment of Functioning
HAMD	Hamilton Depression Rating Scale
HC	Healthy control
IPT-15	Interpersonal Perception Task – 15
IRI	Interpersonal Reactivity Index
LCSPT	Limbic-cortico-striatal-pallidal-thalamo circuit
LTC	Limbic-thalamo-cortical circuit
MASC	Movie for Assessment of Social Cognition
MDD	Major depressive disorder
OFC	Orbitofrontal cortex
RMET	Reading the Mind in the Eyes Test
SAS-SR	Social Adjustment Scale-Self Report
SCID	Structured Clinical Interview for the DSM-IV
TEQ	Toronto Empathy Questionnaire
ToM	Theory of mind
YMRS	Young Mania Rating Scale

## **Declaration of Academic Achievement**

The present thesis is in the sandwich style whereby manuscripts that are prepared for, submitted or published are included in the thesis. The following describes the contribution of each author.

### **Chapter 2**

**Manuscript:** Cusi, A.M., Nazarov, A., Holshausen, K., MacQueen, G.M., & McKinnon, M.C. Behavioural and neural correlates of social cognition in mood disorders: A review.

**Contribution:** A. Cusi helped conceive and direct the project. She also conducted electronic literatures searches, critically interpreted the results, wrote major sections of the manuscript, and critically reviewed and revised the manuscript. A. Nazarov and K. Holshausen conducted electronic literatures searches, and helped write and edit the manuscript. Dr. MacQueen helped design the structure of the manuscript, and helped write and review the article. Dr. McKinnon conceived, supervised and designed the structure of the paper. Dr. McKinnon also helped write the manuscript, and critically reviewed and revised the manuscript. This review was written from January 2009 to July 2011. This chapter constitutes an overview of the current behavioural and neuroimaging literature concerning social cognitive processing in patients with mood disorders. A significantly modified version of this chapter has been accepted to the *Journal of Psychiatry and Neuroscience*.

**Chapter 3, Manuscript 1:** McKinnon, M.C., Cusi, A.M., & MacQueen, G.M. (2010).

Impaired theory of mind performance in patients with recurrent bipolar disorder:

Moderating effect of cognitive load. *Psychiatry Research*, 177(1-2): 261-2.

**Contribution:** Dr. McKinnon conceived, guided and supervised the project. She critically interpreted the data, and critically read and revised the manuscript. A. Cusi was involved in the design of the experiment, performed all experimental work, data analysis and wrote the manuscript. Dr. MacQueen was involved in the design of the experiment, and critically read and revised the manuscript. Data for this study was collected from November 2007 to February 2009, and the paper was written from November 2008 to May 2009. The paper was submitted to *Psychiatry Research* on May 27, 2009 and was accepted on February 6, 2010.

**Chapter 3, Manuscript 2:** Cusi, A.M., MacQueen, G.M., & McKinnon, M.C. Theory of mind deficits in subsyndromal major depressive disorder.

**Contribution:** Dr. McKinnon conceived, guided and supervised the project. She critically interpreted the data, and critically read and revised the manuscript. A. Cusi was involved in the design of the experiment, performed all experimental work, data analysis and wrote the manuscript. Dr. MacQueen was involved in the design of the experiment, and critically read and revised the manuscript. Data for this study was collected from November 2007 to July 2010, and the paper was written from May 2011 to September 2011. This manuscript was submitted for review to the *Journal of Affective Disorders* on October 18, 2011.

## **Chapter 4**

**Manuscript:** Cusi, A.M., MacQueen, G.M., & McKinnon, M.C. Patients with bipolar disorder show impaired performance on complex tests of Theory of Mind.

**Contribution:** Dr. McKinnon conceived, guided and supervised the project. She critically interpreted the data, and critically read and revised the manuscript. A. Cusi was involved in the design of the experiment, performed all experimental work, data analysis and wrote the manuscript. Dr. MacQueen was involved in the design of the experiment, and critically read and revised the manuscript. Data for this study was collected from November 2007 to June 2010 and the paper was written from May 2011 to July 2011. This manuscript was submitted for review to *Psychiatry Research* on September 23, 2011.

**Chapter 5, Manuscript 1:** Cusi, A.M., MacQueen, G.M., & McKinnon, M.C. (2010). Altered self-report of empathic responding in patients with bipolar disorder. *Psychiatry Research*, 178(2): 354-8.

**Contribution:** Dr. McKinnon conceived, guided and supervised the project. She critically interpreted the data, and critically read and revised the manuscript. A. Cusi was involved in the design of the experiment, performed all experimental work, data analysis and wrote the manuscript. Dr. MacQueen was involved in the design of the experiment, and critically read and revised the manuscript. Data for this study was collected from November 2007 to October 2008, and the paper was written from December 2008 to

February 2009. The paper was submitted to *Psychiatry Research* on February 5, 2009 and was accepted on July 15, 2009.

**Chapter 5, Manuscript 2:** Cusi, A.M., MacQueen, G.M., Spreng, R.N., & McKinnon, M.C. (2011). Altered empathic responding in major depressive disorder: Relation to symptom severity and psychosocial outcome. *Psychiatry Research*, 188(2):231-6.

**Contribution:** Dr. McKinnon conceived, guided and supervised the project. She critically interpreted the data, and critically read and revised the manuscripts. A. Cusi was involved in the design of the experiment, performed all experimental work, data analysis and wrote the manuscript. Dr. MacQueen was involved in the design of the experiment, and critically read and revised the manuscript. Dr. Spreng critically read and revised the manuscript. Data for this study was collected from November 2007 to June 2009, and the paper was written from October 2009 to March 2010. The paper was submitted to *Psychiatry Research* on March 10, 2010 and was accepted on April 12, 2011.

**CHAPTER ONE: GENERAL INTRODUCTION**

## **General Introduction**

Major depressive disorder (MDD) and bipolar disorder (BD) are recognized as chronic, debilitating illnesses that have a lifetime prevalence rate of 13.2% and 2.4% respectively (Hasin, Goodwin, Stinson, & Grant, 2005; Merikangas et al., 2011). In addition to significant cognitive impairment (Hammar & Ardal, 2009; Mur, Portella, Martinez-Arán, Pifarré, & Vieta, 2007), MDD and BD are also associated with deficits in multiple domains of functioning, including social functioning (Depp et al., 2010; Romera et al., 2010). For example, individuals with mood disorders often experience a reduction in the frequency of social and leisure activities (Bauwens, Pardoën, Staner, Dramaix, & Mendlewicz, 1998; Ruggero, Chelminski, Young, & Zimmerman, 2007) and less fulfillment from social and family relationships (Dickerson, Sommerville, Origoni, Ringel, & Parente, 2001; Nezlek, Hampton, & Shean, 2000). One concept that has been used to examine the underlying mechanisms of social impairment in neuropsychiatric disorders is social cognition, involving the ability to understand and respond to the thoughts and feelings of others, and thought integral for social behaviour (Adolphs, 2001; Brothers, 1990). This thesis examined two distinct but overlapping social cognitive constructs in patients with BD and MDD, theory of mind (ToM) and empathy. A secondary goal was to examine how theory of mind and empathy relate to key clinical variables, including symptom severity and burden of illness. Finally, the relation between social cognitive performance on experimental tasks and social functioning was investigated.

It has been proposed that performance on social cognition tasks relies upon the joint contribution of cognitive (e.g., working memory and attention) and affective (e.g., emotion recognition) processing resources (McKinnon, Levine, & Moscovitch, 2007; McKinnon & Moscovitch, 2007). Imaging and lesion studies of ToM and empathy suggest that social cognition is mediated by a broad network of regions that subserve cognitive (e.g., dorsolateral prefrontal cortex, anterior cingulate), affective (e.g., orbitofrontal and medial frontal cortex; amygdala) and memory (e.g., posterior cingulate, temporal poles) functions (see Carrington & Bailey, 2009; McKinnon et al., 2007; Shamay-Tsoory, 2011 for recent reviews). Importantly, many of these same regions play an important role in the pathophysiology of mood disorders, showing altered metabolic functioning as well as tissue volume loss (Blumberg et al., 2003; MacQueen et al., 2003; Steele, Currie, Lawrie, & Reid, 2007). Based on the evidence summarized here, we predicted that patients with recurrent mood disorders would exhibit impairments on social cognitive tasks that rely upon the cognitive and affective processing resources subserved by these regions.

In this introductory chapter, we first define ToM in order to provide a conceptual framework. Second, we provide an overview of measures designed to assess ToM ability. We then describe the neuroanatomy of ToM and its putative underlying cognitive and affective mechanisms. We then made similarly constructed sections on empathy. We conclude the chapter by describing the neurocognitive deficits associated with MDD and BD and the underlying neurobiological underpinnings of MDD and BD.

## **1.1. Theory of Mind**

### *i) Constructs*

Theory of mind (ToM) and its often used synonyms “mind reading,” (Whiten, 1991) and “mentalizing” (Frith, Morton, & Leslie, 1991) refer to the ability to interpret mental states such as beliefs, desires, and intentions in oneself and others in order to explain or predict human behaviour (Premack & Woodruff, 1978). Several theoretical models propose that ToM draws on both cognitive (e.g., understanding another’s perspective) and affective (e.g., recognizing another’s emotional state) processing resources (Leslie, Friedman, & German, 2004; McKinnon & Moscovitch, 2007), with a number of researchers proposing that ToM ability involves two component processes. The first component involves being able to accurately decode mental states from available perceptual information such as a person’s facial expressions, tone of voice, or gestures. A second component is necessary for reasoning about mental states by combining contextual information and prior knowledge about an individual person or situation to understand behaviour (Sabbagh, 2004; Tager-Flusberg & Sullivan, 2000). Effectively engaging in these two processes is thought to contribute to successful interpersonal functioning (e.g., Carton, Kessler, & Pape, 1999).

### *ii) ToM Measures*

Researchers have developed several ToM measures that vary in the demands they place on cognitive and affective processing resources. A commonly used ToM reasoning

measure involves using false belief tasks that require the participant to understand that “others can hold false beliefs that are different from one’s own (correct) knowledge” (Brüne & Brüne-Cohrs, 2006, p. 445). A classic example of a false belief measure is the Sally-and-Anne test (Baron-Cohen, Leslie, & Frith, 1985; Wimmer & Perner, 1983). This task involves presenting participants with a comic strip that shows one character (Anne) hiding an object when another character (Sally) leaves a room. In order to pass this test, perspective taking ability is required to recognize that when Sally returns to the room, she will look for the object in the original place she placed it (Brüne & Brüne-Cohrs, 2006). By contrast, first-order false belief questions assess the ability to understand that another person can hold a belief that is different from the actual state of affairs (Perner & Wimmer, 1985; Zobel et al., 2010). A first-order false belief question would ask where Sally will look for the object when she returns to the room. A more advanced ToM measure is a second-order false belief question that examines the ability to infer someone’s false attribution of a belief (Perner & Wimmer, 1985; Zobel et al., 2010). A second-order question in the Sally-and-Anne test would ask where Anne thinks Sally will look for the object.

More complex ToM tasks were developed for participants who could pass false belief tests. One notable example is the Strange Stories Test (Happe, 1994), a story comprehension task that assesses the ability to recognize mental states involving sarcasm, irony, double bluff, misunderstanding, and deception. Another more complex ToM task involves detecting a faux pas. A faux pas occurs when someone says something they should not have said, not realizing their mistake (Brüne & Brüne-Cohrs, 2006).

Understanding that a faux pas has occurred is considered an advanced ToM task because it requires the representation of both the person who committed the faux pas and the listener's mental state as well as an understanding of the listener's feelings or emotional response to the faux pas. An example from McKinnon and Moscovitch (2007) is a case of mistaken identity; a character carelessly identifies a female neighbour as a male. In order to understand that a faux pas has occurred, the participant must hold in mind the conflicting perspectives of the female character that has been mistakenly identified as a male and the clueless neighbour who has no idea that he has made such an error. The participant must also recognize the embarrassment and potential anger the female character is feeling in this scenario.

In Chapter 3 we examine the performance of subsyndromal patients with MDD and BD on a perspective taking task that describes various social vignettes, including social faux pas. We chose to use the Complex Social Scenarios Task because it is a ToM test that varies the level of cognitive and affective processing demands (verified under dual-task conditions) required for performance through the use of questions examining first-order (A thinks/feels X) and second-order (A thinks B thinks/feels X) ToM (McKinnon & Moscovitch, 2007). First-order ToM questions require participants to take into account a single character's perspective, whereas second-order ToM questions require participants to consider the perspective of two characters simultaneously. Thus, administering this ToM measure allowed us to examine the impact of cognitive and affective load on ToM performance in patients with mood disorders.

Another notable example of an advanced ToM decoding test is the Reading the Mind in the Eyes Test (RMET; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). In this task, participants are presented with 36 sets of eyes depicting complex mental states (e.g., jealousy, desire) and are asked to make a forced-choice judgment of the mental state depicted. Although the RMET limits the demands it places on central processing resources because participants are not asked to retain information as it is a self-paced task, it is considered an advanced measure of ToM ability for several reasons: first, the RMET only includes complex mental states such as ‘contemplative’ and ‘caution’ to increase variability in performance. Second, participants must choose the correct mental state from one of four response options, increasing the ability to detect individual differences in performance. Third, the mental state distractor terms (response options) are matched closely in emotional valence to the target word, making it possible to detect subtle differences in performance (Baron-Cohen et al., 2001). To date, three studies have examined the performance of depressed patients on this measure (Lee, Harkness, Sabbagh, & Jacobson, 2005; Wang, Wang, Chen, Zhu, & Wang, 2008; Wolkenstein, Schonenberg, Schirm, & Hautzinger, 2011) and one study administered the RMET to euthymic patients with BD (Bora, Yucel, & Pantelis, 2009). These studies, however, report conflicting findings of performance sparing and impairment on this measure. In Chapter 4, we examine the performance of patients with BD on this task with the aim of clarifying ToM decoding ability in a sample of patients in varying mood states.

Researchers have also developed ecologically valid measures of social cognition. For example, the Interpersonal Perception Task-15 (IPT-15; Costanzo & Archer, 1993)

measures numerous aspects of social cognition, including social perception, and notably, ToM. The IPT-15 is a measure of social intelligence for nonverbal social cues, such as body language, facial expressions, and tone of voice. This test has established reliability and validity, and is accompanied by a standardized scoring manual. The test consists of 15 videotaped scenes, each followed by multiple-choice questions. For example, one scene depicts a woman telling a true and a fabricated life story. Participants are asked, in multiple choice format, to decide “Which is the lie and which is the truth?” According to the test’s authors, each question has an “objectively correct” answer. In this example, one of the stories would in fact be true. In another scene, participants are asked to decide which of two men just won the basketball game. In this case, one of the men *did* just win a basketball game. In Chapter 4 we examine the performance of BD patients in varying mood states on the IPT-15 to determine if these patients show impairments on a complex ToM measure.

### *iii) Neuroanatomy of ToM*

Evidence from imaging and lesion studies indicate that ToM relies on brain areas associated with cognitive processes and affective processes. Neuropsychological studies suggest that ToM ability depends crucially on regions associated with cognitive processes such as working memory (e.g., dorsolateral prefrontal cortex), with damage to these regions resulting in impairments of cognitively-based aspects of task performance. Conversely, damage to regions associated primarily with affective processing (e.g., ventromedial prefrontal cortex, amygdala) may disrupt emotionally-based aspects of task

performance such as understanding another's emotional state. Consistent with this conclusion, Shamay-Tsoory, Tomer, Berger, Goldsher, & Aharon-Peretz (2005) found that relative to patients with posterior lesions and healthy controls, patients with orbitofrontal/ventromedial (but not dorsolateral) prefrontal cortex damage were impaired on ToM tasks drawing heavily on affective processing such as the detection of irony and social faux pas, but not on a task relying primarily on cognitive processes such as working memory and attention (second-order false belief task). Similarly, although studies involving patients with primarily dorsolateral prefrontal lobe damage reveal a link between ToM impairment and executive dysfunction (e.g. Channon & Crawford, 2000; Stone, Baron-Cohen, & Knight, 1998), studies including patients with primarily medial frontal lobe lesions do not demonstrate such an association (Rowe, Bullock, Polkey, & Morris, 2001; Stuss, Gallup, & Alexander, 2001).

Convergent evidence from neuroimaging studies implicate a complex network of neural regions involved in both cognitive and emotional processing that is recruited across a wide variety of ToM paradigms such as the detection of social faux pas, and recognition of mental states (see Carrington & Bailey, 2009; Mar, 2011 for recent reviews). Recent imaging reviews indicate that core regions within this network include: the medial prefrontal cortex and orbitofrontal cortex, involved in forming mental state representations about oneself and others (Amodio & Frith, 2006), as well as higher-order affective processes such as emotion regulation (Adolphs, 2002). Additionally, regions such as the superior temporal sulcus, linked to the perception of biological motion (Aichhorn, Perner, Kronbichler, Staffen, & Ladurner, 2006; Blanke & Arzy, 2005)

including socially relevant directional cues such as the eye gaze of others (Pelphrey, Morris, Michelich, Allison, & McCarthy, 2005; Pelphrey, Viola, & McCarthy, 2004) and the adjacent temporoparietal junction, involved in the perception of intentional behaviour (Gallese, Keysers, & Rizzolatti, 2004; Saxe & Powell, 2006), perspective taking (Frith & Frith, 2006) and a sense of agency (Decety & Lamm, 2007). The posterior cingulate and neighbouring precuneus--linked to memory processes, including episodic memory retrieval (Cavanna & Trimble, 2006; Nielsen, Balslev, & Hansen, 2005) -- and the temporal poles -- thought to be involved in the processing of faces (Mesulam, 1998) and social semantic knowledge (Olson, Plotzker, & Ezzyat, 2007; Ross & Olson, 2010) -- are also activated across neuroimaging studies of ToM. Finally, the amygdala, thought critical to the processing and evaluation of emotional stimuli (Adolphs, 2001), appears to be less consistently activated by ToM tasks (Carrington & Bailey, 2009; Mar, 2011). Recent meta-analyses also appear to confirm that these neural regions subserve ToM ability (Mar, 2011; Van Overwalle, 2009).

Overall, these studies suggest that ToM is subserved by neural regions involved in affective and cognitive processing. Critically, these same regions and processes are known to be affected in patients with long-standing mood disorders (cognitive domains impacted in mood disorders are outlined below in the section entitled “Neurocognitive Deficits in MDD and BD” and affective domains impacted in these disorders are outlined in Chapter 2).

Indeed, emerging evidence suggests that cognitive processes such as executive functions, which include cognitive control mechanisms such as attentional flexibility, inhibition of irrelevant information, and updating in working memory (Bull, Phillips, & Conway, 2008; Miyake et al., 2000) contribute to ToM (see Maylor, Moulson, Muncer, & Taylor, 2002; Rowe et al., 2001 for divergent results). In healthy adults and children, significant associations have been reported between ToM ability and tests of executive function such as inhibition (German & Hehman, 2006; Sabbagh, Xu, Carlson, Moses, & Lee, 2006), working memory (Gordon & Olson, 1998), and cognitive flexibility (Charlton, Barrick, Markus, & Morris, 2009; Hughes, 1998). For example, Gordon and Olsen (1998) demonstrated that working memory performance was positively correlated with measures of false belief, representational change, and appearance-reality in a sample of typically developing children. Moreover, Bailey and Henry (2008) recently demonstrated that deficits in inhibitory control mediated differences in false belief performance between older and younger adults. A growing number of studies have also documented significant correlations between impaired ToM performance and impaired executive functions in individuals with autism (e.g., Joseph & Tager-Flusberg, 2004; Zelazo, Jacques, Burack, & Frye, 2002) and patients with brain injury (Channon & Crawford, 2000; Stone et al., 1998). More direct evidence of the role of executive functions in ToM has been demonstrated in studies using dual-task methodology. For instance, both first- and second-order ToM performance has been shown to be disrupted during the concurrent performance of executive tasks such as working memory (Bull et al., 2008; McKinnon & Moscovitch, 2007), although, predictably, the extent of disruption

is greater for the higher-order, more cognitively demanding second-order task. The results of these dual-task studies highlight the overlap in central processing resources between ToM and executive functions (Bull et al., 2008).

Basic affective functions such as emotion recognition have also been linked to ToM ability (e.g., Bora et al., 2005; Brüne, 2005; Buitelaar & van der Wees, 1997; Dyck, Piek, Hay, Smith, & Hallmayer, 2006; Henry, Phillips, Crawford, Ietswaart, & Summers, 2006 but see Langdon, Coltheart, & Ward, 2006; Phillips, MacLean, & Allen, 2002 for conflicting results). For example, recognition of emotional facial expressions has been shown to positively correlate with performance on the Strange Stories Test (Happé, 1994) in participants with autism (Dyck et al., 2006). Similarly, in a sample of euthymic bipolar patients, Bora et al. (2005) demonstrated that the ability to recognize basic emotions predicted impaired performance on the Reading the Mind in the Eyes Test. Other studies, however, have shown that emotion recognition and ToM function are intercorrelated in healthy comparator groups, but dissociable in lesion patients and individuals with psychiatric disorders. For example, Henry et al. (2006) demonstrated that performance on the Reading the Mind in the Eyes Test was significantly associated with recognition of basic facial emotion in a sample of neurologically intact controls, but not in patients with traumatic brain injury. Similarly, Brüne (2005) found that emotion recognition ability correlated positively with performance on a ToM task assessing false belief and true belief in a healthy comparator group, but were found to be independent of each other in a sample of patients with schizophrenia. The results of these two studies indicate that basic emotion recognition and ToM may rely on distinct neural networks in individuals who

have sustained a traumatic brain injury and patients with schizophrenia, and thus may be affected independently of each other (Brüne, 2005; Henry et al., 2006). These results are also broadly consistent with Frith and Frith's (2006) model suggesting that the perception of emotion recognition is subserved by a disparate, but overlapping neural system than ToM (Brüne, 2005; Henry et al., 2006).

## **1.2. Empathy**

### *i) Constructs*

Empathy refers broadly to the ability to infer and share the feeling states of another (Gallese, 2003) and is thought to promote unselfish, prosocial behaviour (Eisenberg & Miller, 1987). Intact empathic capacity is thought to be essential for developing and maintaining successful social relationships (Batson & Shaw, 1991; Davis, 1996). Similar to ToM, recent research has focused on the possibility that empathy is multidimensional in nature involving both cognitive (e.g. understanding another's perspective) and affective components (e.g. emotional response to the feeling states of others'; emotion recognition) (Davis, 1980, 1983).

Several theoretical models have proposed that empathy relies on a shared representation mechanism through which we understand the mental states of others (including their emotions) by activating neural regions corresponding to those states in ourselves (Singer & Lamm, 2009). Moreover, these theories incorporate the notion that emotional contagion, in which one is affected by another's emotional or arousal state, is a fundamental empathic process. According to the perception-action hypothesis (Preston & de Waal, 2002), perceiving another person's behaviour or emotion automatically engages

the corresponding neural networks necessary for the execution of the same behaviour or emotional state, along with the associated automatic and somatic responses. Another influential theory related to the perception-action hypothesis is the ‘simulation theory’ (Gallese & Goldman, 1998; Gordon, 1986). The simulation theory proposes that we infer the mental state of another individual by matching or simulating that person's experience in our own mind (Gallese & Goldman, 1998; Gordon, 1986). Consistent with these models of shared representation (Decety & Moriguchi, 2007), researchers have proposed that “people are fundamentally egocentric and have difficulty getting beyond their own perspective when anticipating what others are thinking or feeling, especially when trying to understand the states of mind of people who are perceived as being similar to themselves” (Decety & Moriguchi, 2007, Mental flexibility and perspective taking section, para. 2). Thus, it is plausible that impaired empathic ability may stem from difficulties adjusting from one's own self-perspective to another person's perspective (Shamay-Tsoory, 2011). We suspect that individuals with mood disorders may show impaired empathic responding given that prior research has demonstrated that maladaptive self-focused processes such as rumination, defined as focusing on the cause, consequences and symptoms of one's depressed mood (Nolen-Hoeksema, 1991), are prevalent in patients with MDD (Just & Alloy, 1997; Nolen-Hoeksema & Morrow, 1991) and with BD (Knowles, Tai, Christensen, & Bentall, 2005; Thomas & Bentall, 2002).

Empathy is elicited in a variety of contexts, and other, more advanced, forms of empathy require more complex processes, such as a cognitive understanding and appreciation of another's mental state, including the ability to adopt the perspective of

others. This process is known as cognitive empathy, and as previously noted, is thought to be related to and overlapping with the construct of ToM (Davis, 1994; Ickes, 1997).

Indeed, empirical studies support the view that these two constructs are closely related by showing significant correlations between measures of cognitive empathy and ToM (e.g., Shamay-Tsoory et al., 2009; Shamay-Tsoory et al., 2005).

### *ii) Empathy Measures*

Dispositional empathy is typically measured by the administration of self-report questionnaires. For example, the Questionnaire Measure of Emotional Empathy (Mehrabian & Epstein, 1972) was designed to examine emotional empathy. Another questionnaire proposed to assess cognitive empathy is Hogan's Empathy Scale (Hogan, 1969). The most commonly used self-report measure of empathic responding in the literature, however, is the Interpersonal Reactivity Index (IRI; Davis, 1983). This measure has demonstrated efficacy across multiple subject populations, including substance dependence (Alterman, McDermott, Cacciola, & Rutherford, 2003) and schizophrenia (Montag, Heinz, Kunz, & Gallinat, 2007) and has been administered successfully in patients with frontal dysfunction (e.g., Eslinger, 1998; Rankin, Kramer, & Miller, 2005). The IRI is a 28-item instrument containing four 7-item subscales assessing dimensions of dispositional empathy: Perspective Taking and Fantasy as well as Empathic Concern and Personal Distress. Each pair was designed to measure cognitive and affective elements of empathy, respectively. Each item is scored on a 5-point Likert scale ranging from 0 (does not describe me well) to 4 (describes me very well). Whereas the Perspective Taking (the tendency to spontaneously understand the perspective of others and see things from their

point of view) and Fantasy (the tendency to identify with fictional characters in books and movies) subscales are thought to assess cognitive components of empathy, the Empathic Concern (other-oriented feelings of warmth, compassion and concern for others) and Personal Distress (the self-oriented emotional response of fear or discomfort that results from observing another's negative experience) subscales are thought to measure affective components of empathy (Davis, 1983). The IRI has good internal consistency (Christopher, Owens, & Stecker, 1993; Davis, 1980) and correlates with other measures of empathy, providing support for the construct validity of the measure (Davis, 1983).

Empathy is also assessed via interactive paradigms, often used in neuroimaging studies. These paradigms often involve imitating displayed emotions (e.g., Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003), passively viewing other characters in pain (e.g., Singer et al., 2004) or experiencing other emotional states such as disgust (e.g., Jabbi, Swart, & Keysers, 2007) and happiness (e.g., Chakrabarti & Baron-Cohen, 2006; Jabbi et al., 2007). These measures have the advantage of being less vulnerable to confounding factors such as response biases and demand characteristics that are often inherent in self-report questionnaires (e.g., Baldwin, 2000).

In Chapter 5, we administered two standardized self-report measures of empathic responding: The Interpersonal Reactivity Index (Davis, 1983), an instrument that measures both affective and cognitive components of empathy, as well as the Toronto Empathy Questionnaire (TEQ; Spreng, McKinnon, Mar, & Levine, 2009), a measure that represents empathy as a primarily emotional process. Like the IRI, the TEQ has also been

shown to demonstrate strong convergent validity, good internal consistency and high test–retest reliability (Spreng et al., 2009).

*iii) Neuroanatomy of Empathic Responding*

Similar to ToM, empathy has been shown to be mediated by neural regions involved in both cognitive and affective processes. Evidence from lesion studies indicate that patients with damage to the dorsolateral prefrontal cortex show impaired cognitive (e.g., perspective taking), but not emotional empathy, whereas patients with orbitofrontal lesions show the reverse effect (Eslinger, 1998). Similarly, Rankin et al. (2005) showed that damage to orbitofrontal, medial and dorsal prefrontal regions in frontal variant frontotemporal dementia patients is associated with impairments in cognitive aspects of empathy (e.g., perspective-taking), while damage restricted to anterior temporal lobes, amygdala and ventromedial orbitofrontal regions in temporal variant frontotemporal dementia patients is associated with impairments in both cognitive and affective components (e.g., emotional contagion) of empathic responding in social situations. Recent theories also indicate that the mirror neuron system may play a role in social cognition, including ToM (Oberman & Ramachandran, 2007), and the emotional aspects of empathy (Gallese, 2007; Jabbi et al., 2007). The mirror neuron system includes the inferior frontal gyrus, posterior parietal cortex/inferior parietal lobule, and premotor cortex, and is thought to be active when an individual executes a movement and in response to the motor acts of others (see Cattaneo & Rizzolatti, 2009 for a review). For example, recent evidence indicates that lesions in the inferior frontal gyrus are associated with poor emotion recognition skills and reduced levels of affective empathy (Adolphs,

2002; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). These studies highlight the importance of both cognitive and affective processes in normal empathic responding.

Evidence from neuroimaging studies suggests that the cognitive and affective components of empathy may rely on distinct neural networks (Decety & Meyer, 2008; Shamay-Tsoory et al., 2009; Singer, 2006). The affective component of empathy is thought to draw on brain areas that are similarly activated during both first-hand and vicarious affective experiences such as happiness, fear, disgust, and pain (Shamay-Tsoory, 2011; Singer & Lamm, 2009). For example, a growing number of studies indicate that the direct experience of pain activates similar neural regions observed during the perception of another person in pain, including the dorsal anterior cingulate cortex and anterior insula (Jackson, Brunet, Meltzoff, & Decety, 2006; Singer et al., 2004). By contrast, the cognitive component of empathy relies on a network of regions associated with ToM (see evidence summarized above; Decety & Moriguchi, 2007; Shamay-Tsoory, 2011). Empirical evidence provides support for the mirror neuron system and particularly the inferior frontal cortex's role in empathic processes such as the imitation of emotional facial expressions (Carr et al., 2003; Lee, Josephs, Dolan, & Critchley, 2006), passive emotion perception (Chakrabarti & Baron-Cohen, 2006; Jabbi et al., 2007), and emotion recognition (Sabbagh, 2004; Schulte-Ruther, Markowitsch, Fink, & Piefke, 2007; see Fan, Duncan, de Greck, & Northoff, 2011; Farrow et al., 2001 for conflicting findings). Overall, the neuroimaging literature shows that empathic responding is mediated by neural regions involved in cognitive and affective processing,

and that there is significant overlap in the neural regions thought to mediate ToM and empathy.

Similar to ToM, empathy has been proposed to rely on multiple, interacting cognitive processing resources (Decety & Lamm, 2007). Specifically, executive functions such as cognitive flexibility, are thought to be required to shift attention from one's own emotional mental state to that of another, as well as to generate ideas about another's mental state, abilities thought requisite for empathic responding (Rankin et al., 2005). Intact working memory is also needed to maintain and update one's representation of another person's cognitive and emotional state from multiple sources of information (e.g., facial expression, tone of voice, posture; Rankin et al., 2005). Other cognitive processes implicated in empathic responding include basic attention and abstract reasoning, in order to understand the mental states of others on a higher-order level of analysis and evaluation (Rankin et al., 2005). Indeed, empirical evidence supports the notion that empathy is mediated by distinct cognitive processes (Eslinger, 1998; Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003). For example, Rankin et al. (2005) demonstrated that impaired levels of cognitive and affective empathy (as measured by the IRI) were found to correlate significantly with deficits in abstract reasoning involving the generation of verbal and nonverbal information. In a sample of patients with prefrontal lesions, Shamay-Tsoory et al. (2004) demonstrated that cognitive empathy (as assessed by the Perspective Taking scale of the IRI) was significantly correlated with perseveration scores on the Wisconsin Card Sorting Test (Grant & Berg, 1948), a measure of cognitive flexibility thought to tap dorsolateral prefrontal function. By contrast, affective empathy

was found to correlate with accuracy in judging facial expressions of sadness and surprise. Shamay-Tsoory, Shur, Harari, and Levkovitz (2007) also reported that whereas impaired cognitive empathy correlated significantly with deficits on a cognitive flexibility task thought to tap orbitofrontal function (i.e., reversal learning), affective empathy was positively associated with social functioning in a sample of patients with schizophrenia.. Moreover, in a sample of healthy females, high performance on an inhibitory control task predicted higher scores on the Empathy Quotient (Baron-Cohen & Wheelwright, 2004), a self-rated questionnaire that assesses both cognitive and affective aspects of empathy (Hansen, 2011).

In addition to drawing on cognitive processing resources, empathy has been proposed to rely on diverse affective domains (Decety & Jackson, 2004). Numerous studies have implicated emotional contagion as a key component of empathy (e.g., Shamay-Tsoory, 2011). For instance, research indicates that observing another person's emotional facial expression activates the corresponding expressions on one's own face (Dimberg, Thunberg, & Elmehed, 2000). van Baaren et al. (2004) also found that participants whose posture and mannerisms had been mimicked by an experimenter were more helpful and generous compared to participants who had not been mimicked. Accurate recognition of another's emotional state is also thought critical to empathy (Decety & Jackson, 2004). Empirical evidence supports this notion, providing evidence that empathic capacity is associated with performance on tasks that tap emotion recognition ability. For example, in a sample of patients with schizophrenia, impaired empathic capacity as assessed by the self-rated Empathy Quotient (Baron-Cohen &

Wheelwright, 2004) was associated with impaired recognition of emotional facial expressions (Bora, Gokcen, & Veznedaroglu, 2008). Moreover, Carr et al. (2005) showed that the ability to empathize with the affective experiences of others was positively correlated with accuracy scores on a facial emotion recognition task in a group of youth offenders. As mentioned above, Shamay-Tsoory et al. (2007) found that impaired affective empathy as assessed by the Questionnaire Measure of Emotional Empathy (Mehrabian & Epstein, 1972) was positively associated with recognition of specific facial expressions (i.e., sadness, surprise). Finally, emotion regulation, defined as the “processes by which we influence which emotions we have, when we have them, and how we experience and express them” (Gross, 2002, p. 282), has also been proposed to be critical for empathy (Decety & Lamm, 2006). Research has shown that healthy individuals who can regulate their emotions are more likely to demonstrate higher levels of dispositional (Rothbart, Ahadi, & Hershey, 1994; Valiente et al., 2004) and situational empathy (Eisenberg et al., 1994).

Impaired empathic responding has been reported in autism spectrum disorders (Baron-Cohen et al., 2004), as well as in patients with Axis II Developmental and Personality Disorders (Guttman & Laporte, 2000; Tantam, 1995), and frontotemporal lobar dementia (Rankin et al., 2005). However, studies examining empathic responding in mood disorder populations are rare. In Chapter 5 we examine dispositional empathy in patients with BD and MDD.

### **1.3. Neurocognitive Deficits in MDD and BD**

MDD is characterized by deficits across a broad range of cognitive domains. Numerous reports document impairment in memory (Porter, Gallagher, Thompson, & Young, 2003) and attention (Landro, Stiles, & Sletvold, 2001). Additional work demonstrates alterations in executive function domains such as verbal fluency (Ravnikilde et al., 2002), working memory (Taylor Tavares et al., 2007), inhibition (Gohier et al., 2009), and cognitive flexibility (Airaksinen, Larsson, Lundberg, & Forsell, 2004). Cognitive impairments also appear to persist during remission of depressive symptoms in MDD (Paelecke-Habermann, Pohl, & Lelow, 2005).

A wide body of evidence also indicates that patients with BD demonstrate significant cognitive impairment during acute phases of illness. Similar to the MDD literature, recent studies have reported that patients with BD show deficits on a variety of memory (Bearden, Hoffman, & Cannon, 2001; Malhi et al., 2007) and attention-related processes (Depp et al., 2007; Malhi et al., 2007). Other studies also report deficits in executive function, including impairments in verbal fluency (Martinez-Aran et al., 2004), working memory (Taylor Tavares et al., 2007), inhibition (Swann, Lijffijt, Lane, Steinberg, & Moeller, 2009), and cognitive flexibility (Martinez-Aran et al., 2004). A recent meta-analysis by Kurtz and Gerraty (2009) compared patients with BD in manic/mixed and/or depressed states with those in euthymic states. The authors reported that relative to control participants, patients in a manic/mixed phase of illness showed moderate to-large effect-size deficits in measures of sustained visual attention, set-

shifting, concept shifting (perseveration) and verbal fluency. Manic/mixed patients also demonstrated large effect-size deficits in verbal learning and memory. Depressed patients showed moderate-to-large effect-size deficits in processing speed and set-shifting, and large effect-size impairment in verbal learning and phonemic fluency. Euthymic patients demonstrated moderate-to-large effect-sizes for sustained visual attention, processing speed, verbal memory, working memory, set-shifting, concept shifting, and response inhibition.

Recent meta-analyses have focused their attention on neuropsychological function in euthymic patients with BD. For example, Mann-Wrobel et al. (2011) compared euthymic patients with healthy controls and reported deficits of medium-to- large effect sizes across a wide range of cognitive domains, including verbal memory, psychomotor speed, and executive function domains such as set-shifting, working memory, verbal fluency, response inhibition, and problem-solving. These findings are consistent with another meta-analysis that found moderate-to-large effect-size impairment across a host of cognitive domains, including sustained visual attention, memory, executive function and processing speed (Bora et al., 2009).

The few studies that have compared neuropsychological performance between patients with unipolar and bipolar depression have produced inconsistent findings. Some studies report that the pattern of cognitive deficits observed in bipolar depression appears to be similar to that observed in unipolar depression (Godard, Grondin, Baruch, & Lafleur, 2011; Marvel & Paradiso, 2004; Quraishi & Frangou, 2002). However, others have shown that deficits in verbal learning and fluency (Borkowska & Rybakowski,

2001; Wolfe, Granholm, Butters, Saunders, & Janowsky, 1987), and on the Halstad Category Test, a measure that broadly assesses domains such as intelligence and reasoning, appear to be more severe in bipolar depressed versus unipolar depressed patients (Savard, Rey, & Post, 1980).

Although impairment in neuropsychological function is well-established in both BD and MDD, other studies have reported intact cognitive performance (e.g., Ferrier, Stanton, Kelly, & Scott, 1999; Harvey et al., 2004; Landro et al., 2001; van Gorp, Altshuler, Theberge, Wilkins, & Dixon, 1998). A recent meta-analysis conducted in MDD provides a partial explanation for these discrepant findings by showing that an increased severity of depression was related to impairments in executive function, verbal memory, and processing speed (McDermott & Ebmeier, 2009). It must be noted, however, that the effect sizes for all significant findings were relatively small (McDermott & Ebmeier, 2009). A meta-analysis conducted in euthymic BD patients also indicates that burden of illness variables such as an earlier illness onset may moderate impairments in verbal learning and processing speed observed in this population (Bora et al., 2009). In line with these meta-analyses, recent empirical studies also indicate a relation between cognitive impairment, social cognitive impairment, and illness factors such as past course of illness and symptom severity in patients with mood disorders (Basso & Bornstein, 1999; Cusi, MacQueen, & McKinnon, 2010; Kurtz & Gerraty, 2009; MacQueen, Galway, Hay, Young, & Joffe, 2002; Malhi et al., 2007; Martinez-Aran et al., 2007; Schenkel, Marlow-O'Connor, Moss, Sweeney, & Pavuluri, 2008; Summers, Papadopoulou, Bruno, Cipolotti, & Ron, 2006; Wolf, Brune, & Assion, 2010).

Taken together, given that many of these cognitive domains that are impacted in MDD and BD have been implicated in both ToM and empathic responding, we expected that these patient populations would show deficits in social cognitive response. Moreover, consistent with prior work demonstrating that impairment in neurocognitive functioning is associated with clinical variables such as symptom severity and burden of illness, we expected that alterations in ToM and empathic responding would be associated with increased symptom severity and a greater burden of illness.

The pattern of deficits in executive functioning and attention is consistent with altered functioning of anterior cingulate and prefrontal areas found in patients with MDD and BD described in the section below.

#### **1.4. Neurobiological Underpinnings of MDD and BD**

Neurobiological models of depression (Drevets & Raichle, 1992; Mayberg, 1997, 2003) propose that depressive illness arises, in part, due to the disruption of overlapping, but functionally distinct neural networks. For example, work by Mayberg and her colleagues (Mayberg, 1997, 2003; Ressler & Mayberg, 2007) have highlighted the role of cortical, limbic, and subcortical neural regions in the development and treatment of depression. Critically, many of these same neural regions have been implicated repeatedly in social cognitive processes, including theory of mind and empathy. The subgenual cingulate cortex, a region involved in the production of sad emotion, shows increased activation in patients with mood disorders (Mayberg et al., 1999). Brain activity in the subgenual cingulate cortex has been shown to decrease following antidepressant therapy (e.g., Martin, Martin, Rai, Richardson, & Royall, 2001; Mayberg et al., 2000) and

psychological treatment interventions (Brody et al., 2001; Siegle, Carter, & Thase, 2006). Interestingly, baseline metabolic activity in the subgenual cingulate cortex may predict treatment response to antidepressant therapy (Kennedy et al., 2001) and cognitive behavioural therapy (Konarski et al., 2009) in patients with MDD. A similar finding has emerged for the dorsal anterior cingulate cortex (ACC) where baseline activity in this region predicted clinical response to cognitive behavioural therapy (Fu et al., 2008). Structural neuroimaging studies demonstrate volume loss in the subgenual anterior cingulate cortex of patients with MDD and with BD (Hajek, Kozeny, Kopecek, Alda, & Hoschl, 2008; Yucel, McKinnon, et al., 2008).

Patients with MDD (Drevets, 2000; Sheline et al., 2001) and with BD (Drevets et al., 2002; Mah et al., 2007) also show hypermetabolism in the amygdala. Activity in this region decreases with recovery from mood symptoms (Fu et al., 2004; Sheline et al., 2001). Whereas reduced amygdala volumes have been reported in patients with MDD (Caetano et al., 2004; Hastings, Parsey, Oquendo, Arango, & Mann, 2004 but see Bremner et al., 2002; Frodl et al., 2004 for conflicting findings), several studies report enlarged amygdala volumes in BD (Brambilla et al., 2003; Frangou, 2005).

Additional neural regions, also thought to mediate social cognitive processes, have been implicated in mood disorders. For example, Drevets and colleagues (Drevets & Raichle, 1992; Price & Drevets, 2010) have described two extended neural circuits involved in the pathophysiology of BD and MDD. These include a limbic-thalamo-cortical circuit (LTC) that includes the amygdala, medial thalamus, orbital prefrontal cortex and medial prefrontal cortex, and the limbic-cortical-striatal-pallidal thalamic

(LCSPT) circuit that involves the pallidum and striatum (Drevets & Raichle, 1992; Price & Drevets, 2010). The LTC is thought to be associated with an ‘orbital prefrontal network’, consisting of regions in the central and caudal areas of the orbital frontal cortex and the anterior insular cortex, and sensory areas such as the primary olfactory and taste cortex, visual areas in the inferior temporal cortex, and somatic sensory areas in the insula and frontal operculum (Ongur, Ferry, & Price, 2003; Rigucci, Serafini, Pompili, Kotzalidis, & Tatarelli, 2009; Saleem, Kondo, & Price, 2008). The orbital network is thought to not only integrate multi-modal stimuli, but also to assess the affective qualities of stimuli such as their reward value (Ongur & Price, 2000; Price & Drevets, 2010; Rigucci et al., 2009). Critically, reduced tissue volume and gray matter content has been reported in the orbitofrontal cortex of patients with MDD (Lacerda et al., 2004; Lai, Payne, Byrum, Steffens, & Krishnan, 2000) and BD (Chen, Wen, Malhi, Ivanovski, & Sachdev, 2007; Nugent et al., 2006) and hypermetabolism has been reported in this region with mood disorder patients at rest (Biver et al., 1994; Drevets et al., 1992).

By contrast, the LCSPT is connected to the ‘medial prefrontal network’ and consists of areas on the ventromedial aspect of the frontal cortex, the medial edge of the orbital cortex, a small area in the caudolateral orbital cortex (Carmichael & Price, 1996). This network also has extensive connections with limbic and visceral control areas such as the hypothalamus and periaqueductal gray, involved with modulating visceral function to affective stimuli (Ongur & Price, 2000). The medial network is also connected to the dorsal medial prefrontal cortex, rostral superior temporal gyrus and the dorsal bank of the superior temporal sulcus, the entorhinal and parahippocampal cortex, and the anterior and

posterior cingulate cortex (Kondo, Saleem, & Price, 2005; Saleem et al., 2008). This network is thought crucial to self-referential processes (Ongur & Price, 2000), that show disruption in patients with MDD (Lemogne et al., 2009; Sheline et al., 2009). Patients with BD demonstrate left-sided hypoactivation and right-sided hyperactivation in the ventral ACC (reviewed in Savitz & Drevets, 2009) along with volume loss in the posterior cingulate cortex and superior temporal gyrus (Nugent et al., 2006). Moreover, abnormal elevated metabolism has been shown in the anterior insula, accumbens, medial thalamus, and posterior cingulate cortex in both unipolar and bipolar depressed patients (Drevets, 2000; Drevets, Gadde, & Krishnan, 2004). The striatum, another region thought central to the LCSPT circuit, has been reported to be larger in BD (Blumberg et al., 2003; Strakowski et al., 2002) and reduced in MDD (Greenwald et al., 1997; Krishnan et al., 1992). Reduced metabolic activity has been reported in this region in patients with mood disorders (Drevets et al., 1992; Kegeles et al., 2003; Kennedy et al., 2001).

Regions involved in cognitive processes such as memory, attention and executive functioning, processes thought requisite to successful social interactions (Mayberg, 1997; McKinnon et al., 2007; McKinnon & Moscovitch, 2007), also show tissue volume loss and/ or structural abnormalities in patients with mood disorders. For example, volume loss has been reported in the ventrolateral prefrontal cortex (Lyo et al., 2004; Nugent et al., 2006), and dorsolateral prefrontal cortex (Brooks et al., 2009; Konarski et al., 2008) of patients with MDD. Reduced blood flow and hypometabolism in the dorsal PFC has been found consistently in patients with MDD (Biver et al., 1994; Davidson, Irwin, Anderle, & Kalin, 2003) and with BD (Drevets et al., 2002; Kruger, Seminowicz,

Goldapple, Kennedy, & Mayberg, 2003) and appears to normalize after antidepressant treatment (Fales et al., 2009; Kennedy et al., 2001). Hippocampal volume loss on the order of 5 to 8 percent is consistently reported in cross-sectional studies of patients with MDD and has recently been confirmed in a series of meta-analyses (Campbell, Marriott, Nahmias, & MacQueen, 2004; McKinnon, Yucel, Nazarov, & MacQueen, 2009; Videbech & Ravnkilde, 2004). MacQueen and colleagues (MacQueen, Yucel, Taylor, Macdonald, & Joffe, 2008) also reported that, in patients previously untreated for MDD, larger hippocampal volumes at baseline predicted better treatment response to antidepressant medication after 8 weeks. By contrast, hippocampal volume in BD is reported to be preserved relative to matched controls (Blumberg et al., 2003; McDonald et al., 2006) and may increase after treatment with lithium (Yucel et al., 2007; Yucel, Taylor, et al., 2008). Hypermetabolic and hypometabolic activity has been shown in this region in BD and MDD patients, respectively (Bremner, Vythilingam, Vermetten, Vaccarino, & Charney, 2004; de Asis et al., 2001; Ketter et al., 2001; Mah et al., 2007).

### **1.5. Overall Goals**

The primary goal of this thesis was to examine the performance of patients with mood disorders on tasks pertaining to two interrelated aspects of social cognition, ToM and empathy. Consistent with evidence suggesting that individuals with mood disorders demonstrate impairments on tests of ToM and empathic responding, and given that patients with these disorders demonstrate impairment in numerous cognitive processes, including working memory, executive functioning (Bearden et al., 2001; Hammar & Ardal, 2009) and affective processes, such as emotion recognition (Bourke, Douglas, &

Porter, 2010; McClure-Tone, 2009) thought to contribute to ToM and empathic performance, we expected that MDD and BD patients would show deficits on measures of ToM and empathy. In light of recent research suggesting that clinical factors such as illness burden (i.e., number of previous episodes, illness duration) and symptom severity may influence neuropsychological performance (e.g., MacQueen et al., 2002; van Gorp et al., 1998), our secondary aim was to explore the relation between performance on these tests of social cognition and illness variables such as symptom severity and burden of illness. We expected that impaired social cognitive response would correlate significantly with an increased burden of illness and higher levels of symptom severity. Finally, given that recent evidence has shown that cognitive impairment is associated with poor functional outcome in patients with mood disorders (Wingo, Harvey, & Baldessarini, 2009), we also examined the relation between performance on these social cognitive tasks and social functioning. We predicted that impaired ToM and empathic capacity will be associated with poor social functioning.

## **1.6. Thesis Outline**

In the chapters that follow, we examined the performance of patients with MDD and BD on a variety of ToM and empathy measures. Chapter 2 provides a review of the literature to date published on three distinct, but overlapping social cognitive domains, emotion recognition, ToM and empathy in MDD and BD. In the third chapter, presented as two separate papers for BD and MDD, we examined the performance of BD and MDD patients with subsyndromal depressive symptoms on a perspective-taking task that varies in the level of demands placed on central processing processes (McKinnon &

Moscovitch, 2007). Chapter 4 is a study that examines the performance of BD patients in varying states of illness on two cognitively complex measures of ToM responding: the Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001) and the Interpersonal Perception Task-15 (Costanzo & Archer, 1993). In the fifth chapter, presented as two separate papers for BD and MDD, we examined the cognitive and affective aspects of empathic responding in these two disorders. The thesis concludes with an overview of our findings, future research directions, and clinical implications of our research.

It must be noted that the literature reviewed and the methods used are overlapping across the chapters. Moreover, some of the participants described were included in several studies found in this thesis. The participant distribution for each manuscript is described in Table 1 below in the order in which the manuscripts were submitted for publication (from earliest to most recent), and not the order in which they appear in this thesis.

**Table 1.** Participant distribution and inclusion and exclusion criteria for each study

Study	Participants	Inclusion Criteria	Exclusion Criteria
“Altered self-report of empathic responding in patients with bipolar disorder” (Chapter 5, Study 1)	20 BD patients in varying illness states  20 age-matched controls	Patients: met DSM-IV criteria for BD  Controls: no history of psychiatric illness	For patients and comparison subjects:  i) inability to provide informed consent,  ii) history of electroconvulsive therapy or transcranial magnetic stimulation therapy, within one

			<p>year,</p> <p>iii) substance abuse based on DSM-IV criteria in the last six months,</p> <p>iv) current or lifetime history of substance dependence based on DSM-IV criteria,</p> <p>v) current or prior history of untreated significant medical illness (e.g., cancer) or of neurological illness (e.g., Parkinson’s disease, epilepsy),</p> <p>vi) history of traumatic brain injury and/or loss of consciousness (lasting more than 60 seconds),</p> <p>vii) Young Mania Rating Scale score &gt; 10,</p> <p>viii) use of benzodiazepines within 12 hours prior to testing</p> <p>Controls: a first-degree family member with BD or schizophrenia</p>
<p>“Impaired theory of mind performance in patients with recurrent bipolar</p>	<p>14 BD patients with subsyndromal depressive symptoms</p>	<p>Patients:</p> <p>i) met DSM-IV criteria for BD</p> <p>ii) Hamilton</p>	<p>*See above</p>

disorder: Moderating effect of cognitive load” (Chapter 3, Study 1)	14 age- and education- matched controls	Depression Rating Scale score between 7 and 15  Controls: no history of psychiatric illness	
“Altered empathic responding in major depressive disorder: Relation to symptom severity, illness burden, and psychosocial outcome” (Chapter 5, Study 2)	20 MDD patients in varying illness states  20 age- and education- matched controls	Patients: met DSM- IV criteria for MDD  Controls: no history of psychiatric illness	*See above
“Patients with bipolar disorder show impaired performance on complex tests of theory of mind” (Chapter 4)	25 BD patients in varying illness states  25 age-, gender-, and education- matched controls	Patients: met DSM- IV criteria for BD  Controls: no history of psychiatric illness	*See above
“Theory of mind deficits in subsyndromal major depressive disorder” (Chapter 3, Study 2)	20 MDD patients with subsyndromal depressive symptoms  20 age-, gender-, and education- matched controls	Patients:  i) met DSM-IV criteria for MDD  ii) Hamilton Depression Rating Scale score between 8 and 14  Controls: no history of psychiatric illness	*See above

**CHAPTER 2: A REVIEW OF THE NEURAL AND BEHAVIOURAL  
CORRELATES OF SOCIAL COGNITION IN MOOD DISORDERS**

*Foreword to Chapter 2*

Chapter 2 provides a review of behavioural and neuroimaging findings concerning social cognitive processing in patients with MDD and BD. Specifically, we focus on studies investigating three aspects of social cognition: emotion comprehension, ToM, and empathy that have undergone recent investigation in patients with mood disorders. Although these social cognitive domains have been shown to be distinct processes, recent theories show that they also demonstrate considerable overlap conceptually, with empirical evidence supporting this view. Hence, these three domains of social cognition were included in the review in order to provide a broad understanding of social cognition in patients with mood disorders.

This chapter also sets the tone for the remaining chapters by examining the influence of key variables on ToM and empathic performance in mood disorders: mood state, burden of illness, medication status, cognitive factors, and age. The influence of these variables on theory of mind and empathic responding were also examined in each subsequent chapter (with the exception of age for ToM and both age and cognitive factors for empathy).

**A review of the neural and behavioural correlates of  
social cognition in mood disorders**

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### Abstract

**Objective:** This review integrates behavioural and neuroimaging studies of three domains of social cognition, emotion comprehension, theory of mind (ToM) and empathy, in patients with MDD and BD. The influence of key clinical and method variables on social cognitive processing is also examined.

**Methods:** Studies were identified using PsycINFO and PubMed (1967 to May 2011).

The search terms were: fMRI, emotion comprehension, emotion perception, affect comprehension, affect perception, facial expression, prosody, theory of mind, mentalizing, and empathy in combination with “major depressive disorder”, “bipolar disorder”, “major depression”, “unipolar depression”, “clinical depression”, and “mania”.

**Results:** Individuals with MDD and BD demonstrate deficits in the perception of affective facial expressions, voice prosody, ToM, and empathy that may worsen with heightened symptom severity and over the course of illness. The extent of social cognitive impairment in this population appears greatest on tests of emotion comprehension and ToM that involve high levels of cognitive and affective processing demands. Interestingly, deficits in facial emotion recognition appear to be reduced following administration of medication. Taken together, neuroimaging studies of social cognition in patients with mood disorders reveal enhanced activation in limbic and emotion-related structures and attenuated activity within frontal regions associated with emotion regulation and higher cognitive functions.

**Limitations:** Studies that did not include control tasks or a comparator group were included in this review.

**Conclusions:** Illness state, medication, illness burden, and cognitive load may influence social cognitive processing in MDD and BD. Further work is needed to examine the contribution of these key variables and to elucidate further neural networks underlying altered social cognition in patients with mood disorders.

**Key words:** emotion perception, theory of mind, empathy, review, major depressive disorder, bipolar disorder, social cognition, fMRI

## **Introduction**

Major depressive disorder (MDD) and bipolar disorder (BD) are associated with alterations in multiple domains, including interpersonal and social functioning.<sup>1-4</sup> Recent studies have examined the nature of social impairment in mood disorders through the lens of social cognition, involving the ability to understand and respond to the thoughts and feelings of others<sup>5,6</sup> and thought central to successful social interactions.<sup>5,6</sup>

The goal of the present review is to examine the findings of behavioural and neuroimaging studies concerning social cognitive processing in patients with MDD and BD. Here, we focus on studies investigating three different, but overlapping, aspects of social cognition: emotion comprehension, Theory of Mind (ToM), and empathy that have undergone recent investigation in patients with mood disorders. Emotion recognition refers to an individual's ability to infer the emotional state of another from observable information such as prosody and facial expression. By contrast, theory of mind has been defined as the ability to ascribe mental states, such as beliefs, desires, and intentions to oneself and others.<sup>7</sup> Empathy also relies upon the ability to appraise the emotional state of another, as well as to vicariously experience this emotional state.<sup>8,9</sup> Taken together, these theoretical definitions reveal significant overlap, as well as distinct processes, involved in these key components of social cognition. For example, theoretical models propose that the ability to recognize another's emotion is critical to theory of mind<sup>10</sup> and empathy<sup>11</sup> with empirical evidence supporting this view.<sup>11-17</sup> Similarly, the construct of ToM is thought to be related to and overlapping with the construct of 'cognitive empathy', and involves a cognitive understanding and appreciation of another's mental state.<sup>18,19</sup>

Hence, we included these three domains of social cognition in our review in order to provide a broad understanding of social cognition in patients with mood disorders.

In healthy individuals, the neural basis of social cognition consists of a system of a complex network of brain areas involved in cognitive and affective processes (for a recent review, see <sup>20</sup>). Key regions that contribute to this network include prefrontal regions such as the ventromedial prefrontal cortex, an area involved in the regulation of emotion and reward evaluation <sup>21</sup> and the dorsolateral prefrontal cortex implicated in higher-order cognitive processes such as cognitive control and executive functioning.<sup>22, 23</sup> The anterior cingulate cortex, involved in conflict monitoring and integration of information to motivate behavior, has also been implicated.<sup>20</sup> The amygdala, critical to processing and evaluation of emotional stimuli, and the ventral striatum involved in emotional and motivational aspects of behaviour, also constitute important nodes in the social cognition network.<sup>24</sup> Finally, temporal regions such as the temporal parietal junction, involved in a sense of agency as well as perspective-taking and the temporal poles, implicated in diverse memory functions have been shown to recruited across various social cognitive tasks, including theory of mind, empathy, and facial emotion processing.<sup>25-27</sup> Critically, many of the same neural regions thought to mediate the cognitive (e.g., memory; executive functioning) and affective (e.g., emotion evaluation) processes necessary for social cognitive responding have been implicated in patients with BD and MDD, showing altered metabolic functioning and/or structural abnormalities (see <sup>28</sup> for a recent review). Coupled with growing evidence of cognitive and affective processing impairments among patients with MDD and BD,<sup>25, 29-33</sup> we predicted that our

review would reveal performance deficits across a host of social cognitive tasks relying upon cognitive and affective processing resources subserved by these same neural regions (for a review see <sup>34</sup>). Moreover, given the overlap in the neural substrates of social cognition and brain areas implicated in the pathophysiology of major depressive disorder and bipolar disorder, we expected that patients with mood disorders would show alterations in neuronal functioning during social cognitive processing. Specifically, we expected that individuals with MDD and BD would show lowered activation in prefrontal areas involved in emotion regulation and higher-order cognitive processes, and increased activity in subcortical and limbic regions implicated in emotion appraisal and generation, indicating a lack of inhibition of higher-order cognitive centres on limbic and emotion-related structures.

Here, behavioral studies of emotion comprehension, ToM and empathy in patients with mood disorders are first reviewed within the context of factors, including illness burden (e.g., number of affective episodes), illness state (e.g., active versus remitted), medication status, age, and cognitive load, expected to moderate social cognitive processing in this population. The neural basis of each of these social cognitive domains is then briefly outlined prior to discussing the neuroimaging literature concerning each aspect of social cognition in patients with mood disorders. Where possible, results for patients with MDD and with BD are presented separately and subsequently compared, with the exception of social cognitive domains for which little data is available. We conclude the review by discussing future research directions and the clinical implications

of social cognitive deficits with respect to improving treatment interventions and preventing relapse in patients with mood disorders.

An enhanced understanding of the neural and behavioural correlates of social cognition may help improve diagnostic accuracy and early intervention in these disorders. This is particularly pertinent to the study of bipolar disorder, given that patients with this illness experience depression more than hypomania or mania,<sup>35,36</sup> which may result in the misdiagnosis of bipolar depression as major depressive disorder<sup>37,38</sup> and suboptimal treatment and poor outcome.<sup>39,40</sup> Elucidating the neural and behavioral correlates of social cognition may assist in identifying the behavioural and neuroanatomical basis of vulnerability to these disorders. Improved knowledge of the underlying neural mechanisms and nature of social cognitive deficits in mood disorder patients may also assist in clarifying the nature of social dysfunction in MDD and BD and may aid in the development of psychological interventions aimed at improving social perception and adjustment in these patient populations. Patients with mood disorders suffer significant disruptions in interpersonal function<sup>41-45</sup> and deficits in social cognition may underlie these difficulties. Given that patients with MDD and with BD show different profiles on tests of basic cognitive function,<sup>25,30-32</sup> it is important to determine whether similar differences in performance profile characterize social cognitive function.

## **Methods**

A search of the literature using PsycINFO and PubMed (from 1967 to May Week 2 2011) was conducted using the following key words: fMRI, emotion comprehension, affect comprehension, emotion perception, affect perception, facial expression, prosody,

theory of mind, mentalizing, and empathy in combination with the diagnostic terms “major depressive disorder”, “major depression”, “unipolar depression”, “clinical depression”, “bipolar disorder”, and “mania”. References lists of retrieved articles were also manually searched for relevant publications. All articles investigating the perception of affective stimuli (facial expressions and prosody), ToM, and empathic responding in patients with a diagnosis of MDD or BD were evaluated. Given the dearth of papers investigating the domains of ToM and empathic responding in patients with mood disorders, we adopted a liberal approach to the inclusion of relevant articles. Both cross-sectional studies including a patient sample and matched controls, along with longitudinal studies comprised of a patient sample only were included. Only studies that involved an experimental task or survey measuring affective responding, theory of mind, or empathy were included. Studies that recruited patients with a primary diagnosis of MDD or BD as well as those that used recognized diagnostic criteria were included. Given that the majority of studies using neuroimaging technology to examine the neural correlates of social cognitive processing in mood disorders rely upon functional magnetic resonance imaging (fMRI) studies we focused our review on this paradigm. Observational reports, case studies, and studies not written in English were excluded from evaluation. Studies not written in English were excluded. A total of 171 studies met the appropriate criteria and were included in this review.

## **Results**

### **Behavioural Studies of Social Cognition in Patients with Mood Disorders**

#### ***Behavioural Findings: Facial Emotion Processing***

The majority of studies of social cognition in patients with mood disorders have examined the perception and recognition of affective stimuli, particularly facial expressions (see <sup>46</sup> for a review). Given the ubiquitous nature of facial expressions, the ability to recognize facial expressions is crucial for intact interpersonal functioning.<sup>47</sup> Emotion perception paradigms typically consist of tasks that employ identification and discrimination formats. Identification tasks involve labeling the emotion depicted in individual facial expressions from a fixed set of choices. The majority these tasks involve recognizing static or still pictures of facial expressions, however, some studies employ a morphing design that involves dynamic recognition of facial affect by morphing the expression from neutral to beyond the prototypical emotional expression. (i.e., 100% full emotional expression). Discrimination tasks involve presenting participants with a pair of faces and asking them to judge whether the people in the two pictures are expressing the same or a different emotion, or judging the intensity of individual emotional facial expressions.

### **Facial Emotion Processing: Major Depressive Disorder**

#### Mood State

Studies examining facial emotion processing in acutely depressed patients have reported a generalized emotion recognition deficit <sup>48-58</sup> and impaired recognition of happy facial expressions relative to matched controls.<sup>51, 53, 59-67</sup> Enhanced recognition of sad facial expressions has also been consistently reported in acutely depressed patients.<sup>68-74</sup> Other studies have reported evidence of a negative bias during facial expression recognition and detection tasks,<sup>63, 65, 75-82</sup> including a tendency to identify neutral faces as

sad relative to healthy controls in patients with moderate to severe depressive symptoms.<sup>83-85</sup> This bias is accompanied by selective attention to negatively-valenced faces depicting sadness,<sup>59, 72, 81, 86</sup> and anger<sup>87</sup>. Overall, these studies point towards a processing bias involving enhanced attention to and recognition of negatively valenced faces during active states of depression that may be accompanied by a tendency to mislabel positively valenced faces as sad, and to misjudge (i.e., amplify) the amount of negative emotion conveyed in faces.

A number of studies, however, fail to show evidence of alterations in the processing of emotional faces for either static<sup>75, 88-92</sup> or dynamic facial stimuli among patients with mood disorders.<sup>93</sup> For example, Mogg et al.<sup>89</sup> found that patients with MDD did not demonstrate a bias in the attentional processing of sad faces, however, the majority of these patients had a concurrent diagnosis of generalized anxiety disorder, rendering it difficult to determine whether the presence of MDD alone or of co-morbidity accounts for these null findings.<sup>59</sup> Kan et al.<sup>93</sup> did not find any significant differences between MDD patients and controls on a dynamic facial emotion recognition task. It is possible that the dynamic stimuli employed by Kan et al.<sup>93</sup> (i.e., videotaped scenes of actors posing different facial expression) provide more information about the depicted emotion than the static or still images of emotional facial expressions that are typically used in the emotion recognition literature. The study sample also was comprised of patients with a varying illness history (e.g., single depressive episode vs. multiple episodes). Given preliminary evidence that depressed patients experiencing a single episode of illness show less severe impairment on cognitive tasks than do patients

experiencing recurrent episodes,<sup>94, 95</sup> it is possible that the inclusion of first-episode patients limited the authors' ability to detect deficit in their sample (see below). The relatively small sample sizes of these studies may have also been underpowered to detect group differences in emotion processing.

The few studies that have examined facial emotion processing during euthymia or remission in MDD have produced conflicting results rendering it unclear whether remission results in a reduction in alterations in facial affect recognition seen during active illness states. For example, Suslow et al.<sup>66</sup> reported that actively depressed patients were slower to respond to positive and neutral facial expressions, and this impairment was evident during remission. Similarly, Leppanen and colleagues<sup>84</sup> showed that deficits in recognizing neutral faces persisted in a sample of MDD patients even after clinical remission. By contrast, one study found that individuals with MDD show improvements in the recognition of sad and happy faces from the acute phase to remitted phase.<sup>51</sup>

Severity of depressive symptoms may moderate performance across these studies, although the evidence is again inconsistent. The presence of a mood congruent bias in emotion recognition tasks has also been strongly linked to the persistence of depressive symptoms in patients with MDD<sup>61, 81, 96-98</sup> (but see<sup>53, 80, 83, 99-101</sup> for conflicting findings). Among patients with MDD, greater symptom severity is associated with increased difficulty in discriminating negative<sup>69, 98</sup> and positive<sup>102</sup> emotions from facial expressions and with longer reaction times to these stimuli, suggesting a generalized emotion recognition deficit during the more severe phases of illness.<sup>103</sup> Other studies, however, found no evidence of a correlation between impairments in emotion recognition and

severity of depression.<sup>71, 78, 101</sup> Similarly, Canli et al.<sup>104</sup> found no association between depressive symptoms and reaction times during an fMRI task of implicit emotional processing while other studies failed to find any differences in reaction times altogether.<sup>67, 105-107</sup>

### Illness Burden

Few studies have examined the influence of illness burden variables on facial emotion recognition performance in MDD. Dannlowski et al.<sup>100</sup> reported a significant association between a stronger judgmental bias elicited by negative faces and higher scores on a severity index characterizing illness history (illness duration, number of episodes, total hospitalization time, time since first inpatient treatment and time since first outpatient treatment). This finding suggests that the negative bias observed for facial emotion was associated with a more chronic and severe course of illness.

### Medication Status

Little is known about the influence of medication on facial affective performance in patients with mood disorders despite findings that, in healthy subjects, administration of benzodiazepines impairs recognition of anger,<sup>108</sup> and administration of citalopram,<sup>109</sup> reboxetine,<sup>109</sup> and tryptophan<sup>110</sup> reduces perception of negative emotional expressions (see <sup>111</sup> for conflicting findings regarding citalopram).

A recent study by Merens et al.<sup>112</sup> found that, relative to controls, remitted MDD patients on SSRIs or SNRIs show enhanced accuracy when asked to identify fearful facial expressions. Bhagwagar et al.<sup>113</sup> also found enhanced recognition of fearful facial expressions relative to matched controls in a sample of unmedicated euthymic women

with a history of MDD; administration of a single dose of citalopram normalized this enhanced recognition when tested immediately following medication administration. Harmer et al.<sup>64</sup> showed that a single dose of reboxetine increased recognition of happy facial expressions in depressed patients early in treatment, prior to any changes in mood or symptoms. In a related study, Tranter and colleagues<sup>114</sup> found that administration of either citalopram or reboxetine in a sample of depressed patients led to increased recognition of surprise, disgust and happy expressions within two weeks of treatment initiation. In a longitudinal study, Bouhuys et al.<sup>96</sup> reported that, in naturalistically treated depressed patients, recognition of negative emotions from ambiguous faces decreased from the acute to remitted illness phase, however, like Tranter et al.<sup>114</sup> this study did not include a comparator group. Interestingly, improved recognition of happy faces following two weeks of treatment was associated with a more favorable clinical course when measured six weeks after treatment onset, suggesting that early changes in facial emotional processing may also be a causal factor for a favorable response to antidepressants. Taken together, these studies provide provocative new evidence that treatment with SSRIs/ SNRIs may reduce processing biases towards negative faces (but see Lisiecka et al.<sup>115</sup> for contradictory findings) and normalize identification of positively valenced faces in MDD.

Recent studies have also employed acute tryptophan depletion methods to investigate the effects of lowered serotonergic function in patients with depression. Following low-dose tryptophan depletion, euthymic patients with MDD show reduced recognition of happy faces and enhanced recognition of facial expressions of disgust<sup>116</sup>.

In a sample of remitted MDD patients, however, high-dose tryptophan depletion reduced recognition of fearful faces as compared with low-dose tryptophan depletion and baseline.<sup>117</sup> It appears that the direction of the effect of tryptophan depletion on facial emotion recognition remains to be clarified.

### Age

In line with research in adults, a small body of evidence suggests that children and adolescents with MDD also show impairment in the recognition of emotional facial expressions. Deficits recognizing negative emotions such as anger<sup>118, 119</sup> and fear<sup>118</sup> have been reported in depressed youth with acute symptoms. These observations suggest that impaired social cognitive processing is a feature of MDD that is present across the lifespan.

### Section Summary

Taken together, the results of the above studies suggest a mood-congruent bias in facial emotion processing in MDD. Individuals with MDD appear to show a negative bias in detecting, interpreting, and recognizing neutral, emotional, and ambiguous facial expressions. These findings also indicate a reduced sensitivity to positive emotional expressions. The observed biases towards negative stimuli and away from positive stimuli have been reported during other perceptual, cognitive, and memory tasks. For example, depressed individuals demonstrate enhanced recall for depression-relevant items compared to neutral stimuli.<sup>120</sup> More broadly, evidence of negative biases in facial emotion processing supports cognitive theories of depression that posit that depressed patients show negative cognitions and biases in information processing that may play a

role in the maintenance of depressive symptoms.<sup>121, 122</sup> It must be noted that the mood-congruent impairment in facial emotion processing is not consistently reported, likely stemming from underpowered sample sizes and clinical heterogeneity of patient samples. The influence of mood state and burden of illness variables on facial emotion processing in MDD is far from conclusive and future research is warranted. Preliminary evidence indicates that facial emotion processing may improve following antidepressant treatment. It is unclear if facial emotion processing deficits are related to mood state or represent a trait vulnerability marker for major depression. Improvements in facial affect processing are associated with a more favourable clinical course, and may contribute to symptom remission.

### **Facial Emotion Processing: Bipolar Disorder**

#### Mood State

Several studies report that patients with bipolar disorder (BD) experience difficulty decoding facial emotions on facial affect labeling tasks during periods of mania.<sup>123-125</sup> For example, emotion-specific impairments in the identification of sadness,<sup>126</sup> disgust,<sup>124</sup> and fear,<sup>124</sup> as well as a more generalized deficit in facial emotion recognition have been reported in actively manic patients.<sup>29, 123</sup> Increased levels of manic symptoms have been shown to correlate significantly with impaired recognition of sad faces.<sup>124</sup> In a pattern that similar to that observed in patients with unipolar illness, studies examining BD patients in a depressed phase of illness reveal a mood congruent bias in emotion perception tasks, including difficulties labeling happy faces,<sup>127, 128</sup> and a tendency to misinterpret neutral facial stimuli as sad,<sup>69, 107</sup> and happy faces as angry,<sup>129</sup>.

Individuals with bipolar depression are also more accurate when identifying facial expressions of disgust.<sup>90</sup> (but see <sup>107</sup> for conflicting findings). Finally, these patients show a reduction in sensitivity to happy facial expressions<sup>90, 130, 131</sup> that is amplified in the presence of more severe depressive symptoms.<sup>130</sup> Hence, whereas mania appears associated with a reduction in the ability to recognize negative facial emotions, the presence of depressive symptoms in patients with bipolar disorder appears to result in the over-identification of negative emotion and difficulty recognizing positive affect in faces.

By contrast, the literature examining facial emotion recognition in clinically stable patients with bipolar disorder (euthymic or in remission) is conflicting, with an equal number of studies reporting performance sparing<sup>124, 132-137</sup> and impairment.<sup>131, 138-140</sup> For example, in a number of studies, compared to healthy controls, euthymic BD patients demonstrate generalized facial emotion recognition deficits,<sup>125</sup> and difficulties identifying fearful<sup>139</sup> and surprised faces.<sup>131</sup> Others have shown increased reaction times for identification of sad faces.<sup>141</sup> Consistent with findings in depressed unipolar and bipolar patients,<sup>90</sup> an enhanced ability to identify facial disgust has also been observed among euthymic BD patients.<sup>142</sup> An equal number of studies, however, fail to show these effects.<sup>124, 132-136</sup> The noted discrepancies concerning facial emotion recognition ability in remitted patients with BD may be due to variations in sample size as well as the use of different analyses when examining emotion recognition performance (e.g., examining emotion specific and generalized emotion impairments).<sup>143</sup>

The presence of residual mood symptoms in some patients at the time of testing may also provide a partial account for these conflicting findings. For example, Summers

and colleagues<sup>131</sup> found that BD patients with residual depressive symptoms (Beck Depression Inventory score >10) were less sensitive than controls to happiness and underperformed relative to patients without residual depressive symptoms on sensitivity to anger expressions. Similarly, Vaskinn et al.<sup>135</sup> found a significant negative relation between depressive symptom severity and facial emotion performance among patients with mixed states of BD. Other studies of clinically stable patients with BD, however, have failed to find an association between level of residual symptoms and facial emotion identification ability.<sup>136-138, 142</sup> It is also possible that task differences may contribute to equivocal findings in remitted patients with BD.

Investigations examining the performance of patients with BD on facial affect discrimination tasks have resulted in mixed findings. For example, two studies reported deficits in facial affect matching in euthymic BD patients<sup>29, 132</sup> while other studies report no evidence of impairment.<sup>133, 135</sup> It is difficult to determine whether the presence of residual manic or depressive symptoms may account for these discrepant findings, as mean mania and depression severity scores were quite low in studies reporting both facial discrimination deficits<sup>29</sup> and performance sparing.<sup>133</sup> Mean duration of illness was also similar across these studies [ranging from 11.5-13 years, although this data was not reported in Edwards et al.<sup>133</sup>], rendering it unlikely that this variable accounts for the discrepant findings. Indeed, Bozikas et al.<sup>29</sup> found that impaired emotion matching performance was not attributable to illness factors such as residual manic or depressive symptoms.

### Illness Burden

Factors relating to illness burden, including number of past episodes of illness and mean duration of illness, are rarely reported in studies examining facial emotion recognition in euthymic BD patients, although it is notable that most patient samples reported in the literature are significantly heterogeneous with respect to these variables.<sup>134-136</sup> Two studies have examined the relation between age of onset of symptoms, duration of illness and emotion processing performance but failed to find significant association between these variables; these studies had small patient samples, however, limiting power.<sup>29, 135</sup> By contrast, in a larger sample, Schenkel et al.<sup>138</sup> found that an earlier age of onset of illness correlated positively with the extent of impairment. Venn et al.<sup>136</sup> however, included a significant proportion of rapid-cyclers ( $\geq 4$  episodes or more each year), and both Summers and colleagues<sup>131</sup> and Malhi et al.<sup>134</sup> included patients with multiple past episodes of depression and/or mania. Despite a high illness burden in these samples, euthymic BD patients performed comparably to controls on all emotion comprehension tasks, rendering it unclear whether an enhanced illness burden exerts its impact only during periods of active illness.

In a related study, Derntl et al.<sup>143</sup> found that BD-I, but not BD-II patients, performed significantly worse in emotional face identification. The authors, however, failed to find any associations between performance deficits and mood state, illness burden, or medication. Further work is required to determine whether emotion recognition abilities decline over the course of multiple illness episodes in BD, as has been suggested for other aspects of cognitive function.<sup>94, 95</sup>

### Medication Status

Investigations examining the effect of medication on facial emotion performance in BD are rare. Schenkel et al.<sup>138</sup> found that treatment with either lithium and risperidone or with divalproex sodium and risperidone failed to resolve impaired facial emotion performance in a euthymic pediatric sample. Getz and colleagues<sup>123</sup> did not find any performance differences between bipolar patients receiving mood stabilizers, antipsychotics, antidepressants and benzodiazepines and those who were not receiving these treatments. The authors, however, were not able to examine the influence of multiple medications on facial emotion processing because of the small study sample size. Similarly, Venn et al.<sup>136</sup> examined the effect of antidepressant use on perception of facial affect and found no differences in performance between those BD patients receiving antidepressants and those who were not. Patients in this sample also received antipsychotic drugs or mood stabilizers, or a combination of both.

Similar results have been reported in pediatric samples, where, for example, Brotman et al.<sup>144</sup> found no effect of medication for the performance deficits seen during presentations of child and adult emotional facial expressions in children with BD. In another pediatric study showing that BD and at-risk youth require higher levels of depicted emotional intensity before correctly identifying facial emotion, medication status was not found to be a factor.<sup>145</sup> Although at present, the majority of studies suggest that medication does not resolve alterations in emotion identification in patients with BD, it will be critical for future studies of BD patients to examine the effect of specific medication classes (e.g., lithium; SSRIs) in larger and more adequately powered samples of patients in active, manic and depressed phases of illness.

### Age

Consistent with findings in adult patients (for a recent review see <sup>146</sup>), adolescents with BD also demonstrate facial expression recognition deficits.<sup>125, 129, 138, 144, 147, 148</sup> that have been shown to be significantly associated with altered social reciprocity skills.<sup>148</sup> For example, global emotion recognition deficits have been reported in heterogeneous samples of euthymic and symptomatic BD patients,<sup>144, 145, 147</sup> as well as hypomanic/mixed bipolar youth<sup>144, 148</sup>. Relative to controls and medicated euthymic patients, unmedicated pediatric patients in mixed and manic states showed deficits in differentiating between subtle variations of happy or sad facial expressions.<sup>138</sup> Moreover, acutely ill and euthymic BD adolescents have been shown to misjudge emotionally intense happy and sad faces relative as moderate in intensity.<sup>138</sup> Finally, euthymic bipolar youth demonstrate difficulties labeling disgusted and happy faces.<sup>148</sup> The presence of co-morbid anxiety may moderate these effects where youth in a pediatric BD sample with a co-morbid anxiety disorder showed a bias towards threatening faces, while healthy individuals and BD youth without an anxiety disorder did not.<sup>149</sup> Interestingly, youth with a first degree BD relative also show global emotion recognition deficits suggesting that altered emotion recognition performance may represent an endophenotype of this disorder.<sup>144, 145</sup>

### Section Summary

Taken together, the results of these studies indicate a mood-congruent positive bias in bipolar patients, specifically these patients demonstrate deficits in recognizing negatively valenced faces but not positively valenced faces.<sup>124, 126</sup> By contrast, depressed

bipolar patients demonstrate a mood-congruent negative bias during facial emotion processing tasks.<sup>69, 130</sup> These results are consistent with evidence suggesting a negative bias in facial emotion processing in patients with MDD (see above). Divergent findings in facial emotion processing are observed in euthymic and remitted BD patients where some studies have found performance deficits,<sup>131, 138-140</sup> while others report intact performance.<sup>124, 132-137</sup> Moreover, the influence of manic and depressive symptom severity on facial emotion recognition in BD is unclear, with some studies showing elevated levels of deficit with increasing symptom severity and other studies failing to reveal any such relation. These discrepant findings in the literature may reflect the limited sample sizes found across studies as well as the heterogeneous status of patient samples in terms of mood state, illness history, and medication. The effects of medication status on facial emotion performance in BD are seldom examined and although primarily null, remain to be investigated.

### ***Behavioral Findings: Affective prosody recognition in MDD and BD***

#### **Mood State and Illness Burden**

Preliminary evidence indicates that individuals with mood disorders experience difficulty in the recognition of affective prosody. In a pattern similar to the results reported for identification of facial emotion, a bias towards interpreting neutral prosodic emotions (i.e., surprise) as negative,<sup>78, 93</sup> and intact recognition of sad emotional tones,<sup>150</sup> has been reported in homogeneous samples of acutely depressed patients. In a related study, Murphy and Cutting<sup>151</sup> presented neutral, angry, surprised, and sad sentences to a heterogeneous sample of manic and depressed patients, some of whom had co-morbid

psychosis. Both patient groups were significantly impaired relative to matched controls in recognizing emotional prosody. Moreover, the depressed group made more errors identifying sad tones than did controls. In a related study, Peron et al.<sup>152</sup> presented participants with pseudowords uttered in happy, sad, angry, fearful, and neutral tones and found that relative to controls, actively depressed patients performed more poorly than controls in recognizing fear, happiness and sadness. Moreover, compared to controls, MDD patients rated levels of negative emotions such as fear and sadness higher after being primed with auditory happy stimuli. These deficits may be apparent into remission in patients with BD.<sup>153</sup>

Other studies, however, report performance sparing for affective prosody recognition among patients with mood disorders. For example, Edwards et al.<sup>133</sup> found that patients with first-episode affective psychoses performed as well as healthy controls on an affective prosody recognition task, perhaps reflecting a sparing of affective recognition in the early stages of illness. Similarly, a recent study by Vaskinn et al.<sup>135</sup> found no evidence of emotional prosody deficits in a sample of predominantly euthymic BD patient; Bozikas et al.<sup>153</sup> however, reported impairments in affective prosody recognition in a sample of remitted BD patients that were specific to female participants and to the emotions of fear and surprise. These conflicting findings may stem from the limited sample sizes included in the studies. Moreover, the emotion perception paradigms found in Vaskinn et al.'s<sup>135</sup> study had comparatively few positively valenced emotional stimuli relative to negatively valenced stimuli, precluding the author's ability to examine performance on specific emotions or valence.

The effects of illness variables such as mood state and illness burden on affective prosody recognition are rarely examined. Peron et al.<sup>152</sup> reported that the impaired recognition of affective prosody is related to depressive symptom severity in a sample of actively ill patients with MDD. Similarly, Bozikas et al.<sup>153</sup> found that depression severity tended to correlate with performance on fear and neutral stimuli in remitted bipolar patients. Other studies, however, found no relation between symptom severity and accuracy scores on affective prosody tasks in patients with MDD or BD.<sup>78, 93, 135</sup> With respect to illness burden, an initial study found emotional prosody recognition to be independent of illness duration in individuals with BD.<sup>135</sup> Similarly, Peron et al.<sup>152</sup> failed to find a relation between the length of time since the first symptoms of the first episode and recognition of emotional prosody in MDD.

### Cognitive Factors

There is preliminary evidence that cognitive processing demands across tasks moderate the extent of deficit observed in studies of affective prosody recognition. For example, Uekermann et al.<sup>150</sup> reported emotion comprehension deficits in patients with MDD on a task placing high demands on domain-general resources such as inhibition, and executive functioning (i.e., naming emotional tone of prosody with incongruent semantic content); no such impairment was observed for a task placing less demands on cognitive resources (i.e., identifying the emotional tone of prosody with congruent semantic content). Previous work has demonstrated that the recognition of affective prosody in sentences with incongruent semantic content relies heavily on executive processing resources, including inhibition.<sup>154</sup> In line with this finding, both Uekermann et

al.<sup>150</sup> and Peron et al.<sup>152</sup> found that the extent of emotional prosody comprehension deficits in patients with MDD was positively associated with impaired performance on tests of executive functioning, including working memory, inhibition, and set shifting suggesting that impairments in these cognitive processing resources may contribute to diminished performance on emotion recognition tasks reliant upon them.<sup>155</sup>

### Medication Status

The influence of psychotropic medication on affective prosody recognition is seldom examined. Recent studies conducted in MDD have reported no significant association between medication usage<sup>150</sup> or dose<sup>93</sup> and task performance.

### Age

To date, no study has examined the influence of age on affective prosody recognition in patients with MDD.

### Section Summary

Taken together, the recognition of affective prosody appears to be impaired in patients with MDD.<sup>78, 93, 151, 152, 156</sup> Moreover, the negative bias observed for negative emotional stimuli in MDD is not only specific for facial expressions, there is preliminary evidence that this mood-congruent bias extends to prosodic stimuli.<sup>78, 93, 152</sup> The available data examining affective prosody recognition in patients with BD is mixed: two preliminary studies report impairment in actively ill and remitted patients,<sup>151, 153</sup> while another study failed to show deficits in affective prosody recognition in a sample of mainly euthymic patients with BD.<sup>135</sup> It remains unclear whether factors such as age, medication, illness burden, or symptom severity moderate the extent of deficit observed

on affective prosody tasks administered to patients with mood disorders. It is plausible that the level of central processing demands across tasks may moderate the performance of mood disorders patients in this social cognitive domain.<sup>156</sup> It also remains indeterminate whether affective prosody impairments in patients with mood disorders stem from a specific deficit in emotion perception, from domain-general cognitive impairments (e.g., in executive function) or a combination of these factors.<sup>152</sup>

### ***Behavioural Findings: Theory of Mind***

Theory of mind (ToM) refers to the ability to infer the mental states of other individuals, including their beliefs, desires, and intentions in order to explain or predict human behaviour.<sup>157</sup> Recent theoretical models propose that ToM draws on both cognitive (e.g., understanding another's perspective) and affective (e.g., emotional response to feeling states of others) processing resources.<sup>155, 158</sup>

Recent theories have also proposed that ToM ability encompasses two separate aspects: 1) decoding mental states from available information such as facial expressions, tone of voice, or gestures, 2) reasoning about mental states by combining contextual information and prior knowledge about an individual person or situation to understand behavior.<sup>159, 160</sup> Interestingly, very preliminary evidence suggests that impaired ToM ability may be associated with poor clinical and functional outcome in patients with mood disorders. Inoue et al.<sup>161</sup> showed that deficit on higher-order ToM tasks was related to poorer prognosis (increased risk of relapse) at 1-year follow-up in a heterogeneous sample of unipolar and bipolar individuals who had recently recovered from a major depressive episode.

## **Theory of Mind: Major Depressive Disorder**

### Mood State

Although it is widely acknowledged that autistic children and adults with Asperger's syndrome are impaired in appreciating the mental states of other individuals,<sup>162-165</sup> theory of mind ability in patients with mood disorders remains an under-explored area of research.<sup>166</sup> Several studies have examined theory of mind performance in actively depressed patients with MDD. One initial study reported deficits on the Reading the Mind in the Eyes Test (RMET;<sup>167</sup>), in a female MDD sample that was actively depressed at the time of testing.<sup>168</sup> The RMET is a classic ToM task that involves decoding the mental states of individuals from photographs of pairs of eyes.<sup>167</sup> Similarly, two recent studies showed severely depressed patients with psychotic and non-psychotic symptoms<sup>169</sup> and a sample of MDD patients in varying illness states (partial remission and significant residual symptoms)<sup>170</sup> were impaired relative to controls on the same task. In contrast to these studies, Wolkenstein et al.<sup>171</sup> did not find decoding deficits in a mixed sample of patients with acute depressive symptoms as well as participants with milder forms of depressive illness, such as dysthymia, suggesting that ToM ability may be less impacted in patients with less severe illness. Interestingly, however, the same patient sample was impaired on the more cognitively demanding naturalistic Movie for Assessment of Social Cognition,<sup>172</sup> a standardized paradigm that involves the presentation of a short film and evaluates participants' ability to recognize the mental states of the depicted characters<sup>171</sup> (but see<sup>173</sup> for contradictory results in patients with varying levels of symptom severity).

ToM has also been examined in remitted patients with MDD. Inoue et al.<sup>174</sup> found that a combined sample of remitted patients with unipolar and bipolar depression were impaired on ToM tasks shown previously to place high demands on domain-general resources such as working memory and executive functioning (i.e., second-order false-belief questions); however, the patient group had comparable scores to controls on tasks involving lower-level ToM reasoning (i.e., first-order false belief stimuli). Hence, only performance on cognitively complex ToM tasks may be impacted in remitted patients with MDD.

The influence of mood state on ToM performance in MDD has also been investigated by examining the relation between symptom severity and ToM ability. For example, Uekermann et al.<sup>175</sup> reported a significant association between reduced ToM performance and level of depression in a sample of MDD inpatients. Wolkenstein et al.<sup>171</sup> also found that impaired performance on MASC emotional ToM stimuli was associated with increased depressive symptom severity in patients with major depression. However, other studies report no such associations between ToM ability and symptom severity in MDD.<sup>168, 173</sup>

### Illness Burden

Recent work has begun to examine the performance of acutely depressed patients with a chronic course of illness. For example, Zobel et al.<sup>176</sup> found that these patients demonstrated impaired performance on both first- and second-order questions ToM tests involving the detection of cooperation, deception, and intentions, suggesting that deficits on both lower level (i.e., first-order) and cognitively challenging (i.e., second-order) ToM

tasks may emerge in patients with an extended course of illness. Other studies, however, found no relation between illness duration<sup>171, 174</sup> and ToM performance in patients with MDD.

### Cognitive Factors

As noted, the level of cognitive and affective processing resources required for task performance may also account for inconsistent findings across studies. Specifically, preliminary research suggests that remitted patients are impaired on higher-order ToM tests<sup>174</sup> that draw on cognitive processing resources that remain affected despite remission of mood symptoms (e.g.,<sup>31, 32</sup>). Patients with acute depressive symptoms seem to show deficits on ToM tasks that place low demands on cognitive and affective processing resources (e.g., first-order false belief tasks), as well as tasks that rely heavily on central processing resources (e.g., second-order false belief tasks, Movie for Assessment of Social Cognition).<sup>168-171, 176</sup>

Indeed, recent studies also reported ToM impairment in acutely ill MDD patients that correlated significantly with the extent of deficit observed on neuropsychological measures of executive functioning<sup>171, 175, 176</sup> and verbal fluency.<sup>169</sup> These findings support the idea that ToM ability in MDD may differ with the level of cognitive processing resources required for task performance. Moreover, the significant associations between cognitive performance and ToM are consistent with evidence documenting the contribution of such cognitive factors to ToM performance.<sup>34, 177, 178</sup>

### Medication Status and Age

The influence of medication status and age on ToM performance in MDD has not yet been examined.

## **Theory of Mind: Bipolar Disorder**

### Mood State

ToM ability has also begun to be examined in patients with bipolar disorder. Recent reports have demonstrated that euthymic patients with bipolar disorder are impaired on ToM tests that involve high levels of cognitive processing demands,<sup>13, 179, 180</sup> but perform comparably to matched controls on ToM tasks that require fewer cognitive demands.<sup>181</sup> For example, Bora et al.<sup>13</sup> found that euthymic patients with BD showed impaired ToM decoding ability on the Reading the Mind in the Eyes Test.<sup>167</sup> A recent study by Montag et al.<sup>182</sup> evaluated ToM performance in euthymic bipolar patients using the Movie for Assessment of Social Cognition (MASC). The authors found that BD patients performed more poorly than controls in cognitive mental state reasoning (“What is X thinking/intending?”) but showed preserved emotional mentalizing abilities (“What is X feeling?”). By contrast, Kerr et al.<sup>183</sup> found deficits in BD patients who were acutely depressed or manic on tasks involving both lower-level (i.e., first-order false belief; “A thinks X”) and higher-order ToM reasoning (i.e., second-order false belief; “A thinks B thinks X”); remitted patients were unimpaired relative to controls for both tasks in this study. Interestingly, the extent of ToM impairment among patients with active illness in this study did not differ across the first- and second-order tasks, despite the greater cognitive demands inherent in the second-order task. Bazin and colleagues<sup>184</sup> recently reported that a sample of actively manic patients (but not depressed patients) were

significantly impaired relative to healthy controls on a cognitively challenging ecological video task thought to tap ToM, most notably the ability to infer others' intentions. Recent work from our laboratory<sup>185</sup> has shown that BD patients experiencing sub-syndromal symptoms of illness perform more poorly than control subjects for both first-order and second-order ToM questions, however, these deficits are more pronounced for cognitively demanding second-order stimuli.

Taken together, these studies suggest a gradient of ToM impairment among BD patients in euthymic, sub-syndromal, and active phases of illness. This gradient in ToM performance among patients with BD appears to be similar to the pattern of ToM impairment observed in MDD (see above). Specifically, it appears that euthymic patients show deficits on ToM tasks that involve high levels of cognitive processing demands. This impairment on higher-order ToM tasks may be related to neuropsychological deficits that persist into the clinically stable phase of illness.<sup>13, 186-188</sup> By contrast, sub-syndromal patients appear to show deficits on high-level and low-level ToM tasks, with greater impairment found on the higher-order ToM stimuli.<sup>185</sup> Finally, acutely ill patients appear impaired on both resource-free ToM tasks drawing primarily on affective processes (e.g., emotion comprehension) and cognitively demanding ToM tasks that rely on the joint contribution of cognitive (e.g., working memory, executive functioning) and affective processing resources.<sup>183</sup> Consistent with the notion that the extent of ToM impairment in BD varies with cognitive processing demands, recent studies demonstrate that deficits in ToM are linked with poor performance on tests of executive functioning,<sup>13, 180, 189</sup> attention,<sup>13</sup> and non-verbal reasoning<sup>189</sup> in bipolar patients. Impaired ToM performance

has also been shown to be significant after controlling for level of intellectual functioning and performance on tests of executive functioning, suggesting that some elements of ToM performance (e.g., emotion comprehension) are independent of cognitive variables.<sup>189</sup>

The influence of mood state on ToM performance in bipolar disorder has also been investigated by examining the relation between symptom severity and ToM ability. We found a negative relation between severity of depression and ToM performance in patients with sub-syndromal symptoms of BD.<sup>185</sup> Schenkel et al.<sup>190</sup> also found that impaired ToM performance was associated with elevated manic symptoms in acutely ill pediatric patients with BD. However, other studies report no such associations between ToM ability and symptom severity in patients with BD.<sup>13, 189</sup>

### Illness Burden

Few studies have examined the moderating influence of illness burden on ToM performance in patients with bipolar disorder, despite evidence that patients with multiple episodes of illness show greater cognitive impairment relative to those with a single episode of illness.<sup>94, 191</sup> Several studies found no relation between number of previous affective episodes,<sup>13</sup> illness duration,<sup>13, 174</sup> and ToM performance in patients with BD. Recent studies conducted in acutely ill<sup>190</sup> and remitted bipolar patients,<sup>189</sup> however, reported that impaired performance on complex ToM tasks were associated with an earlier illness onset. Moreover, McKinnon et al.<sup>185</sup> found that poor performance on higher-order ToM tests was associated with an extended duration of illness in BD patients experiencing sub-syndromal symptoms. Similarly, Montag et al.<sup>182</sup> found that the

euthymic bipolar patients with a greater number of hypomanic episodes performed worse on emotional mentalizing questions.

Additional, longitudinal, investigations will be required to clarify the relation between illness burden and ToM responding in mood disorders and determine whether a gradual offset of ToM ability occurs in these patients.

### Cognitive Factors

The influence of cognitive factors on ToM performance in BD has been reviewed with the context of its interaction with mood state (see above).

### Medication Status

Few studies have examined the influence of psychotropic medication on ToM performance in patients with BD, making it difficult to draw any firm conclusions about the moderating effect of this clinical variable. These studies that do exist have reported no significant association between medication type and ToM performance in these patients.<sup>13, 181</sup> It should be noted that the small sample sizes of these studies precluded the analysis of any specific effects of different medication classes and may have limited the authors' ability to detect potential effects of medication on performance.

### Age

To date, only one study has examined the moderating effect of age on ToM performance in BD. Schenkel et al.<sup>190</sup> found that relative to controls, patients with pediatric BD showed deficits on ToM measures of false-belief and on a Hinting Task that involved inferring the real intentions of characters behind indirect comments. Moreover, BD youth with a co-morbid diagnosis of attention deficit hyperactivity disorder (ADHD)

performed more poorly on the Hinting Task relative to patients without co-morbid ADHD. Future studies examining ToM ability among PBD youth with and without co-morbid ADHD are warranted.

### Section Summary

Overall, it appears that individuals with BD and MDD show deficits on ToM tasks involving both decoding (e.g., RMET) and reasoning (e.g., false-belief, MASC) components. The extent of ToM deficit observed may be moderated by illness state and level of cognitive and affective demands of task performance. Further studies comparing ToM ability in larger samples of mood disorder patients in varied illness states are needed to more adequately assess the influence of mood state on this social cognitive domain. The available knowledge examining the impact of illness burden variables on ToM performance in mood disorders is inconclusive; further investigation is needed to clarify the relation between burden of illness and ToM. The influence of psychotropic medication on ToM remains to be examined.

### ***Behavioral Findings: Empathy***

Empathy refers broadly to the ability to infer and share the feeling states of another<sup>192</sup> and is thought to promote unselfish, prosocial behaviour.<sup>193</sup> Intact empathic ability is thought to be fundamental for establishing and supporting social relationships and important for higher social functioning.<sup>194, 195</sup> Similar to work involving ToM, recent research has focused on the possibility that empathy is multidimensional in nature involving both cognitive (e.g. understanding another's perspective) and affective

components (e.g. emotional response to the feeling states of others’).<sup>8, 196</sup> As noted above, cognitive empathy is conceptually related to the construct of theory of mind.

### **Empathic Responding: Major Depressive Disorder**

#### Mood State

Impaired empathic responding has been reported in autism spectrum disorders,<sup>194</sup> as well as in patients with Axis II Developmental and Personality Disorders,<sup>197, 198</sup> and frontotemporal lobar dementia.<sup>22</sup> Studies examining empathic responding in patients with mood disorders are rare. In one recent study, Donges et al.<sup>199</sup> found that relative to healthy controls, patients with acute MDD exhibited a lower emotional awareness as assessed by the Levels of Emotional Awareness Scale, a measure not designed to measure empathy specifically. This impairment improved following 7 weeks of treatment in a psychotherapeutic program targeted at recognizing and labeling emotional responses.<sup>199</sup>

The few studies examining directly the cognitive and affective components of empathy in MDD reveal mixed findings. Wilbertz et al.<sup>173</sup> found that chronically depressed patients reported reduced levels of Perspective-Taking and elevated levels of Personal Distress on the Interpersonal Reactivity Index (IRI).<sup>196</sup> The IRI is a standardized self-rated measure that assesses four dimensions of dispositional empathy: Perspective-Taking and Fantasy as well as Empathic Concern and Personal Distress. Each pair was designed to measure cognitive and affective elements of empathy, respectively. By contrast, Cusi et al.<sup>200</sup> found that MDD patients in varying states of illness reported significantly reduced levels of empathy measured broadly by the Toronto Empathy Questionnaire and specifically in cognitive (‘Perspective Taking’) and affective

(‘Empathic Concern’) domains captured by the IRI. These discrepant findings in cognitive and affective empathy domains may be influenced by the differing mood state of the participants in the two studies, specifically the majority of patients in Wilbertz et al.’s<sup>173</sup> were moderately to severely depressed and those in Cusi et al.’s<sup>200</sup> study were in varying illness states, including euthymia and sub-syndromal depression. Indeed, preliminary evidence suggests that alterations in empathic responding are associated with higher levels of depressive symptoms in MDD.<sup>199</sup> It is plausible that levels of empathic concern may differ with illness state, suggesting that impaired empathic responding in MDD may represent a state-like phenomenon rather than stable trait. Given the self-rated nature of the Interpersonal Reactivity Index, it is also possible that the discrepant findings on affective empathy domains were influenced by social desirability.

#### Illness Burden

In one study, Cusi and colleagues<sup>200</sup> demonstrated that a greater number of previous depressive episodes was associated with reduced IRI Perspective Taking abilities in MDD patients.

#### Cognitive Factors, Medication Status, and Age

The moderating influences of cognitive factors, medication status, and age on empathic responding in patients with MDD have yet to be examined.

### **Empathic Responding: Bipolar Disorder**

#### Mood State

Early evidence of altered empathic responding has also been shown in patients with bipolar disorder. A recent study found that euthymic patients with BD reported

significantly lower levels of cognitive empathy ('Perspective Taking) and increased affective personal discomfort in response to others' distress ('Personal Distress'), as assessed by the Interpersonal Reactivity Index.<sup>196</sup> Cusi et al.<sup>201</sup> replicated these findings in a sample of bipolar patients in varied mood states. Moreover, similar to MDD patients,<sup>199</sup> elevated IRI Personal Distress increased with higher levels of depression in patients with BD.<sup>201</sup>

### Illness Burden

The moderating influence of illness burden on empathic responding in BD has only been examined in single study, and the authors failed to find relation between course of illness variables (number of mood episodes, illness duration, onset of illness) and empathic response in their sample.<sup>201</sup>

### Medication Status

A single study found that medication type did not influence empathic responding in euthymic patients with BD.<sup>181</sup>

### Cognitive Factors

A preliminary study found that alterations in cognitive empathy are associated with poor performance on a measure of executive function in a sample of euthymic patients with BD.<sup>181</sup>

### Age

The moderating influence of age on empathic responding in patients with BD has yet to be examined.

### Section Summary

Taken together, preliminary findings from studies in patients with MDD and BD suggest impaired abilities in both cognitive and affective empathy domains. The observed findings of reduced perspective taking in patients with MDD and BD are consistent with reports of ToM deficits in these patient populations outlined in the previous section. Perspective-taking is one of many processes related to ToM.<sup>18, 195</sup> Reduced levels of perspective-taking in mood disorder populations suggests that these individuals may experience difficulties in suppressing self-perspective to take on the viewpoint of another.<sup>202</sup> Increased Personal Distress or affective discomfort in response to another person's suffering is consistent with research documenting deficits in emotion regulation in both MDD<sup>203-205</sup> and BD.<sup>206</sup> Elevated levels of Personal Distress as assessed by the IRI is also in accordance with the notion of 'simulation theory', that proposes that we understand the mental states of others by matching or simulating their states/experiences in our own mind.<sup>207, 208</sup> It is possible that patients with BD and MDD may "oversimulate" others' mental states or experiences,<sup>181</sup> and become "overwhelmed by their own affective reaction to be able to focus on the other person" (<sup>173</sup>, pg. 268). This in turn may result in the reduced levels of cognitive empathy (Perspective taking) and theory of mind observed in these patient populations.<sup>181</sup> Evidence of alterations in certain facets of empathic response and intact ability in other aspects is accordance with the idea that empathy is a multi-dimensional construct.<sup>18</sup> It is unclear if the empathy deficits observed in individuals with MDD and BD are state- or trait-based; however, it appears that elevated levels of depression may lead to greater impairment in this social cognitive domain. The impact of psychotropic medication on empathic responding remains to be

clarified. One of the major limitations of the above studies is that the measures of empathic responding used are self-rated questionnaires, which have been shown to be susceptible to inherent biases.<sup>209</sup> Again, small sample sizes found in these studies limit the interpretability of these results. Future work may benefit from the use of on-line measures of empathy or caregiver ratings.

Interestingly, in a pattern similar to recent findings in the ToM literature,<sup>161, 185</sup> early evidence from our laboratory suggests that impaired empathic capacity may be associated with poor psychosocial functioning in mood disorders. Altered empathic responding, as assessed by the IRI correlated significantly with decreased family, social and occupational functioning in patients with BD.<sup>201</sup>

### **Neuroimaging Studies of Social Cognition in Patients with Mood Disorders**

#### ***Neural Correlates of Facial Emotion Processing***

Lesion and neuroimaging studies have revealed a complex neural network involved in the processing of emotional faces. For example, whereas the fusiform gyrus and superior temporal sulcus have been implicated in the perception of facial expressions, the amygdala, anterior insula, orbitofrontal cortex, and ventral striatum have been shown to be involved in recognizing emotion and generating emotional reactions in response to provocation stimuli (see<sup>210</sup> for a review). Anterior cingulate cortex and prefrontal cortical regions have also been shown to play a prominent role in the regulation of emotion (see<sup>211, 212</sup> for a review). Specifically, recent theoretical models of emotion regulation implicate both top-down and emotion regulation processes in prefrontal cortical regions and the anterior cingulate cortex and bottom-up subcortical and limbic regions involved in

emotion appraisal and generation.<sup>213-215</sup> The dorsolateral prefrontal cortex, implicated in working memory and cognitive control, may be involved in the generation and maintenance of emotional reappraisal strategies, or ways of transforming/reframing the meaning of an emotional event or stimuli.<sup>216-218</sup> The medial prefrontal cortex is thought to be involved in self-monitoring processes,<sup>218, 219</sup> including evaluating internal states relative to external stimuli.<sup>220</sup> The dorsal anterior cingulate cortex has been implicated in conflict error and monitoring,<sup>221</sup> including the interference between top-down and bottom-up processes involved in emotion reappraisals and generation.<sup>220</sup> These models posit that prefrontal regions such as the lateral prefrontal cortex, medial prefrontal cortex, orbitofrontal cortex, lateral prefrontal cortex, and dorsal anterior cingulate modulate activity in subcortical (e.g., amygdala) and limbic regions.<sup>215, 218</sup> The amygdala has been implicated in the unconscious and rapid detection of emotionally salient stimuli, including faces,<sup>222-224</sup> and a more detailed evaluation of the significance of the emotional stimulus takes place in paralimbic (e.g., thalamus, hippocampus) and cortical regions.<sup>225, 226</sup>

## **MDD Neuroimaging Findings: Facial Emotion Processing**

### Mood State

Evidence from studies involving functional magnetic resonance imaging (fMRI) suggests that patients with acute MDD differ from healthy controls in the pattern of neural responding arising from exposure to a variety of emotional facial expressions (see<sup>227</sup>). Specifically, increased activation in the amygdala, ventral striatum, and orbitofrontal cortices, regions key to the representation of emotion and to the processing of reward, has been reported in response to masked<sup>74, 100, 228, 229</sup>; and unmasked<sup>104, 230-234</sup> displays of

negatively-valenced faces (e.g., expressions of fear, sadness, disgust) in these patients (see <sup>105, 106, 235, 236</sup> for conflicting findings). As is the case for the behavioural literature reviewed above, conflicting findings in the neuroimaging literature concerning facial emotion may stem from different emotional processing paradigms as well as differences in the clinical status of patients in terms of medication use, illness burden, comorbidity, and depression severity. For example, Scheuerecker et al.<sup>235</sup> recruited a heterogeneous sample of patients experiencing first-episode and recurrent depression and failed to find differences from controls in patterns of neural activation in response to emotional faces.

Actively depressed patients also show increased neural responses to positive and negative facial expressions in the subgenual portion of the anterior cingulate cortex, a region involved in the physiological response of emotional processing.<sup>237-240</sup> Increased activity in the subgenual cingulate cortex suggests that individuals with MDD show stronger autonomic emotional responses compared to controls.<sup>237</sup> By contrast, reduced amygdala activation in response to positive stimuli has been demonstrated across a small number of studies.<sup>229, 241</sup> Suslow and colleagues<sup>229</sup> suggest that amygdala hyperactivity to negative stimuli in MDD is associated with negative biases during automatic stages of affective processing,<sup>100</sup> including facial affect recognition. Hyporesponsivity of the amygdala to positive stimuli on an automatic processing level is conversely thought to stem from a reduced allocation of cognitive resources for positive stimuli.<sup>229, 242</sup> A recent report by Lee et al.<sup>243</sup> also demonstrated reduced activation in the dorsolateral prefrontal cortex in response to the passive presentation of negative facial stimuli among patients with MDD. Similarly, Fales et al.<sup>239</sup> found that during an emotional distractor task,

patients with MDD showed increased amygdala activity and a failure to recruit the dorsolateral prefrontal cortex in response to unattended fearful faces. By contrast, controls demonstrated increased activity in the dorsolateral prefrontal cortex and no activation differences in the amygdala when ignoring fearful faces. These findings are in line with theories of emotion regulation that posit that prefrontal regions such as the dorsolateral prefrontal cortex inhibit activity in subcortical (e.g., amygdala) and cortical regions involved in emotional appraisal and emotion generation systems (e.g.,<sup>213, 214</sup>).

Recent research has also begun to examine the interactions between prefrontal and subcortical regions in MDD patients. Specifically, during negative facial processing tests (implicit and explicit) consisting of angry and sad facial expressions, the dorsal anterior cingulate, and the precuneus, a region implicated in self-related mental representations, show reduced connectivity with the orbitofrontal cortex in unmedicated patients with depression.<sup>244</sup> Decreased connectivity between the dorsal anterior cingulate and orbitofrontal cortex may contribute to dysfunction in the cognitive control of emotional processing (e.g., rewarding value of stimuli) mediated by orbitofrontal regions. The precuneus has been strongly implicated in the mental representation of self and related processes such as autobiographical recollection and first-person perspective taking; decreased connectivity with the orbitofrontal cortex may contribute to the disturbances in self-related processes in patients with mood disorders. Finally, functional connectivity between the orbitofrontal cortex and dorsolateral prefrontal cortex was increased in patients relative to controls during negative facial processing; enhanced connectivity between the orbitofrontal region and this key cognitive region, respectively, may give rise

to the negative processing bias inherent in the disorder.<sup>244</sup> Similarly, another study found that a chronic and recurrent course of illness was significantly associated with reduced functional connectivity between the amygdala and dorsolateral prefrontal cortex while passively viewing angry and sad faces.<sup>245</sup> Finally, disruptions in functional coupling between the amygdala and subgenual cingulate, a region also implicated in assessing the salience of emotion and regulating of emotions, have been reported during facial processing tasks.<sup>231, 246</sup>

By contrast, few studies have examined the neural correlates of facial affective processing in euthymic patients with MDD. Preliminary findings demonstrate elevated dorsolateral prefrontal cortex activation to fearful faces in euthymic patients relative to controls.<sup>247</sup> In this study, levels of amygdala activation did not differ between patients and matched controls during the presentation of fearful faces. These authors interpreted the increased level of dorsolateral prefrontal activation as a compensatory cortical control mechanism that acts to limit emotional dysregulation in limbic regions, including the amygdala, in patients with remitted illness. A recent study by Victor et al.<sup>74</sup>, however, found that remitted patients with MDD showed exaggerated responses in the amygdala to masked sad faces and a lack of amygdala response to masked happy faces relative to controls. A possible reason for the discrepant findings in amygdala activation in euthymic MDD patients may stem from differences in method variance, specifically, Victor et al.<sup>74</sup> used an implicit or masked emotional face paradigm, whereas Norbury et al.<sup>247</sup> used an explicit facial emotion task which likely engaged the dorsolateral prefrontal cortex to

regulate amygdala activity.<sup>214, 218</sup> The dorsolateral prefrontal cortex has been shown to be activated by explicit emotional tasks relative to tasks that are more implicit in nature.<sup>248</sup>

Preliminary work has also examined the relation between patterns of neural activation in response to emotional facial expressions and mood state. For example, level of depression severity has been shown to correlate negatively with the extent of activation in the fusiform gyrus<sup>233, 249</sup>, anterior cingulate cortex<sup>250</sup>, and amygdala<sup>229, 251</sup> in response to happy and negative faces<sup>232</sup>. It should be noted, however, that an equal number of studies failed to find a significant association between level of depression and neural activity to facial emotions.<sup>100, 105, 106, 235, 252, 253</sup> These studies were likely not able to detect a relation between this illness variable and neuronal response because of their limited sample sizes and the inclusion of patients with varying levels of depression.

### Illness Burden

Few studies have examined the relation between burden of illness variables and neural activity during a facial emotion task. Suslow et al.<sup>229</sup> reported that amygdala responsiveness to masked sad and happy faces was independent of illness burden variables such as number of episodes or duration of illness. Similarly, Dannlowski et al.<sup>100</sup> were unable to detect an association between course of illness variables (duration of illness, number of episodes, total hospitalization time, time since first inpatient treatment and time since first outpatient treatment) and amygdala activity in response to masked displays of angry, sad and happy facial expressions. However, the same study group found that amygdala–dorsolateral prefrontal cortex connectivity was significantly

associated with illness severity, indicating that MDD patients with reduced connectivity between these regions had a more pervasive and severe course of illness.<sup>254</sup>

Taken together, these findings provide evidence for down-regulation in prefrontal regions involved in top-down emotional processes up-regulation in limbic and paralimbic systems implicated in bottom-up emotional processes.<sup>213, 215</sup> It remains unclear if clinical variables such as mood state and illness burden interact to influence the pattern of neural response during facial emotion processing.

### Medication Status

Antidepressant therapy may normalize patterns of neuronal responding to affective facial stimuli. For example, a recent study by Fu et al.<sup>249</sup> examined responding to positive stimuli in patients with MDD relative to matched controls, and found reduced activation in subcortical (basal ganglia), limbic (hippocampus), and extrastriate regions among acutely ill patients with MDD; this pattern was attenuated following treatment with fluoxetine. Similarly, Keedwell and colleagues<sup>255</sup> found that severely depressed patients showed increased visual cortex responses to sad faces and reduced neural response in these same regions to happy faces in the early stages of antidepressant treatment. Following continued antidepressant therapy and clinical improvement, these patterns were reversed. Moreover, consistent with prior findings demonstrating subgenual cingulate activity as a marker of treatment response (e.g.,<sup>256, 257</sup>), reductions in subgenual cingulate activity was associated with reductions in depression scores.<sup>255</sup> Further analysis of data arising from Keedwell et al.'s study<sup>255</sup> showed that increased activity in the right visual cortex and subgenual cingulate to sad but not happy facial

expressions in the first few weeks of treatment were predictive of a greater clinical recovery.<sup>258</sup> By contrast, enhanced responses to happy and sad stimuli in the ventrolateral prefrontal cortex were associated with a poor clinical outcome. Similarly, Victor et al.<sup>74</sup> found that an exaggerated response in the amygdala to masked sad faces and reduced amygdala activity to masked happy faces were reversed following administration of a four-week treatment regimen of sertraline. These findings indicate that the negative bias towards sad faces improves, and a positive bias towards happy faces emerges, with antidepressant treatment.

Similar to the effects of antidepressant treatment on neural response to emotional facial expressions, administration of erythropoietin, a novel treatment of psychiatric disorders (e.g.,<sup>259</sup>) that exerts neurotrophic and neurorestorative effects, reduced neural responses in the amygdala and hippocampus to fearful relative to happy faces.<sup>260</sup>

A recent study has also examined the connectivity of the orbitofrontal cortex, a key region in the emotion regulation circuit, to other brain areas in patients with MDD. Lisieka et al.<sup>115</sup> found that during a facial emotion identification task, at baseline, an increase in functional coupling between the orbitofrontal cortex (OFC) and motor areas and internally within the right middle OFC was associated with positive response to treatment with antidepressants (mirtazapine and venlafaxine). By contrast, increased connectivity between the OFC and cerebellum was associated with lack of response to antidepressant treatment. The magnitude of response to antidepressant treatment was also positively correlated with functional coupling between left OFC and the caudate nuclei

and thalamus. This study highlights the utility of using functional connectivity patterns of regions implicated in the affect regulation circuit as a marker of treatment response.

Overall, these results suggest that conventional antidepressants and novel treatments may dampen hyperactive responses to negative stimuli and enhance the salience of positive stimuli. These findings are also in accordance with the notion that antidepressants may work by remediating the negative bias in information processing found in depression.<sup>261</sup>

#### Psychological Treatment Status

Psychological interventions have also been found to alter patterns of neuronal response to affective stimuli among patients with MDD. Specifically, Fu et al.<sup>262</sup> found that hyperactivation in the amygdala and hippocampus in response to sad faces appeared to normalize following sixteen weeks of cognitive behavioral therapy (CBT). Moreover, consistent with prior work showing a significant relation between anterior cingulate activity and clinical response to antidepressant medication (e.g.,<sup>230</sup>), elevated dorsal anterior cingulate activity associated with cognitive control has been shown to be associated with treatment response to CBT.<sup>262, 263</sup>

#### Age

Finally, neuroimaging studies conducted in children and adolescents with major depressive disorder also show greater activation in the amygdala<sup>251, 264, 265</sup> and orbitofrontal cortex<sup>251</sup> in response to emotional facial expressions (see<sup>266</sup> for conflicting findings).

#### Section Summary

Taken together, these suggest that individuals with MDD demonstrate altered neural responsiveness to both positively and negatively valenced facial stimuli, whether they are presented inside or outside of conscious awareness. These results may provide a neural mechanism for the negative bias in facial emotion processing in MDD described in a previous section of this review. Specifically, this negative bias in emotion processing may reflect top-down dysfunction in brain areas implicated in the cognitive control of attention such as the dorsolateral prefrontal cortex and dorsal anterior cingulate cortex.<sup>220,</sup>

<sup>221</sup> The above studies demonstrate hypoactivity and reduced levels of connectivity in these regions in MDD. These findings may be interpreted as deficits in the cognitive control of emotion, during the processing of emotionally salient stimuli (faces).<sup>100, 220, 221,</sup>

<sup>239</sup> This negative bias may also stem from deficits in brain areas implicated in bottom-up emotion processes such as the amygdala and ventromedial prefrontal cortex function (including the subgenual cingulate).<sup>215, 218</sup> Hyperactivity in the amygdala in response to negative facial stimuli has been demonstrated across numerous studies in MDD and a small number of studies indicate hypoactivity in this region in response to positive facial stimuli. Increased activity in the subgenual cingulate during baseline rest conditions (e.g.,<sup>267, 268</sup>) has been consistently reported and emerging body of research suggests that this region is hyperactive during the processing of emotional faces. Elevated activity and altered connectivity of the amygdala and ventromedial regions such as the subgenual cingulate may result in the negative processing bias inherent in the disorder.<sup>239</sup>

Preliminary evidence suggests that dysfunction in these key emotion processing areas is reversed in the remitted or euthymic state in MDD. These suggest that after mood

symptoms remit, MDD patients are able to recruit the dorsolateral prefrontal cortex and dorsal anterior cingulate to suppress activity in the amygdala and related regions and the impact of emotional stimuli, especially negative stimuli. Moreover, preliminary evidence suggests that dysfunction in these key emotion processing regions appears to resolve with antidepressant treatment<sup>74, 269</sup> and cognitive behavioural therapy.<sup>263</sup> Similar to the behavioural literature, the influence of depressive symptom severity and burden of illness variables on neuronal activity during facial emotion processing in MDD remains to be determined.

### **BD Neuroimaging Findings: Facial Emotion Processing**

#### Mood State

Functional neuroimaging studies of facial affect processing in BD have revealed mixed findings regarding neural activity in brain regions associated with cognitive and affective processing during facial emotion tasks. In a sample of BD patients with mixed illness states, amygdala activity was greater in unmedicated patients, but lower in medicated patients compared to controls in response to happy faces.<sup>270</sup> Moreover, relative to controls, rostral anterior cingulate activation was reduced in unmedicated BD whereas, medicated BD patients demonstrated similar levels of rostral anterior cingulate activation.<sup>270</sup> Killgore et al.<sup>271</sup>, however, found that a sample of bipolar patients in varying mood states, demonstrated less activation than controls within the putamen, caudate, anterior cingulate gyrus, orbitofrontal cortex, and superior temporal pole. In addition to the small sample sizes of these studies, heterogeneity within the participant

sample in terms of mood state and symptom severity may partially account for these discrepant findings.

In depressed bipolar patients, relative to healthy controls, heightened activation in fronto-striato-thalamic regions, including the superior frontal gyrus, ventral frontal gyrus, precentral gyrus, cingulate, putamen, and thalamus in response to happy faces has been demonstrated.<sup>272</sup> Depressed bipolar patients have also shown elevated activity in the amygdala<sup>127</sup> and attenuated responses in the orbitofrontal cortex and dorsolateral prefrontal cortex to neutral and negative faces (angry, afraid, sad).<sup>41</sup> Evidence of greater left amygdala-orbitofrontal cortex connectivity in response to sad faces and reduced bilateral connectivity between these same regions to happy faces has also been reported in depressed but not euthymic BD patients.<sup>128</sup>

These overall findings of elevated levels of neuronal activation in limbic and emotion-related structures and attenuation of activity in areas subserving primarily executive and cognitive processes are similar to those observed in patients with MDD during the performance of similar tasks (see above). Unlike MDD, however, there is little evidence that this pattern remits with the offset of depressive symptoms. In euthymic BD patients, compared with healthy controls, studies have demonstrated increased hippocampal activity<sup>273</sup> along with enhanced amygdala activity,<sup>274</sup> and diminished dorsolateral prefrontal cortex activation, when viewing fearful faces.<sup>137, 273, 274</sup> (see<sup>137, 275</sup> for conflicting findings). A preliminary study by Surguladze et al.<sup>276</sup> reported that euthymic BD patients also show enhanced activity in the medial prefrontal cortex and amygdala in response to happy facial expressions. It is plausible that the discrepant

findings in subcortical activations in both actively ill and euthymic patients may stem from failure to account for co-morbid disorders. For example, Hassel et al.<sup>140</sup> reported significant associations between co-morbid symptoms of substance abuse and eating disorder and neural activity in the prefrontal cortex and subcortical striatal (caudate nucleus, putamen) regions in response to happy and neutral faces.

A number of neuroimaging studies have examined facial affect processing in manic patients. Here, a contrasting pattern of reduced amygdala and subgenual cingulate activation in response to sad but not happy facial expressions has been reported, in conjunction with a mood-congruent deficit in recognizing sad facial affect.<sup>126</sup> Chen et al.<sup>272</sup> also found that manic patients showed increased activity in the fusiform gyrus in response to sad faces perhaps leading to enhanced perceptual processing of these stimuli. In this study, a neural response to sad faces was modulated by level of attentional processing. That is, whereas implicit processing of sad faces was associated with enhanced activation in the amygdala, anterior cingulate cortex, lateral temporal cortex and medial prefrontal cortex, explicit processing of sad faces was associated with attenuation of these same regions. Altshuler et al.<sup>277</sup> reported increased neural response in the amygdala and reduced orbitofrontal cortex response during an emotion discrimination task. Similar to findings in MDD, Foland and colleagues<sup>278</sup> also found reduced functional connectivity between the ventrolateral prefrontal cortex and the amygdala during a facial emotional labeling task in line with reduced inhibitory frontal control over amygdala reactivity. Interestingly, reduced connectivity between the ventrolateral prefrontal cortex and amygdala was associated with increased manic

symptoms. Moreover, consistent with findings in MDD, BD patients in a variety of mood states, showed reduced connectivity between the amygdala and anterior cingulate cortex in response to negatively-valenced faces.<sup>279</sup>

Severity of depressive or manic symptoms may influence neural response to affective facial stimuli in BD, although the evidence is again inconsistent. For example, patients with more severe depressive illness show significantly enhanced hippocampal activation while viewing sad faces compared to those with lesser symptoms of illness.<sup>241</sup> Moreover, increased depressive symptom severity was associated with lower activation in the medial frontal gyrus in response to angry faces.<sup>280</sup> However, other studies have failed to find significant associations between levels of brain activation and mood state<sup>279, 281</sup> or symptom severity in BD patients.<sup>137, 144, 270, 282</sup>

#### Studies Comparing Patients with Unipolar and Bipolar Depression

A small number of neuroimaging studies comparing individuals with unipolar versus bipolar depression while performing facial affective processing tasks suggest that different pathophysiological mechanisms may distinguish these two types of depression. Almeida et al.<sup>283</sup> found that recurrent MDD was associated with a top-down negative connectivity between the orbitomedial prefrontal cortex and amygdala to positive (happy) faces suggesting a top-down prefrontal ‘inhibition’ of amygdala activity to positive facial expressions. Moreover, in MDD patients, the greater the medication load, the more positive (less abnormal) the effective connectivity between these two regions. By contrast, BD depression was associated with a bottom-up disconnectivity between the amygdala and orbitomedial prefrontal cortex, suggesting reduced inhibitory control over

amygdala reactivity in this disorder. Depressed bipolar patients have also shown enhanced activation in the amygdala to neutral and sad faces relative to controls, remitted BD patients, and depressed individuals with MDD.<sup>127</sup> Finally, Lawrence and colleagues<sup>241</sup> also found enhanced levels of activity in limbic and emotion-related structures in patients with BD relative to MDD. Specifically, these authors reported that a heterogeneous sample of euthymic and depressed bipolar patients showed greater activations in subcortical and ventral prefrontal regions to positive and negative facial expressions relative to patients with unipolar depression and controls. Overall, these data suggest that patients with bipolar depression may be biased towards negative mood congruent facial expressions, whereas unipolar depression is characterized by an attentional bias away from positive expressions.<sup>127</sup>

### Illness Burden

A limited number of studies have examined the relation between burden of illness variables and neural activity during affective facial processing in BD. Recent work has demonstrated significant associations between an earlier illness onset and both amygdala hyperactivity<sup>137</sup> and decreased activity within the dorsolateral prefrontal cortex.<sup>274</sup> A greater illness onset was associated with reduced functional connectivity between the amygdala and orbitofrontal cortex in response to sad faces in a mixed sample of patients in depressed and remitted mood states.<sup>128</sup> Foland et al.<sup>278</sup> also found that reduced connectivity between the ventrolateral prefrontal cortex and amygdala was associated with number of previous manic episodes and illness duration in manic patients. It should be noted, however, that Blumberg et al.<sup>270</sup> did not find any significant associations

between level of brain activation and variables such as illness duration, or age of onset illness. Critically, however, BD patients with a longer illness duration and earlier age of illness onset were found to have greater dorsal prefrontal cortex and reduced amygdala activity in response to negatively valenced faces, suggesting an ameliorating effect of a greater illness burden on neural response.<sup>127, 140</sup>

### Medication Status

As in MDD, administration of pharmacological agents may alter the neural circuits underlying the perception and recognition of facial emotion in BD. Specifically, two recent studies report that BD patients treated with 12 weeks of lamotrigine monotherapy demonstrated ‘normalized’ (increased) activations within the neural circuitry involved in facial affect processing (e.g., medial frontal cortex, precentral and anterior cingulate gyri, middle temporal gyrus) in response to angry<sup>284</sup> and sad faces.<sup>285</sup>

### Age

Finally, neuroimaging studies conducted in adolescents with bipolar disorder similarly show enhanced activations in subcortical limbic regions and hypoactivation in prefrontal regions in response to emotional faces.<sup>41, 146, 286</sup> These findings have been shown in euthymic youth with BD (e.g.,<sup>287-289</sup> and heterogeneous samples of patients in a variety of mood states.<sup>280-282, 290</sup> Finally, relative to controls, BD youth demonstrate reduced connectivity between the amygdala and neural regions thought to be involved in facial expression processing and emotional stimuli (posterior cingulate/precuneus and fusiform gyrus/parahippocampal gyrus).<sup>291</sup>

### Section Summary

Taken together, these neuroimaging findings support theories proposing abnormally increased activity in subcortical and limbic emotion-processing regions (e.g., amygdala) and reduced response in prefrontal cortical emotion-regulation regions in BD.<sup>206</sup> These dysfunctional patterns of neural activity and connectivity are observed in both manic and depressed bipolar patients (e.g.,<sup>278, 283</sup>). However, in contrast to patients with MDD, evidence suggests that in BD patients, alterations in regions implicated in emotion appraisal, generation, and regulation may not normalize with remission of mood symptoms.<sup>273, 274, 276</sup> These findings, however, were not consistently observed in euthymic BD patients.<sup>137, 275</sup> Preliminary research indicates that treatment with a mood stabilizer (lamotrigine) may ameliorate dysfunction in neuronal regions involved in the generation and regulation of emotion,<sup>284, 285</sup> a similar pattern observed after depressive symptoms remit.<sup>292</sup> Finally, early evidence of differences in connectivity patterns between the amygdala and orbitofrontal cortex in response to displays of facial emotion in bipolar depression may be a potential biomarkers of this illness that is not present in unipolar depression.<sup>127</sup> Preliminary evidence indicates that co-morbid symptoms, and in particular the presence of anxiety, eating disorder, and substance abuse symptoms may contribute to observed patterns of dysfunction in neural circuits involved in mood regulation in BD, highlighting the need for future studies to consider co-morbidities in their analyses.<sup>137, 140</sup> Relatively small sample sizes and variable emotion processing paradigms employed in these studies may also have contributed to discrepant findings observed in subcortical regions such as the amygdala across mood states.

#### Facial Emotion Processing Paradigms

It must be noted that studies investigating facial emotion comprehension in mood disorders employ diverse methods such as attention bias (non-fMRI:<sup>59, 63, 72, 81, 86, 87, 89, 130, 131</sup>; fMRI:<sup>74, 100, 149, 229, 239</sup>), emotion identification (non-fMRI:<sup>29, 48-53, 56, 57, 60-62, 64, 65, 67, 68, 70, 71, 73, 75, 80, 83-85, 93, 97, 101-103, 107, 112-114, 116-119, 123-125, 129-133, 135, 136, 142, 145, 293</sup>; fMRI:<sup>41, 58, 74, 90, 100, 105, 106, 115, 128, 134, 139-141, 143, 145, 229, 231, 232, 235, 239, 244, 247, 251, 252, 260, 275, 277, 278, 280, 284, 285, 289, 291</sup> 147, 283, 294), and spatial processing (non-fMRI:<sup>66, 81</sup>). This list expands to include gender identification<sup>104, 137, 140, 238, 244, 246, 263, 269, 276, 279, 281, 295, 296</sup> and passive viewing paradigms<sup>54, 237, 253-255, 260, 264-266, 270, 271, 282, 287, 291, 293, 297, 298</sup> when utilizing fMRI to uncover the neural mechanisms underlying emotion processing in mood disorders. Generally, all paradigms reveal deficits in behavioural measures of emotion processing (i.e., reaction time, accuracy, or attention bias). For instance, individuals with MDD and BD demonstrate generalized emotion recognition deficits.<sup>29, 48-58, 123</sup> Although the evidence is less consistent, both disorders appear to demonstrate deficits in recognizing happy<sup>51, 53, 61</sup> and neutral<sup>69, 83-85, 107</sup> expressions, as well as an enhanced ability to detect facial disgust.<sup>90, 142</sup> Both unipolar and bipolar depressed patients appear to show a negative response bias during facial processing tasks, including a reduction in sensitivity to positively valenced facial expressions and an increase in sensitivity to negatively valenced faces.<sup>63, 65, 75-82, 90, 130, 131</sup> Similarly, patients with MDD and BD demonstrate an attentional bias to negative facial expressions<sup>59, 72, 81, 86, 87, 149</sup>. Although spatial detection of positive facial emotion is impaired in MDD,<sup>62, 66</sup> no study has examined this emotion processing ability in BD. During passive viewing paradigms, patients with BD and MDD demonstrate hypoactivity in the dorsolateral prefrontal cortex and orbitofrontal cortex,

and hyperactivity in the amygdala, anterior cingulate (subgenual and pregenual anterior cingulate), although evidence is less consistent for subcortical regions such as the amygdala and paralimbic regions.<sup>145, 237, 253, 265, 270, 287, 293, 297</sup> During gender identification tasks, patients with MDD and BD demonstrate elevated amygdala responses,<sup>269, 276, 281, 295</sup> and reduced connectivity between the amygdala and anterior cingulate cortex.<sup>246, 279</sup> By contrast, preliminary evidence suggests that during gender identification paradigms, patients with MDD show increases in the subgenual anterior cingulate<sup>238</sup> and orbitofrontal cortex<sup>234</sup>; whereas patients with BD demonstrate lower activity in the dorsolateral prefrontal cortex<sup>140</sup> and higher activity in the medial prefrontal cortex<sup>276</sup>.

Some divergent patterns may emerge when these behavioural measures are compared to its counterparts within fMRI studies. For instance, when comparing accuracy and reaction time of facial emotion identification, most fMRI studies state no differences, whereas studies exploring only behavioural measures tend to report deficits in patient samples. This discrepancy could be due to several factors. Since neuroimaging studies are inherently placed under a temporal constraint, a decreased number of trials may be used in order to shorten the scan duration, consequently decreasing the statistical power during within-subject comparisons. Reduced statistical power for behavioural measures in fMRI is also seen due to smaller samples. Bourke et al.<sup>33</sup> previously noted relatively low sample sizes in facial emotion studies in MDD.

Task complexity is another issue that may contribute to the inconsistency seen during facial emotion recognition. Some fMRI studies<sup>235, 278</sup> appear to employ emotion recognition tasks that are not difficult or cognitively challenging (e.g.,<sup>235, 278</sup>). The goal of

these studies is generally to elicit activation from specific brain regions of interest and not necessarily to investigate performance differences emotion recognition and discrimination.<sup>278</sup> While it is beneficial to increase the number of emotions examined for identification in order to improve ecological validity, this type of complexity may engage supplementary neural regions (primarily related to ToM) that may be hard to disentangle from neural regions that are predominantly affected in the identification of basic emotions.<sup>299</sup> As is generally seen in the neuroimaging literature of emotion identification, while patients with mood disorders may perform comparably to healthy individuals on behavioural measures, the neural processing of that information is extensively altered (e.g.,<sup>139, 244</sup>). Another shortfall of the comparison of results within the emotion identification paradigm is the number and types of emotions presented. Although this point was highlighted when comparing fMRI and non-fMRI studies, this variation is seen within these groups as well. For instance, while some studies might only present angry and neutral faces, others only present angry and happy expressions, making it difficult to yield firm conclusions regarding the potential emotion-specific recognition deficits.

### ***Neural Correlates of Affective Prosody Recognition***

Recognition of emotional prosody is thought to draw upon multiple processing resources mediated by a complex neural network found primarily in the right superior temporal region.<sup>300, 301</sup> Wildgruber et al.<sup>301</sup> recently proposed a neuroanatomical model implicating right-sided primary and association audition areas in the temporal lobe in the perception and extraction of auditory information,<sup>302-304</sup> whereas posterior regions of the right superior temporal sulcus are thought to be involved in representing the meaning of

the acoustic sequences.<sup>298, 303</sup> By contrast, evaluative aspects of affective prosody identification are believed to be mediated by the bilateral inferior frontal cortex<sup>302, 304, 305</sup>, reviewed in<sup>306</sup> and<sup>301</sup>.

### **Neuroimaging Findings: Affective Prosody Recognition in Patients with Mood Disorders**

The neural correlates of altered affective prosody recognition in mood disorders remain relatively unexplored. One preliminary study by Mitchell et al.<sup>307</sup> compared the neural response of controls and patients with schizophrenia and bipolar disorder to recorded scenarios presented in happy, sad, and neutral intonations. Subjects were scanned while passively listening to affective prosody stimuli and while actively attending to the emotional intonation of each phrase. During the passive listening task, relative to healthy controls, the bipolar group demonstrated less activation in the amygdala, uncus, bilateral superior temporal gyrus and right inferior frontal gyrus in response to pure emotional prosody and greater activation of the left superior temporal gyrus in response to unfiltered emotional prosody. The lack of activation found in the right-sided prefrontal and temporal areas implicated in affective prosody recognition (see above), suggests a reduced neural capacity to process this type of emotional stimuli.<sup>307</sup>

#### Mood State, Illness Burden, Medication Status, Age

The influence of mood state, illness burden, medication status, and age on neural response during affective prosody processing remains to be investigated.

#### ***Neural Correlates of Theory of Mind Responding in Patients with Mood Disorders***

Neuroimaging and patient studies of ToM implicate a core network of neural regions that serve diverse functions, and include cognitive (e.g., dorsolateral prefrontal cortex;<sup>23, 308, 309</sup>, affective (e.g., medial prefrontal cortex;<sup>194, 310-313</sup>; anterior paracingulate cortex;<sup>314, 315</sup> and memory systems (e.g., posterior cingulate; temporal poles;<sup>314</sup>; see McKinnon et al.<sup>34</sup>, for a review). Moreover, neuroimaging evidence also implicates the posterior superior temporal sulcus, involved in biological motion perception<sup>316, 317</sup> including socially relevant directional cues such as the eye gaze of others,<sup>318, 319</sup> and the adjacent temporoparietal junction, involved in perspective-taking as critical for ToM ability.<sup>7, 321, 322</sup>

### **Neuroimaging Findings: Theory of Mind**

#### Mood State

To date, two preliminary investigations have examined the neural correlates of ToM in samples of euthymic patients with BD. Malhi et al.<sup>323</sup> instructed BD patients and matched controls to observe computer-animated ToM stimuli depicting complex mental states such as bluffing, persuading, surprising, and mocking. Patients performed more poorly than controls on this task. These authors also found that, relative to controls, BD patients demonstrated a diminished pattern of activation in the supramarginal, angular, and middle temporal gyri. These regions have been shown previously to have strong functional connectivity with the temporoparietal junction and superior temporal sulcus,<sup>324</sup> regions thought crucial to ToM. Moreover, the patient sample showed a reduced neural response in the insula and bilateral inferior frontal gyri during viewing of these stimuli. These regions are strongly implicated in the mirror neuron system involved in decoding

the actions and intentions of others (<sup>325</sup>; see Empathy section below for further description of the mirror neuron system).

In a separate study, Kim et al.<sup>326</sup> examined the performance of euthymic bipolar patients on a social cognitive task that involved inferring the reason for the expressed emotion of a virtual human (avatar) based on emotional cues (facial expression of avatar and verbal description of experience). Similar to Malhi et al.<sup>323</sup>, euthymic BD patients showed hypoactivation in mirror neuron system regions such as the right inferior frontal gyrus, right insula, as well as the right premotor cortex during happy and angry emotional conditions.<sup>326</sup> Moreover, although the BD group performed comparably to controls on the social cognitive task, they showed significantly delayed response times during the emotional conditions.

### Medication Status

Kim et al.<sup>326</sup> found that neither the number of medications nor medication dosage was found to influence performance or neuronal activation during ToM performance.

### Illness Burden, Age

The effect of illness burden and age on neuronal activation during ToM performance in mood disorders remains an underexplored area of research.

### *Neural Correlates of Empathic Responding*

Although few studies have examined the neural correlates of empathy, preliminary evidence suggests enhanced activations of regions involved in cognitive processing including the dorsolateral prefrontal regions,<sup>327</sup> as well as affective regions including the medial and orbitofrontal prefrontal cortex,<sup>327, 328</sup> paracingulate,<sup>328</sup> and the amygdala<sup>328</sup> during empathic responding. Furthermore, regions implicated in recollective memory function are also recruited during empathic responding including the anterior and posterior cingulate, and temporal poles.<sup>328</sup> Recent evidence also indicates that the mirror neuron system may play a role in social cognition, including emotion recognition,<sup>329</sup> ToM,<sup>330</sup> and the emotional aspects of empathy.<sup>331-333</sup> The mirror neuron system includes the inferior frontal gyrus, posterior parietal cortex, premotor cortex, and insula, and is thought to be active when an individual executes a movement and in response to the motor acts of others (see<sup>334</sup> for a review). Interestingly, whereas patients with damage to the dorsolateral prefrontal cortex show impaired performance on cognitive (e.g., perspective taking), but not emotional aspects of empathic responding, patients with orbitofrontal lesions show the opposite effect.<sup>195</sup> In line with these findings, Rankin et al.<sup>22</sup> found that damage to orbitofrontal, medial and dorsal prefrontal regions in patients with frontal variant frontotemporal dementia resulted in impairments to cognitive aspects of empathy (e.g., perspective taking). Damage restricted to the anterior temporal lobes, amygdala and ventromedial orbitofrontal regions in patients with temporal variant frontotemporal dementia, however, was associated with impairments in both cognitive and affective components (e.g., emotional contagion) of empathic responding in social situations. As noted above, many of these same regions show volume loss and/or

regional metabolic changes in patients with mood disorders, however, the neural correlates of empathic responding in patients with mood disorders have yet to be examined.

## **Conclusions**

Studies examining social cognition in patients with mood disorders reveal deficits on several overlapping social cognitive domains including the perception and recognition of affective facial expressions and prosody, ToM, and empathy. Specifically, the majority of studies reviewed indicated that patients with MDD are impaired in the recognition of affective facial expressions and prosodic stimuli and show a mood-congruent bias during emotion recognition tasks. By contrast, conflicting patterns of deficit and performance sparing emerge among studies investigating emotion recognition in affective facial and prosodic stimuli among patients with BD. Impairments in performance across a variety of ToM tasks are observed in both MDD and BD. Patients with BD report reduced levels of cognitive empathy and elevated levels of affective empathy. However, a variable pattern of empathic response emerges in MDD. Critically, a small number of studies indicated that these deficits in emotion comprehension, ToM, and empathy persist into the remitted state in MDD and BD. A small body of research indicates that deficits in social cognitive ability may worsen with elevated levels of mania and depression and over the course of illness in mood disorders; these results are not consistently reported. The effect of course of illness variables, such as duration of illness and number of previous mood episodes, remains an underexplored area of research. Discrepant findings in the emotion processing literature in mood disorders may result

from differences in these illness variables. Studies that systematically examine the moderating influence of these variables on social cognitive performance in patients with mood disorders are required. The mixed pattern of findings within each social cognitive domain may be also explained by the fact that the majority of these studies recruited relatively small samples. The discrepant findings may also stem from differences in mood state, symptom severity, course of illness variables, comorbidities, and differences in paradigms employed to examine social cognitive response.

The level of cognitive and affective processing resources required for task performance also appears to moderate social cognitive performance in mood disorders. Patients with MDD and BD show greater deficits on tests of emotion comprehension and ToM that involve high levels of cognitive and affective processing demands relative to social cognitive tests that are resource free. These deficits may be mediated by well-documented impairments in cognitive and affective domains found in these patient populations.<sup>30, 31, 33, 146</sup> Future studies are warranted to investigate the interaction of cognitive (e.g., executive functioning) and affective (e.g., emotion recognition) processing resources across social cognitive tasks in mood disorder populations.

Alterations in social cognitive functioning in patients with mood disorders are likely related to alterations in patterns of neuronal activation observed during performance of these tasks. Functional neuroimaging studies of facial emotion processing in MDD and BD implicate altered interactions between subcortical and ventral prefrontal regions associated with emotion identification and production, and dorsal anterior cingulate cortex and dorsolateral prefrontal regions associated with emotion

regulation and higher cognitive functions, that may vary with the emotional valence (i.e., positive, negative) of affective stimuli.

Preliminary evidence suggests this pattern is attenuated following treatment with psychotropic medication and with psychological interventions. Few studies have examined neural response to emotional prosody and ToM; however, no studies have examined the neural correlates of empathy in mood disorders.

There is very preliminary evidence that alterations in social cognitive functioning, specifically emotion recognition, appear to be reduced following administration of medication. Indeed, a recent review by Harmer et al.<sup>335</sup> suggests that antidepressants alter emotion processing abilities in healthy individuals and depressed patients early in the course of treatment and may contribute to later changes in mood and depressive symptoms. In line with this suggestion, very limited evidence suggests that facial emotion recognition may improve following administration of antidepressants such as citalopram and reboxetine in MDD. It will be critical for future studies to examine the effect of different medication classes and dosages on social cognitive function in patients with mood disorders.

Early evidence suggests that social cognitive dysfunction, specifically facial emotion and ToM deficits, may be associated with poor clinical outcome in major depressive disorder and bipolar disorder. The mood congruent bias in facial emotion processing observed in mood disorder patients may also be related to the persistence and maintenance of depressive symptoms.<sup>96-98</sup> It is possible that a heightened sensitivity to negative stimuli and situations (e.g.,<sup>336</sup>) may lead to a reduction in the number of social

interactions and may increase depression severity.<sup>59</sup> Alterations in ToM and empathic responding are associated with reduced functioning in multiple psychosocial domains in these patients. Conversely, it is possible that impaired social interactions may negatively influence social cognitive behavior. Further studies examining the relation between social cognitive and clinical outcome are required, particularly in light of evidence suggesting that deficits in cognitive functioning, which are thought to contribute social cognition ability, including ToM, are strong predictors of outcome in mood disorder patients (e.g.,<sup>337</sup>).

Substantial overlap exists in the pattern of social cognitive response observed in MDD and in BD, particularly on tests of affective processing. Nonetheless, preliminary findings point towards differences, for example, in the patterns of neural activation observed in response to affective stimuli in actively ill and remitted patients with unipolar and with bipolar depression. Dissociations have also been demonstrated in the domain of empathy, where different facets of empathic responding appear affected across patients with MDD and with BD when tested in the same self-report measures. Variables such as mood state at the time of testing (e.g., acute depression vs. euthymia) may contribute to preliminary differences observed across groups. Further behavioural and neuroimaging studies that compare directly the performance of patients with MDD and with BD on tests of affective processing, ToM and empathy will be required, as well as longitudinal investigations that examine how changes in social cognitive performance emerge across the two courses of illness.

A nascent literature suggests that youth with MDD and BD show impaired performance on tests of facial emotion processing. Social cognitive abilities such as emotion comprehension, ToM, and empathy undergo an extended development from early childhood to adolescence.<sup>338-340</sup> Adolescence, a period of time characterized by marked changes in social relationships with peers and family,<sup>341, 342</sup> is also associated with increased vulnerability to depression and bipolar disorder.<sup>343-345</sup> It is possible that any alterations in social cognitive processes during this period of development may contribute to the early onset of mood disorders. Alternatively, the development of psychiatric morbidity during adolescence could alter or delay the development of social cognitive abilities. A better understanding of social cognition in mood disorders as well as factors that may influence social cognitive functioning could improve early intervention efforts aimed at reducing the peak morbidity and mortality observed in youth.

The study of social cognitive processing in patients with mood disorders remains in an early stage of discovery, where many outstanding questions remain concerning, for example, the influence of medications, course of illness variables, and cognitive status on task performance and patterns of neuronal activation. Given the heterogeneous profile of these disorders, in terms of symptom severity, chronicity, recurrence, co-morbidities, and treatment status, it will be important for future studies to incorporate larger sample sizes to take into account the influence of these variables on social cognitive processing. In particular, small sample size in a number of studies, particularly those involving fMRI paradigms may have constrained the ability to detect performance differences among

groups (e.g.,<sup>59, 82, 92, 104, 236, 250</sup>). Longitudinal studies, for example, will be necessary to determine whether social cognitive deficits are trait markers of vulnerability for mood disorder patients. Investigations recruiting individuals who are at risk for developing mood disorders will also address this issue. Future studies may also determine further whether known alterations in neuronal structure (e.g., reduced hippocampal volume) in MDD and BD are associated with altered patterns of social cognitive performance in these disorders. An enhanced understanding of social cognition in patients with mood disorders may contribute to new advances in the treatment of these illnesses.

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**CHAPTER 3: PERSPECTIVE TAKING IN PATIENTS WITH BD AND MDD**

*Foreword to Chapter 3, Study 1*

Those studies of ToM taken to date in patients with BD reveal a pattern of mixed findings which may be moderated by mood state and level of cognitive and affective demands of task performance (Shamay-Tsoory et al., 2005). Although a significant number of patients with BD exhibit subsyndromal depressive symptoms that do not meet criteria for a full affective episode (Judd et al., 2003), no studies have investigated ToM performance in this patient population. The objective of this study was to examine the performance of subsyndromal patients with BD on a task that varied in the demands it placed on cognitive processing resources. Specifically, we administered a ToM test consisting of a series of first- ('A thinks X') and second-order ('A thinks B thinks or feels X') questions (McKinnon and Moscovitch, 2007). In view of BD patients' well-documented deficits in cognitive (e.g., executive functioning) and affective (e.g., emotion recognition) processing resources (Summers et al., 2006) and consistent with preliminary evidence demonstrating that patients with BD show impairments on tests of ToM ability (Kerr et al., 2003), we hypothesized that subsyndromal patients with BD would be impaired relative to controls on both first- and second-order ToM tasks. We also predicted that the increased cognitive load of the second-order questions would result in a greater level of impairment among BD patients.

We also examined the relation between symptom severity, illness burden (i.e., duration of illness, age at illness onset, and number of depressive episodes), and ToM ability. Consistent with prior evidence documenting relations between cognitive impairment, brain tissue volume loss, and illness variables, it was hypothesized that

deficits in ToM performance would be associated with increased levels of symptom severity and an increased burden of illness in our BD sample.

The full author list and citation information for this article are provided below:

McKinnon, M.C., Cusi, A.M., & MacQueen, G.M. (2010). Impaired theory of mind performance in patients with recurrent bipolar disorder: Moderating effect of cognitive load. *Psychiatry Research*, 177(1-2): 261-2.

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**Impaired theory of mind performance in patients with recurrent bipolar disorder:  
moderating effect of cognitive load**

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**ABSTRACT**

The aim of this study was to investigate theory of mind (ToM) performance on tasks that varied in the demands they placed on cognitive processing resources in a sample of 14 bipolar patients with subsyndromal illness and 14 controls. Patients showed impaired performance on cognitively demanding second-order ToM tasks. Reduced ToM performance was associated with longer illness duration, and with increased symptom severity.

**Keywords:** Bipolar disorder; subsyndromal; Theory of mind

## 1. Introduction

Theory of mind (ToM) refers to the ability to infer the mental states of other individuals and to distinguish these mental states from our own. Studies examining the performance of patients with bipolar disorder (BD) on ToM tasks reveal a conflicting pattern of performance sparing and impairment (Kerr et al., 2003; Inoue et al., 2004; Bora et al., 2005; Olley et al., 2005) that may vary with mood state and the extent of cognitive resources required for task performance (Shamay-Tsoory et al., 2005). Although many patients with BD exhibit subsyndromal depressive symptoms that do not meet criteria for a full affective episode (Judd et al., 2003), no studies have investigated ToM performance in subsyndromal patients.

Here, we administered a complex ToM test consisting of a series of first- and second-order false-belief questions (McKinnon and Moscovitch, 2007) to BD patients with subsyndromal illness. Given that ToM ability depends on a wide range of cognitive (e.g., executive functioning) and affective (e.g., emotion recognition) processing resources that are affected in BD (Summers et al., 2006), we predicted that patients would show deficits on both the first- and second-order ToM tasks. We expected, however, that the extent of this deficit would be greatest for second-order ToM tasks drawing most heavily on cognitive processing resources thought impacted in this population. Finally, in light of recent findings suggesting a relation between cognitive impairment, structural brain changes, and clinical variables such as past course of illness (MacQueen et al., 2002), we examined the association between illness burden, symptom severity and ToM performance.

## 2. Methods

### 2.1. Participants

Fourteen subsyndromal patients who met DSM-IV criteria for bipolar disorder (mean age = 47.5, S.D. = 10.4; mean years of education=16.2, S.D. = 3.8; 10 women; 8 Bipolar I; 5 Bipolar II; 1 Bipolar NOS patients) were recruited from the Mood Disorders Program at St. Joseph's Healthcare Hamilton. On average, patients had experienced 52.3(S.D. = 67.6) episodes of past illness, with an overall illness duration of 27.2 (S.D. = 13.2) years (mean age of onset=20.3, S.D. = 10.7). Subsyndromal status was defined as a 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) score between 7 and 15 (mean of sample = 10.8, S.D. = 2.4 ) and a Young Mania Rating Scale (YMRS; Young et al., 1978) score (mean = 3.2, S.D. = 2.0) less than 10 at testing. All were on medication at testing: lithium ( $N = 7$ ), anticonvulsants ( $N = 16$ ), antipsychotic drugs ( $N = 8$ ), SSRIs ( $N = 3$ ), tricyclic antidepressants ( $N = 1$ ), monoamine oxidase inhibitors ( $N = 1$ ), trazadone ( $N = 1$ ), bupropion ( $N = 1$ ), stimulants ( $N = 1$ ), benzodiazepines ( $N = 9$ ), and sedative/hypnotics ( $N = 1$ ). Fourteen matched healthy comparison (HC) subjects (mean age = 43.1, S.D. = 13.4; mean years of education = 16.4, S.D. = 2.9; 9 women) with no history of psychiatric illness and no known family member with BD or schizophrenia were included.

Exclusion criteria were: inability to provide informed consent; history of electroconvulsive therapy or transcranial magnetic stimulation within one year; substance abuse in the last six months; current or lifetime history of substance dependence; current or prior history of untreated significant medical illness or of neurological illness; history

of traumatic brain injury and/or loss of consciousness (lasting more than 60 seconds); use of benzodiazepines within 12 h prior to testing.

The study was approved by the local ethics board and written informed consent was obtained from all participants.

## *2.2. Theory of Mind Task*

The theory of mind test used includes eight scenarios that describe complex social situations, such as social faux pas, followed by four first-order and four second-order ToM questions (see McKinnon and Moscovitch, 2007 for details). Each answer is scored 0 (error) or 1 (correct) following scoring criteria for a maximum score of 32 on each question type. Responses were scored by one of the creators of the test (M.M.) blind to clinical diagnosis.

## *2.3. Statistical Analyses*

Mixed-design analyses of variance were used to examine differences in ToM response between the bipolar and HC groups. Post-hoc group differences were assessed using independent-sample *t* tests. Alpha was set at 0.05 for all analyses. The relation between ToM ability, illness burden, and symptom severity was explored with two-tailed Pearson's *r* correlation coefficients.

## **3. Results**

There was a main effect of stimulus type [ $F(1, 26) = 48.82, P < 0.001$ ], and group membership [ $F(1, 26) = 10.07, P = 0.004$ ], and a significant interaction between Stimulus Type and Group [ $F(1, 26) = 46.45, P = 0.04$ ]. Patients with BD performed poorly

compared to HCs for second-order questions [ $t(26) = -2.86, P = 0.008$ ] and tended to perform worse than controls on first-order questions [ $t(26) = -1.89, P = 0.07$ ] (see Figure 1).

There were significant negative relations between HAM-D scores and first- ( $r = -0.38, P = 0.04$ ) and second-order ( $r = -0.47, P = 0.01$ ) ToM scores. A significant negative relation was found between illness duration and second-order ToM performance ( $r = -0.65, P = 0.01$ ). The correlations between ToM performance and age of onset (first-order ToM:  $r = 0.25, P = 0.38$ ; second-order ToM:  $r = 0.26, P = 0.36$ ), number of illness episodes (first-order ToM:  $r = -0.22, P = 0.50$ ; second-order ToM:  $r = -0.10, P = 0.76$ ) or YMRS scores (first-order ToM:  $r = -0.25, P = 0.19$ ; second-order ToM:  $r = -0.10, P = 0.60$ ) were not statistically significant.

#### 4. Discussion

BD patients with subsyndromal depressive symptoms showed impaired performance relative to matched controls on a cognitively challenging task that required them to integrate two perspectives simultaneously (second-order ToM questions). There was also a trend toward poor performance on a less demanding first-order ToM task (McKinnon and Moscovitch, 2007). Our results suggest a gradient in ToM performance among BD patients in remitted, subsyndromal and active phases of illness. Specifically, prior research indicates that BD patients with active illness show impairment on both cognitively demanding and resource-free ToM tasks (Kerr et al., 2003). Here, subsyndromal patients were impaired on a cognitively demanding ToM task, and to a

lesser extent, showed poor performance on a version of the task with fewer cognitive demands. By contrast, euthymic patients are impaired only on those ToM tasks that rely heavily upon cognitive processing resources thought affected despite illness remission (Inoue et al., 2004, Bora et al., 2005; Olley et al., 2005).

Subsyndromal patients with a longer duration of illness were more likely to show poor performance on the second-order ToM task, suggesting that ability on complex tests of ToM is associated with a greater burden of illness and may worsen over time. This finding is consistent with prior studies in acutely ill patients with pediatric BD (Schenkel et al., 2008) and with schizophrenia (Montag et al., 2007), where an extended course of illness also predicted ToM impairment. The offset of ToM ability may also coincide with the increased cognitive impairment seen in patients with recurrent illness (MacQueen et al., 2002).

More severe depressive symptoms were associated with worse performance on the first- and second-order ToM tasks in our sample, providing preliminary evidence that alterations in ToM responding may be a state-dependent deficit in this illness. These results are in contrast with Bora et al. (2005) who found no relation between ToM performance and symptom severity in euthymic patients with BD. The restricted range of HAM-D and YMRS scores in the Bora et al. (2005) sample likely limited these authors' ability to detect this relation.

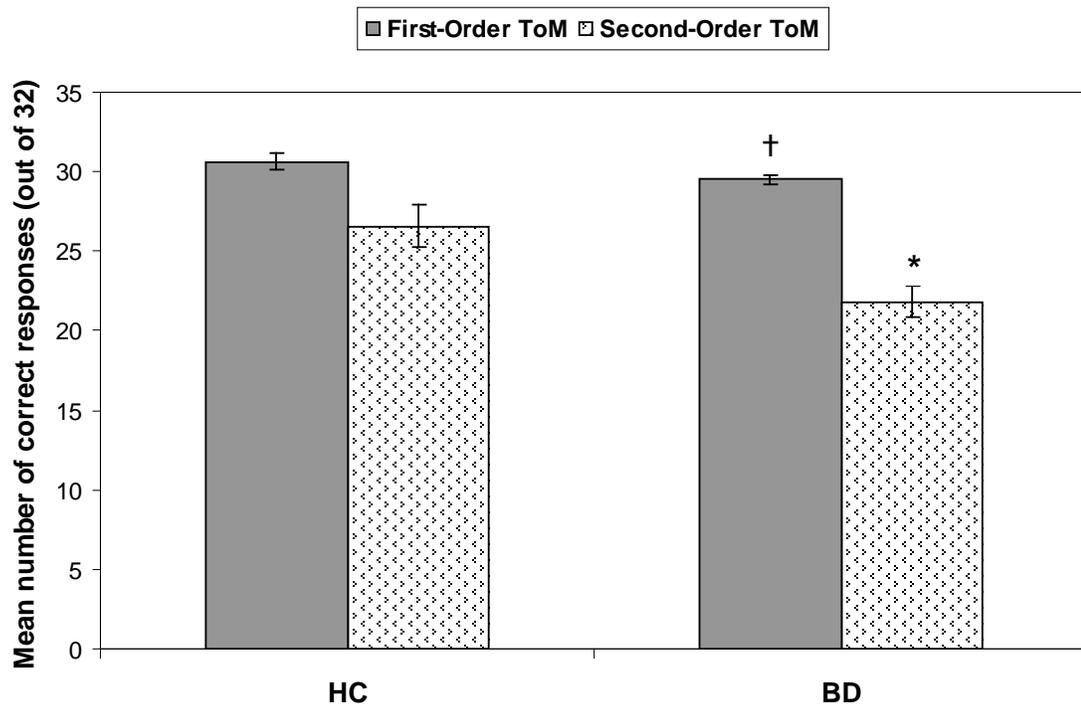
This preliminary study provides provocative evidence of impaired ToM ability in a sample of BD patients with subsyndromal depressive symptoms and indicates that cognitive processing demands may moderate this impairment. Caution is warranted in

the interpretation of these results, however given the low sample size that may have obscured group differences and the heterogeneous medication status of participants. Future longitudinal studies are awaited to confirm these findings.

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**Figure 1.** Mean number of correct responses by healthy controls and by patients with BD



**Abbreviations:** BD, bipolar disorder group; HC, healthy controls; ToM, theory of mind

\*  $P < 0.01$

†  $P = 0.07$

*Foreword to Chapter 3, Study 2*

Similar to the BD literature, those studies of ToM taken to date in patients with MDD reveal a pattern of mixed findings which may stem from differences in illness state and the amount of central processing resources required for task performance. Moreover, to date, no study has examined ToM ability in patients with subsyndromal MDD. This is surprising in light of evidence suggesting that patients with subsyndromal symptoms are vulnerable to increased rates of relapse (Judd et al., 1998a). The objective of this study was to examine the performance of subsyndromal patients with MDD on a task that varied in the demands it placed on cognitive processing resources. We hypothesized that our subsyndromal sample would be impaired relative to controls on both first- and second-order ToM tasks, consistent with well-documented deficits in cognitive and affective processing thought requisite for ToM response, and also found in MDD (e.g., Demenescu et al., 2010). We also predicted that the increased cognitive load of the second-order questions would result in a greater level of impairment among MDD patients.

We also examined the relation between symptom severity, illness burden, and ToM ability. Consistent with prior evidence documenting relations between cognitive impairment, brain tissue volume loss, and illness variables (e.g., MacQueen et al., 2002), it was hypothesized that deficits in ToM performance would be associated with increased levels of symptom severity and an increased burden of illness in our MDD sample.

This paper was submitted for review to the *Journal of Affective Disorders* on October 18, 2011.

**Theory of mind deficits in subsyndromal major depressive disorder**

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## ABSTRACT

**Background:** Findings regarding theory of mind (ToM) in patients with major depressive disorder (MDD) are conflicting suggesting that key variables, such as task complexity and symptom severity, may moderate performance on ToM tasks. The aim of this study was to investigate ToM ability in a sample of MDD patients with subsyndromal symptoms of illness using a measure that varied in the demands it placed on cognitive processing resources. The relation of ToM performance to symptom severity, past burden of illness, and psychosocial function was also examined.

**Methods:** Twenty MDD patients with subsyndromal symptoms and 20 control subjects completed a task consisting of first- and second-order ToM stimuli, and the Social Adjustment Scale Self-Report, a measure of psychosocial functioning.

**Results:** The MDD group demonstrated worse performance than control subjects on second-order ToM questions; no such deficit was observed for first-order ToM stimuli. Impaired ToM performance was related to symptom severity but was independent of burden of illness. Reduced ToM ability was also associated with poor psychosocial functioning.

**Limitations:** This study represents a preliminary investigation of ToM ability in patients with MDD. Additional studies, involving larger samples, are required to more adequately characterize the effects of current mood state and illness burden on social cognitive performance in this population.

**Conclusions:** This preliminary study provides the first evidence of altered ToM responding in MDD patients with subsyndromal symptoms. Difficulties inferring the mental states of others may result in compromised social interactions found in this population.

**Keywords:** Major depressive disorder; subsyndromal symptoms; Theory of mind; psychosocial function

## 1. Introduction

Theory of mind (ToM) has been described as the ability to infer the mental states of others in order to understand and predict their behaviour (Premack and Woodruff, 1978). Intact theory of mind ability is thought integral to navigating the social world (Mar, 2011; Watson et al., 1999) and to the maintenance of interpersonal relationships (Tomasello et al., 2005). Recent work has examined the performance of patients with major depressive disorder (MDD) on tests of social cognition, demonstrating deficits in the perception and recognition of affective stimuli, including faces, in this population (Asthana et al., 1998; Bouhuys et al., 2006; Csukly et al., 2009). Numerous studies have also demonstrated deficits across a broad range of cognitive (e.g., executive functioning) and affective (e.g., emotion comprehension) domains in MDD (see Demenescu et al., 2010; Hasselbalch et al., 2011 for recent reviews) that are required for performance on higher-order social cognition tasks, including ToM (e.g., Bailey and Henry, 2008; Bora et al., 2005). Accordingly, a small number of studies examining ToM performance in patients with MDD point towards deficits in this ability among this population (e.g., Lee et al., 2005; Wang et al., 2008), however, these results remain conflicting. It is probable that a number of key variables moderate ToM performance among this population, including task complexity, which has been identified as impacting performance across a host of cognitive tasks in patients with mood disorders (e.g., King et al., 2010; McKinnon et al., 2010). Here, we examined the performance of patients with subsyndromal MDD on a ToM task that varied in the cognitive demands placed upon participants. To date, no study has examined ToM performance in depressed patients experiencing subsyndromal

symptoms although research has shown that patients experiencing sub-clinical symptoms are at risk for a poor prognosis (Judd et al., 1998a) and cognitive impairment (Preiss et al., 2009). Although controversial, numerous studies have also pointed towards a cumulative burden of illness on tests of social (e.g., Uekermann et al., 2008) and cognitive (e.g., MacQueen et al., 2002) performance in patients with mood disorders; hence, we examined the relation of ToM performance to illness burden. The relation of ToM performance to an index of psychosocial functioning was also examined.

To date, a small number of studies have examined ToM performance in patients with MDD. Two studies reported ToM deficits on the Reading the Mind in the Eyes Test (RMET), a measure of mental state decoding, in severely depressed patients (Lee et al., 2005) and in actively depressed patients with psychotic and non-psychotic symptoms (Wang et al., 2008). Another study did not, however, find any evidence of RMET deficits in a mixed sample of patients with varying levels of depression, including milder forms such as dysthymia (Wolkenstein et al., 2011). The inclusion of patients experiencing milder symptoms may have contributed to the lack of ToM deficits in this study. Interestingly, this same sample did show performance deficits on a more complex ToM task, the ecologically-valid Movie for Assessment of Social Cognition, a standardized paradigm that assesses participants' ability to recognize the intentions, thoughts, and emotions of multiple movie characters (Wilbertz et al., 2010). ToM has also been examined in remitted patients with MDD. Inoue et al. (2004) reported ToM deficits in a combined sample of remitted patients with unipolar and bipolar depression on cognitively challenging second-order false-belief questions that involve considering the perspective

of two different characters simultaneously (i.e., “A thinks B believes X”); no such impairments were observed for first-order false belief stimuli that involve adopting the perspective of a single character (i.e., “A thinks X”) (Inoue et al., 2006) .

Critically, performance deficits have been shown to emerge on less cognitively challenging ToM tasks in studies involving actively ill patients with a chronic course of illness. Zobel et al. (2010) found one such sample of MDD patients performed below controls on both first-order false belief tasks involving lower-level ToM reasoning and second-order false-belief tasks placing high demands on cognitive processing resources including working memory and executive functioning.

Taken together, the results of these studies point towards a number of key variables that may moderate ToM performance in patients with MDD, providing a partial account for discrepancies observed across studies. Inconsistencies across studies may be, in part, attributable to differences in symptom severity among patient samples, as well as the inclusion of participants with differing subtypes of depression. For example, Wilbertz et al. (2010), who did not find any evidence of ToM impairment in their study of chronically depressed patients, included patients with varying levels of depressive symptom severity. Wolkenstein et al. (2011) recruited a heterogeneous sample consisting of patients experiencing an acute depressive episode as well as participants with milder forms of depression such as dysthymia. Noted discrepancies may also reflect differences in the level of cognitive and affective resources required for task performance. Specifically, patients with active illness may show impairment on ToM tasks with both low and high demands on cognitive and affective processing resources, remitted patients

are impaired only on those ToM tasks that tap cognitive processing resources that remain affected despite remission of illness states (Hasselbalch et al., 2011; Preiss et al., 2009).

We explored this possibility further in a sample of MDD patients with subsyndromal symptoms of depression. Crucially, approximately one third of patients with MDD experience subsyndromal symptoms (Judd et al., 1998b; Paykel et al., 1995; Romera et al., 2010) that may put them at greater risk for future major depressive episodes (Paykel et al., 1995) and rapid rates of relapse (Judd et al., 1998a). Notably, the presence of subsyndromal depressive symptoms is also associated with significant functional disability among this patient population (Johnson et al., 1992; Judd et al., 1997; Judd et al., 1996; Sherbourne et al., 1994; Wells et al., 1989) and with persistent cognitive deficits (Preiss et al., 2009; Weiland-Fiedler et al., 2004).

In the present study, we examined ToM performance in patients with subsyndromal illness, examining whether performance varied as a function of the cognitive load of the ToM tasks administered. We employed a theory of mind test consisting of a series of first- ('A thinks X') and second-order ('A thinks B thinks or feels X') belief questions (McKinnon et al., 2007; McKinnon and Moscovitch, 2007); the differing cognitive load of these conditions has been confirmed under dual-task conditions. First-order ToM tasks assess the ability to understand the perspective of a single character, whereas second-order belief questions examine the ability to compare and contrast two different character's perspectives. Given MDD patients' known deficits in cognitive (e.g., working memory, executive functioning) and affective (e.g., emotion recognition) processing resources and consistent with preliminary evidence demonstrating

that patients with MDD show impairments on tests of ToM ability, we predicted that subsyndromal patients with MDD would show deficits on both first- and second-order ToM tasks.

Although deficits in ToM ability has shown to be associated with poorer social functioning and outcome in neuropsychiatric populations such as autism (Peterson et al., 2007; Tager-Flushberg, 2003) and schizophrenia (Bora et al., 2006; Brüne et al., 2007; Romera et al., 2010), the relation between ToM impairment and social functioning has not been examined in major depressive disorder. This is relevant given that individuals with MDD experience reductions in multiple domains of social functioning (Broadhead et al., 1990; Hays et al., 1995; Wells et al., 1989). Preliminary evidence also suggests that poor performance on tests of ToM is associated with a worsening of functional outcome in patients with MDD (Inoue et al., 2006). Hence, we investigated the relation of ToM ability to psychosocial functioning in our patient sample using a well-validated measure of functional outcome, the Social Adjustment Scale Self-Report (SAS-SR; Weissman and Bothwell, 1976). We expected that reduced ToM performance would be significantly associated with poor social functioning. Finally, recent findings indicate a relation between cognitive impairment, social cognitive impairment, and illness factors such as past course of illness (e.g., Basso and Bornstein, 1999; MacQueen et al., 2002) and symptom severity (e.g., O'Connor et al., 2002; Uekermann et al., 2008) in patients with MDD. Thus, we examined the relation between symptom severity, illness burden (i.e., duration of illness, age at illness onset, and number of depressive episodes), and theory of

mind ability. We predicted that impaired ToM performance would be associated with increased levels of depression and an increased burden of illness in our sample.

## **2. Methods**

### *2.1. Participants*

Formal written informed consent was obtained from all participants. The study was approved by the Research Ethics Board of St. Joseph's Healthcare Hamilton/McMaster University. Twenty subsyndromal patients who met DSM-IV criteria for major depressive disorder (mean age = 46.95; S.D. = 9.38; mean years of education = 15.78, S.D. = 2.61; 14 women) were recruited from the outpatient Mood Disorders Program at St. Joseph's Healthcare in Hamilton. Symptom severity was assessed using the 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) and the Global Assessment of Functioning Scale (GAF; American Psychiatric Association, 1994). Subsyndromal status was defined as a 17-item HAM-D (Hamilton, 1960) score between 8 and 14. Twenty healthy comparison (HC) subjects matched for age (mean age = 47.60, S.D. = 10.75; mean years of education = 17.31, S.D. = 2.54) and gender (14 women) with no history of psychiatric illness and no known family member with BD or schizophrenia were also recruited. Patients and control subjects did not differ with respect to age, years of education, and gender distribution. Demographic and clinical characteristics of the study sample are presented in Table 1.

Exclusion criteria included: i) inability to provide informed consent, ii) history of electroconvulsive therapy or transcranial magnetic stimulation therapy, within one year, iii) substance abuse based on DSM-IV criteria in the last six months, iv) current or

lifetime history of substance dependence based on DSM-IV criteria, v) current or prior history of untreated significant medical illness (e.g., cancer) or of neurological illness (e.g., Parkinson's disease, epilepsy), vi) history of traumatic brain injury and/or loss of consciousness (lasting more than 60 seconds), vii) use of benzodiazepines within 12 hours prior to testing.

## *2.2. Materials*

### **2.2.1. Theory of Mind Task**

#### *Complex Social Scenarios Task*

The theory of mind test used was administered previously in neurologically intact adult participants (McKinnon and Moscovitch, 2007) and patients with bipolar disorder (McKinnon et al., 2010). The test includes eight scenarios that describe complex social situations, such as social faux pas. For example, one scenario describes a case of mistaken identity; a female is carelessly identified as a male. Each of the stories was followed by four first-order ToM questions and four second-order ToM questions (see Appendix 1 for an example). Prior to the test session, participants completed a practice story and answered practice questions. Each answer is scored 0 (error) or 1 (correct), yielding a total score of 32 for each ToM question type (first- and second-order). All the scenarios and ToM questions were available to inspection until a response was made. The data was scored by one of the creators of the ToM test (M.C.M.) who was blind to the clinical diagnosis (MDD or HC) of each participant.

### 2.2.2. Psychosocial Measure

The *Social Adjustment Scale Self-Report (SAS-SR)* assesses a broad range of social domains including work/school role, social/leisure activities, relationship with extended family, marital role, parental role and membership within family unit (Weissman and Bothwell, 1976). Individual scores are obtained in each of these areas, and an overall score for psychosocial adjustment is generated. In this self-rated questionnaire, scores range from 1 (optimal functioning) to 5 (extremely poor functioning).

### 2.3. Procedures and Statistical Analyses

The data for the Complex Social Scenarios task were not normally distributed. Accordingly, we applied a Winsorization procedure to the data by which outliers (i.e., scores exceeding 1.5X the intraquartile range above the third quartile or below the first quartile) were rescaled to be  $\pm 2.5$  SD from the mean (calculated excluding outliers). This procedure reduces the impact of extreme observations without changing the size of the sample. The ToM data were then analyzed using a 2 Between (Group: MDD, HC) X 2 Within (ToM Stimulus Type: first-order versus second-order) mixed-design analysis of variance (ANOVA). Post-hoc independent sample *t* tests that treated group as a between-subjects variable explored differences in performance between patients with MDD and control participants. Estimated effect sizes were analyzed by partial eta square values. The relation between ToM ability and social functioning was explored with two-tailed Pearson's *r* correlation coefficients. Alpha was set at 0.05 for all analyses.

### 3. Results

#### 3.1. Performance on the Complex Social Scenarios Task

There was a main effect of stimulus type [ $F(1, 38) = 84.12, p < 0.001, \eta_p^2 = 0.69$ ]; participants were more accurate in responding to first-order than to second-order ToM questions. There was also an effect of group membership [ $F(1, 38) = 6.30, p = 0.02, \eta_p^2 = 0.14$ ] and a significant interaction between Stimulus Type and Group [ $F(1, 38) = 4.16, p = 0.049, \eta_p^2 = 0.10$ ]. The post-hoc analyses revealed that although subsyndromal MDD participants were as accurate as controls for the first-order ToM stimuli [ $t(38) = -1.08, p = 0.29$ ], they were impaired on second-order ToM questions [ $t(38) = -2.56, p = 0.01$ ] (see Figure 1).

#### 3.2. Relation between clinical variables and ToM performance

HAM-D 17 scores tended to be associated with second-order ToM performance [ $r(40) = -0.31, p = 0.05$ ], but not first-order ToM scores ( $p = 0.44$ ). Performance on second-order ToM tasks was also positively associated with GAF scores [ $r(40) = 0.34, p = 0.03$ ]. No significant associations emerged between burden of illness variables (i.e., duration of illness, age at illness onset, and number of depressive episodes) and ToM performance.

#### 3.3. Relation between social functioning and ToM performance

Second-order ToM scores were negatively associated with total SAS-SR scores [ $r(37) = -0.359, p = 0.029$ ], Social/Leisure Activities [ $r(37) = -0.377, p = 0.021$ ],

indicating that deficits in ToM performance were associated with poorer levels of functioning on global and leisure domains. A significant negative relation was also observed between first-order ToM performance and the Relationship with Extended Family domain [ $r(37) = -0.402, p = 0.033$ ], suggesting that impaired ToM ability was associated with poor relationships with family members. No other significant associations emerged [ $p$ 's  $> 0.105$ ].

#### **4. Discussion**

The main finding of this study was that patients with subsyndromal symptoms of MDD show reduced performance on a complex second-order theory of mind task. In line with our hypothesis that the cognitive complexity of the ToM task would moderate performance, performance on a less cognitively challenging first-order ToM task was intact in this sample. This is the first study to demonstrate altered theory of mind ability in a well-characterized sample of subsyndromal MDD patients. Reduced performance on second-order ToM stimuli was associated with increased levels of depressive symptom severity and a lower level of overall functioning on the GAF in the entire sample suggesting that this social cognitive ability may be compromised with active mood symptoms. Furthermore, impaired ToM performance was found to be related to poor social functioning indicating that declines in the frequency of social activities and quality of interpersonal relationships may stem from impairments inferring the mental states of others.

Relative to healthy controls, subsyndromal patients with MDD were impaired on a complex ToM task that requires participants to integrate two perspectives simultaneously (second-order questions). However, no such deficits were observed in our patient sample on first-order questions that involve adopting the perspective of a single character. These results are broadly consistent with previous reports of ToM deficits in patients with MDD (e.g., Lee et al., 2005; Wang et al., 2008; Zobel et al., 2010). Moreover, taken together with past findings, our results suggest that ToM performance may differ among MDD patients in remitted, subsyndromal and acute phases of illness. Specifically, remitted patients appear to have deficits only on those ToM tasks that are demanding of cognitive and affective resources (Inoue et al., 2004; 2006). By contrast, the subsyndromal patients examined here only demonstrated poor performance on the cognitively demanding second-order ToM stimuli. Finally, patients in an active state of illness have deficits on ToM tasks that place both low and high demands on central processing resources (Lee et al., 2005; Uekermann et al., 2008; Wang et al., 2008; Wolkenstein et al., 2011; Zobel et al., 2010). This gradient in ToM performance among patients with MDD appears to be similar to the pattern of ToM impairment observed in bipolar disorder (see McKinnon et al., 2010).

Our finding of reduced ToM performance in patients with MDD is also consistent with prior reports of reduced cognitive empathy in this patient population. Cognitive empathy, the ability to understand the mental state of another, is a construct thought to be closely related, but dissociable from ToM. Cusi et al. (2011) and Wilbertz et al. (2010) found that patients with MDD reported reduced levels of cognitive empathy on the

Interpersonal Reactivity Index, a validated measure of empathic responding (Davis, 1983). As mentioned, patients with MDD show impairment on a host of cognitive domains (Gualtieri et al., 2006; Landro et al., 2001; Porter et al., 2003), that are thought to contribute to ToM ability. Indeed, recent studies demonstrate that ToM deficits in MDD may be associated with impairment on tests of executive function, memory, and attention (Uekermann et al., 2008; Wolkenstein et al., 2011; Zobel et al., 2010). However, future work is needed to investigate the relation between ToM deficits and neuropsychological functioning in MDD.

Deficits in ToM performance were associated with mood state at the time of testing and level of functioning as assessed by the GAF. These findings are in accordance with other studies in MDD which report significant associations between level of depression and ToM (Uekermann et al., 2008; Wolkenstein et al., 2011). For instance, Uekermann et al. (2008) found that increased depressive symptom severity was associated with poor performance on a humour comprehension task that involved inferring the perspective of various characters. Moreover, Wolkenstein et al. (2011) reported a significant association between depression severity scores and impaired performance on the Movie for Assessment of Social Cognition. These results, however, stand in contrast to previous work demonstrating that certain social cognitive domains such as facial emotion recognition and theory of mind are not related to level of depressive symptom severity in MDD (e.g., Lee et al., 2005; Leppänen et al., 2004; Wolkenstein et al., 2011). Future work will be required to address this issue by employing larger sample sizes that include participants with varying levels of symptom severity.

We did not find any significant associations between ToM ability and any burden of illness variables. These findings suggest that deficits in ToM are independent of course of illness variables in subsyndromal MDD. Preliminary research examining the relation between burden of illness variables and social cognitive performance in MDD reveal a mixed pattern of findings; with one study reporting a significant association between perspective-taking ability and number of depressive episodes (Cusi et al., 2011) and another showing no evidence of a correlation between illness duration and ToM ability (Wolkenstein et al., 2011). The relation between ToM performance and course of illness variables in MDD requires further research and remains to be clarified.

We also found a significant association between second-order ToM responding and impaired functioning in the social and leisure domain. Ours is the first study to report a significant relation between real-world psychosocial functioning and ToM ability in MDD; a related study found no such association between empathic capacity and social functioning in a sample of patients in varying illness states (Cusi et al., 2011). Future investigations that include larger sample sizes are needed to address these conflicting findings. This finding is in line with prior research in patients with schizophrenia, where impaired ToM performance has been shown to be a significant predictor of altered social behaviour (Brüne, 2005). This result also suggests that individuals with MDD experience difficulties in social processing and communication, stemming from deficits in their ability to understand the viewpoints and feelings of others. The present findings suggest that these impairments have important implications for real-world functioning not tapped by our laboratory-based measures.

Future studies are needed to determine if ToM impairment is a state- or trait marker of MDD. Inoue et al. (2004) reported deficits in ToM performance among a sample of remitted patients with unipolar and bipolar depression. In a follow-up study, these authors also demonstrated that mood disorder patients with ToM deficits had significantly greater relapse rates than patients who did not demonstrate such a deficit (Inoue et al., 2006). Taken together, these preliminary studies indicate that ToM impairment may be a trait-like phenomenon that is present in patients with mood disorders. Future investigations examining populations at risk for developing MDD and longitudinal research that follow patients across euthymic and active illness states will more conclusively address this issue.

Our preliminary study provides the first evidence of impaired ToM ability in a sample of MDD patients with subsyndromal symptoms and warrants further investigations of ToM responding in this patient cohort. Given known alterations in the structure and function of prefrontal and temporal brain regions in patients with major depressive disorder (see Price and Drevets, 2010 for a recent review), and the importance of these regions to ToM ability (e.g., Carrington and Bailey, 2009; Mar, 2011), it is possible that ToM impairments may be related to these neuronal alterations. Future work is awaited to examine the neural mechanisms underlying ToM ability in MDD. Evidence of impaired ToM performance, together with evidence of a relation between ToM ability and social functioning among patients with MDD, have important clinical implications. Improved knowledge of social cognitive deficits in major depressive disorder may assist in clarifying the nature of social dysfunction in this disorder and may aid in the

development of psychological interventions aimed at improving social perception and adjustment in this patient population.

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**Table 1.** Clinical and demographic characteristics of study sample

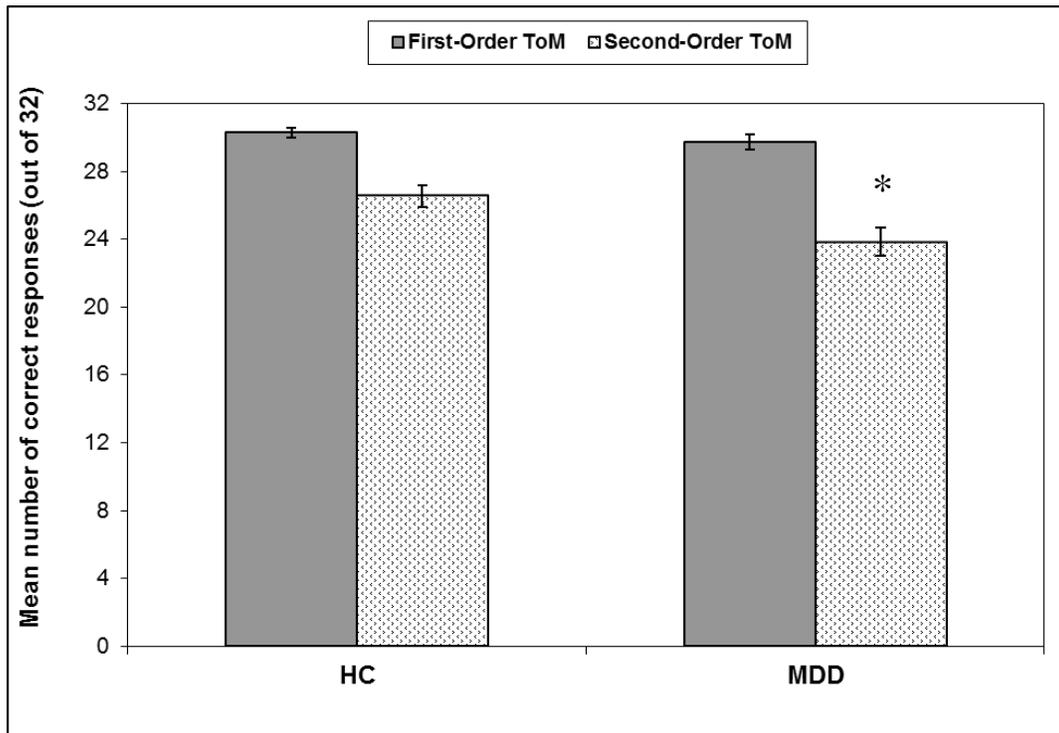
<i>Characteristic</i>		<b>Controls</b> (n=20)	<b>MDD patients</b> Total sample (n=20)
		<i>n</i>	<i>n</i>
<b>Sex</b>	Male	6	6
	Female	14	14
		<i>Mean</i>	<i>Mean</i>
<b>Age</b>		47.60(10.75)	46.95(9.38)
<b>Education</b>		17.31(2.54)	15.78(2.61)
<b>Number of affective episodes</b>			4.61(2.75)
<b>Onset of illness (in years)</b>			24.95(10.70)
<b>Duration of illness (in years)</b>			22.0(13.09)
<b>Ham-D score</b>		2.05(2.86)	11.50(1.76)*
<b>GAF score</b>		79.20(3.69)	61.60(5.68)*

Values are *n* or mean (standard deviation).

**Abbreviations:** MDD, major depressive disorder group; Ham-D, 17-item Hamilton Depression Rating Scale; GAF, Global Assessment of Functioning Scale.

\* Significant results ( $P < 0.05$ ).

**Figure 1.** Mean number of correct responses by healthy controls and by patients with MDD.



Abbreviations: MDD, major depressive disorder group; HC, healthy controls; ToM, theory of mind.

\* $P = 0.033$

**Appendix 1.** Example from Social Scenarios Task

Ellen’s hockey team has just defeated Brad’s hockey team. The teams were evenly matched, but Ellen’s team worked harder and won. When Brad sees Ellen, he says, “Congratulations on your victory. It’s too bad our goalie was so ill.”

What does Ellen believe Brad is thinking when he makes this comment?

How does Ellen think Brad feels when he makes this comment?

What does Brad believe Ellen will think when he makes this comment?

How does Brad think Ellen will feel when he makes this comment?

Why does Ellen think her team won the competition?

How does Ellen feel when Brad makes this comment?

Why does Brad think Ellen’s team won the competition?

How does Brad feel when his team loses the competition?

**CHAPTER 4:**

**COMPLEX THEORY OF MIND PERFORMANCE IN BIPOLAR DISORDER**

*Foreword to Chapter 4*

The literature concerning ToM performance in BD is conflicting, and indicates that performance is likely moderated by a number of key variables, with more severe deficits emerging in patients with increased illness severity and for ToM tasks of greater cognitive complexity. The goal of the present study was to further elucidate the nature of ToM dysfunction in BD by administering two standardized tests: 1) the Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001); and 2) The Interpersonal Perception Task-15 (Costanzo and Archer, 1993). In light of evidence that patients with BD demonstrate deficits on cognitive and affective domains (e.g., Bozikas et al., 2007) thought requisite to ToM responding (e.g., Bailey and Henry, 2008), it appears likely that patients with BD will show performance deficits on tests of ToM. Our secondary goal was to evaluate the relation of symptomatology and illness burden to ToM ability. Given that impaired cognitive and social affective performance among patients with BD has been shown to be associated with increased symptom severity and a prolonged course of illness (e.g., Cusi et al., 2010), we hypothesized that ToM performance would be negatively associated with these illness variables. Psychosocial functioning was also measured in our sample and its relation to ToM performance explored. Consistent with preliminary evidence suggesting that deficits on tests of social cognition are associated with higher rates of relapse (Inoue et al., 2006) and lowered social functioning (Cusi et al., 2010) in mood disorders, we expected that poor ToM performance in patients with BD would be associated with lower levels of social functioning in a real-world context.

This paper was submitted for review to *Psychiatry Research* on September 23, 2011.

**Patients with bipolar disorder show impaired performance on complex tests of theory of mind**

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**Abstract**

The literature concerning social cognitive performance in people with bipolar disorder (BD) reveals a mixed pattern of findings. We compared performance between patients with BD and matched controls on two complex theory of mind tasks that involved: i) the decoding of mental states from pictures of eyes (Reading the Mind in the Eyes Test), and ii) a video-based test that requires participants to discriminate social cues to make interpersonal judgments (Interpersonal Perception Task-15; IPT-15). We also sought to evaluate the association between symptom severity, social functioning, and theory of mind ability in patients with BD. Relative to controls, patients with BD were impaired at discriminating mental states from pictures of eyes and in making complex social judgments. Impaired responding on the IPT-15 was also associated with reduced psychosocial functioning. These results provide evidence of impaired performance on complex tests of theory of mind in patients with BD. Impairments in mental state attribution may be associated with well-documented declines in the frequency of social interactions and development of interpersonal relationships found in this patient population.

**Key words:** social cognition; mood disorders; social inference; social functioning

## 1. Introduction

Bipolar disorder (BD) is characterized by impairment in multiple domains, including interpersonal and social functioning (Elgie and Morselli, 2007; Depp et al., 2010). Accordingly, a number of investigations indicate a reduction in social interactions (Bauwens et al., 1991; Bauwens et al., 1998), and lower rates of development of socially meaningful relationships among individuals with BD (Judd et al., 2003). Recently, there has been increased interest in utilizing a cognitive framework, such as theory of mind, to understand the cognitive and affective underpinnings of alterations in social functioning among patients with neuropsychiatric disorders (e.g., Lahera et al., 2008; McKinnon et al., 2010). Theory of mind (ToM) refers to the ability to infer the mental states of others, including their beliefs, desires, and intentions in order to explain or predict their behaviour (Premack and Woodruff, 1978). Although a growing body of research has begun to examine the performance of patients with BD in decoding non-verbal signals such as facial emotion (e.g., George et al., 1998; Getz et al., 2003; Bozikas et al., 2006; Gray et al., 2006), and in detecting emotional prosody (Bozikas et al., 2006), other facets of social cognition, including theory of mind remain an under-explored area of research (Brüne and Brüne-Cohrs, 2006; McKinnon et al., 2010). The goal of the present study was to further elucidate the nature of ToM dysfunction in BD, as well as to examine the relation between ToM performance, symptom severity, and illness burden. Psychosocial functioning was also measured in our sample and its relation to ToM performance explored.

Recent theoretical models propose that ToM ability draws on both cognitive

and affective processing resources (Leslie et al., 2004; McKinnon and Moscovitch, 2007). Indeed, the results of neuroimaging and lesion studies suggest that ToM is a complex, multifaceted process, mediated by a network of multiple brain regions involved in cognitive (e.g., dorsolateral prefrontal cortex; temporoparietal junction; Stone et al., 1998; Channon and Crawford, 2000; Shamay-Tsoory et al., 2005; Frith and Frith, 2006; Saxe and Powell, 2006; Decety and Lamm, 2007), affective (e.g., medial and orbitofrontal prefrontal cortex; amygdala (Fletcher et al., 1995; Goel et al., 1995; Rowe et al., 2001; Stuss et al., 2001; Baron-Cohen and Wheelwright, 2004); and memory functions (e.g., posterior cingulate; temporal poles; (Gallagher et al., 2000; see McKinnon et al., 2007; Carrington and Bailey, 2009; Mar, 2011 for reviews). Notably, many of the same neural regions show altered structure and/ or function in patients with BD (e.g., Blumberg et al., 2003a, 2003b; Adler et al., 2005; Altshuler et al., 2005; Kruger et al., 2006; Yucel et al., 2007; Bearden et al., 2008; Foland et al., 2008; Yucel et al., 2008), suggesting that these patients may demonstrate impaired performance on complex ToM tasks that have been shown to rely on these cognitive and affective processing resources. Moreover, given that patients with BD demonstrate deficits on a wide variety of cognitive and affective tasks (Altshuler et al., 2004; Bearden et al., 2006; Bozikas et al., 2006; Bozikas et al., 2007; Malhi et al., 2007; Mur et al., 2007) thought requisite to ToM responding (e.g., Bora et al., 2005; Bailey and Henry, 2008), it appears likely that patients with BD will show performance deficits on tests of ToM.

Research examining ToM responding in patients with BD, however, has revealed mixed findings. One study reported deficits in a combined sample of remitted patients

with unipolar and bipolar depression on cognitively challenging ToM tasks that involve integrating and understanding the perspective of two characters simultaneously (i.e., second-order false-belief questions) but not on less challenging ToM tests that involve inferring the perspective of a single character (i.e., first-order false-belief question; Inoue et al., 2004). In patients with sub-syndromal illness, however, deficits emerge on both first-order and second-order ToM questions; notably the magnitude of deficit observed here is greater for the more cognitively challenging second-order ToM tasks (McKinnon et al., 2010). Kerr et al. (2003) also reported deficits on both first- and second-order ToM tests in BD patients who were actively depressed or manic; remitted patients, however, were unimpaired. Recent reports also point towards performance deficits on cognitively demanding tests of mental state attribution among euthymic patients with BD (Bora et al., 2005; Olley et al., 2005; Lahera et al., 2008). Taken together, these results suggest that ToM performance among patients with BD is likely moderated by a number of key variables, with more severe deficits emerging in patients with heightened illness severity and for ToM tasks of greater cognitive complexity.

In line with these findings, Bora and el. (2005) reported that, relative to matched controls, euthymic patients with BD showed impaired mental state discrimination on the Reading the Mind in the Eyes Task (RMET; Baron-Cohen et al., 2001), an advanced ToM task that involves inferring the mental state of a person from their eye gaze, and thus decoding the mental state depicted by the eyes' expression. In contrast to Bora et al.'s (2005) study, however, Shamay-Tsoory and colleagues (2009) reported that euthymic patients showed intact recognition of both basic and complex emotions depicted in sets of

eyes. Importantly, Shamay-Tsoory et al.'s (2009) task may not have been as cognitively challenging for the patient sample, as participants were required to choose the most accurate mental state from one of two mental state descriptors, rather than four mental state words that is found in the original RMET task (Baron-Cohen et al., 2001). The performance of patients with BD in mood states other euthymia on the RMET task are unknown.

The primary goal of the present study was to examine ToM responding in patients with BD in varying illness states and matched controls using two standardized tests: 1) the RMET; and 2) The Interpersonal Perception Task-15 (IPT-15; Costanzo and Archer, 1993). The IPT-15 is a complex and naturalistic test that is thought to tap multiple elements of social cognitive processing, including ToM. We predicted that, relative to healthy volunteers, patients with BD would demonstrate ToM deficits on both the RMET and IPT-15. Our secondary goal was to evaluate the relation of symptomatology and illness burden to ToM ability. Given that impaired cognitive and social affective performance among patients with BD has been shown to be associated with increased symptom severity and a prolonged course of illness (Summers et al., 2006; Malhi et al., 2007; Martinez-Aran et al., 2007; Schenkel et al., 2008; Kurtz and Gerraty, 2009; Cusi et al., 2010; Wolf et al., 2010), we hypothesized that ToM responding would be negatively associated with these illness variables. Preliminary investigations indicate that deficits on tests of social cognition, including theory of mind and empathy, are associated with higher rates of relapse (Inoue et al., 2006) and lower social functioning (Cusi et al., 2010), but the relation between ToM ability and psychosocial functioning has not been well-

characterized. Hence, we investigated the relation of ToM ability to psychosocial functioning in our patient sample using a well-validated measure of functional outcome, the Social Adjustment Scale Self-Report (SAS-SR; Weissman and Bothwell, 1976). We expected that poor performance on the ToM measures in patients with BD would be associated with lower levels of social functioning in a real-world context.

## **2. Methods**

### *2.1. Participants*

Twenty-five patients (7 males, 18 females) who met DSM-IV criteria for BD (APA, 2000) were recruited from the Mood Disorders Program outpatient clinic at St. Joseph's Healthcare Hamilton. Eighteen patients met DSM-IV diagnostic criteria for bipolar type I, 7 patients were diagnosed with bipolar type II, and 1 patient was diagnosed with bipolar not otherwise specified. We also recruited 25 healthy comparison subjects who were matched for age, gender, and education. Controls were excluded if they reported a personal history of a psychiatric disorder or if they had a family member with BD or schizophrenia. In order to assess the relation between level of symptom severity and ToM ability, patients in varying mood states were recruited. The severity of manic symptoms was assessed using the Young Mania Rating Scale (YMRS; Young et al., 1978). Depressive symptoms were examined using the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960). Overall functioning was evaluated using the Global Assessment of Functioning Scale (APA, 1994). The demographic and clinical characteristics of the sample are shown in Table 1.

Exclusion criteria for patients and controls included: i) history of electroconvulsive therapy or transcranial magnetic stimulation therapy, within one year ii) substance abuse based on DSM-IV criteria in the last six months, iii) current or lifetime history of substance dependence based on DSM-IV criteria, iv) current or prior history of untreated significant medical illness or of neurological illness, v) history of traumatic brain injury and/or loss of consciousness (lasting more than 60 seconds), vi) use of benzodiazepines within 12 hours prior to testing.

The study received ethical approval from the St. Joseph's Healthcare Hamilton Ethics Board and all participants provided written informed consent.

## *2.2. Statistical Methods*

To investigate significant differences in ToM between patient and control groups, a one-way ANOVA was applied to dependent variables (RMET total score, IPT-15 total and subscale scores). This procedure was repeated for the SAS-SR data. Partial eta-squared scores as a measure of effect sizes were also calculated. Associations between the scores on the RMET and IPT-15 and the demographic and clinical data were analyzed using Pearson's  $r$  correlations. Level of significance was set at 0.05, and all reported results were two-tailed.

## *2.3. ToM Tasks*

### *2.3.1. Reading the Mind in the Eyes Test*

In this task, participants were presented with 36 sets of eyes depicting complex mental states (e.g., jealousy, desire; Baron-Cohen et al., 2001). Four adjectives corresponding to mental state descriptors (e.g., “hateful,” “panicked”) were displayed on each slide. Three of the adjectives were distractors, while one of the adjectives correctly described the mental state of the person in the photograph. Participants were required to decide which of 4 mental state descriptors best described what the individual in the photograph was thinking or feeling. Stimuli were presented on a computer screen and both reaction time and error rates recorded. There was no time limit for responses. Participants were instructed to consult a glossary of all mental state words found in the task when they were unsure of the meaning of a word, following the same procedures used by Baron-Cohen et al. (2001). Scores were calculated as the total number of correct responses for all 36 items.

### *2.3.2. Interpersonal Perception Task-15*

The Interpersonal Perception Task-15 (IPT-15; Costanzo and Archer, 1993) is a measure of social intelligence consisting of 15 videotaped scenes, depicting one to four individuals interacting or speaking. Each vignette is followed by a multiple choice question. Each question has an objectively correct answer. For example, one scene depicts a short interaction between two people and then the viewer is asked to judge which of the two people is the boss. The scenes are edited so that there are no obvious verbal clues are present when answering each question. The task includes five different types of social judgements, including kinship, intimacy, deception, competition, and status, with three scenes in each area. The maximum score for each subscale is 3 and the

maximum total score for the test is 15. The IPT-15 has established reliability and validity (Costanzo and Archer, 1993).

## *2.4. Social Functioning*

### *2.4.1. Social Adjustment Scale Self-Report*

The Social Adjustment Scale Self-Report (SAS-SR; Weissman and Bothwell, 1976) assesses a broad range of social domains including work/school role, social/leisure activities, relationship with extended family, marital role, parental role and membership within a family unit. Individual scores are obtained in each of these areas, and an overall score for psychosocial adjustment is generated. In this self-rated questionnaire, scores range from 1 (optimal functioning) to 5 (extremely poor functioning). The SAS-SR has been found to have adequate reliability and validity (Weissman and Bothwell, 1976; Weissman and Staff, 1999; Zweig and Turkel, 2007).

## **3. Results**

### *3.1. Performance on ToM Measures*

Table 2 summarizes the descriptive statistics for the two groups along with the effect size of each measure.

### 3.1.1. RMET Performance

Relative to controls, patients with BD showed diminished accuracy on the RMET [ $F(1, 48) = 5.74; p = 0.02$ ], suggesting impairments in discriminating complex mental states among this sample.

### 3.1.2. IPT-15 Performance

On the IPT-15 total score, the BD group performed significantly worse than the HC group [ $F(1, 48) = 4.89, p = 0.03$ ], suggesting that individuals with BD show impairments in making judgments about everyday social situations. Moreover, the BD group scored lower than controls on the IPT Competition subscale [ $F(1, 49) = 4.46, p = 0.04$ ] and tended to perform worse on the IPT-15 Kinship scale [ $F(1, 49) = 3.62, p = 0.06$ ]. No significant group differences were found for the IPT Intimacy, Status, and Deception subscales ( $p$ 's  $> 0.05$ ).

## 3.2. Relation between ToM performance and Demographic and Clinical Variables

RMET accuracy scores were negatively associated with YMRS scores [ $r(49) = -0.37, p = 0.01$ ], suggesting that individuals with higher levels of manic symptoms performed worse on this ToM task. A significant positive association emerged between RMET performance and duration of illness in the BD group, [ $r(23) = 0.47, p = 0.03$ ]. We also found a significant positive relation between the Global Assessment of Functioning Scale and IPT-15 total [ $r(49) = 0.30, p = 0.03$ ] and IPT-15 Status subscale [ $r(49) = 0.28, p = 0.05$ ] scores. These results indicate that participants who performed poorly on the

IPT-15 also had a lower level of overall functioning. The IPT-15 Intimacy scale was negatively associated with the YMRS [ $r(49) = -0.31, p = 0.03$ ]. No significant correlations were found between the measures of ToM abilities (RMET, IPT-15) and depressive symptom severity as assessed by the HAM-D.

### *3.3. Social functioning*

On the SAS-SR, individuals with BD were impaired in overall functioning [ $F(1, 42) = 16.92, p < 0.001$ ] as well as Social/Leisure Activities [ $F(1, 42) = 11.46, p = 0.02$ ], and Membership within Family Unit [ $F(1, 42) = 4.28, p = 0.04$ ]. No other significant group differences emerged on the SAS-SR ( $p$ 's  $> 0.10$ ).

### *3.4. Relation between ToM scores and Social Functioning*

A significant negative association was found between the IPT-15 total score and the SAS-SR Parental Role Domain [ $r(23) = -0.47, p = 0.02$ ]. The IPT-15 Kinship scale was also negatively associated with the Marital Dole domain of the SAS-SR [ $r(29) = -0.44, p = 0.02$ ]. RMET performance was not associated with any domain of the SAS-SR for all analyses ( $p$ 's  $> 0.05$ ).

## **4. Discussion**

The primary goal of the present study was to investigate ToM ability in patients with BD using both complex and ecologically valid measures. We predicted that individuals with BD would show impaired ToM performance on the tasks assessed, and that these deficits would be associated with a higher level of symptom severity and

increased burden of illness. Patients were less accurate than control participants in attributing mental states from pictures of eyes and showed impaired performance on a complex task that required social inferencing. These deficits appear to have implications for interpersonal relationships held by patients with BD; impaired responding on the IPT-15 was associated with reduced self-reported levels of psychosocial functioning.

Our finding of impaired performance by patients with BD on the RMET is in line with a prior study reporting deficits in mental state recognition from eye expressions in euthymic individuals with BD (Bora et al., 2005) and extends these findings to include patients in a sub-syndromal illness state. By contrast, Shamay-Tsoory et al. (2009) failed to report a deficit in discriminating complex mental states from eye expressions among euthymic patients with BD, however, the task used in this study may have been less cognitively challenging as it involved two rather than four response choices. The present finding of a deficit on the RMET among patients with BD is also in line with numerous studies reporting a general impairment in facial emotion recognition among this population (see McClure-Tone, 2009; Kohler et al., 2011 for recent reviews; but see Harmer et al., 2002; Venn et al., 2004; Vaskinn et al., 2007; Schaefer et al., 2010 for contradictory findings).

Consistent with our hypotheses, patients also showed overall reduced performance on the IPT-15, which relies heavily on social inferencing. This deficit was particularly apparent on the IPT Competition subscale, where patients with BD had difficulty decoding social cues to determine who had won a sporting match in each competition scene. Individuals with BD also tended to score lower than controls on the IPT-15

Kinship scale, indicating that patients experienced difficulties interpreting the nature of the relationship between individuals depicted in each kinship scene. Taken together, these findings suggest that patients with BD experience difficulties interpreting social cues to make interpersonal judgments. Similar to the RMET results, these findings are consistent with prior studies that show impairment in social perception in this patient population, including the recognition of emotion in facial stimuli (McClure-Tone, 2009) and on naturalistic tests of ToM ability and social inference (Bazin et al., 2009; Montag et al., 2010). Importantly, analyses of the other IPT-15 subscales showed that patients with BD performed comparably to controls in detecting lies (Deception subscale), levels of intimacy between individuals (Intimacy subscale), and the status of individuals relative to one another (Status subscale). Intact performance on these IPT-15 subscales suggest that social perceptual ability is not entirely impacted in this patient sample, and is consistent with the idea that ToM is a complex psychological construct that involves the interaction of multiple cognitive and affective processes (e.g., McKinnon et al., 2007; Carrington and Bailey, 2009; Mar, 2011). These results of impaired performance on these ToM tasks are also broadly consistent with research demonstrating that individuals with BD report reduced levels of cognitive empathy (Shamay-Tsoory et al., 2009; Cusi et al., 2010), involving the cognitive understanding and comprehension of another person's mental state, a psychological construct thought to be closely related to ToM. Specifically, Shamay-Tsoory et al. (2009) and Cusi et al. (2010) found that relative to controls, patients with BD rated themselves lower on the Perspective Taking subscale of the Interpersonal Reactivity Index (Davis, 1983), a standardized measure of empathic responding.

An extended duration of illness was associated with enhanced performance on the RMET. These findings stand in contrast to preliminary evidence that an earlier illness onset (Schenkel et al., 2008; Wolf et al., 2010) and greater illness duration (McKinnon et al., 2010) are associated with ToM deficits in bipolar patients. One possible explanation for this unexpected finding is that a more chronic course of illness might be related to less satisfactory social interactions and thus these patients may be highly attuned to social cues. We failed to find any additional significant associations between ToM performance and other burden of illness variables (number of affective episodes, age at onset of illness). This absence of an association is in line with recent studies (Inoue et al., 2004; Bora et al., 2005) that did not find any relation between course of illness variables and social cognitive response in BD. Given the small size of our sample, however, further research is needed to clarify the relation between burden of illness and ToM.

No significant associations were found between depressive symptom severity and ToM performance. We found limited evidence that YMRS scores were negatively associated with RMET accuracy scores. Prior work examining the relation between symptom severity and ToM ability in patients with BD report a similar pattern of conflicting findings. McKinnon et al. (2010) found a negative relation between severity of depression and both first- and second-order ToM scores in a sample of patients with sub-syndromal BD. Other studies, however, report no such associations between ToM ability and symptom severity in BD (Bora et al., 2005; Wolf et al., 2010). Further studies including larger patient samples in different mood states will be required to address adequately the association between symptomatology and ToM response.

Finally, impaired performance on the IPT-15 was associated with poor functioning in the Parental Role domain of the SAS-SR. These findings support the notion that disruptions in social cognitive processing may be associated with declines in patients' social functioning (Cusi et al., 2010). These results are also in accord with findings suggesting that poor performance on tests of ToM is associated with a poorer prognosis in patients with major depressive disorder and BD (Inoue et al., 2006). Poor interpersonal functioning is also associated with impairments in ToM abilities in other psychiatric disorders such as schizophrenia and autistic spectrum disorders (Baron-Cohen et al., 2005; Schenkel et al., 2005; Shamay-Tsoory et al., 2007). Due to our relatively small sample size this finding is preliminary in nature and further studies are needed to determine the association between altered social cognitive performance and everyday functioning in BD.

Given the cross-sectional nature of our study, future research is required to examine whether impaired ToM ability is a state-like phenomenon or a stable trait in individuals with BD. Previous research suggests that patients with BD demonstrate ToM deficits during euthymia (Inoue et al., 2004; Bora et al., 2005; Olley et al., 2005; Shamay-Tsoory et al., 2009), suggesting that impairment in this social cognitive ability reflects a trait marker of vulnerability for this disorder. However, future studies should incorporate longitudinal designs and follow individuals who are at risk for BD and patients through acute and remitted phases of illness to address this issue.

In summary, the present study provides additional empirical evidence for impaired ToM in patients with BD. The ability to make accurate inferences about the mental states

of others and correctly perceive social cues are essential for day-to-day social interactions. Preliminary findings from this study indicate that deficits in interpersonal functioning may stem from impairments on theory of mind tasks in BD. The ability to understand and appreciate mental states and to perceive social information should be taken into consideration in treatment interventions for BD. Treatment approaches that incorporate social skills training may help improve the social dysfunction that accompanies this disorder.

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**Table 1.** Demographic and clinical characteristics of study sample

<i>Characteristic</i>		<b>Controls</b> (n=25)	<b>BD group</b> Total sample (n=25)
		<i>n</i>	<i>n</i>
<b>Sex</b>	Male	7	7
	Female	18	18
		<i>Mean</i>	<i>Mean</i>
<b>Age</b>		44.2(11.8)	45.2(10.8)
<b>Education</b>		16.7(3.0)	15.3(2.6)
<b>Number of affective episodes</b>			18.2(10.9)
<b>Onset of illness (in years)</b>			22.8(11.0)
<b>Duration of illness (in years)</b>			23.1(11.2)
<b>HAM-D score</b>		1.9(2.7)	8.1(6.2)*
<b>YMRS</b>		0.2(0.7)	2.0(2.0)*
<b>GAF score</b>		79.6(4.1)	67.2(9.6)*

Values are *n* or mean (standard deviation).

**Abbreviations:** BD, bipolar disorder group; HAM-D, 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; GAF, Global Assessment of Functioning Scale.

\* Significant results ( $P < 0.05$ ).

**Table 2.** Group Differences on Theory of Mind Tests

Theory of Mind Measures	Controls	BD Group	Results	Effect size (partial eta-squared)
RMET Total Score	26.2(3.1)	23.9(3.6)	$F = 6.96, df = 1, P = 0.02^*$	0.17
IPT-15 Total Score	10.3(1.5)	9.4(1.6)	$F = 4.86, df = 1, P = 0.03^*$	0.09
IPT-15 Kinship Score	2.3(0.8)	1.9(0.8)	$F = 3.62, df = 1, P = 0.06$	0.07
IPT-15 Intimacy Score	1.8(0.7)	1.6(0.9)	$F = 0.84, df = 1, P = 0.36$	0.017
IPT-15 Competition Score	2.6(0.6)	2.2(0.7)	$F = 4.46, df = 1, P = 0.04^*$	0.085
IPT-15 Status Score	2.4(0.7)	2.3(0.6)	$F = 0.19, df = 1, P = 0.67$	0.004
IPT-15 Deception Score	1.3(0.8)	1.5(0.9)	$F = 0.43, df = 1, P = 0.51$	0.009

Values are mean (standard deviation).

**Abbreviations:** BD, bipolar disorder group; IPT-15, Interpersonal Perception Task 15; RMET, Reading the Mind in the Eyes Test.

Significantly different from control group at \*  $P < 0.05$

**CHAPTER 5:  
EMPATHIC RESPONDING  
IN  
PATIENTS WITH MOOD DISORDERS**

*Foreword to Chapter 5, Study 1*

Similar to ToM, recent theoretical models have proposed that empathy is multidimensional in nature, involving both cognitive (e.g., understanding another's perspective) and affective (e.g., emotional response to the feeling states of others) components (Davis, 1983) with empirical evidence supporting this view (e.g., Vollm et al., 2006). Although recent investigations have demonstrated deficits in facial affect processing (e.g., Getz et al., 2003) and in ToM (e.g., Kerr et al., 2003) in patients with BD, at the time this study was conducted, empathic responding had not been assessed directly in this patient sample.

The objective of this study was to examine the performance of patients with BD on a well-validated measure of empathic responding, the Interpersonal Reactivity Index (IRI; Davis, 1983). The IRI assesses both cognitive and affective components of empathy. The association of empathic responding with the clinical characteristics and social functioning of this sample was also investigated. Consistent with well-documented deficits in emotion regulation (Phillips et al., 2008) among patients with BD, we predicted that our sample would report difficulties in emotional self-control as measured by the IRI Personal Distress Scale. In light of recent work that shows impaired perspective taking ability in patients with BD (Kerr et al., 2003), we expected patients in our sample to report lower levels of IRI Perspective Taking than controls. Because alterations in cognitive functioning have been shown to worsen with disease progression in patients with mood disorders (e.g., van Gorp et al., 1998), we expected impaired empathic performance to be associated with a greater burden of illness and symptom severity.

Finally, we predicted that empathic responding would be significantly associated with poor social functioning.

The full author list and citation information for this article are provided below:

Cusi, A.M., MacQueen, G.M., & McKinnon, M.C. (2010). Altered self-report of empathic responding in patients with bipolar disorder. *Psychiatry Research*, 178(2): 354-8.

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**Altered self-report of empathic responding in patients with bipolar disorder**

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### ABSTRACT

Despite evidence of impairments in social cognition in patients with bipolar disorder (BD), systematic investigations of empathic responding in this population have not been conducted. The objectives of the current study were to investigate empathic responding in patients with BD in varying states of illness and to determine whether course of illness variables and symptom severity predicted responding. Twenty well-characterized patients with BD and twenty matched healthy control subjects completed the Interpersonal Reactivity Index (IRI) and the Social Adjustment Scale Self-Report (SAS-SR), self-report measures of cognitive and emotional empathy and of psychosocial functioning, respectively. Patients with BD reported significantly reduced levels of cognitive empathy ('Perspective Taking') and higher levels of personal distress in response to others' negative experiences than did controls. Altered affective empathic abilities correlated significantly with reduced psychosocial functioning in family, social and occupational domains and with increased symptom severity. This study provides preliminary evidence of alterations in empathic responding in patients with BD. Alterations in the ability to adopt the perspective of others may contribute to the difficulties in social communication inherent in this patient population. Additional studies, involving larger samples, are required to determine the contribution of social cognitive performance to impaired social functioning in BD.

**Keywords:** Empathy; Social cognition; Bipolar disorder; Social functioning

## 1. Introduction

People with bipolar disorder (BD) experience significant disruptions in social functioning, which may negatively impact the quality of life of patients, family members and other supports (e.g., Begley et al., 2001; Lepine, 2001; Kessler et al., 2006). Poor social functioning may result in part from deficits in social cognition, involving the ability to understand and respond to the thoughts and feelings of others. Recent investigations have demonstrated impairments in facial affect processing (e.g., George et al., 1998; Lembke and Ketter, 2002; Getz et al., 2003) and in theory of mind (e.g., Kerr et al., 2003; Inoue et al., 2004, 2006; Bora et al., 2005) in patients with BD. Less attention has been paid, however, to other aspects of social cognition, including empathy. In the present study, we examine the performance of patients with BD on a well-validated measure of empathic responding, the Interpersonal Reactivity Index (Davis, 1983), and the association of empathic responding with the clinical characteristics and psychosocial functioning of this sample.

Empathy refers broadly to the ability to infer and share the feeling states of another (Gallese, 2003). Empathic skills are thought to be essential for successful social communication and interactions (Baron-Cohen and Wheelwright, 2004) and important for promoting unselfish, prosocial behaviour (Eisenberg and Miller, 1987). Recent theoretical models have proposed that empathy is multidimensional in nature, involving both cognitive (e.g., understanding another's perspective) and affective (e.g., emotional response to the feeling states of others) components (Davis, 1980, 1983; Rankin et al., 2005). Neuroimaging and patient studies of empathy confirm this view, implicating a core

network of neural regions that serve diverse functions, and include cognitive (e.g., dorsolateral prefrontal cortex), affective (e.g., orbitofrontal and medial frontal; amygdala) and memory systems (e.g., hippocampus; anterior and posterior cingulate, temporal poles; Eslinger, 1998; Farrow et al., 2001; Völlm et al., 2006; see McKinnon et al., 2007 for a review).

Many of the regions included in these neural network models are affected in patients with BD, showing altered metabolic functioning (e.g., Blumberg et al., 2003a; Altshuler et al., 2005; Krüger et al., 2006; Foland et al., 2008) and volumetric abnormalities (e.g., Blumberg et al., 2003b; Adler et al., 2005; Bearden et al., 2008; McKinnon et al., 2009). Combined with well-established evidence of impairments on cognitive tasks in this population (Altshuler et al., 2004; Bearden et al., 2006; Malhi et al., 2007; Mur et al., 2007; see also MacQueen et al., 2005), which worsen with disease progression (MacQueen et al., 2002), there is substantial reason to suspect that patients with BD will have altered performance on social tasks that rely on the processing resources (e.g., executive functioning, emotion comprehension) subserved by these regions and thought to contribute to social cognitive performance, including empathy (McKinnon and Moscovitch, 2007).

To date, little work has been conducted concerning empathic responding in patients with mood disorders. Donges et al. (2005) found that depressed patients had reduced awareness of others' emotional states compared with healthy controls. They used the Levels of Emotional Awareness Scale, however, which is not a direct measure of empathy, although this finding is in keeping with the preoccupation with the self and

negative self cognitions that form the core symptoms of this illness (Raes et al., 2006). Another study reported that patients with major depression score higher than controls on measures of altruism (O'Connor et al., 2002), a process linked closely to empathy, although not directly analogous to it. Hence, empathic responding has not been assessed directly in patients with BD, despite knowledge of impairments in social functioning in this population (Blairy et al., 2004). Moreover, the relation between performance on social reasoning tasks and measures of real-world social functioning has not been adequately examined.

This preliminary study was designed to investigate empathic responding in a sample of patients with established BD and matched healthy comparison subjects. We administered a standardized self-report measure of empathic responding: the Interpersonal Reactivity Index (IRI; Davis, 1983). This measure has demonstrated efficacy across multiple subject populations, including substance dependence (Alterman et al., 2003) and schizophrenia (Montag et al., 2007), and has been administered successfully in patients with frontal dysfunction (e.g., Eslinger, 1998). The IRI assesses four dimensions of dispositional empathy: Perspective-Taking and Fantasy as well as Empathic Concern and Personal Distress. Each pair was designed to measure cognitive and affective elements of empathy, respectively. Given well-documented deficits in emotion regulation (Phillips et al., 2008) among patients with BD, we predicted that our sample would report difficulties in emotional self-control as measured by the Personal Distress Scale (e.g., “In emergency situations I feel apprehensive and ill at ease”). By contrast, recent evidence points towards impaired perspective taking ability in patients

with active (Kerr et al., 2003) and sub-syndromal BD (McKinnon et al., submitted). Hence, we expected patients in our sample to report lower levels of perspective taking (e.g., “I sometimes find it difficult to see things from the ‘other guy’s’ point of view”) than matched controls. The Fantasy subscale of the IRI has been described as best assessing imagination (e.g., “I daydream and fantasize with some regularity about things that might happen to me”; Baron-Cohen and Wheelwright, 2004); we did not expect patients with BD to show deficits on this scale as impairments in imagination have not been reported in this population. Finally, given the dearth of study regarding empathic concern in patients with BD (e.g., “I would describe myself as a pretty soft-hearted person.”), we were unable to make predictions for this subscale.

Because alterations in cognitive functioning have been shown to worsen with disease progression in patients with mood disorders (e.g., van Gorp et al., 1998; Lebowitz et al., 2001; MacQueen et al., 2002; but see Nehra et al., 2006 and Pavuluri et al., 2006 for conflicting findings), we also examined the relation between illness burden and empathic responding. Finally, we explored relations between psychosocial functioning and performance on the IRI by administering a reliable and well-validated measure of psychosocial functioning, the Social Adjustment Scale Self-Report (SAS-SR; Weissman and Bothwell, 1976).

## **2. Methods**

### *2.1. Participants*

Twenty patients with bipolar disorder (mean age = 43.0, S.D. = 8.9; 14 women) were recruited from the outpatient Mood Disorders Clinic at St. Joseph’s Healthcare in

Hamilton. A primary diagnosis of BD was confirmed by the Structured Clinical Interview for DSM-IV (SCID; First et al., 2001). Fourteen bipolar type I and 6 bipolar type II patients were recruited in total. The healthy comparison (HC) group consisted of 20 subjects with no history of psychiatric illness matched to the patients in terms of age (mean age = 40.2, standard deviation (S.D.) = 15.1) and gender distribution (12 women). Control subjects had no known family member with BD or schizophrenia. Demographic and clinical characteristics of the study sample are presented in Table 1.

Patients were tested in varying states of illness, allowing for an examination of the relation between symptom severity and empathic responding. Symptom severity was assessed using the 17-item Hamilton Depression Rating Scale (Ham-D; Hamilton, 1960), Young Mania Rating Scale (YMRS; Young et al., 1978), and the Global Assessment of Functioning Scale (GAF; American Psychiatric Association, 1994). Healthy controls also received these measures to rule out the presence of subthreshold psychiatric illness.

Exclusion criteria for patients and comparison subjects were: i) inability to provide informed consent, ii) history of electroconvulsive therapy or transcranial magnetic stimulation therapy, within 1 year, iii) substance abuse based on DSM-IV criteria in the last 6 months, iv) current or lifetime history of substance dependence based on DSM-IV criteria, v) current or prior history of untreated significant medical illness (e.g., cancer) or of neurological illness (e.g., Parkinson's disease, epilepsy), vi) history of traumatic brain injury and/or loss of consciousness (lasting more than 60 s), vii) YMRS score > 10, viii) use of benzodiazepines within 12 h prior to testing.

All participants provided written informed consent. The study was approved by the Research Ethics Board of St. Joseph's Healthcare Hamilton and was performed in accordance with the ethical standards laid down by the 1964 Declaration of Helsinki.

## 2.2. *Materials*

The Interpersonal Reactivity Index (IRI) is a 28-item instrument containing four 7-item subscales assessing different dimensions of empathy: Perspective Taking (PT), Empathic Concern (EC), Personal Distress (PD), and Fantasy (FS) (Davis, 1980; 1983). Each item is scored on a 5-point Likert scale ranging from 0 (*does not describe me well*) to 4 (*describes me very well*). Whereas the Perspective Taking (the tendency to spontaneously understand the perspective of others and see things from their point of view) and Fantasy (the tendency to identify with fictional characters in books and movies) subscales are thought to assess cognitive components of empathy, the Empathic Concern (other-oriented feelings of warmth, compassion, and concern for others) and Personal Distress (the self-oriented emotional response of fear or discomfort that results from observing another's negative experience) subscales are thought to measure affective components of empathy (Davis, 1983). The IRI has good internal consistency (Christopher et al., 1993; Davis, 1980) and correlates with other measures of empathy, providing support for the construct validity of the measure (Davis, 1983).

The Social Adjustment Scale Self-Report (SAS-SR) assesses performance in six major areas of functioning including work/school role, social/leisure activities, relationship with extended family, marital role, parental role and membership within a family unit. Based on individual scores in these areas, an overall score for psychosocial

adjustment is generated. Higher scores are indicative of greater social dysfunction or impairment. This self-rated instrument has been used in patients with a variety of psychiatric disorders (Calabrese et al., 2004; Fallon et al., 1991; Furukawa et al., 2001) and has been confirmed to correlate significantly with and to be comparable to interviewer-rated assessments (Weissman and Bothwell, 1976).

### *2.3. Procedures and statistical analyses*

Participants completed the self-report questionnaires in a counterbalanced order. These data were analyzed using a multivariate analyses of variance (MANOVA) treating Group (BD, HC) as a fixed variable and score for each of the IRI (PT, EC, FS, PD) subscales as a dependent variable. This procedure was repeated for the SAS-SR. Alpha was set at 0.05. Correlational analyses (Pearson's  $r$ ; two-tailed; alpha = 0.05) were used to explore the relation between social functioning and empathic responding. Spearman's correlation coefficient was used to evaluate the relation between number of previous episodes and empathic responding.

## **3. Results**

### *3.1. Performance on the IRI*

Patients with BD scored lower on the Perspective Taking subscale [ $F(1, 38) = 4.53, P < 0.05, \eta_p^2 = 0.11$ ] and higher on the Personal Distress subscale [ $F(1, 38) = 5.98, P < 0.05, \eta_p^2 = 0.14$ ] than healthy controls (See Table 2). No other significant effects emerged.

### *3.2. Psychosocial functioning*

As expected, the Work/Academic functioning [ $F(1, 14) = 10.93, P < 0.01, \eta_p^2 = 0.44$ ], Social/Leisure activities [ $F(1, 14) = 8.51, P < 0.05, \eta_p^2 = 0.38$ ], Relationship with Outside Family [ $F(1, 14) = 4.75, P < 0.05, \eta_p^2 = 0.25$ ], Parental Role [ $F(1, 14) = 5.51, P < 0.05, \eta_p^2 = 0.28$ ] and Membership within a Family Unit [ $F(1, 14) = 22.54, P < 0.001, \eta_p^2 = 0.62$ ] domains were impaired in patients with BD relative to controls. Overall social adjustment was also impaired in these patients [ $F(1, 14) = 12.61, P < 0.01, \eta_p^2 = 0.47$ ]. No other significant differences emerged.

### *3.3. Relation between psychosocial functioning and empathic responding*

There were significant positive relations found between the IRI Personal Distress scale and global social functioning ( $r = 0.48, P < 0.01$ ), Work/School Role ( $r = 0.38, P < 0.05$ ), Social/Leisure Activities ( $r = 0.47, P < 0.01$ ), and Relationship with Extended Family ( $r = 0.34, P = 0.05$ ) in our sample, suggesting that individuals who demonstrated elevated personal distress in negative social situations also showed reduced social functioning. Moreover, individuals who demonstrated lower scores on the IRI Empathic Concern scale also showed reduced functioning on the Social/Leisure activities scale of the SAS-SR ( $r = -0.34, P < 0.05$ ).

### *3.4. Relation between clinical variables and empathic responding*

There was limited evidence that scores on the IRI Personal Distress scale correlated with greater symptom severity as assessed by the Ham-D 17 ( $r = 0.33, P = 0.05$ ) and GAF ( $r = -0.33, P = 0.05$ ). No significant correlations emerged between

burden of illness (number of previous episodes, duration of illness) and performance on any of the IRI subscales ( $P$ 's > 0.05).

#### **4. Discussion**

To our knowledge, this is the first study to examine directly empathic responding in patients with BD. The main findings in this preliminary study were the reduced perspective taking and elevated levels of personal discomfort reported by BD patients in response to others' distress. Altered empathic responding, as assessed by these scales, was associated with decreased family, social and occupational functioning. Very preliminary evidence emerged that personal distress increased with higher levels of symptom severity.

Individuals with BD showed deficits on the 'Perspective Taking' subscale of the IRI, a measure of cognitive empathy. This result is consistent with previous investigations demonstrating social cognitive deficits, including impaired theory of mind, in BD (Kerr et al., 2003; Inoue et al., 2004, 2006; Bora et al., 2005; Olley et al., 2005; Lahera et al., 2008; Schenkel et al., 2008). Theory of mind, the ability to infer the thoughts and beliefs of others (Premack and Woodruff, 1978), is often described as overlapping with the construct of cognitive empathy (understanding another's emotional state). Deficits on the IRI Perspective Taking scale and other theory of mind paradigms suggest that patients with BD may experience difficulty shifting from an egocentric viewpoint in order to adopt the perspective of someone else (Vogeley et al., 2001). Previous work in both neurologically-intact and patient populations has highlighted the contribution of domain-general cognitive resources such as working memory to perspective taking ability (e.g., X believes Y thinks

A; Leslie et al., 2004; McKinnon and Moscovitch, 2007). We speculate that reduced perspective taking ability in our sample may stem, in part, from well-documented declines in executive functioning and memory resources in patients with BD (Altshuler et al., 2004; Bearden et al., 2006; MacQueen et al., 2005; Malhi et al., 2007; Mur et al., 2007), although further work is required to confirm the specificity of this relation, as well as identify other illness factors that may contribute to altered perspective taking.

Patients with BD also scored higher on the ‘Personal Distress’ subscale of the IRI, indicating that they were more likely to experience self-oriented feelings of discomfort and anxiety in response to stressful social situations, such as emergencies. This result is in line with previous reports of alterations in emotional perception (Bozikas et al., 2007) and in emotional regulation (Phillips et al., 2008) in patients with BD. Prior work in healthy participants also indicates an association between enhanced personal distress and prefrontal dysfunction (Spinella, 2005). Moreover, high levels of personal distress, as reflected by elevated scores on the PD scale of the IRI, have been shown previously to reflect impaired social cognitive functioning in neurologically-intact control samples, perhaps indicating a hyper-reflexive style of affective response (Spreng et al., 2009). Given the roles of the medial and lateral prefrontal cortices in social cognitive function, including empathy and theory of mind (e.g., see McKinnon et al., 2007 for a review), we speculate that structural (Blumberg et al., 2003b) and functional (Altshuler et al., 2005) abnormalities in prefrontal regions in patients with BD may also contribute to the impairments reported in this sample, but future studies are awaited to investigate this possibility.

Our patient sample showed preserved function on two subscales of the IRI: Empathic Concern and Fantasy. Previous work (Davis et al., 1983) confirms that each of the IRI subscales represents dissociable elements of the multi-factorial system underlying empathic responding. Here, patients with BD reported feelings of warmth, compassion, and concern for others equivalent to that experienced by matched controls. Our results suggest that although patients with BD may experience an exaggerated level of distress at the discomfort and anxiety experienced by others in stressful social situations, the ability to experience basic emotions felt in response to others' emotional states remains intact in these patients. Patients with BD also identified with fictional characters in books and movie at a rate equivalent to that reported by matched controls, indicating that imagination, as it relates to empathy, is also spared. Our finding of impairments in specific aspects of empathic responding, and preservation in others, is consistent with the notion that empathy is a multi-factorial process.

In keeping with a sizable body of literature that has reported significant impairments in various psychosocial domains in patients with BD (e.g., Bauwens et al., 1991; Serretti et al., 1999; Blairy et al., 2004), our patient sample was impaired in their occupational, social/leisure, family and global psychosocial functioning compared with healthy controls. Moreover, we found significant correlations between empathic responding ('Personal Distress'; 'Empathic Concern') and these various psychosocial domains. These findings are in line with previous findings in healthy individuals, where higher levels of personal discomfort in tense interpersonal situations were associated with greater levels of social dysfunction (Davis, 1983). The reciprocal may also be true, where

alterations in social networks and associated distress may have contributed to alterations in empathic responding, including the elevation in discomfort and anxiety experienced by patients in response to stressful social situations due to repeated negative interactions with others. In BD, an inability to disengage from self-oriented thought processes may also contribute to difficulties maintaining successful familial and social relationships, as well as occupational and leisure activities. Overall, these significant associations between affective empathy and psychosocial adjustment are important given that intact empathic skills have been found to contribute to higher social functioning (Baron-Cohen and Wheelwright, 2004; Brüne, 2005; Spreng et al., 2009).

We found very preliminary evidence that alterations in empathic responding were associated with higher levels of symptom severity. By contrast, empathic responding was not related to burden of illness. These findings are in line with previous reports where number of previous mood episodes and illness duration do not appear to contribute to impaired theory of mind performance in patients with BD (Inoue et al., 2004; Bora et al., 2005). Moreover, these results provide an early indication that alterations in empathic responding may be a state, rather than trait, marker of BD, reflecting a preoccupation with the self, negative ruminations, and negative cognitions about the self that are hallmark symptoms of mood disorders (Beck, 1967; Raes et al., 2006). Consistent with this viewpoint that depression is characterized by negatively biased information processing and distorted self-perceptions (e.g., Beck, 1967), individuals in a depressed state demonstrate a negative bias in their self-evaluations of task performance (Fu et al., 2005), personality (McKendree-Smith and Scogin, 2000), and competence in multiple domains

(e.g., social acceptance, academic competence, physical appearance; Hoffman et al., 2000). Despite this negative bias, there is significant evidence indicating that individuals with depression are more realistic and accurate judges of their social competence and general performance than non-depressed individuals (Lewinsohn et al., 1980; Ducharme and Bachelor, 1993), a phenomenon known as depressive realism (Alloy and Abramson, 1979; Colin, 1998). Additional studies involving larger numbers of subjects with a varied course of illness will be required to determine the strength of this preliminary finding and the association between alterations in empathic responding and declines in social functioning observed among patients with BD.

The preliminary results of this study provide initial evidence of alterations in select aspects (i.e., perspective taking; personal distress) of empathic responding in BD and suggest that these alterations are associated with impairments in family, social and occupational functioning. Interestingly, both the ability to engage in fantasy as it relates to the emotional responses of others, as well as more basic empathic concern, appear spared in this population. Longitudinal studies are necessary to determine whether social cognitive deficits are trait markers of vulnerability for BD. Our sample was comprised of patients in varying states of illness and a range of Bipolar I and Bipolar II illness; the extent to which these alterations persist across mood states and different illness presentations remains unknown. Future studies are also required to determine whether known alterations in neuronal structure and function in BD are associated with altered empathic responding in this disorder. Enhanced knowledge of these processes will improve our basic knowledge of the clinical and behavioural correlates of social cognition

and may further the goal of reducing the impact of BD on day-to-day functioning in these patients.

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**Table 1.** Clinical and demographic characteristics of study sample

		Controls ( <i>n</i> = 20)	BD patients ( <i>n</i> = 20)	Effect size (Cohen's <i>d</i> )
Sex	Male	<i>n</i> = 8	<i>n</i> = 6	
	Female	<i>n</i> = 12	<i>n</i> = 14	
Age		40.1(15.1)	43.0(8.9)	
Education		16.1(2.7)	15.7(2.6)	
Number of affective episodes			52.3(65.5)	
Onset of illness (in years)			20.4(8.5)	
Duration of illness (in years)			23.2(9.6)	
Ham-D score		1.5(1.8)*	11.3(6.9)*	-1.9
YMRS score		0.1(0.3)*	3.0(2.1)*	-2.0
GAF score		80.4(2.0)*	63.6(11.7)*	2.0

Values are *n* or mean (standard deviation).

**Abbreviations:** BD, bipolar disorder group; Ham-D, 17-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; GAF, Global Assessment of Functioning Scale.

\* Significant results ( $P < 0.01$ ).

**Table 2.** Interpersonal Reactivity Index subscale scores by group

IRI	Controls	BD Patients	Results	Effect size (partial eta-squared)
Perspective taking	20.2(5.6)*	17.0(3.7)*	$F = 4.53, df = 1, P < 0.05$	0.11
Empathic concern	22.2(3.2)	20.6(3.7)	$F = 2.29, df = 1, P > 0.05$	0.06
Fantasy	13.4(5.4)	12.4(4.9)	$F = 0.42, df = 1, P > 0.05$	0.01
Personal distress	8.2(5.4)*	12.3 (5.4)*	$F = 5.98, df = 1, P < 0.05$	0.14

Values are *n* or mean (standard deviation).

**Abbreviations:** BD, bipolar disorder group

\* Significant results ( $P < 0.05$ ).

*Foreword to Chapter 5, Study 2*

When this study was conducted, there were no studies that directly assessed the cognitive and affective components of empathy in a sample of outpatients with MDD. Prior reports only included depressed inpatients (O'Connor et al., 2002) or only examined processes linked closely to empathy such as emotional awareness (Donges et al., 2005). In this study we examined empathic responding in a sample of outpatients with MDD, examining the relation of performance to symptom severity, illness burden, and psychosocial function. We administered two standardized self-rated measures of empathic responding, the Toronto Empathy Questionnaire (TEQ; Spreng\*, McKinnon\*, et al., 2009) to assess empathic ability broadly and the IRI to specifically assess cognitive and affective facets of empathic responding. We expected that depressed patients would show impaired cognitive and affective empathic abilities, as a result of well-documented deficits in cognitive (e.g., perspective taking) and affective (e.g., emotion recognition) processing found in this patient population (Phillips et al., 2003). Deficits on other aspects of social cognition, including theory of mind, is associated with poor functional outcome in individuals with mood disorders (Inoue et al., 2006). To date, however, there have been no studies examining the relation between cognitive and affective empathic responding and standardized measures of social functioning in patients with MDD. Hence, we examined the relation between empathic abilities and psychosocial functioning. We predicted that altered empathic performance in patients with MDD would be associated with poor functioning. Finally, in light of recent findings showing that patients with a chronic and recurrent illness history show greater impairment on tests

of social (McKinnon et al., 2010) and cognitive function, (e.g., MacQueen et al., 2002), we examined the relation between illness burden and empathic responding. We expected that alterations in empathic performance would correlate significantly with a greater burden of illness.

The full author list and citation information for this article are provided below:

Cusi, A.M., MacQueen, G.M., Spreng, R.N., & McKinnon, M.C. (2011). Altered empathic responding in major depressive disorder: Relation to symptom severity and psychosocial outcome. *Psychiatry Research*, 188(2):231-6

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**Altered empathic responding in major depressive disorder: relation to symptom severity, illness burden, and psychosocial outcome**

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**ABSTRACT**

Individuals with major depressive disorder (MDD) demonstrate deficits in multiple social cognitive domains; however, systematic investigations of empathic responding have not been performed. Twenty patients with MDD completed two measures of empathy, the Interpersonal Reactivity Index (IRI: Davis, 1980, 1983) and the Toronto Empathy Questionnaire (TEQ: Spreng et al., 2009). Relative to matched controls, patients with MDD reported significantly reduced levels of empathy measured broadly on the TEQ and specifically in cognitive ('Perspective Taking') and affective ('Empathic Concern') domains captured by the IRI. A higher illness burden (i.e., greater number of past depressive episodes) was associated with greater reductions in perspective taking ability. This study provides early evidence of impaired empathic abilities in patients with MDD that may worsen with illness progression. Alternatively, reductions in perspective taking ability may contribute to a more severe course of illness in this population. Further longitudinal work is needed to characterize the relation between social cognitive performance and social functioning in this population.

**Keywords:** Empathy, Depression, Social functioning

## **1. Introduction**

Empathy refers broadly to the ability to infer and share the feeling states of others in reference to oneself (Decety and Moriguchi, 2007), playing a central role in successful interpersonal engagement and higher social functioning (Baron-Cohen and Wheelwright, 2004). Investigators have adopted a multidimensional approach to the study of empathy, proposing that this psychological construct involves both cognitive (e.g., inferring another's mental state) and affective (e.g., affective response to the feeling state of another) components (Davis, 1983; for a review see McKinnon et al., 2007). Critically, many of the same cognitive (e.g., executive functioning; working memory) and affective (e.g., emotion comprehension) processes are affected in patients with MDD (Mikhailova et al., 1996; Landro et al., 2001; Surguladze et al., 2004; Gualtieri et al., 2006), rendering it probable that patients with this disorder will demonstrate reduced empathic abilities that rely on these same processing resources. To date, however, few studies of empathic responding have been conducted in patients with MDD. Here, we examine empathic responding in a sample of outpatients with MDD, examining the relation of performance to symptom severity, illness burden, and psychosocial function.

Studies examining social cognitive performance in patients with MDD reveal a conflicting pattern of performance impairment and sparing. For example, a wide body of evidence reveals that patients with MDD are impaired in the recognition of affective facial expressions (see Leppänen, 2006 for a review). Here, individuals with MDD demonstrate a mood-congruent bias during facial emotion recognition tasks, showing deficits in the recognition of happy faces (Mandal and Bhattacharya, 1985; Rubinow and

Post, 1992; Mikhailova et al., 1996; Suslow et al., 2001; Gotlib et al., 2004; Surguladze et al., 2004; LeMoult et al., 2009), enhanced recognition of sad facial expressions (Mandal and Bhattacharya, 1985; David and Cutting, 1990; Surguladze et al., 2004; Goeleven et al., 2006), as well as a tendency to identify neutral faces as sad relative to healthy controls (David and Cutting, 1990; Wright et al., 2009). A number of studies, however, fail to show evidence of alterations in the processing of emotional faces among patients with MDD (Gaebel and Wolwer, 1992; Mogg et al., 2000; Kan et al., 2004; Hertel et al., 2009). Patients with MDD also demonstrate a negative bias during the processing of affective prosodic stimuli by interpreting neutral prosodic emotions as negative (Kan et al., 2004) and showing enhanced recognition of sad emotional tones (Uekermann et al., 2008a). Few studies have examined theory of mind, the ability to infer the mental states (e.g., belief, intentions, emotions) of others to understand and predict their behaviour (Premack and Woodruff, 1978) in patients with MDD. Theory of mind is a term related to but dissociable from the construct of ‘cognitive empathy’, and involves a cognitive understanding and appreciation of another’s mental state. In these studies, actively ill patients show impairment on a variety of theory of mind tasks placing demands on cognitive and affective processing resources (Lee et al., 2005; Uekermann et al., 2008b; Wang et al., 2008). Overall, the literature concerning social cognitive performance in MDD reveals a mixed pattern of findings, underscoring the need for further investigation. The primary goal of this study is to examine specifically empathic responding in a sample of patients with MDD, an area of social cognitive performance remaining underexplored in this population.

Deficits in empathic responding have been reported in neuropsychiatric populations such as schizophrenia (Montag et al., 2007; Shamay-Tsoory et al., 2007) and autism spectrum disorders (Baron-Cohen et al., 2001; Rogers et al., 2007), however, to date, very few studies have assessed empathic responding in patients with mood disorders. Early evidence of reduced empathic capacity has been reported in individuals with bipolar disorder (Shamay-Tsoory et al., 2009; Cusi et al., 2010). Both Shamay-Tsoory et al. (2009) and our group (Cusi et al., 2010) found that relative to healthy controls, patients with bipolar disorder (BD) reported decreased cognitive empathy ('Perspective Taking') and elevated levels of affective personal discomfort in response to others' distress ('Personal Distress'), as assessed by the Interpersonal Reactivity Index (IRI; Davis, 1983). In our study, impaired affective empathic abilities were associated with greater depressive severity but not number of past mood episodes or illness duration suggesting that changes in empathic responding in bipolar disorder may represent a state, rather than trait, marker of illness. Interestingly, these alterations in affective distress were associated with reduced psychosocial functioning (as assessed at the time of testing) in our sample of BD patients, most of whom were mildly ill; it is unclear at present whether further reductions in psychosocial function would arise with more severe illness or remit over the course of euthymia.

Prior investigations provide preliminary evidence of alterations in abilities associated with empathic responding in individuals with MDD. For example, Donges et al. (2005) found that *inpatients* with acute MDD showed intact awareness of their own emotions, but reduced awareness of others' emotions compared to matched controls. This

decrease in emotional awareness for others was associated with elevated symptoms of depression. Interestingly, emotional awareness improved significantly following treatment in a psychotherapeutic program targeted at recognizing emotional responses and their situational origins (Donges et al., 2005). Only one study has assessed directly the cognitive and affective components of empathy in patients with MDD. O'Connor and colleagues (2002) found that depressed *inpatients* reported elevated levels of distress and discomfort in response to other's negative situations on the IRI Personal Distress subscale; greater levels of depression severity were associated with higher scores on this subscale. These patients also scored significantly higher than healthy controls on self-rated measures of altruism, a process linked closely to empathy, although not directly analogous to it.

In the present study, we conducted a preliminary assessment of empathic responding in a sample of MDD *outpatients* in varying states of illness. First, we used two standardized self-rated measures of empathic responding, the Toronto Empathy Questionnaire (TEQ; Spreng et al., 2009) to assess empathic ability broadly and the IRI to specifically assess cognitive and affective facets of empathic responding. We expected that depressed patients would show impaired cognitive and affective empathic abilities, as a result of well-documented deficits in cognitive (e.g., perspective taking) and affective (e.g., emotion recognition) processing found in this patient population (Phillips et al., 2003; Lee et al., 2005; Uekermann et al., 2008a). Notably, impairments on tests of social cognition, most prominently, theory of mind (Inoue et al., 2006), is associated with poor functional outcome in individuals with mood disorders. To date, however, there have

been no studies examining the relation between cognitive and affective empathic responding and standardized measures of social functioning in patients with MDD. Hence, we examined the relation between empathic abilities and psychosocial functioning using a well-validated measure of functional outcome, the Social Adjustment Scale Self-Report (SAS-SR; Weissman and Bothwell, 1976). We predicted that similar to patients with BD, altered empathic performance in patients with MDD would be associated with impaired functioning. Finally, in light of recent findings showing that patients with a chronic and recurrent illness history show greater impairment on tests of social (McKinnon et al., 2010) and cognitive function, (e.g., Basso and Bornstein, 1999; MacQueen et al., 2002), we examined the relation between illness burden (e.g., number of depressive episodes, illness duration) and empathic responding.

## **2. Methods**

### *2.1. Participants*

Twenty patients who had experienced at least one prior episode of MDD (6 males and 14 females) and 20 age- and education-matched controls (7 males and 13 females) with no history of psychiatric illness participated in the present study. The demographic and clinical characteristics of the study sample are summarized in Table 1. Patients were tested in varying states of illness, allowing for an examination of the relation between symptom severity and empathic responding. Current level of symptom severity was assessed using the 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) and the Global Assessment of Functioning Scale (GAF; American Psychiatric Association, 1994). The study sample consisted of 5 euthymic patients (HAM-D 17 score

less than 7), 13 patients with sub-syndromal depression (HAM-D 17 score between 7 and 14), and 2 patients with moderate depression (HAM-D 17 score between 15 and 30). Our patient sample was free of psychotic symptoms. Medication consisted of selective serotonin reuptake inhibitors ( $N = 7$ ), serotonin and noradrenaline reuptake inhibitors ( $N = 4$ ), tricyclic antidepressants ( $N = 3$ ), monoamine oxidase inhibitors ( $N = 2$ ), stimulants ( $N = 1$ ), antipsychotic drugs ( $N = 3$ ), anticonvulsants ( $N = 5$ ), benzodiazepines ( $N = 3$ ), sedative/hypnotics ( $N = 6$ ), bupropion ( $N = 2$ ), mirtazapine ( $N = 1$ ), and no medication ( $N = 1$ ). Two patients were on anti-parkinson drugs (ropinirole) for restless leg syndrome. We were not able to obtain medication information for one participant. Participants with a history of neurological disease, traumatic brain injury and/or loss of consciousness (lasting more than 60 s), electroconvulsive therapy or transcranial magnetic stimulation therapy within 1 year, substance dependence, and untreated significant medical illness were excluded.

All participants provided written informed consent and the research protocol was approved by the Research Ethics Board of St. Joseph's Healthcare Hamilton/ McMaster University.

## 2.2. Materials

The *IRI* (Davis, 1980, 1983) is a 28-item self-report instrument that measures both cognitive and emotional aspects of empathy. Items are rated on a scale ranging from 0 (*does not describe me well*) to 4 (*describes me very well*). The cognitive subscales comprise the Perspective Taking and Fantasy scales. Whereas the Perspective Taking (PT) scale measures the tendency to spontaneously understand the psychological point of

view of others (i.e. *I sometimes find it difficult to see things from the "other guy's" point of view*), the Fantasy subscale assesses the tendency to identify with fictional characters (i.e. *I daydream and fantasize, with some regularity, about things that might happen to me*). The emotional subscales of the IRI comprise the Empathic Concern and Personal Distress scales. The Empathic Concern subscale evaluates the respondent's feelings of warmth and compassion for others (i.e. *I often have tender, concerned feelings for people less fortunate than me*). The Personal Distress scale measures self-oriented feelings of distress and discomfort in response to difficult interpersonal situations (i.e. *I sometimes feel helpless when I am in the middle of a very emotional situation*). The IRI has been shown to have good test-retest reliability, internal consistency, and adequate levels of convergence with other measures of empathy (Davis, 1980,1983; Christopher et al., 1993).

The *TEQ* (Spreng\*, McKinnon\*, et al., 2009) is a 16-item empirically-derived self-report measure. This measure represents empathy as a primarily emotional process, by tapping constructs similar to those measured by the IRI Empathic Concern scale. The *TEQ* has demonstrated good internal consistency, high test-retest reliability and strong convergent validity.

The *Social Adjustment Scale Self-Report* (SAS-SR; Weissman and Bothwell, 1976) is a 54-item self-rated questionnaire that assesses role performance in six domains of functioning including work/school role, social/leisure activities, relationship with extended family, marital role, parental role and membership within a family unit. Each item is scored on a 5-point scale, with higher scores indicative of greater social

impairment. Individual subscale and total scores are calculated by averaging all applicable items. The SAS-SR has shown high internal consistency, good test–retest reliability, and has shown good agreement with the interviewer-rated version of this measure (Weissman and Bothwell, 1976; Davis, 1980, 1983; Christopher et al., 1993; Weissman and Staff, 1999).

### *2.3. Procedures and statistical analyses*

These data were analyzed using a multivariate analyses of variance (MANOVA) treating Group (MDD, HC) as a fixed variable and score for each of the IRI (PT, EC, FS, PD) subscales as a dependent variable. This procedure was repeated for the SAS-SR. In order to examine group differences on the TEQ, a univariate ANOVA was conducted. Estimated effect sizes were analyzed by partial eta square values.

Partial correlations after adjusting for age and gender were computed to examine the relation between empathic responding, illness burden (e.g., depression severity, illness duration, age at onset of illness, number of depressive episodes) and social functioning. Alpha was set at 0.05 for all analyses.

## **3. Results**

### *3.1. Performance on the TEQ*

Relative to controls, the MDD group reported reduced levels of empathic responding as assessed by the TEQ [ $F(1, 38) = 6.96, P = 0.01, \eta_p^2 = 0.16$ ].

### *3.2. Performance on the IRI*

Table 2 displays the participants' performance on the IRI. Patients with MDD reported lower levels of Perspective Taking [ $F(1, 38) = 7.65, P = 0.009, \eta_p^2 = 0.17$ ] and

Empathic Concern [ $F(1, 38) = 4.86, P = 0.03, \eta_p^2 = 0.11$ ] than did healthy controls. No other significant effects emerged.

### *3.3. Psychosocial functioning*

As expected, the Work/Academic functioning [ $F(1, 13) = 12.59, P = 0.004, \eta_p^2 = 0.49$ ], Membership within a Family Unit [ $F(1, 13) = 4.85, P = 0.04, \eta_p^2 = 0.27$ ] domains, and overall social adjustment [ $F(1, 13) = 5.83, P = 0.031, \eta_p^2 = 0.31$ ] were impaired in the MDD patients relative to controls. No other significant differences emerged.

### *3.4. Relation between psychosocial functioning and empathic responding*

No significant relations emerged between levels of SAS-SR functioning and performance on the TEQ and IRI subscales ( $P$ 's > 0.05).

### *3.5. Relation between clinical variables and empathic responding*

Within the MDD group, there was evidence that lower scores on the IRI Perspective Taking scale correlated with a higher number of depressive episodes ( $r = 0.60, P = 0.02$ ). No significant correlations emerged between symptom severity, burden of illness (age at onset of illness, duration of illness) and performance on any of the IRI subscales ( $P$ 's > 0.05). No significant relations were found between performance on the TEQ and any of the clinical variables ( $P$ 's > 0.05).

#### 4. Discussion

To our knowledge, this is the first report of altered empathic abilities in a sample of *outpatients* with MDD. Critically, we found preliminary evidence that patients with MDD reported significantly lower levels of both cognitive (Perspective Taking) and affective (Empathic Concern) empathy relative to matched controls. A higher number of depressive episodes were also associated with reduced perspective taking abilities, suggesting a gradual worsening in the ability to mentalize about other's affective states with illness progression.

The current finding of reduced 'Perspective Taking' ability among patients with MDD is consistent with prior reports of impairments in the closely related domain of theory of mind in patients with MDD (Inoue et al., 2004; Lee et al., 2005; Uekermann et al., 2008b; Wang et al., 2008) and are consistent with the notion that depressed individuals have difficulties detaching from an egocentric viewpoint in order to adopt the perspective of another (Vogelely et al., 2001). These results are also consistent with recent studies conducted in bipolar disorder, documenting reduced perspective taking ability in individuals in varying states of illness (Cusi et al., in 2010; McKinnon et al., 2010), including euthymia (Shamay-Tsoory et al., 2009). We suspect that impaired perspective taking ability in our sample may be mediated by deficits in executive functioning and other cognitive processes, including cognitive flexibility, closely associated with perspective taking ability (e.g., Eslinger, 1998; McKinnon and Moscovitch, 2007) and reported routinely in patients with MDD (e.g., Porter et al., 2003). Future studies, however, are required to test the relation between empathic ability and

cognitive functioning in MDD, through, for example, the utilization of neuropsychological test batteries along with measures of empathic responding.

Our results also provide early evidence that individuals with MDD report less feelings of care and concern in response to someone else's emotional experience; patients reported lower levels of empathic concern on the Empathic Concern subscale of the IRI. Individuals with MDD also reported reduced empathic responding on the TEQ. These findings are consistent with the notion that depression is characterized by a preoccupation with the self and negative ruminations (Beck, 1967; Raes et al., 2006), that is enhanced with more severe illness (Joormann and Gotlib, 2010). These findings are, however, in contrast with previous reports of intact Empathic Concern in a sample of depressed inpatients, where O'Connor et al. (2002) reported elevated levels of personal distress, but not reduced empathic concern, in response to others' concerns in a sample comprised of acutely ill inpatients with MDD. Taken together with the current findings, we suggest that levels of empathic concern may fluctuate with illness state such that a variable profile of empathic responding emerges across active, sub-syndromal and euthymic states of depressive illness. Notably, individuals with bipolar disorder also show differing levels of empathic responding across active and euthymic illness states (Shamay-Tsoory et al., 2009; Cusi et al., 2010), suggesting that alterations in empathic responding in patients with mood disorders may represent a state, rather than trait, marker of illness.

As reviewed, the literature concerning social cognitive performance in patients with MDD is conflicting. Consistent with these findings, the results of this study provide evidence of both impaired and intact empathic capacity in MDD. Although patients with

MDD reported reduced levels of care and concern for others (IRI Empathic Concern scale, TEQ), they reported similar levels of distress in response to difficult interpersonal situations (IRI Personal Distress scale) as controls. Patients with MDD also rated themselves comparably to controls in identifying with fictional characters found in books and movies (Fantasy subscale), a finding in line with previous studies conducted in depressed (O'Connor et al., 2002) and bipolar (Shamay-Tsoory et al., 2009; Cusi et al., 2010) samples. Baron-Cohen and Wheelwright (2004) have suggested that the Fantasy subscale of the Interpersonal Reactivity Index contains items that measure constructs broader than empathy, including imagination. On balance, our finding of impairments in specific aspects of empathic responding captured by the IRI, and preservation in others, is consistent with the notion that empathy is multidimensional in nature (Davis, 1994).

Empathic responding has been shown to rely on a complex network of neural regions that serve diverse cognitive (e.g., dorsolateral prefrontal cortex), affective (e.g., orbitofrontal and medial frontal; amygdala; subgenual cingulate) and memory functions (e.g., anterior and posterior cingulate, temporal poles; Eslinger, 1998; Farrow et al., 2001; McKinnon et al., 2007; Zahn et al., 2009). Critically, many of the same neural regions thought to mediate the cognitive and affective processes necessary for empathic responding have been implicated in patients with MDD, showing altered metabolic functioning and/or structural abnormalities (see Price and Drevets, 2010 for a recent review). For example, the medial prefrontal cortex, a region implicated in cognitive perspective taking (Eslinger, 1998; Shamay-Tsoory et al., 2009) and theory of mind (Gallagher and Frith, 2003; Mar, 2011), shows hyperactivity (Biver et al., 1994;

Nofzinger et al., 2005) and reduced tissue volume (Lai et al., 2000; Lacerda et al., 2004) in patients with MDD. The dorsolateral prefrontal cortex (DLPFC), shows tissue volume loss (Coffey et al., 1993; Konarski et al., 2008; Brooks et al., 2009) and hypometabolism in patients with MDD (Biver et al., 1994; Dunn et al., 2002; Davidson et al., 2003) and may contribute to reductions in cognitive flexibility and the generation of ideas also thought requisite to empathic responding (Eslinger, 1998; Rankin et al., 2005).

Moreover, tissue volume loss (Sheline et al., 1998; Caetano et al., 2004; Hastings et al., 2004) and hypermetabolism (Drevets, 2000; Sheline et al., 2001) has been reported in the amygdala, a region involved in modulating attention to emotionally salient stimuli (thought to be necessary to understand and respond to the feeling states of others).

Finally, the subgenual cingulate cortex, a region implicated in the generation of negative affect (thought to be necessary for generating emotional responses to social situations and the feelings of others), shows abnormally elevated activity in patients with MDD (Drevets and Raichle, 1992; Drevets et al., 2008). Impairments in empathic concern in our sample may be further mediated by deficits in emotion recognition (e.g., amygdala) and the generation (e.g., subgenual cingulate) and regulation of emotional responses (e.g., orbitofrontal cortex) also found in this disorder (see Phillips et al., 2003 for a review). On balance, we speculate that empathy draws on a host of cognitive and affective processing resources and the locus of deficits in this and other social cognitive domains is likely to be multi-faceted. Future studies, however, are awaited to explore this hypothesis and to identify specifically the neural underpinnings of social cognitive performance deficits in MDD.

Patients in our sample with a higher burden of illness (i.e., greater number of depressive episodes) were more likely to have reduced IRI Perspective Taking scores, suggesting a gradual deterioration of this social cognitive ability with illness progression or, alternatively, that overall reductions in perspective taking ability among patients with MDD contribute to a more severe course of illness. This finding is similar to that of a recent study (Schenkel et al., 2008) that found an extended course of illness also predicted theory of mind impairment in patients with acute and sub-syndromal bipolar disorder; it is notable, however, that bipolar disorder involves a different course of illness than MDD and these findings cannot be directly linked. Alterations in cognitive functioning, including memory and executive functioning, have also been shown to worsen with disease progression in patients with recurrent unipolar and bipolar illness (van Gorp et al., 1998; Lebowitz et al., 2001; MacQueen et al., 2002; but see Nehra et al., 2006; Pavuluri et al., 2006 for conflicting findings). The ability to adopt the perspective of another is important for guiding successful social behaviour (Baron-Cohen and Wheelwright, 2004). Compromised perspective taking skills may lead to the inappropriate interpretation of social cues, resulting in changes in mood and interpersonal functioning, and may represent a risk factor for having a more deteriorative course of illness. The cross-sectional nature of the study, however, limits our ability to determine if deficits in perspective taking and associated cognitive processes contribute to the development of mood symptoms or conversely, if an increased illness burden negatively impacts cognitive functioning and perspective taking. Specifically, prospective, longitudinal

studies are needed to explore how empathic responding changes over the course of illness in individuals with major depressive disorder.

Neither cognitive nor affective empathy scores were significantly associated with mood state at the time of testing, a result consistent with prior research showing that some aspects of social cognitive performance (e.g., theory of mind, facial emotion recognition) are independent of symptom severity in MDD (e.g., Leppänen et al., 2004; Lee et al., 2005). Other investigations (O'Connor et al., 2002; Donges et al., 2005), however, have reported significant negative associations between altered empathic responding and level of depression. The discrepant finding in the present study may be due, in part, to the limited range of HAM-D scores in our sample, and the inclusion of sub-syndromal patients. Further studies with larger sample sizes and participants in varying mood states, including acute depression and euthymia, are required to determine the association between empathic responding and symptom severity.

Our preliminary study provides the first evidence of impaired cognitive *and* affective empathic abilities in a sample of MDD outpatients and warrants further investigations of empathic responding in this patient population. Future work would benefit from including objective measures of empathic responding given that self-report measures show inherent biases (Baldwin, 2000). Further, this study provides the first evidence that an impaired ability to adopt another person's viewpoint is related to past burden of illness in MDD; the directionality of this relation has yet to be established. Future studies of empathic responding that follow patients longitudinally in active and in euthymic illness states, and that examine performance in clinically unaffected first-degree

relatives of patients with MDD are needed to determine if alterations in this social cognitive ability represent a trait characteristic of MDD. Additional work is required to characterize the relation between social cognitive performance and social functioning, where reduced levels of empathic responding were not associated with poor psychosocial functioning in our sample, likely due to the small sample size. Given that intact empathic skills are essential for higher social functioning (Baron-Cohen and Wheelwright, 2004; Spreng et al., 2009; Cusi et al., 2010), the non-adaptive nature of empathy deficits in MDD is at odds with recent claims that depression increases analytic skills in a manner that is evolutionarily "adaptive" (Andrews and Thomson, 2009). Future research is required to determine whether these empathy deficits have adaptive value (e.g., providing protection from further emotional arousal under stressful or dangerous situations). Finally, future studies utilizing structural and functional neuroimaging methods to examine the neural substrates of social cognition in MDD will provide significant information concerning the putative neural mechanisms underlying social dysfunction in this illness.

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**Table 1.** Clinical and demographic characteristics of study sample

<i>Characteristic</i>		<b>Controls</b> (n=20)	<b>MDD patients</b> Total sample (n=20)
		<i>n</i>	<i>n</i>
<b>Sex</b>	Male	7	6
	Female	13	14
		<i>Mean</i>	<i>Mean</i>
<b>Age</b>		44.5(11.2)	45.1(11.4)
<b>Education</b>		17.553(2.7)	15.78(2.9)
<b>Number of affective episodes</b>			7.3 (7.8)
<b>Onset of illness (in years)</b>			31.7(9.4)
<b>Duration of illness (in years)</b>			18.8(11.4)
<b>Ham-D score</b>		1.33(2.7)*	9.2(5.5)*
<b>GAF score</b>		81.2(3.8)*	64.6(10.0)*

Values are *n* or mean (standard deviation).

**Abbreviations:** GAF, Global Assessment of Functioning Scale; Ham-D, 17-item Hamilton Depression Rating Scale; MDD, major depressive disorder

\* Significant results ( $P < 0.05$ ).

**Table 2.** Interpersonal Reactivity Index and Toronto Empathy Questionnaire scores by diagnostic group

Empathy Scales	Controls	MDD Patients	Results	Effect size (partial eta-squared)
TEQ	67.1(6.3)*	61.4(7.2)*	$F(1, 38) = 6.96, P < 0.05$	0.16
IRI Perspective taking	21.4(4.3)*	17.8(3.8)*	$F(1, 38) = 7.65, P < 0.05$	0.17
IRI Empathic concern	22.8(3.7)*	20.4(3.6)*	$F(1, 38) = 4.86, P < 0.05$	0.11
IRI Fantasy	14.4(5.9)	15.1(5.0)	$F(1, 38) = 0.12, P > 0.05$	0.003
IRI Personal distress	8.4(6.2)	11.4(4.5)	$F(1, 38) = 2.86, P > 0.05$	0.07

Values are *n* or mean (standard deviation).

**Abbreviations:** IRI, Interpersonal Reactivity Index; MDD, major depressive disorder group; TEQ, Toronto Empathy Questionnaire

\* Significantly different from control group at  $P < 0.05$

## **CHAPTER 6: GENERAL DISCUSSION**

## **General Discussion**

The main goal of this thesis was to determine if patients with mood disorders demonstrate impairments on two overlapping, but dissociable social cognitive domains: ToM and empathy. We found evidence that subsyndromal depressed patients with BD and MDD show deficits on second-order ToM questions that required participants to compare and contrast the differing perspectives of two different characters involved in complex social scenarios. Subsyndromal patients with BD tended to perform poorly on first-order ToM questions that required the integration of only one character's perspective on the same measure; by contrast subsyndromal MDD patients did not show deficits on first-order ToM questions. Bipolar patients in varying illness states also showed impaired mental state discrimination on the Reading the Mind in the Eyes Test and deficits on a ToM task that required social inferencing. Consistent with our ToM results, both BD and MDD patients reported reduced levels of cognitive empathy (Perspective Taking) but differed on affective empathy domains. Specifically, patients with BD reported increased levels of Personal Distress, whereas patients with MDD rated themselves lower on the Empathic Concern subscale of the IRI. Preliminary evidence indicated that deficits in ToM and empathic responding were associated with reduced levels of social functioning. We also found early evidence that symptom severity may be associated with altered ToM and empathic ability. Illness burden was not found to be consistently associated with ToM or empathic responding.

*ToM*

In Chapter 3, we demonstrated that patients with mood disorders with subsyndromal depressive symptoms performed poorly on a ToM reasoning task that involved perspective taking. Bipolar patients with subsyndromal depressive symptoms tended to perform worse than controls on first-order ToM tasks that required adopting the perspective of a single character by inferring their thoughts and feelings in various complex social scenarios; however, the extent of deficit was greater for second-order ToM measures that required participants to integrate two perspectives simultaneously (Study 1). Similarly, subsyndromal patients with MDD were also impaired on second-order ToM questions, but showed preserved performance for first-order ToM questions (Study 2). The tendency for subsyndromal BD but not MDD patients to show impairments on the less challenging first-order ToM stimuli and exhibit deficits on the cognitively demanding second-order ToM questions is consistent with research demonstrating that bipolar depression is characterized by more severe cognitive deficits relative to unipolar depression (Borkowska & Rybakowski, 2001; Savard et al., 1980; Wolfe et al., 1987). These studies are the first to date that have assessed social cognitive ability in patients with mood disorders experiencing subsyndromal depressive symptoms.

Taken together, these findings are consistent with our view that variables such as symptom severity and the level of cognitive processing demands required for task performance may contribute to ToM in patients with mood disorders (Chapter 2). Specifically, remitted patients appear to be impaired on those ToM tasks that require a greater level of cognitive and affective resources (Bora et al., 2005; Inoue, Tonooka, Yamada, & Kanba, 2004; 2006; Kerr, Dunbar, & Bentall, 2003; Olley et al., 2005). Here,

we presented evidence that subsyndromal patients with BD show deficits on a cognitively demanding ToM task (second-order ToM questions), and tended to perform poorly on first-order ToM stimuli that require fewer cognitive and affective processing resources; by contrast, subsyndromal patients with MDD examined here only demonstrated poor performance on the cognitively challenging second-order ToM stimuli. Finally, mood disorder patients in an active state of illness show impairment on ToM tasks that place both low and high demands on central processing resources (Kerr et al., 2003; Lee et al., 2005; Uekermann et al., 2008; Wang, Wang, Chen, Zhu, & Wang, 2008; Wolkenstein, Schonenberg, Schirm, & Hautzinger, 2011).

The results presented in Chapter 3 are also consistent with evidence demonstrating that central processing resources such as working memory contribute to ToM performance. For example, Gordon and Olsen (1998) demonstrated that ToM performance in typically developing children correlated significantly with a measure of working memory. Moreover, recent work suggests that cognitive variables such as working memory, attention, and set-shifting are associated with ToM performance among patients with MDD (Wolkenstein et al., 2011; Zobel et al., 2010) and BD (Bora et al., 2005; Olley et al., 2005; Wolf et al., 2010). The findings presented here contribute to this line of research by demonstrating differential impairment on a task that varied in the level of cognitive and affective load in mood disorder populations that have well-documented deficits in multiple cognitive and affective domains.

In Chapter 4, we administered two complex measures of ToM in a sample of bipolar patients in varying illness states, demonstrating that individuals with BD perform poorly on an advanced ToM task that involves decoding the mental state of a person from their eye gaze. We extend prior work reporting deficits in mental state attribution from eye expressions in euthymic individuals with BD (Bora et al., 2005) by demonstrating impairment in patients in various states of illness, including subsyndromal status. The present finding of a deficit on the RMET among patients with BD is also in accord with a large body of evidence demonstrating impairment in facial emotion recognition among this population (McClure-Tone, 2009).

We also found evidence that patients with BD are impaired on a naturalistic measure of social perception (IPT-15). This finding is consistent with prior work documenting deficits in social perception in this patient population, including poor performance on ecologically valid ToM paradigms (Bazin et al., 2009; Montag et al., 2010) as well as the the recognition of facial emotion (McClure-Tone, 2009).

Interestingly, our patient sample showed impaired performance on certain subscales of the IPT-15 and preserved performance on others. This finding is in line with the viewpoint that ToM is a multi-faceted constructed that relies upon the joint contribution of numerous cognitive and affective processes (e.g., Carrington & Bailey, 2009; Mar, 2011; McKinnon et al., 2007).

Overall, the results of Chapter 3 and 4 are broadly consistent with previous reports of ToM deficits in patients with MDD (e.g., Lee et al., 2005; Wang et al., 2008; Zobel et

al., 2010) and BD (e.g., Bora et al., 2005; Olley et al., 2005). Caution is warranted in the interpretation of these results, however, given the low sample sizes and relatively small effect sizes observed across studies. We suspect that deficits in central processing resources (e.g., cognitive and affective) required for task performance contribute to the impairments observed across these ToM studies. Future tests are awaited to determine the contribution of specific cognitive and affective processing resources to ToM ability among patients with MDD and BD, although early evidence indicates that measures of executive functioning and emotion recognition may moderate ToM performance (Bora et al., 2005; Olley et al., 2005).

### *Empathic Responding*

In Chapter 5, we examined the performance of patients with BD and MDD on standardized measures of empathic responding. We demonstrated that patients with BD reported reduced levels of Perspective Taking and increased levels of Personal Distress on the Interpersonal Reactivity Index (Davis, 1983). Perspective taking, a measure of cognitive empathy, is thought to be closely related to the construct of ToM (Eslinger, 1998). This finding is in line with prior studies reporting deficits in ToM in patients with BD (e.g., Bora et al., 2005; Inoue et al., 2004; Inoue et al., 2006; Kerr et al., 2003; Lahera et al., 2008; Olley et al., 2005; Schenkel et al., 2008). Deficits on the IRI Perspective Taking scale and other ToM paradigms among patients with BD and MDD suggest that these patients may experience difficulty shifting from self-perspective in order to adopt the perspective of another (Vogeley et al., 2001). By contrast, increased levels of Personal

Distress reported by our patient sample indicates that patients with BD experience elevated levels of self-oriented feelings of discomfort in response to tense interpersonal situations. The high levels of affective empathy (Personal Distress) reported in this study is consistent with research reporting difficulties with emotion regulation in patients with BD (Phillips, Ladouceur, & Drevets, 2008). Elevated Personal Distress is also in accordance with the notion that empathy relies on a shared representation mechanism such as the perception-action hypothesis (Preston & de Waal, 2002) and simulation theory (Gallese & Goldman, 1998; Gordon, 1986), and that emotional contagion is exaggerated in individuals with BD compared to healthy controls. It is plausible that enhanced levels of emotional contagion, as demonstrated by increased levels of IRI Personal Distress, may result from a lack of inhibition of higher-order cognitive empathy processes, which are also compromised in BD (Perspective Taking) on this more basic facet of emotional empathy (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003).

In a second study (Chapter 5, Study 2), we presented evidence that patients with MDD in varying illness states report reduced levels of empathy as assessed broadly by the Toronto Empathy Questionnaire and in both cognitive (Perspective Taking) and affective (Empathic Concern) empathy facets as measured by the IRI. The low scores on the Perspective Taking scale of the IRI is consistent with prior reports of ToM deficits in individuals with MDD (e.g., Lee et al., 2005; Wang et al., 2008) and preliminary research indicating reduced cognitive empathy in depressed patients (Wilbertz, Brakemeier, Zobel, Harter, & Schramm, 2010). Similar to our BD findings summarized above, impaired

levels of perspective taking indicate that patients with MDD may experience difficulty understanding the feelings and viewpoint of others.

We also provided the first evidence that individuals with MDD reported less feelings of warmth and compassion for others on the Empathic Concern Subscale of the IRI. Moreover, patients with MDD reported reduced levels of empathic responding on the Toronto Empathy Questionnaire, a measure that contains many items that tap constructs closely related to the Empathic Concern Subscale of the IRI. These results are in contrast with prior reports of intact Empathic Concern in samples of patients with MDD (O'Connor, Berry, Weiss, & Gilbert, 2002; Wilbertz et al., 2010). O'Connor et al. (2002) found that, although acutely ill patients with MDD reported increased levels of Personal Distress relative to healthy controls, there were no differences between the groups on the remaining cognitive and affective empathy subscales of the IRI. Moreover, a recent study conducted by Wilbertz et al. (2010) reported reduced cognitive empathy (Perspective Taking) and increased Personal Distress in a sample of chronically depressed patients. Taken together with the current findings, it is plausible that affective empathic responding may vary with mood state. Specifically, our sample was comprised mainly of euthymic and subsyndromal patients with MDD who reported less feelings of care and concern in response to someone else's emotional experience; this measure of affective empathy may only be impaired during these particular mood states. By contrast, increased levels of personal distress or discomfort in response to stressful social situations may only be present in patients with more severe symptoms such as those found in Wilbertz et al.'s (2010) and O'Connor et al.'s (2002) studies.

Taken together, the results of Chapter 5 indicate impairment in certain empathy domains and intact ability in others. This is line with the notion that empathy is a multi-dimensional construct that consists of both cognitive and affective components (Davis, 1994). Our findings of impaired empathic responding in individuals with BD and MDD is consistent with the idea that individuals with mood disorders display self-focused tendencies such as rumination (Just & Alloy, 1997; Knowles et al., 2005; Nolen-Hoeksema & Morrow, 1991; Thomas & Bentall, 2002). Similar to our ToM findings, however, the results of these two studies are constrained by their limited sample sizes and small effect sizes. Future studies that incorporate larger samples are needed to confirm these findings.

#### *Symptom Severity*

We presented preliminary evidence that depressive symptom severity was found to be negatively associated with both first- and second-order ToM performance in a sample of BD patients with subsyndromal depressive symptoms and matched controls (Chapter 3, Study 1). We also found early evidence that an increased level of depression was associated with elevated self-oriented distress during negative social situations (IRI Personal Distress) in a sample of patients with BD and healthy controls (Chapter 5, Study 2). Prior research has shown significant associations between depressive symptom severity and other social cognitive domains such as facial emotion recognition in patients with BD (e.g., Vaskinn et al., 2007), but the correlations reported here are the first to extend these findings to ToM and empathy domains. Taken together, these findings suggest that individuals with BD with elevated symptoms of depression may have

difficulties understanding the thoughts and feelings of others because of difficulties suppressing an egocentric viewpoint to consider the perspective of another (Vogeley et al., 2001). These findings are also consistent with the notion that individuals with BD engage in self-oriented thought processes (Knowles et al., 2005).

We found preliminary evidence that YMRS and IPT-15 scores were negatively associated with RMET accuracy scores. It must be noted that no relations were found between RMET, IPT-15 accuracy scores and depressive symptom severity. Prior studies, however, have reported no such associations between measures of symptom severity and ToM in euthymic (Bora et al., 2005; Montag et al., 2010) and symptomatic patients with BD (Wolf et al., 2010). Further studies including larger patient samples in different mood states will be required to address adequately the association between symptomatology and ToM ability.

Similar to our BD findings, we presented evidence that impaired performance on second-order ToM stimuli tended to be associated with increased depression severity and significantly correlated with reduced levels of overall functioning on the Global Assessment of Functioning Scale (Chapter 3, Study 2) in a sample of patients with sub-syndromal MDD. In contrast to our bipolar findings, we failed to find any significant associations between cognitive and affective empathy scores and level of depression in a sample of patients with MDD and matched controls (Chapter 5, Study 2). The lack of associations between empathic responding and symptom severity is in line with work demonstrating that certain domains of social cognition (e.g., theory of mind, facial emotion recognition) are independent of depressive symptom severity in MDD (e.g., Lee

et al., 2005; Leppänen, Milders, Bell, Terriere, & Hietanen, 2004). The inability to detect any relations between level of depression and empathy scores in this particular study is not consistent with prior research that have shown significant associations between altered empathic responding and mood state at the time of testing (e.g., O'Connor et al., 2002). It is possible that the limited range of depressive symptom scores in our sample may partially account for these discrepant findings found in in this study.

Overall, these significant associations between impaired ToM and empathic ability and symptom severity provide preliminary evidence that social cognitive performance may be compromised with active mood symptoms. These preliminary findings indicate that these deficits in social cognitive performance may be a state-related marker of illness in patients with mood disorders. Given the correlational nature of our findings, it is plausible that the opposite may be true, specifically that impairments in social cognitive ability may exacerbate mood symptoms. The cross-sectional nature of our study makes it difficult to make any firm conclusions about the directionality of these associations, highlighting the importance of future longitudinal studies that examine how social cognition changes over the course of illness in individuals with mood disorders. An inability to find consistent evidence of associations between severity of mood symptoms and social cognitive performance indicates that although variation in mood symptoms may contribute to ToM and empathic ability to a certain extent, the influence of mood state may only be one of many factors influencing social cognitive impairment in patients with mood disorders.

### *Illness Burden*

Contrary to our expectations, the only significant relation to arise between social cognitive ability and burden of illness variables among our BD studies was found between impaired second-order ToM performance and an extended duration of illness in a sample of patients with sub-syndromal depressive symptoms (Chapter 3, Study 1). This preliminary finding indicates that poor performance on complex, cognitively challenging ToM measures is associated with long-standing illness and may worsen with illness progression. This finding corresponds to prior research conducted in acutely ill patients with pediatric BD (Schenkel et al., 2008) and remitted bipolar patients (Wolf et al., 2010), that found that an earlier illness onset was associated with ToM impairment. Moreover, similar associations have been reported in studies examining general neurocognitive abilities in patients with BD (e.g., van Gorp et al., 1998). The deterioration of ToM may correspond to the increased cognitive impairment observed among mood disorder patients with recurrent illness (MacQueen et al., 2002; Robinson & Ferrier, 2006).

We failed to find any relations between course of illness variables (number of mood episodes, illness duration, onset of illness) and accuracy scores on the RMET and IPT-15 (Chapter 4). Similarly, neither cognitive nor affective empathy scores on the IRI were found to be related to illness burden variables (Chapter 5, Study 1). An inability to detect any associations between course of illness variables and both ToM and empathy among patients with BD is in line with prior research reporting non-significant correlations between ToM performance and variables such as number of affective episodes (Bora et al., 2005) and illness duration (Bora et al., 2005; Inoue et al., 2004).

Similar to our BD findings, increased impairment on the Perspective Taking scale of the IRI was associated with an extended illness burden as measured by number of depressive episodes in a sample of patients with MDD (Chapter 5, Study 2). This is the first study to report such an association between empathic response and a course of illness variable in MDD. This finding indicates that more pronounced impairments in perspective-taking ability may develop with recurrent illness. This finding is also consistent with Zobel et al. (2010) who found that a sample of MDD patients with a chronic course of illness was impaired on both first- and second-order ToM questions. This result is also in line with prior research indicating that cognitive domains such as memory and executive functioning may progressively decline in patients with mood disorders (e.g., MacQueen et al., 2002). By contrast, we failed to find an association between ToM ability and any burden of illness variables in a sample of patients with subsyndromal symptoms (Chapter 3, Study 2). This finding is in line with recent work that reported no relation between illness duration and ToM performance in patients with MDD (Inoue et al., 2004; Wolkenstein et al., 2011).

Taken together, we found very limited evidence that burden of illness variables may influence ToM and empathic ability in patients with mood disorders. Prior research examining the relation between burden of illness variables and social cognitive performance in both MDD and BD also reveals a conflicting pattern of findings. The relation between ToM, empathy, and course of illness variables in patients with mood disorders requires further research in studies with larger sample sizes and longitudinal designs.

*Relation to Social Functioning*

Consistent with our predictions, we found preliminary evidence that poor performance on the IPT-15 was associated with reduced levels of social functioning on the SAS-SR in a sample of patients with BD and healthy controls. We also evidence that measures of affective empathy ('Personal Distress'; 'Empathic Concern') correlated significantly with various psychosocial domains in a sample of patients with BD and matched controls. These findings indicate that individuals with BD experience difficulties in social processing and communication, stemming from deficits in their ability to understand and share the perspectives and feelings of others. These findings provide the first evidence that significant disruptions in ToM and empathic responding are related to poor social functioning in individuals with BD.

We also found the first evidence that poor performance on second-order ToM stimuli was associated with impaired social functioning in a sample of MDD patients with subsyndromal symptoms and healthy controls. By contrast, neither cognitive nor affective empathy measures were found to be associated with social functioning in patients with MDD. The inability to detect a relation between empathic responding and psychosocial functioning may be due to our limited sample size.

The significant associations between social cognitive performance and psychosocial functioning found in this thesis are in line with studies indicating that poor performance on tests of ToM are associated with a poorer prognosis in patients with MDD and BD (Inoue et al., 2006). These findings are also consistent with prior research

in patients with schizophrenia and autism spectrum disorders, where impaired ToM and empathic responding has been shown to be a significant predictor of altered interpersonal behaviour and functioning (Baron-Cohen, Knickmeyer, & Belmonte, 2005; Schenkel, Spaulding, & Silverstein, 2005; Shamay-Tsoory et al., 2007). The present findings suggest that these impairments have important implications for day-to-day functioning not tapped by our laboratory-based measures.

#### *Limitations and Future Directions*

Several limitations of this thesis need to be acknowledged. First, the relatively modest sample sizes of the studies likely limited the statistical power of the findings and may have obscured group differences on ToM and empathy measures, as well as associations between social cognitive response and clinical and social variables. Future studies that recruit larger sample sizes and homogeneous patient groups that are similar in terms of mood state, symptom severity, illness duration, onset, and number of affective episodes would allow for more accurate comparisons across studies and may reconcile the divergent findings found in the social cognition literature.

Another limitation of this study was the use of self-rated questionnaires such as the Interpersonal Reactivity Index and Toronto Empathy Questionnaire to assess empathic responding. It is possible that our findings on these measures may be confounded by our participants' propensity to answer these questionnaires in a socially desirable manner. However, it must be noted that prior work has used questionnaires to investigate this social cognitive domain in neuropsychiatric populations, including

schizophrenia (Shamay-Tsoory et al., 2007) and mood disorders (O'Connor et al., 2002; Shamay-Tsoory et al., 2009; Wilbertz et al., 2010). Future studies may benefit from more objective measures that assess empathy during naturalistic or real-world settings (Zaki, Bolger, & Ochsner, 2008).

Another limitation includes the near ceiling performance found in both healthy controls and individuals with mood disorders on first-order ToM questions in both studies in Chapter 3. Thus, it is difficult to conclude whether significant performance differences between the patient and comparator groups would arise if the first-order questions were more cognitively challenging.

The majority of patients found in these studies were heterogeneous in terms of medication status. Although preliminary evidence indicates that an association between social cognitive ability and medication is unlikely in patients with mood disorders (e.g., Kan, Mimura, Kamijima, & Kawamura, 2004; Shamay-Tsoory et al., 2009), other studies suggest that certain psychotropic medications may potentially affect social cognitive function (e.g., Merens, Booij, & Van Der Does, 2008; Tranter et al., 2009). For instance, recent work indicates that impairments in facial emotion processing appear to improve following antidepressant treatment in patients with MDD (Merens et al., 2008; Tranter et al., 2009). We were not able to examine in a principled way at medication status because of the small sample size, and future research would benefit from examining the influence of particular medication classes on social cognitive ability in mood disorders.

Although we speculate the impairments observed in ToM and empathic responding in patients outlined in this thesis stem from impairments in cognitive and affective processing resources, we did not include a neuropsychological battery to assess cognitive functioning nor a measure of affective responding such as a basic emotion recognition task. Future work that includes measures of cognitive and affective performance will more adequately assess the contribution of these central processing resources to social cognitive ability.

Findings from this thesis suggest that individuals with BD and MDD demonstrate emotion dysregulation that may potentially impede higher-order cognitive skills such as perspective taking. This idea is consistent with research documenting that the neural systems thought to be involved in both ToM and empathic responding (Mar, 2011; Shamay-Tsoory, 2011) are also implicated in the pathophysiology of BD and MDD (Price & Drevets, 2010). It is possible the deficits observed in ToM and empathic ability here may stem from alterations in neuronal functioning found in these patient populations. Indeed, numerous studies examining facial emotion processing in patients with MDD and BD report reduced levels of activation in prefrontal areas involved in emotion regulation and higher-order cognitive processes, and increased activity in subcortical and limbic regions implicated in emotion appraisal and generation, indicating a lack of inhibition of higher-order cognitive centres on limbic and emotion-related structures. Prospective, longitudinal studies that follow patients across euthymic and active illness states are needed to determine the influence of neuronal function in the emergence of impairments in ToM and empathic responding.

*Clinical Implications*

The ability to infer and share the mental states of others is crucial for successful social interactions. Treatment interventions for patients with MDD and BD should take into account impairments in theory of mind and empathic responding. Incorporating social cognitive training into treatment protocols may address these deficits and improve social perception and interpersonal functioning in these disorders.

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