Theory of Mind in Bipolar Disorder: A Pilot Descriptive Study

by

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Abstract

Objective: Primarily, to determine if affective Theory of Mind (ToM) decoding differs between patients with bipolar disorder who are experiencing mania, euthymia, or depression. Secondarily, to determine if a bias in ToM in patients experiencing different affective episodes is related to a positive, negative, or neutral valence of the target. Finally, to determine if mental state decoding is related to the severity of depressive, manic, or anxious symptoms

Methods: A prospective, cross-sectional, study of ToM in patients with bipolar disorder experiencing mania ($n = 14$), depression ($n = 25$), or euthymia ($n = 20$), using the “Reading the Mind in the Eyes Task” (Eyes Task) and the Animal Task developed to control for nonsocial response demands of the Eyes Task. Measures of depressive and anxious symptoms were taken using self-report scales. Interview measures of depressive and manic symptoms were also conducted. A review of patient records was conducted to collect information regarding medications, and course of illness variables.

Results: Patients experiencing mania were significantly impaired in mental state decoding compared to euthymic and depressed patients with bipolar disorder. No significant difference was observed between the depressed and euthymic groups. These relationships were maintained when controlling for age of illness onset and Animal Task accuracy. No effect of valence was found. Manic symptom severity was negatively correlated to Animal Task accuracy but no other relationships between Eyes and Animal Tasks and the severity of manic, depressive, or anxious symptoms were found. Group differences in Eyes Task performance were not due to differences in demographics, axis I comorbidities, history of psychosis, or course of illness measures.
**Limitations:** The sample was too small to assess differences between acutely and chronically ill patients. There was no assessment of neurocognition or intelligence using tasks previously validated with manic patients. **Conclusions:** Patients with bipolar disorder experiencing mania were significantly impaired in mental state decoding compared to patients who were depressed or euthymic. The deficit in ToM decoding in manic patients independent of indicators of illness severity may be indicative of qualitative differences in interpersonal dysfunction between mania, depression, and euthymia in patients with bipolar disorder.
Co-Authorship

Dr R. Milev, Dr. M. David, and Dr. K. Harkness, of the Department of Psychiatry and the Department of Psychology and Dr. M. Sabbagh of the Department of Psychology contributed to the study design. Dr. R. Milev, L. Lazowski, and J. Joannette, were responsible for participant recruitment and the study visits. Dr. Milev assisted with analysis and preparation of this document.
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Chapter 1
Introduction

Over the last decade there has been increased interest in cognitive dysfunction associated with bipolar disorder. The traditional Kraepelin concept (Kraepelin, 1913) of bipolar disorder consisting of relapse and remission has been replaced with heterogeneous reports of continued impairments into the euthymic phase (Jamrozinski, 2010). Patients with bipolar disorder present with significant deficits in social functioning such as reduced number of social relationships or interactions and less fulfillment from social and family relationships (Dickerson et al., 2001; Malhi et al., 2007). In addition, a reduced level of social functioning has been reported to continue into remission in patients with bipolar disorder (Brissos et al., 2008).

In order to understand the mechanisms underlying social dysfunction, researchers have studied social cognition in patients with bipolar disorder. Social cognition is described as the higher cognitive processes underlying social interactions, which require the ability to appreciate the intentions and perspectives of others (Brothers, 1990). Social cognition includes subcategories such as “relationship dynamics”, “social knowledge” and “social perception” (see Green et al., 2008). The majority of empirical studies of social cognition in patients with bipolar disorder involve emotion recognition (de Almeida Rocca, van den Heuvel, Caetano, & Lafer, 2009). This is unsurprising considering the affective symptoms experienced in manic and depressed episodes of bipolar disorder.
Recently, social cognitive research investigating theory of mind (ToM) in bipolar disorder has gained popularity. ToM is a term used to describe the ability to conceptualize mental states such as beliefs, desires, intentions, and emotions within oneself and others (Premack & Woodruff, 1978). Also referred to as “social intelligence” and “mentalizing”, ToM is regarded as the primary manner in which individuals interpret and predict the behaviour of others (Baron-Cohen et al., 2001). ToM has considerable overlap with empathy, and some researchers even use the terms interchangeably (see Baron-Cohen et al., 2001). It is important to note, however, that ToM is specifically the ability to recognize mental states and does not imply a vicarious emotional response to another person (Shamay-Tsoory, 2008).

The Reading of the Mind in the Eyes Task (Baron-Cohen et al., 2001) is a measure of ToM that explicitly addresses the ability to recognize emotional content in the mental states of others. It is a self-paced task that requires participants to infer mental states by observing only the eye region of characters. Participants must choose the best one of four descriptive words that represent the mental state expressed.

The Eyes Task is not cognitively taxing so it does not rely on aspects of cognition known to be affected in bipolar disorder. For example, the Eyes Task is not related to memory unlike ToM tasks that require story comprehension (e.g. Kerr et al., 2003). Euthymic patients with bipolar disorder present with cognitive deficits that are exacerbated during affective episodes such as verbal memory, sustained attention, and executive functioning (Bora et al., 2009a; Robinson & Ferrier, 2006; Trivedi et al., 2008). Acknowledging these deficits by using a task such as the Eyes Task that is not heavily
tied to non-social cognitive function may give a clearer understanding of ToM ability in patients with bipolar disorder.

An additional benefit is that, although cognitively simple, the Eyes Task is challenging and sensitive to subtle differences in ability. One recent study compiled the Eyes Task performance of healthy control groups from six independent studies and found an average accuracy of 73.1% (Fertuck et al., 2009). This is of particular importance as other ToM tasks that do not rely on memory, such as comic tasks, suffer from ceiling effects in many clinical samples (Bazin et al., 2009; Sarfati et al., 1997).

The Eyes Task is sensitive enough to subtle ToM differences to be used in non-clinical settings. One trend has been in dissociating ToM ability from measures of empathy. Recent reports using the Eyes Task found that stage actors had enhanced ToM ability but not empathy (Goldstein et al., 2009) and the opposite was true for professional psychics (Dziobek et al., 2005). The Eyes Task has also been used to investigate trait related deficits in schizophrenia. A study found no impairment in the Eyes Task with unaffected first-degree relatives of patients with schizophrenia (Kelemen et al., 2004). With these results, Kelemen et al. argued that ToM is not associated with schizophrenia liability although these findings have been disputed (Yucel et al., 2009). As group differences have been demonstrated in healthy adults using the Eyes Task, it is expected that it would be effective in detecting differences within clinical samples.

The Eyes Task has been shown to be sensitive to mood in non-clinical samples of students with mild to moderate levels of depressed symptoms. Enhanced Eyes Task
accuracy was found in dysphoric university students (Harkness et al., 2005) and is sensitive to mood induction in university students with past major depression (Harkness et al., 2009). Harkness et al. suggest that more accurate mental state decoding in people with dysphoria or a history of past depression may indicate that enhanced ToM may be related to increased risk of depression. ToM deficits associated with dysphoria broaden the understanding of how ToM is related to psychiatric disorders and supports the sensitivity of the Eyes Task to differences in mood.

Researchers investigating ToM have reported significant findings using the Eyes Task with different clinical groups. Patients with chronic and first-episode schizophrenia (Craig et al., 2004; Kettle et al., 2008), and women with anorexia nervosa (Russell et al., 2009) or clinical depression (Lee, Harkness, Sabbagh, & Jacobson, 2005) all performed poorly on the Eyes Task compared to healthy controls. On the other hand, no impairment in psychopathic individuals (Richell et al., 2003) and enhanced ToM decoding ability in patients with borderline personality disorder (Fertuck et al., 2009) have been reported in studies using the Eyes Task. Finally, Eyes Task accuracy is a better predictor of social functioning in patients with schizophrenia than more complex tasks that simulate social interactions (Bora et al., 2006). As dysfunctional and enhanced ToM ability has been found with the Eyes Task in clinical groups and it is predictive of social functioning, the Eyes Task is an appropriate measure of ToM in patients with bipolar disorder.

The current study is a pilot investigation of mental state decoding in patients with bipolar disorder across manic, depressed, and euthymic episodes. Investigation of ToM ability in general is limited in patients with bipolar disorder. Using the Eyes Task, Bora et
al. (2005) found significant deficits in euthymic patients with bipolar disorder compared to healthy controls. To the author’s knowledge, the Eyes Task has not been used to study ToM in patients with bipolar disorder in depressed or manic episodes. As the Eyes Task is sensitive to differences in mood (Harkness et al., 2009) and has been used in different psychiatric samples, it is appropriate for investigating ToM between manic, depressed, and euthymic patients with bipolar disorder.
Chapter 2
Literature Review

2.1 Bipolar Disorder

2.1.1 Diagnostic Criteria

Bipolar disorder is a mood disorder characterized by the presence of one or more mood episodes clinically referred to as manic episodes or, if less severe, hypomanic episodes (American Psychiatric Association, 2000). Individuals with bipolar 1 disorder present with a past or current manic episode and usually a past or current episode of depression. Individuals with bipolar 2 disorder usually present with recurrent depressive episodes and at least one hypomanic episode. Although some patients can switch between episodes of mania and depression, it is common for patients to experience periods of symptom remission, or euthymia (Basco, 1996). Experiencing mixed episodes, which have a combination of depressive and manic symptoms, is also common.

The Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR; American Psychiatric Association, 2000) defines manic episodes as “distinct periods of abnormally and persistently elevated, expansive, or irritable mood lasting at least one week”, though the time stipulation is waived if the patient is hospitalized. Each episode must consist of at least three of the following symptoms (four if the episode mood is irritable) with considerable persistence and severity: 1) increased self-esteem or feelings of grandiosity, 2) decreased need for sleep, 3) increased talkativeness or subjective
feelings of greater pressure to speak, 4) subjective experiences of mind racing or flight of ideas, 5) increased distractibility, 6) increased psychomotor agitation or goal-directed activity, and 7) disproportionate involvement in pleasure seeking activities that hold great risk of serious consequences (e.g. sexual indiscretion, excessive shopping, unsound investments).

Depressive episodes experienced by patients with bipolar disorder are consistent with those experienced by patients with major depressive disorder. The DSM IV-TR (2000) recognizes major depressive episodes as five or more of the following symptoms which cause either significant distress or decreased function and occur nearly every day for a period of at least two weeks: 1) depressed mood for most of the day, 2) considerably decreased interest or pleasure in most or all activities, 3) markedly increased or decreased unintentional change in weight 4) insomnia or hypersomnia, 5) psychomotor agitation or retardation, 6) fatigue, 7) feelings of worthlessness, or excessive guilt 8) reduced ability to think, concentrate, or make decisions, and 9) recurrent thoughts of death.

2.1.2 Prevalence

The prevalence of bipolar disorder is reported to be from 1.5-3% of the North American population (Narrow et al., 2002) with rates increasing as the definition of bipolar disorder becomes less restrictive (Waraich et al., 2004). Despite fluctuations, a 1-year prevalence rate of 0.8% and a lifetime prevalence of 1.0% for bipolar 1 disorder are relatively consistent across most international studies (Merikangas & Pato, 2009). Bipolar 2 disorder is often excluded from epidemiological studies as it is generally believed that hypomanic episodes are difficult to assess outside of the clinical environment. The
National Comorbidity Study-Replication (NCS-R), a major population survey in the United States, reported a 4.5% lifetime prevalence of hypomania (Merikangas & Pato, 2009). Although this value seems high, it has clinical relevance as the symptoms reported mirror those of patients in outpatient treatment programs (Kessler et al., 2005).

Many recent reports of sociodemographics relating to bipolar disorder use three nationally representative samples in the United States (NCS-R, National Health and Nutrition Examination Survey, Epidemiologic Catchment Area Study). These studies demonstrate that the prevalence rates for bipolar disorder are consistently inversely related to income and level of education and are not related to race or gender (Grant et al., 2005; Jonas et al., 2003; Merikangas & Pato, 2009). Although there is a trend for more women in psychiatric care for bipolar disorder than men (Blanco et al., 2002), equal prevalence is further supported in studies of pediatric and adolescent bipolar disorder (Soutullo et al., 2005). Some researchers report different manifestations of bipolar disorder between men and women. For example, a study of pediatric bipolar disorder found that boys had higher rates of manic episodes whereas girls had higher rates of depressed episodes (Duax et al., 2007). Men are also more likely than women to report manic episodes at onset (Kawa et al., 2005). When bipolar 2 disorder is considered, a prevalence rate comparable to the 2:1 female to male ratio found in major depressive disorder is observed. (Benazzi, 2006).
2.1.3 Burden

Bipolar disorder is associated with significant psychological suffering, social and occupational dysfunction, and economic burden (Yatham et al., 2004). A report from the World Health Organization found that bipolar disorder, in terms of years lived with a disability, is the sixth highest-ranked cause of disability internationally. It is estimated that bipolar disorder outranks cancers and primary neurological disorders such as Alzheimer’s disease and epilepsy due to an early onset and relatively stable lifetime chronicity (Lopez & Murray, 1998).

Functional recovery, a primary goal for treatment of bipolar disorder, can be very difficult to achieve. With a classification of functional recovery as the ability to achieve the level of functioning the patient had prior to their most recent episode, many studies have found striking evidence for maintenance of impairment (Cardoso et al., 2010). For example, in a 1-year follow-up study of manic or mixed episode patients, 48% of patients reached clinical (syndromic) recovery but only 26% reached symptomatic recovery and only 24% reached functional recovery (Keck et al., 1998). A low level of functional and symptomatic recovery is indicative of the chronicity of impairment associated with bipolar disorder. Furthermore, the severity of social and cognitive dysfunction observed in bipolar disorder is comparable to that found in schizophrenia (Brissos et al., 2008; Dickerson et al., 2001). A study of patients receiving treatment through community and rehabilitation services found comparable social and cognitive deficits between patients with bipolar 1 disorder to patients with schizophrenia. Of 41 measures of social and cognitive functioning, 36 measures did not differ significantly between the two patient
groups (Dickerson et al.). Patients with bipolar disorder present with social and functional impairments of considerable chronicity and severity highlighting a need for further investigation of social cognitive functioning in bipolar disorder.

A relationship between quality of life and severity of affective symptoms when depressed and euthymic has been reported (Piccinni et al., 2007). As well, poorer quality of life has been shown to persist in remitted patients (Brissos et al., 2008). Brissos et al. found that patients with remitted bipolar 1 disorder had significantly lower quality of life scores in physical, psychological, social, and environmental domains compared to healthy controls. When controlling for both depressive and manic symptoms only psychological and social domains remained significant, suggesting that other factors aside from subsyndromal affective symptoms contribute to low quality of life score in remitted phases. Interestingly, quality of life was strongly related to psychopathology and neurocognitive deficits, especially executive functioning and verbal abstraction. It has been suggested that neurocognitive measures are negatively related to functional outcome (Atre-Vaidya et al., 1998) and are better at predicting long-term rather than current quality of life (Fujii et al., 2004). As quality of life and functional recovery are associated with social and cognitive dysfunction, researchers have turned to developing a coherent understanding of cognitive dysfunction in bipolar disorder to better identify treatment targets.
2.1.4 Neurocognitive Deficits

Bipolar disorder is associated with significant cognitive impairment. Patterns of cognitive dysfunction in manic and depressed episodes have a great deal of overlap. The deficits most commonly reported across episodes of mania and depression are found in: executive function (Martinez-Aran et al., 2004), verbal learning and memory (Wolfe et al., 1987), attention (Clark & Goodwin, 2004), visual memory (Coffman et al., 1990) and psychomotor speed (Malhi et al., 2007). Some studies were unable to define differences in cognitive deficits between manic and depressed episodes despite very different clinical presentations (Bulbena & Berrios, 1993; Goldberg et al., 1993). Some researchers have argued that different patterns of dysfunction can result in comparable task scores. For example, patients with bipolar depression often make inattentive errors and have trouble shifting tasks whereas manic patients tend to make response pattern errors of impulsiveness and lower focused attention (Murphy et al., 1999; Sax et al., 1995). These clinically relevant differences have caused similar performance scores on primary measures while secondary measures were very different (Murphy et al., 1999).

A great deal of research in cognitive dysfunction is focused on patients who are euthymic. In a recent meta-analysis of studies that compared euthymic patients with bipolar disorder to healthy controls, Bora et al. (2009a) found deficits of moderate to large effect size in executive functioning, verbal memory, sustained attention, and psychomotor speed that persisted in euthymic patients despite publication bias. This is consistent with the results of another meta-analytical study of euthymic bipolar disorder
by Robinson et al. (2006) although they also found a large effect size for response inhibition.

The pattern of deficits in executive functioning and memory is consistent with a ‘hypoactive prefrontal cortex’ model of bipolar disorder (Kronhaus et al., 2006; Olley et al., 2005). Neuroimaging studies support a role of dysfunction in the anterior cingulated cortex (AC) and prefrontal cortex (PFC), especially the ventromedial and dorsolateral regions as the potential neurological underpinning of bipolar disorder (Blumberg et al., 2000; Simpson et al., 2001). Although there are trait and affective state abnormalities observed in neuroimaging studies of bipolar disorder (e.g. Blumberg et al., 2003), neurocognitive deficits have been attributed to the inability to engage prefrontal regions in both affective episodes and euthymia in bipolar disorder (Monks et al., 2004). Expanding research involving PFC function from customary neurocognitive testing to include cognitive domains like ToM which also rely on PFC functioning (Carrington & Bailey, 2009) may be beneficial in assessing illness severity in clinical settings.

2.2 Theory of Mind

2.2.1 Constructs

As methods for testing ToM ability range in difficulty and differ in the involvement of other cognitive domains, researchers have defined constructs of ToM in an effort to explain differential findings. One distinction deals with the extent of social information required. ToM decoding uses immediately available information (e.g. facial expressions or actions) to presume the mental state of others; generally addressing
questions involving the type of mental state expressed. ToM reasoning relies on the ability to combine the information immediately available with prior knowledge about the individual or the situation in order to make judgments on more complex theory or mind tasks; generally addressing questions involving why someone is in their current state (Sabbagh, 2004). There is also a distinction made between cognitive and affective aspects of ToM. Cognitive ToM involves inferences about knowledge or intention whereas affective ToM involves inferences on emotional state (Montag et al., 2010; Sabbagh, 2004). With researchers employing different tasks to assess ToM, contradictory findings in clinical samples may be due to different aspects of ToM assessed.

The typical structure of a ToM task involves the presentation of a story through text, images, or audio, alone or in combination. The participant is then asked questions regarding their comprehension of the story. The most common cognitive ToM tasks require the participant to accurately ascribe false belief or ignorance to characters. First order false belief questions involve asking about a character’s belief whereas second order questions are based on inferring the mental state a character would ascribe to another character, or beliefs of beliefs. For example, the common Sally-and-Anne test (Baron-Cohen et al., 1985; Wimmer & Perner, 1983) presents one character hiding an object while another character leaves the room. Perspective taking ability is required to recognize that, upon return, the character that left the room will think that the object has not been moved and will look for it in its original place (Brüne & Brüne-Cohrs, 2006). A first order false belief question would ask where the character will first look for the object. A second order question would ask where one character thinks the other character
will look for the object first. Typically developing children can pass first and second order false belief tasks like the Sally-and-Anne task around the age of 4-6 (Baron-Cohen et al., 1985).

Another common type of ToM task involves detecting a faux pas. These are considered to be more advanced ToM reasoning tasks as they require the representation of both the speaker and listener’s mental states as well as an appreciation for the listener’s affective response. An example presented by Baron-Cohen et al. (1999) is when a character, after identifying an old acquaintance as a good friend, mistakes their name. In order to correctly recognize a faux pas has occurred, the participant must recognize the unintentional false belief of the first character as well as the emotional impact their false belief has on the second character. Baron-Cohen et al. (1999) found that some children with Asperger syndrome or high functioning autism, two disorders associated with impaired ToM, were able to pass both false belief and faux pas tasks. When individuals who have disorders associated with ToM deficits pass these tasks, it raises concerns of specificity with dissociating ToM ability from general cognitive deficits when used in other patient groups for which ToM has not been so well documented (Bora et al., 2005).

Two notable ToM tasks in the literature specifically address advanced ToM decoding ability while limiting the cognitive demands of typical social interactions. The first is the “Yoni” task which combines verbal cues, eye gaze, and facial expressions to address first and second order questions for both cognitive and affective ToM (Baron-Cohen & Goodhart, 1994; Shamay-Tsoory et al., 2007). This task, although beneficial in detecting deficits in gloating and envy recognition, is not sensitive to subtle affective and
cognitive ToM deficits in adults with Asperger syndrome or high functioning autism (Shamay-Tsoory, 2008). The second is the Eyes Task (Baron-Cohen et al., 2001), which specifically addresses advanced affective ToM decoding and is designed for individuals who pass false belief tasks.

2.2.2 Neuroanatomical Aspects of ToM Constructs

A great deal of neuroimaging studies have worked towards mapping the regions of the brain responsible for ToM. Carrington and Bailey (2009) reviewed 38 functional magnetic resonance imaging (fMRI) studies of healthy participants during many different types of ToM tasks. The medial prefrontal and orbitofrontal cortices and the superior temporal sulcus were the areas most often activated. The temporoparietals, anterior- and para-cingulate cortices were also considered “core” regions. Beyond identifying ToM regions of the brain, researchers have started differentiating affective and cognitive ToM on a neuroanatomical basis.

A trend for investigating neuronal activity associated with deficits in affective ToM preceded that of cognitive ToM. Patients with localized orbitofrontal/ventromedial, and especially right ventromedial prefrontal lesions, had dysfunctional affective ToM (faux pas detection) but intact cognitive ToM ability (second order false belief; Shamay-Tsoory, Tomer, Berger, Goldsher, & Peretz, 2005). In this study patients with posterior cortex lesions and healthy controls were unimpaired in both tasks. A similar investigation of patients with traumatic brain injury compared patients with focal ventromedial to dorsolateral prefrontal lesions. Both patient groups had poor scores on the Eyes Task however only the patients with ventromedial lesions did poorly on a faux pas task (Geraci
et al., 2010). Combined, these studies support a role of the ventromedial PFC in affective ToM in both decoding and reasoning tasks.

A focus on neuroanatomical substrates of cognitive ToM is less common in the literature but the studies undertaken have found interesting trends. In an fMRI study of cognitive and affective perspective-taking tasks, Hynes et al. (2006) found that cognitive perspective taking was associated with the dorsolateral prefrontal cortex whereas affective perspective taking was most strongly related to medial orbitofrontal cortex activation. The dorsolateral prefrontal cortex as well as the right temporoparietal junction were also found to be activated in a study using false belief tasks (Sommer et al., 2007). Finally, one study interested in dissociating cognitive from affective ToM used repetitive transcranial magnetic stimulation (TMS; Kalbe et al., 2010). Stimulation of the dorsolateral prefrontal cortex improved response time in cognitive but not affective ToM tasks or physical tasks using the “Yoni” ToM task (Kalbe et al.). The neuroanatomical dissociation of cognitive and affective ToM has been studied in healthy participants but the same cannot be said for patients with bipolar disorder.

The only study to date which has used fMRI to investigate ToM ability in bipolar disorder compared euthymic patients to healthy matched controls (Malhi et al., 2008). Malhi et al. used animation sequences of triangles which moved in a manner that implied complex mental states by mimicking human behaviour. All activations related to the ToM task were stronger in the healthy controls. Healthy controls had robust activation in ToM related areas such as bilaterally in the supramarginal angular, and middle temporal gyri as well as prefrontal and subcortical regions. In contrast, patients with bipolar
disorder had activation that was limited to the anterior cingulate, percuneus and cuneus. Furthermore, any significant ToM related activation in the euthymic group was lost when statistically compared to the activation of healthy controls. Malhi et al. argue that activation in the percuneus and cuneus suggests that euthymic patients are capable of forming internal representations of first- and third-person perspectives. It may be problems with elaboration of these perspectives, requiring activation of surrounding areas seen in healthy controls, causing ToM and social deficits in patients with bipolar disorder.

A great deal of research involving ToM ability in patients with bipolar disorder involves the use of cognitive ToM tasks, often to represent a general ToM ability. As there is strong neuroanatomical evidence that cognitive and affective ToM exist as separate constructs, there is also a need for investigation into the separate ToM constructs in bipolar disorder.

2.2.3 Investigation of ToM in Euthymic State

In an effort to determine to what extent ToM dysfunction exists in euthymic phases, researchers have used different tasks to study ToM ability in euthymic bipolar disorder. A study of executive functioning and cognitive ToM ability in euthymic patients found that ToM deficits were related to increased verbal demands (Olley et al., 2005). Euthymic patients with bipolar disorder did significantly worse than healthy controls on a ToM story comprehension task but had comparable scores on non-ToM stories and non-verbal comic ToM tasks. The euthymic group, however, did not reach a level of impairment in the verbal ToM task with less than one standard deviation from the
healthy controls. Considering the relative ease of story tasks, tests of more subtle ToM may be more applicable in understanding ToM in patients with bipolar disorder (Baron-Cohen et al., 1999). Results comparable to the study by Olley et al. were reported in a study by Montag et al. (2010) of both cognitive and affective ToM ability in euthymic patients using the Movie for Assessment of Social Cognition (MASC; Dziobek et al., 2006). The MASC is a naturalistic task that consists of short videos of four characters in different social situations; the videos are followed by forced choice questionnaires. The reason for using tests of this nature is to increase sensitivity to ToM ability as well as mimic the cognitive demands of typical social interactions. Montag et al. found that patients with bipolar disorder had dysfunctional cognitive ToM abilities while affective ToM abilities remained intact. The cognitive ToM deficit was maintained when controlling for verbal memory, physical inferencing, or resistance towards interference, supporting an argument for specific social cognitive deficits.

Contrary to the results of Montag et al. (2010), Bora et al. (2005) found deficits in both affective and cognitive ToM. Compared to healthy controls, euthymic patients had poorer scores in the Eyes Task. Bora et al. also used a Hinting Task which is a series of audio clips ending in one character hinting to another developed to assess ToM in patients with schizophrenia (Corcoran et al., 1995). The participant must accurately infer the real intentions of the characters which suggests that this is primarily a measure of cognitive ToM reasoning. Interestingly, although deficits were observed in both the Eyes Task and Hinting Task in the euthymic group, performance in each task did not correlate with each other.
There seems to be some consistency with researchers finding cognitive ToM deficits in euthymic patients with bipolar disorder when compared to healthy controls. In contrast, reports of affective ToM in euthymia are less consistent. This pattern of inconsistent reporting continues in studies that investigate ToM ability across depression, mania and euthymia in bipolar disorder.

2.2.4 Neuropsychological Investigation of ToM in Manic and Depressed States

There are only four well known studies that investigate ToM ability in patients with bipolar disorder across depressed, manic, and euthymic phases. Furthermore, a great deal of ToM research in mania is from studies of schizophrenia that employed patients experiencing mania as control subjects.

The first study to compare ToM ability in patients with bipolar disorder experiencing mania, depression, and euthymia used a story based task (Kerr et al., 2003). This task was originally designed to assess ToM in patients with schizophrenia (Frith & Corcoran, 1996). The task required participants to listen to 6 short stories while viewing a complementary comic strip. The questions asked following each story involved first or second order false beliefs and a control question based on the event depicted. Patients experiencing depression and mania did poorer on ToM and event-related control questions than remitted patients and healthy controls. Although described by Kerr et al. as a general ToM measure, the use of false belief questions suggests that the study is specific to cognitive ToM ability.
Another study of cognitive ToM found results contradictory to those reported by Kerr et al. (2003). Wolf, Brüne, and Assion, (2010) found significant ToM impairment in patients with bipolar disorder compared to controls regardless of affective episode. They used a comic sequencing task combined with a multiple-choice questionnaire involving first and second order false beliefs, cheater detection, and cooperation. Although patient groups did not significantly differ overall, there was a trend for the remitted patients to do poorer than the patients who were manic or depressed. The significant difference between combined patient groups and healthy controls in ToM ability was maintained when verbal and practical IQ, executive planning, and cognitive flexibility were statistically controlled for. Although this suggests some partial selectiveness of ToM deficits similar to that reported by Montag et al. (2010), Wolf et al. (2010) stress that significant correlations between ToM scores and other cognitive tasks indicate that they are not independent of each other.

Two additional studies that compared manic, depressed and euthymic patients with bipolar disorder investigated ToM in pediatric patients. The first was limited by the use of non-typical tasks. McClure et al. (2005) used tests of facial emotion recognition and language pragmatics - the generation of socially appropriate responses to interpersonal scenarios - to assess social cognition in patients. They found significant differences between healthy controls, and patients with bipolar disorder, but no differences in social cognition between symptomatic and euthymic patients. The second study used pediatric and adolescent patients age 8 to 18 in euthymic, mixed, manic, and depressed episodes, however between-episode comparison was limited to correlations...
between ToM and symptom severity (Schenkel et al., 2008). In their study, Schenkel et al. used the Hinting Task as well as the Affective Story Task which they developed. Patients performed significantly worse than healthy controls on both tasks with more severe manic symptoms predicting poorer performance. Although these studies used pediatric samples, a relationship between manic symptoms and ToM is of clinical relevance and worth further investigation in the current study.

A study of ToM reasoning ability in patients with schizophrenia used patients with bipolar disorder who were experiencing mania or depression as comparison groups. The Versailles-Situational Intention Reading task consists of video clips of complex social interactions and a scoring system based on likelihood of the multiple-choice responses (Bazin et al., 2009). Bazin et al. found that patients who were manic or depressed had comparable scores which were significantly worse than healthy controls. Furthermore, patients who were manic did not differ in ToM ability from patients with schizophrenia. The same study found no group differences in a more rudimentary comic sequencing task named the Inference Intention Task (see Sarfati et al., 1997). The Inference Intention Task may not be a good indicator of subtle cognitive ToM deficits as, Safarti et al., when introducing the task, found that only patients with schizophrenia who suffered from thought and speech disorganization were impaired. In-patients with major depression or schizophrenia without thought or speech disorganization were not impaired.

The studies described above indicate heterogeneous findings when trying to determine the extent of ToM dysfunction in patients with bipolar disorder. Although
some studies (e.g. Wolf et al., 2010; Bazin et al., 2009) investigated subtle differences in cognitive or undifferentiated ToM ability, there has not been a study of subtle differences in affective ToM ability between patients with bipolar disorder experiencing depression, mania and euthymia. Of note are the consistent reports of comparable ToM deficits in patients experiencing mania and depression. Despite the report from Schenkel et al. (2008) of an overall inverse relationship between ToM and manic symptoms, no study explicitly reported significant differences between depressed and manic patients in ToM ability.

2.3 Aim of the Present Study

The aim of the current study is to compare affective ToM decoding between manic, depressed and euthymic phases of bipolar disorder using the Eyes Task. This is the first study, to the author’s knowledge, that uses a task that does not rely on memory to investigate subtle ToM differences between affective episodes, and it is the first to use the Eyes Task with manic patients.

To support the investigation of ToM ability between mania, depression, and euthymia, four general concerns will be addressed. The first is possible covariates such as differences in demographics, medications, and measures of illness severity such as comorbidities or illness progression. The second is an investigation of Eyes Task performance based on the valence of the target items. The third is a consideration for the severity of depressed, manic, and anxious symptoms and how they relate to Eyes and Animal Task accuracy. Finally, a speed vs. accuracy trade-off in Eye Task performance will be considered. Each of these concerns are addressed in the following sections.
2.4 Covariates Considered

The field of neurocognitive research involving patients with bipolar disorder has highlighted many factors relating to cognition that if not considered can artificially skew results. The relationships between cognitive function, affective episode, and covariates available through the review of patient records are examined here with information relating to Eyes Task performance reported where available. The following demographic and clinical measures will be investigated in an effort to strengthen the comparison of ToM ability between depressed, manic, and euthymic groups.

2.4.1 Comorbidity

Comorbidity is of great concern when investigating ToM functioning in bipolar disorder. Approximately 90% of patients with lifetime bipolar disorder 1 or 2 in the NCS-R study also met DSM-IV criteria for another Axis I lifetime disorder, and over 70% had a history of at least three additional disorders (Merikangas & Kalaydjian, 2007). As comorbidity with bipolar disorder is relatively common, it is important to consider associated cognitive implications.

2.4.1.1 Comorbid Anxiety Disorders

Anxiety disorders are of particular concern to the study of bipolar disorder. The NCS-R study found 80% of patients with bipolar disorder had a lifetime history of a DSM-IV anxiety disorder; of that 80%, 70% reported a history of panic attacks (Merikangas & Kalaydjian, 2007). A recent review of epidemiological studies reported a range from 2-67% for current comorbidity of anxiety disorders such as PTSD, OCD, and GAD, in patients with bipolar disorder which was significantly more than reported
comorbid anxiety disorders in patients with MDD or those without an affective disorder (Cardoso et al., 2010).

Anxiety in patients with bipolar disorder seems to be a marker of poorer outcome. In particular, history of panic attacks has been strongly correlated with nonremission in bipolar disorder (Feske et al., 2000). Patients with anxious bipolar disorder have also been shown to have higher rates of suicidality, lower quality of life, and reduced role functioning compared to patients with nonanxious bipolar disorder even while controlling for affective symptoms (Otto et al., 2006). As anxiety disorders are often observed in patients with bipolar disorder, comorbidity of an anxiety disorder may be a marker of illness severity that can be controlled for when investigating between-episode ToM differences.

Deficits in neuropsychological performance reflecting frontal lobe and subcortical dysfunction observed in patients with bipolar disorder are also observed in patients with anxiety disorders (Veale et al., 1996). Deficits in executive functioning, visual memory, visuospatial processes, verbal learning and memory, have been well documented in patients with obsessive compulsive disorder (Purcell et al., 1998), as well as panic and social anxiety disorders (Asmundson et al., 1994). A relationship between anxiety and impairment in nonsocial cognition lends further support for the use of comorbid anxiety disorders as an indicator of illness severity when comparing ToM between affective episodes.
A relationship between anxiety and ToM in patients with bipolar disorder has not been investigated previously, though there are contrasting reports regarding a relationship between ToM and anxiety in other clinical populations. A recent study found that patients with an anxiety disorder had comparable ToM deficits to those with schizophrenia using the Eyes Task and Hinting Task (Morrison & Myhr, 2010). Comorbidity of anxiety disorders has not been associated with further ToM deficits in pediatric bipolar disorder (McClure et al., 2005) or borderline personality disorder (Fertuck et al., 2009). As reduced level of functioning is associated with anxious bipolar disorder (Otto et al., 2006) and patients with anxiety disorder have deficits in Eyes Task performance (Morrison & Myhr), it is anticipated that patients with comorbid anxiety disorder will have poorer Eyes Task performance. As measures of anxiety often correlate with measures of depression, there is concern for comorbid anxiety to affect the between-episode comparison of Eyes Task performance making anxious comorbidity a potential covariate of concern.

2.4.1.2 Comorbid Substance Use Disorders

Substance use disorders, especially involving alcohol abuse and dependence, are common comorbidities associated with bipolar disorder. Patients with bipolar disorder are at higher risk for developing a comorbid substance abuse disorder than any other axis I disorder (Weiss, 2004). Comorbid substance disorder is associated with treatment non-adherence, poor insight, increased suicidality, greater illness severity, and poorer cognitive function (Mitchell et al., 2007). A history of comorbid substance dependence in patients with bipolar disorder is predictive of cognitive deficits. A study comparing
patients with euthymic bipolar disorder, both with and without a history of alcohol dependence, to healthy controls found significant cognitive dysfunction related to substance abuse (van Gorp et al., 1998). Although both patient groups had deficits in verbal memory, patients with prior comorbid alcohol dependence had further deficits in many executive tasks (van Gorp et al.). The current study included patients with a history of substance abuse but not substance dependence. As measures of executive functioning have been reported as significant covariates when comparing euthymic patients with bipolar disorder to healthy controls with ToM task batteries (e.g. Olley et al., 2005; Montag et al., 2010) and comorbid substance dependence is related to executive functioning, an effect of substance abuse on Eyes Task accuracy will be investigated. Patients with bipolar disorder and comorbid substance abuse disorder generally have increased distractability, a disproportionate number of depressive symptoms, and increased consumption of alcohol and illicit substances during manic and depressed episodes (Salloum & Thase, 2000). As comorbid substance abuse is related to cognitive deficits and presents differently in affective episodes, substance abuse is an important clinical indicator to be considered as a covariate.

2.4.1.3 Comorbid Attention-Deficit/Hyperactivity Disorder (ADHD) Comorbidity of ADHD, oppositional defiant disorder, and conduct disorder (Lewinsohn et al., 2002) is common in pediatric patients with bipolar disorder. Though research is limited in the implications of these comorbidities with regards to social cognition in adults, some work has been done in pediatric samples. Comorbidity of ADHD in pediatric patients with bipolar disorder was associated with further deficits in
attention and executive functioning (Pavuluri et al., 2006). ToM deficits were found to be worse in pediatric patients with comorbid ADHD but not comorbid anxiety (McClure et al., 2005). Comorbid ADHD may be related to ToM ability in adults as symptoms of ADHD such as problems in sustained attention and executive functioning are associated with ToM ability in patients with bipolar disorder (e.g. Wolf et al., 2010) it is expected that comorbid ADHD will be associated with poorer ToM ability in the current study. Exaggerated symptoms of ADHD such as distractability and impulsivity during mania makes ADHD comorbidity a covariate to be considered.

Comorbid disorders are reliably reported in patient records in accordance with good clinical practice. As some studies discussed previously have found a relationship between comorbidity and further social and nonsocial cognitive deficits, a past diagnosis of a comorbid disorder could be an appropriate indicator of illness severity to consider in support of investigating between-episode differences in ToM ability.

2.4.1.4 History of Psychosis

Impaired ToM is a popular research topic in patients with schizophrenia. A relationship between psychosis and ToM dysfunction in schizophrenia has been investigated in an effort to understand delusional cognitive misrepresentations (Brüne, 2005). From this, a relationship between ToM functioning and psychotic symptoms has been explored. Lahera et al. (2008) used the Strange Story Task to investigate effects of psychosis on ToM ability in euthymic patients with bipolar disorder. They found no effect for history of psychosis although people with bipolar disorder did significantly worse than healthy controls on executive functioning, verbal learning, and ToM tasks. In
a study of general cognition in euthymic patients (Bora et al., 2007), a history of psychotic mood episodes was only related to poorer cognitive flexibility. Still, conflicting results using a Hinting Task have been reported. In a comparison of healthy controls to patients with schizophrenia or affective disorders, Marjoram et al. (2005) found that high levels of delusions and hallucinations predicted poor ToM performance regardless of diagnosis. In a study investigating patients with schizophrenia and depression, paranoid delusions were linked to both executive functioning and performance on a ToM story task even when controlling for IQ (Bentall et al., 2009). Despite reports of a relationship between ToM and psychosis, many studies do not report further ToM deficits. In a review of ToM in schizophrenia, only half of the reviewed papers that compared ToM and paranoia found a significant relationship and even less found a relationship between ToM and delusions or hallucinations (Harrington, Siegert, & McClure, 2005). With conflicting results regarding a relationship between ToM and psychosis that is confounded by the use of different ToM tasks, a history of psychosis is worth documenting when considering group differences in ToM ability. Still, as history of psychosis was related to ToM (Marjoram et al.) it is anticipated that a history of psychosis will be related to poorer ToM performance in the current study.

2.4.1.5 Past Suicide Attempts

It is estimated that more than 25% of patients with bipolar disorder attempt suicide at least once (Voltenen et al, 2006). A history of suicide attempts in patients with bipolar disorder is associated with poorer psychosocial adaptation (Allen et al., 2005) and blunted emotional processing in men (Simon et al., 2007).
A history of suicidality is a covariate of interest in the current study due to an overlapping neural substrate in the orbitofrontal cortex for history of suicide attempts, social cognition, and affective decision making. Suicidality is associated with reduced serotonergic activity in the orbitofrontal cortex (Mann, 1998) which is considered one of the core regions for ToM (Carrington & Bailey, 2009). Orbitofrontal and medial temporal regions are activated when healthy participants perform the Eyes Task (Sabbagh, Moulson, & Harkness, 2004) and during an affective perspective taking task (Hynes et al., 2006). In an fMRI study, men with histories of suicide attempts compared to depressed men with no attempts had increased activity in the orbitofrontal cortex when they were shown angry faces (Jolant et al., 2008).

Although a direct link between suicidality and ToM ability is not established in the literature, patients with abnormalities in the orbitofrontal cortex, either from lesions or fronto-temporal dementia, present with characteristic deficits in decision making and ToM (Torralva et al., 2007). Individuals with a history of suicide attempts had deficits in a task of affective decision making named the Iowa Gambling Task, comparable to patients with orbitofrontal lesions (Jolant et al., 2005). A history of suicide attempts was also predictive of poorer performance on the Iowa Gambling Task in patients with bipolar 1 disorder (Malloy-Diniz et al., 2009). These findings point to a shared neural substrate in the orbitofrontal cortex for ToM, decision making, and suicidality. Although patients with fronto-temporal dementia had poor performance on the Iowa Gambling Task, Eyes Task and the Hinting Task, scores were not correlated to each other (Torralva et al.). It is anticipated that a history of suicide attempts will be related to poorer ToM
performance. As attempted suicide predicts poorer decision making in bipolar disorder and suicide ideation is commonly exaggerated in depressed episodes, the addition of suicidality as an indicator of illness severity and a potential covariate of Eyes Task performance between affective groups is worthwhile.

2.4.2 Age

The effect of age on cognition in patients with bipolar disorder is addressed in three manners: age at testing, age of onset, and length of illness. As patient groups were not matched with clinical or demographic measures, any differences in these measures of age will be investigated further.

2.4.2.1 Age at Testing

Certain cognitive abilities, such as executive function, decline with age in healthy adults (Charlton et al., 2009). Some measures of cognition decline more rapidly in patients with bipolar disorder such as attention (Mahlberg et al., 2008), executive function (Martinez-Aran et al., 2004), and problem solving capacity (Savard et al., 1980). Inconsistent results have been reported regarding age and ToM ability. Studies of ToM ability in healthy aging found no relationship between age and verbal ToM reasoning (MacPherson et al., 2002). One study, using Happé's Strange Story Task (see Happé, 1994), found verbal ToM reasoning to be negatively related to age in healthy participants aged 50-90, however the relationship was fully mediated by executive function processing speed, and performance intelligence and partially mediated by verbal
intelligence (Charlton et al., 2009). Age was not correlated to Eyes Task performance in clinically depressed women or euthymic patients with bipolar disorder (Lee et al., 2005; Bora et al., 2005), or false belief tasks in affective and euthymic bipolar disorder (Kerr et al., 2005; Olley et al., 2005). Nonetheless, some significant relationships between age and ToM have been reported. A study using the Eyes Task found that healthy participants age 60-80 had significant deficits in mental state decoding compared to participants age 20-40 (Phillips et al., 2002). Age was a significant covariate in regression analyses that compared euthymic patients with bipolar disorder to healthy controls in both cognitive and affective ToM measures in the MASC task (Montag et al., 2010). It is expected that a negative relationship between age and ToM ability will be found.

2.4.2.2 Age of Onset

Age of onset is of particular interest in bipolar disorder research. Although there are interesting genetic differences between early and late-onset patients (Faraone et al., 2003), a popular complementary argument is that bipolar disorder interferes with development of social-cognitive skills so the earlier the onset the more likely the patient is to experience social deficits (Schenkel et al., 2008). Early onset bipolar disorder is generally associated with a more severe disease course (Tohen et al., 2000; van Gorp et al., 1998), greater rates of neuropsychological deficits (Taylor & Abrams, 1981), and deficits in aspects of executive functioning in euthymic adults with bipolar disorder (Martinez-Aran et al., 2004).

The relationship between age of onset and ToM ability has been inconsistently reported in research literature. Age of onset in pediatric bipolar disorder was negatively
related to both cognitive and affective ToM performance using the Hinting Task and Affective Story Task (Schenkel et al., 2008). Cognitive ToM scores on a cartoon sequencing and questionnaire task was correlated to age of onset in adult remitted patients but not patients experiencing mania or depression (Wolf et al., 2010). Onset was not related to ToM using the Eyes Task (Bora et al., 2005) or first and second order false belief tasks (McKinnon et al., 2010) in euthymic patients with bipolar disorder. In the current study, it is anticipated that a positive relationship between Eyes Task and age of onset will be found.

2.4.2.3 Duration of Illness

Duration of illness is a common clinical measure with bipolar disorder. A short duration of illness is related to increased chance of recovery and a shorter recovery time (Keck et al., 1998). Meanwhile, longer illness duration is associated with neuropsychological dysfunction in patients with bipolar disorder. For example, Illness duration is negatively correlated to sustained attention, executive functioning, and verbal memory (Clark & Goodwin, 2004; Martinez-Aran et al., 2004). A relationship between illness duration and ToM ability has been reported. Interestingly, illness duration, but not age of onset, was related to second order false belief tasks in euthymic patients with bipolar disorder (McKinnon et al., 2010). Although duration is intrinsically related to age and age-of-onset, researchers often discuss duration of illness as an indicator of chronicity with course of illness measures such as number of affective episodes and hospitalizations. It is expected that a negative relationship between length of illness and ToM ability will be found in the current study.
2.4.3 Number of Affective Episodes

Neurocognitive studies often use the number of experienced affective episodes as an index of illness severity based on an argument for cognitive decline due to neurotoxic hypercortisolemia (increased cortisol levels in the brain) observed during affective episodes (Altshuler, 1993). It is also argued that the number of episodes is a better indicator of illness severity than length of illness. For example, the number and length of affective episodes were stronger predictors of cognitive deficits in euthymic patients with bipolar disorder than illness duration (Kessing, 1998). Increased number of manic episodes but not depressed episodes has been associated with poorer memory (Denicoff et al., 1999; Robinson & Ferrier, 2006), and executive functioning (Nehra et al., 2006; van Gorp et al., 1998). Although many studies of non-social cognition have found that controlling for number of episodes has reduced differences between healthy controls and patients with bipolar disorder (Clark et al., 2002), a similar relationship between ToM and number of episodes is not well established.

Reports regarding a relationship between ToM and the number of episodes are limited. The number of manic or depressed episodes experienced in euthymic patients with bipolar disorder was not related to Eyes Task (Bora et al., 2005). In a study of cognitive and affective ToM abilities in euthymic patients with bipolar disorder, the number of mistakes in an affective ToM task due to ‘undermentalizing’ was significantly correlated to the number of combined hypomanic and manic episodes (Montag et al., 2010). The same was not found for number of depressed episodes or measures involving cognitive ToM (Montag et al.). There is disagreement in the literature as to if manic or
depressive episodes differ in destructive influence on cognitive function. Some studies have reported greater cognitive deficits with repeated manic but not depressed episodes (e.g. Altshuler et al., 1993), whereas others have argued the opposite (e.g. Summers, Papadopoulou, Bruno, Cipolotti, & Ron, 2006). Due to specific reports of poorer performance with a greater number of affective episodes in two affective ToM tasks (Bora et al.; Montag et al.) it is expected that there will be a negative relationship between Eyes Task and number of affective episodes in the current study. Consideration for the number of affective episodes as a covariate is important as patients who experience more affective episodes have more exposure to research opportunities while experiencing affective episodes than individuals who experience less affective episodes. The same may not be the case for the euthymic group.

2.4.4 Education

Neurocognitive studies have found interesting relationships between level of education and cognitive function in patients with bipolar disorder. In a recent meta-analysis, euthymic participants with higher levels of education had decreased impairments in executive functioning and working memory tasks but greater impairment in verbal learning compared to euthymic patients with less education (Kurtz & Gerraty, 2009). Level of education is an important aspect for researchers to consider as it can account for significant group differences in cognitive functioning. For example, differences in education accounted for differences in verbal fluency between functionally recovered and unrecovered patients with bipolar disorder (Wingo et al., 2010).
Level of education has been controlled for in many studies of ToM as with other studies of cognitive function. Bora et al. (2005) found that duration of education was significantly correlated to Eyes Task accuracy in euthymic patients with bipolar disorder. Education was not a covariate in the relationship between Eyes Task and bipolar disorder (Bora et al.) or clinical depression (Lee et al., 2005). Duration of education was also not significantly correlated to affective or cognitive ToM task accuracy in patients with schizophrenia (Shamay-Tsoory et al., 2007). It is anticipated that level of education will be positively related to Eyes Task performance consistent with reports by Bora et al.

2.4.5 Medications

Publications investigating iatrogenic factors in bipolar disorder vary in the reported impact of medication on cognition in bipolar disorder. Furthermore medication regimens vary greatly between patients with bipolar disorder. That said there have been notable findings regarding a relationship between medication and cognitive function in patients with bipolar disorder.

Reduced psychomotor speed and verbal memory are generally accepted with long-term administration of lithium (Honig et al., 1999) and psychotropic medications (Bora, Yucel, & Pantelis, 2009b). Although a recent investigation of monotherapy with lithium or valproate in remitted patients with bipolar disorder found impairments only in verbal memory (Senturk et al., 2007). Administration of mood stabilizers, although considered to be of limited detriment to cognition (Joffe et al., 1988), has been shown to negatively impact affective processing (Csukly et al., 2009). This may be related to
reported side effects of ‘lessened enthusiasm’ and ‘dullling of the senses’ observed with long-term administration (Goodwin & Jamison, 1990).

Limited cognitive improvement has been documented with antipsychotic medication in bipolar disorder (Macqueen & Young, 2003). A study with similar cognitive improvement found in patients with schizophrenia, however, did not find improvement in social cognition (Sergi et al., 2007). ToM differences associated with the type of antipsychotic prescribed have been reported. An interesting study comparing olanzapine and clozapine to traditional antipsychotics in patients with schizophrenia found that patients taking olanzapine or clozapine had improved ToM scores using faux pas, second order false belief, and comic sequencing tasks (Savina & Beninger, 2007).

Studies involving the effects of medication require a great deal of experimental controls or large samples, both of which are not present in the current study. A patient’s medication regimen may change in response to an episode onset such as treatment augmentation or an increase in medication dosage. As medication may differ between groups and may have differential effects on ToM, the classes of medication prescribed will be considered as potential covariates.

2.4.6 Valence

A benefit of the Eyes Task is the ability to test for mood congruent biases. Harkness et al. (2005) separated the items of the Eyes Task into positive, negative, and neutral valence groups based on the expression of the pictured individual. They found response times for negative valence targets were faster than for positive or neutral
valence targets in women who were dysphoric or clinically depressed. An effect of valence is of interest in the current study as mood congruent responses have been observed in patients with bipolar disorder using other cognitive tasks. A mood congruent bias was found in inhibitory control processes in mania and depression (Murphy et al., 1999). Murphy et al. used a go/no-go task that required participants to respond to target stimuli as quickly as possible and inhibit responses to distractor stimuli. Depressed and manic patients with bipolar disorder had attentional biases for valenced words congruent with their current mood state (Murphy et al.). This has also been found in patients with MDD who had slower response times for sad words in a modified Stroop task which improved with symptom improvement (Gotlib & Krasnoperova, 1998). The current study will investigate if a mood congruent bias in the Eyes Task is present in patients experiencing manic and depressive episodes.

Patients with bipolar disorder generally show a mood-congruent bias in emotion recognition tasks. A study of emotion recognition comparing manic to euthymic patients with bipolar 1 and bipolar 2 disorder found that patients experiencing a manic episode had a decreased overall ability to recognize emotions (Lembke & Ketter, 2002). More importantly, the manic patients had a mood-congruent response bias. The manic group performed worse than healthy controls on fear and disgust recognition but did not make any errors in recognition of happy emotions. Manic patients most consistently mistook fear for surprise and disgust for anger and there was a negative correlation found between sad face recognition and YMRS scores. Conversely, euthymic patients had an enhanced fear response. Intact positive emotion recognition in mania is consistent with other
findings such as neural response to happy stimuli in manic patients comparable to healthy controls (Lennox, Jacob, Calder, & Lupson, 2004). An extreme example of a mood-congruent bias associated with mania is that university students assessed as high risk for experiencing a manic episode, when positive mood induced, were exceptionally good at recognizing subtle happiness. (Trevisani, Johnson, & Carver, 2008). Mood-congruent findings have been found with depressed episodes as well (Csukly, Czobor, Unoka, Takacs, & Simon, 2009; Gray et al., 2006) with BDI correlating to poorer happiness recognition (Csukly et al., 2009; George et al., 1998).

The only study that investigates ToM in the context of emotional valence in patients with bipolar disorder involves a pediatric sample. Schenkel et al. (2008) investigated ToM reasoning with the Hinting Task as well as false belief accuracy on stories with positive, negative and neutral emotional valences. Patients with bipolar disorder performed significantly more poorly on the positively and negatively valence but not the neutral stories in the Affective Story Task compared to healthy controls. Schenkel et al. also found a significant effect of valence within the patient group. Patients had significantly worse performance on the negatively valenced stories than the neutral stories and there was a trend for poorer performance for the negative compared to positive stories. Of note, is that an effect of valence on performance was unique to the patient group with no effect of valence in healthy controls. It is anticipated that a mood-congruent response bias will be found in the current study with manic patients showing an accuracy bias for positive items and depressed patients showing an accuracy bias for negative items.
2.4.7 Symptom Severity

Psychosocial functioning is strongly related to the severity of affective symptoms regardless of polarity in patients with bipolar disorder (Gitlin et al., 1995). A relationship between the severity of affective symptoms and cognitive deficits has been reported in some studies. Ferrier et al. (1999) argue that trait related deficits observed in bipolar disorder may instead be related to affective symptoms continued into euthymic phases. Impairments of executive functioning have been found to be related to subsyndromal symptoms in euthymic patients (Ferrier et al., 1999; Martínez-Arán et al., 2004). The findings, however, are often conflicting. One study that primarily investigated the relationship between depressive symptoms and executive functioning in bipolar disorder found that only spatial working memory and visual recall in a battery of 10 neurocognitive tasks were related to depressive symptom severity (Summers et al., 2006).

Mixed findings have likewise been reported in studies investigating ToM in bipolar disorder. Manic symptoms were associated with poorer ToM performance using the Hinting Task and Affective Story Task in pediatric and adolescent patients with bipolar disorder (Schenkel et al., 2008). McKinnon et al. (2010) found that first and second order ToM task performance was significantly correlated to depressive symptoms in subsyndromal patients with bipolar disorder. These results contradict those of Bora et al. (2005) that did not find a relationship between affective symptoms and Eyes and Hinting Tasks. McKinnon et al. suggest that this discrepancy may be due to the limited range of symptoms expressed in the participants in the study by Bora et al. as they had more restrictive criteria for euthymia. It is worth noting that a lack of relationship
between affective symptoms and ToM have been reported in studies of ToM in euthymic (Montag et al., 2010) or symptomatic (Wolf et al., 2010) patients with bipolar disorder, major depression (Lee et al., 2005), and in-patients with schizophrenia (Morrison and Myhr, 2010). As affective symptoms are the primary feature of bipolar disorder it is necessary to determine if a relationship between severity of affective symptoms and ToM ability exists. It is expected that the current study will find a negative relationship between the severity of depressive and manic symptoms and Eyes Task accuracy.

Although ToM deficits may be associated with a diagnosis of an anxiety disorder, a specific relationship between ToM and anxious symptoms is not commonly reported in clinical samples. Anxious symptoms were not related to Eyes Task performance in patients with borderline personality disorder (Fertuck et al., 2009) anxiety disorders or schizophrenia (Morrison & Myhr, 2010). Furthermore, Lee et al. (2005) found that severity of anxious symptoms was significantly negatively correlated to both Eyes and Animal Task performance in clinically depressed women which suggests that the impact of anxious symptoms on cognition is not specific to ToM ability. Harkness et al. (2005) found that severity of anxious symptoms was a significant negative covariate of Eyes Task performance when comparing dysphoric and nondysphoric university students, however zero-order correlations between anxious symptoms and Eyes Task accuracy were not significant. The addition of anxious symptom severity as a covariate strengthened the argument for improved ToM performance associated with dysphoria in university students. As Harkness et al. found a relationship between anxious symptoms and Eyes Task performance, it is expected that the severity of anxious symptoms will
have a negative relationship to Eyes Task performance in the current study of chronically ill patients with bipolar disorder.

2.4.8 Speed vs. Accuracy Trade-Off

In their study of ToM in dysphoric university students, Harkness et al. (2005) found that while dysphoric students had enhanced accuracy on the Eyes Task compared to nondysphoric students, they also had slower response times. Harkness et al. concluded that better accuracy in the dysphoric group was not due to a potential relationship between increased accuracy and taking more time to respond. Although psychomotor slowing is found in patients experiencing mania and depression (e.g. Mahlberg, Adli & Bschor, 2008), a pattern of errors related to impulsiveness in mania (Sax et al., 1995) may lead to a speed vs. accuracy trade-off that influences between-episode comparison of ToM ability.

2.5 Anticipated Findings

2.5.1 Preliminary Hypotheses

It is reasonable that exaggerated ToM deficits will be found in more severely ill patients. Although there is limited evidence for a relationship between ToM and individual clinical measures, comorbidity of anxiety or substance abuse disorders, a history of suicide attempts, or a history of psychosis are expected to predict poorer ToM performance in the current study. An inability to maintain employment or reduced academic achievements is expected to relate to Eyes Task performance similar to general cognition. Furthermore, it is anticipated that due to considerable changes in medication
regimens between episode groups, there will be a relationship between class of medication prescribed and ToM ability. It is anticipated that greater age, lower age of onset, and measures of illness progression such as higher length of illness and number of affective episodes will be related to poorer ToM ability. The potential relationships between Eyes Task accuracy and these measures will be investigated only in an effort to identify potential covariates in support of the between-episode investigation of ToM.

2.5.2 Primary Hypothesis

The primary hypothesis is that patients experiencing manic and depressed episodes will be significantly more impaired in the Eyes Task than euthymic patients with bipolar disorder. As there are trends for poorer ToM performance in manic vs. depressed patients reported in previous studies (e.g. Bazin et al., 2009; Kerr et al., 2003) it is hypothesized that the manic group will perform more poorly than the depressed group in the Eyes Task.

2.5.3 Secondary Hypotheses

2.5.3.1 Valence Effect

It is hypothesized that a mood-congruent bias will be found in the current study consistent with both emotionally valenced ToM tasks (e.g. Schenkel et al., 2008) and emotion recognition tasks (e.g. Lembke & Ketter, 2002; Murphy et al., 1999). It is expected that manic patients will have higher scores in positively valenced items than negatively valenced items and the opposite pattern in depressed patients.
2.5.3.2 Symptom Severity

It is hypothesized that the severity of manic, depressive, and anxious symptoms will be negatively related to Eyes Task accuracy similar to previous reports (e.g. Schenkel et al., 2008; McKinnon et al., 2010).

2.5.3.3 Speed vs. Accuracy Trade-Off

Due to the psychomotor agitation and patterns of impulsivity observed in patients experiencing mania, it is expected that a speed vs. accuracy trade-off may influence between-episode differences in ToM. It is anticipated that faster response times will relate to poorer performance in the current study.
Chapter 3
Methods

This is a prospective, cross-sectional, study of the relationship between affective ToM decoding ability and mood episodes in people with bipolar disorder. This study includes a retrospective component involving a review of patient medical charts in order to investigate the effects of medication and course of illness. This study was approved by the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board and the Providence Continuing Care Centre Research Review Committee.

3.1 Participants

Participants in this study were male and female in-patients and out-patients from specialized mood disorder clinics in Kingston, Ontario. Participants had a current diagnosis of bipolar disorder type I or II as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 1994) and were above the age of 18 (\(M = 46.7, SD = 10.0\)). Demographic information of the patient sample is presented in Table 1. Patients with a current diagnosis of a psychotic disorder, substance dependence, or with a serious medical condition that in the opinion of the investigator might have been the cause of the mood disorder (e.g. hypothyroidism) were excluded from the study. Patients with a developmental disability were also excluded from the study.
Table 1 Demographic and Clinical Measures of the Sample by Group

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Depressed</th>
<th>Manic</th>
<th>Euthymic</th>
<th>Pearson χ²</th>
<th>p (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.494</td>
</tr>
<tr>
<td>Female (N = 59)</td>
<td>24</td>
<td>12</td>
<td>48%</td>
<td>4</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>35</td>
<td>13</td>
<td>52%</td>
<td>10</td>
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<td></td>
<td></td>
<td></td>
<td>.034</td>
</tr>
<tr>
<td>Elementary school (N = 52)</td>
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<td>6</td>
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<td>1</td>
<td>8%</td>
<td>1</td>
</tr>
<tr>
<td>High school</td>
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<td>3</td>
<td>14%</td>
<td>7</td>
<td>58%</td>
<td>5</td>
</tr>
<tr>
<td>College/ University</td>
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<td>12</td>
<td>55%</td>
<td>2</td>
<td>17%</td>
<td>12</td>
</tr>
<tr>
<td>Graduate degree</td>
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<td>5%</td>
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<td>17%</td>
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<td>Occupation</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Unemployed/Disability (N = 55)</td>
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<td>21</td>
<td>84%</td>
<td>6</td>
<td>50%</td>
<td>7</td>
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<tr>
<td>Employed</td>
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<td>2</td>
<td>8%</td>
<td>2</td>
<td>17%</td>
<td>9</td>
</tr>
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<td>Retired</td>
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<td>1</td>
<td>4%</td>
<td>2</td>
<td>17%</td>
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<tr>
<td>Homemaker</td>
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</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.199</td>
</tr>
<tr>
<td>Single (N = 58)</td>
<td>34</td>
<td>17</td>
<td>68%</td>
<td>9</td>
<td>64%</td>
<td>8</td>
</tr>
<tr>
<td>Married/Common law</td>
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<td>8</td>
<td>32%</td>
<td>5</td>
<td>36%</td>
<td>11</td>
</tr>
<tr>
<td>Number of children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.512</td>
</tr>
<tr>
<td>0 (N = 53)</td>
<td>18</td>
<td>9</td>
<td>38%</td>
<td>5</td>
<td>42%</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
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<td>4</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>4</td>
<td>17%</td>
<td>5</td>
<td>42%</td>
<td>5</td>
</tr>
<tr>
<td>3+</td>
<td>13</td>
<td>7</td>
<td>29%</td>
<td>2</td>
<td>17%</td>
<td>4</td>
</tr>
<tr>
<td>Number of depressed episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.220</td>
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<tr>
<td>Less than 5 (N =26)</td>
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<td>1</td>
<td>8%</td>
<td>1</td>
<td>17%</td>
<td>1</td>
</tr>
<tr>
<td>Many</td>
<td>13</td>
<td>8</td>
<td>62%</td>
<td>4</td>
<td>67%</td>
<td>1</td>
</tr>
<tr>
<td>Cycling</td>
<td>10</td>
<td>4</td>
<td>31%</td>
<td>1</td>
<td>17%</td>
<td>5</td>
</tr>
<tr>
<td>Number of manic episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.116</td>
</tr>
<tr>
<td>Less than 5 (N = 26)</td>
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<td>1</td>
<td>9%</td>
<td>3</td>
<td>43%</td>
<td>1</td>
</tr>
<tr>
<td>Many</td>
<td>9</td>
<td>6</td>
<td>55%</td>
<td>2</td>
<td>29%</td>
<td>1</td>
</tr>
<tr>
<td>Cycling</td>
<td>12</td>
<td>4</td>
<td>36%</td>
<td>2</td>
<td>29%</td>
<td>6</td>
</tr>
<tr>
<td>Number of hospitalizations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.379</td>
</tr>
<tr>
<td>None (N = 55)</td>
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<td>8</td>
<td>36%</td>
<td>1</td>
<td>7%</td>
<td>5</td>
</tr>
<tr>
<td>Less than 5</td>
<td>24</td>
<td>8</td>
<td>36%</td>
<td>7</td>
<td>50%</td>
<td>9</td>
</tr>
<tr>
<td>More than 5</td>
<td>17</td>
<td>6</td>
<td>27%</td>
<td>6</td>
<td>43%</td>
<td>5</td>
</tr>
<tr>
<td>Number of suicide attempts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.604</td>
</tr>
<tr>
<td>None (N = 55)</td>
<td>38</td>
<td>13</td>
<td>57%</td>
<td>11</td>
<td>79%</td>
<td>14</td>
</tr>
<tr>
<td>Less than 3</td>
<td>12</td>
<td>7</td>
<td>30%</td>
<td>2</td>
<td>14%</td>
<td>3</td>
</tr>
<tr>
<td>More than 3</td>
<td>7</td>
<td>3</td>
<td>13%</td>
<td>1</td>
<td>7%</td>
<td>3</td>
</tr>
<tr>
<td>Age (N = 59)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>M SD</td>
<td>47</td>
<td>8</td>
<td>46</td>
<td>12</td>
<td>47</td>
<td>11</td>
</tr>
<tr>
<td>Age of onset (N = 59)</td>
<td>25</td>
<td>11</td>
<td>26</td>
<td>13</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>Length of illness (N = 59)</td>
<td>23</td>
<td>13</td>
<td>21</td>
<td>12</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>HDRS-21 (N = 59)</td>
<td>19.72</td>
<td>4.92</td>
<td>7.21</td>
<td>4</td>
<td>5.55</td>
<td>3.98</td>
</tr>
<tr>
<td>YMRS (N = 59)</td>
<td>3</td>
<td>3</td>
<td>18</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>BDI† (N = 58)</td>
<td>30</td>
<td>13</td>
<td>12</td>
<td>10</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>BAI† (N = 58)</td>
<td>18</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>10</td>
<td>8</td>
</tr>
</tbody>
</table>

†BDI and BAI Depressed (n=24)
Of 68 participants recruited, nine participants were excluded. Two participants were removed because they did not complete the Eyes Task. Four patients classified as experiencing a mixed episode, were excluded because they did not fit into either manic or depressed groups and as such affected the validity of the outcomes. Three participants were excluded due to violations of the inclusion criteria found during chart review (schizophrenia, drug induced mania, alcohol dependence). This left 59 patients for analysis.

This study used two sites to recruit patients. Fifty-four patients were recruited from the primary site, Providence Care Mental Health Services (PC-MHS). Five patients, all in the manic episode group, were recruited from Hotel Dieu Hospital (HDH). As the HDH site specializes in acutely ill patients, clinical measures for manic patients separated by site will be considered

3.2 Measures

3.2.1 Demographics

During the interview, patients were asked their age, level of education, occupation, marital status, and number of children.

3.2.2 Course of Illness and Medications

In order to better understand the heterogeneous sample, information about the course of illness was collected from patient records such as approximate age of onset and length of illness, DSM-IV Axis I comorbidities, number of previous episodes and hospitalizations, and history of delusions or schizoaffective traits. Further, the most
recent prescriptions for 55 of the 59 patients were recorded during the chart review to
determine if there were any relationships between medication type and Eyes Task
performance. The four classes of medications investigated were sleep aides,
antipsychotics (both typical and atypical combined), antidepressants, and mood
stabilizers. Comorbidity and medication information is reported in Table 2.

3.2.3 Severity of Depressed Symptoms

The 21-item Hamilton Depression Rating Scale interview, (HDRS-21; Hamilton, 1960) was administered to assess episode status and the severity of depressive
symptomatology. The HDRS-21 is used extensively in mood disorder research and has
robust psychometric properties (Rehm & O'Hara, 1985). A high score represents more
severe symptoms of depression with a score of >17 indicative of a depressive episode.

The Beck Depression Inventory- II (BDI-II; Steer, Ball, Ranieri, & Beck, 1999) is
a 21-item self-report questionnaire used to assess the severity of depressive
symptomatology. Each item has a four-point scale ranging from 0 to 3. Items are summed
for a total score from 0-63 with a higher score indicating more severe symptoms. The
BDI-II is widely used and has been validated with many clinical populations including
psychiatric outpatients (Steer et al., 1999).
<table>
<thead>
<tr>
<th>Medication type</th>
<th>Total</th>
<th>Depressed</th>
<th>Manic</th>
<th>Euthymic</th>
<th>p (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N= 55)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Sleep aides</td>
<td>18</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>0.55</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>44</td>
<td>17</td>
<td>12</td>
<td>14</td>
<td>0.64</td>
</tr>
<tr>
<td>Mood stabilizer</td>
<td>45</td>
<td>15</td>
<td>12</td>
<td>18</td>
<td>0.28</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>33</td>
<td>18</td>
<td>6</td>
<td>9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Attention deficit hyperactivity disorder</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0.39</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.91</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Post traumatic stress disorder</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0.79</td>
</tr>
<tr>
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<td>1</td>
<td>0</td>
<td>1</td>
<td>0.70</td>
</tr>
<tr>
<td>Obsessive compulsive disorder</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>0.50</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>10</td>
<td>7</td>
<td>0</td>
<td>3</td>
<td>0.04</td>
</tr>
<tr>
<td>Anxiety disorder compiled</td>
<td>16</td>
<td>9</td>
<td>2</td>
<td>5</td>
<td>0.17</td>
</tr>
<tr>
<td>History of panic attacks</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0.47</td>
</tr>
<tr>
<td>History of delusions</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>0.50</td>
</tr>
<tr>
<td>No known comorbidities</td>
<td>27</td>
<td>8</td>
<td>8</td>
<td>11</td>
<td>0.29</td>
</tr>
</tbody>
</table>
3.2.3 Severity of Manic Symptoms

The Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) is an 11-item scale completed by the researcher based on the participant’s responses and behaviour during the interview. A higher score indicates more severe manic symptoms with scores >25 indicating severe mania, 24-15 moderate mania, 14-9 mild mania, and 8-0 not clinically significant (Young et al.). It was administered in this study to assess episode status and severity of manic symptoms. The YMRS is used for both adult and adolescent clinical populations and has strong psychometric properties (Double, 1990).

3.2.4 Severity of Anxious Symptoms

The Beck Anxiety Inventory (BAI; Beck & Steer, 1990) is a 21-item self-report questionnaire designed to measure the behavioural, cognitive, and physiological symptoms of anxiety that are separate from symptoms of depression. It consists of a list of symptoms rated on a four-point scale from “not at all” (0) to “severely” (3). With a maximum score of 63, scores below 15 indicate mild anxiety whereas scores above 26 indicate severe anxiety (Beck & Steer). The BAI has high internal consistency and high one-week test-retest reliability ($\alpha = .92$, $r (85) = .75$; Beck & Steer). The BAI is widely used as a screening tool for global anxiety in psychiatric populations with particular discriminant validity in detecting panic disorders (Leyfer, Ruberg, & Woodruff-Borden, 2006).
3.3 Reading of the Mind in the Eyes Task, Revised

The patients participated in the *Reading the Mind in the Eyes Task Revised Edition* (Eyes Task). The Eyes Task is an experimental test designed to measure ToM decoding ability by asking participants to infer the mental state of the target based on information expressed only in the eye region (Baron-Cohen et al., 2001). The Eyes Task consists of a series of 36 black-and-white magazine photographs depicting the eyes of both men and women. The pictures are adjusted to only show from the middle of the nose to just above the eyebrows; the size of each picture is standardized (15cm x 6cm). The task involves a forced choice of one of four adjectives (one target and three distracters) that best describes the complex mental state expressed in each picture. All words are equally spaced from the centre of the picture and the target answer location is counterbalanced. Patients were not given feedback as to how well they performed on the Eyes Task at any point. The pictures in the Eyes Task have also been separated into three categories based on the valence of the expressed mental states: positive, negative, and neutral (*see* Harkness et al., 2005; Lee et al., 2005).

The Animal Task was used as a control task to ensure that group differences on the Eyes Task could be attributed to selective differences in ToM rather than to more general differences in cognitive and/or perceptual abilities. The Animal Task uses the same format as the Eyes Task but instead depicts 12 black-and-white photos of full animals and asks the participant to choose one of four descriptive words that best describes the animal. This control task was developed to mimic the Eyes Task in response demand while not requiring mental state decoding (*see* Harkness et al.).
Participants used a computerized version of the task that randomly combined the Animals task and Eyes Task into a block of 48 trials. Participants responded by pressing one of four keys (S, K, X, M) that were spatially analogous to the words displayed. Using a digital version of the Eyes Task allowed for the collection of response accuracy, and response time for each trial (Harkness et al.). Samples of the Eyes Task and Animal Task are displayed in Figure 1.

The Eyes and Animal Tasks have been validated with previous studies, showing that the targets are consistently chosen more than the distracters and at rates higher than chance (Harkness et al.). Reliability analyses were run for the Eyes Task and Animal Task accuracy scores. Five items from the 36-item Eyes Task were removed to improve reliability from Cronbach’s $\alpha = .688$ to Cronbach’s $\alpha = .748$. Of the five items, three had a neutral valence (insisting, cautious, skeptical) and two had a negative valence (accusing, hostile). Three items were removed from the 12-item Animal Task to improve reliability from Cronbach’s $\alpha = .494$, to Cronbach’s $\alpha = .543$.

### 3.4 Procedure

All participants, prior to testing, provided written informed consent. Patients then completed the sociodemographic and clinical interviews and self-report questionnaires with a trained study coordinator before completing the combined Eyes and Animal Tasks. Patients received $20 as compensation for their participation.
Figure 1: Sample items from (a) the Eyes Task with panicked as the correct answer, and (b) the Animal Task with ferocious as the correct answer.
3.5 Episode Classification

The 59 patients included in analysis were separated into episode groups based on HDRS-21 and YMRS values. The depressed group (n = 25) consisted of patients with a HDRS-21 score of 17 or more and an YMRS score of 8 or less (Rehm & O’Hara, 1985). Patients in the manic group (n = 14) had HDRS-21 scores of 7 or less and YMRS scores of 15 or more (Young et al., 1978). Patients with HDRS-21 scores of 7 or less and YMRS scores of 8 or less were included in the euthymic group (n = 20). Patients experiencing a mixed episode had a score of at least 17 on the HDRS-21 and a score of at least 15 on the YMRS, but as mentioned before they were excluded from the study.

3.6 Statistical Approach

Preliminary univariate analyses (e.g., Mann-Whitney U-tests, chi-square tests, t-tests, correlations) were first conducted to determine (a) if there were any differences in Eyes or Animal Task performance between the two study sites (PC-MHS vs. HDH), and (b) if there were any relations of any of the demographic (i.e., age, sex, marital status, socio-economic status) or clinical (i.e., medication status, age of onset of illness, number of previous episodes, comorbidity) variables to group or to Eyes or Animal Task performance. Any demographic or clinical variables that emerged as significant were included in the primary analyses as covariates. Statistical significance was set at p < .05.

To determine if there were significant differences between depressed, manic, and euthymic groups in Eyes Task accuracy, a one-way ANCOVA was performed with
episode group as the between-group factor and Eyes Task accuracy as the dependent variable. Animal Task accuracy was included as a covariate along with any of the significant demographic or clinical variables. Significant group effects were followed up using Bonferroni corrected $t$-tests. Missing values for age of onset ($n = 8$) were treated as missing.

To determine the effect of group on Eyes Task accuracy by valence of the eyes, a repeated-measures ANCOVA was performed. The within-subject factor was valence (positive vs. negative vs. neutral), the between-subject factor was group (depressed vs. manic vs. euthymic), and Animal Task accuracy and relevant demographic and/or clinical variables were included as covariates.

To determine if Eyes or Animal Task accuracy was related to the severity of depressed, manic, or anxious symptoms, correlations using the Eyes and Animal Task scores, HDRS, BDI, YMRS, and BAI were conducted.

A speed vs. accuracy trade-off with Eyes Task performance was considered in three separate tests. First, an ANOVA comparing the Eyes Task response time between manic, depressed, and euthymic patient groups was conducted. Second, a correlation between Eyes Task response time and Eyes Task accuracy was conducted. Finally, an ANCOVA comparing episode groups in Eyes Task accuracy with response time as a covariate was conducted.
Chapter 4
Results

4.1 Preliminary Analysis

4.1.1 Site Comparison

Clinical measures, sociodemographics, and Eyes Task results for manic patients at the HDH \((n = 5)\) and PC-MHS \((n = 9)\) sites are displayed in Table 3. There were no significant differences between patients at HDH and PC-MHS with all of the clinical measures; HDRS-21, BDI, and BAI \((ps > .34)\). There was a trend for HDH patients to have higher YMRS scores than PC-MHS patients but this was not significant \((z = -1.68, p = .09)\). Based on YMRS scores, two patients were identified as experiencing severe mania and all other patients in the manic group were identified as moderate. Age, time since first diagnosis, age of onset, level of education, or employment status were also not significantly different between sites \((ps > .15)\).

The manic patients from PC-MHS did not differ significantly from manic patients from HDH with regards to Eyes Task accuracy \((z = -1.2, p = .23)\). The HDH patients had significantly poorer scores on the Animal Task than PC-MHS patients \((z = -2.05, p = .04)\). Furthermore, HDH patients had significantly slower Eyes Task and Animal Task response times than PC-MHS patients \((z = -2.33, p = .02, z = -2.20, p = .03\) respectively).
Table 3 Demographic and Clinical Characteristics as well as Reading of the Mind in the Eyes Task: Revised (Eyes Task) Results of Manic Patients by Clinic Site

<table>
<thead>
<tr>
<th></th>
<th>Location†</th>
<th>PC-MHS (n = 9)</th>
<th>HDH (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>Eyes Task</td>
<td>0.6</td>
<td>0.21</td>
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†PC-MHS: Providence Care Mental Health Services, HDH: Hotel Dieu Hospital
4.1.2 Demographic and Course of Illness Relationships to Episode Group and Eyes Task Accuracy

Patients in the depressed, manic, and euthymic episode groups did not significantly differ in demographic measures of age, gender, marital status, level of education, and number of children. Using Kruskal-Wallis tests, significant between group differences in occupation were observed, \( \chi^2(2) = 8.18, p < .02 \). The depressed group had a significantly higher number of patients who were unemployed or on disability insurance than the euthymic group \((z = -2.74, p < .01)\) but not the manic group. No differences in occupation were observed between the euthymic and manic group.

There were no group differences in the of number of depressed and manic episodes, hospitalizations, suicide attempts, age of onset, comorbidity of schizoaffective disorder, attention deficit hyperactivity disorder, post traumatic stress disorder, social anxiety disorder, obsessive compulsive disorder, or a history of delusions or panic attacks. Seven patients in the depressed group and three patients in the euthymic group had comorbid generalized anxiety disorder whereas no patients in the manic group did. When anxiety disorders were compiled, there were no significant differences between groups in number of comorbidities \( \chi^2(2) = 3.51, p = .17 \). Furthermore, four patients in the manic group, three in the depressed group but no patients in the euthymic group had a recent history of substance abuse.

Eyes Task accuracy was not significantly related to level of education and employment status \((\chi^2(4) = 8.30, p = .081, F(3, 47) = 2.48, p = .07\) respectively).
Further, Eyes Task accuracy was not significantly associated with substance abuse history. Patients with a recent history of substance abuse ($M = .77, SD = .13$) did not differ from those with no history of substance abuse ($M = .68, SD = .15$) in Eyes Task accuracy ($t(48) = 1.35, p = .25$). Patients with comorbid generalized anxiety disorder ($M = .67, SD = .13$) were also not significantly different to those without comorbid generalized anxiety ($M = .69, SD = .16$) in Eyes Task accuracy ($t(48) = -.314, p = .76$).

Age of onset was not significantly different between mood episode groups ($p = .82$). Age of onset was significantly positively correlated to Eyes Task accuracy ($r = .37, p = .01$), but not Animal Task accuracy ($r = -.03, p = .83$). A correlation between age of onset and Eyes Task accuracy approaches significance within the depressed group ($r = .41, p = .05$) but not in the euthymic ($r = .19, p = .47$) or manic groups ($r = .48, p = .11$).

4.1.3 Medications and Eyes Task Accuracy

Episode groups did not differ in the number of prescriptions per patient or the percentage of patients with prescriptions for sleep aids, antipsychotics, or mood stabilizers ($ps > .27$). Using Mann-Whitney U tests, the depressed group ($n = 18$ of 21) had significantly more patients with antidepressant prescriptions than the manic group ($n = 6$ of 14; $z = -2.64, p < .01$) or the euthymic group ($n = 9$ of 20; $z = -2.71, p < .01$). There was no significant difference in the number of antidepressant prescriptions between manic and euthymic groups.

To determine if taking a certain class of medication was related to Eyes Task accuracy, two-tailed t-tests were performed comparing patients with a recent prescription
to patients without. There were no significant differences between patients prescribed a certain medication and those without a prescription ($ps > .2$).

**4.2 Main Analysis: Mood Episode and Eyes Task**

An ANCOVA model with Animal Task accuracy and age of onset included as covariates was used to investigate the relationship between episode group and Eyes Task accuracy. The covariate, age of onset, was significantly related to Eyes Task accuracy, $F(1, 54) = 7.77, p = .01, \eta^2 = .13$. That is, Eyes Task accuracy was higher with a later age of onset. The covariate, Animal Task accuracy, was not significantly related to Eyes Task accuracy, $F(1, 54) = 2.18, p = .15$. This suggests that individual performance on the Animal Task is not related to performance on the Eyes Task.

There was a significant effect of mood episode on Eyes Task accuracy after controlling for the effects of Animal Task accuracy and age of onset, $F(2, 54) = 4.73, p = .01, \eta^2 = .15$ (Figure 2). Using Bonferroni post hoc tests, the depressed and euthymic groups performed significantly better than the manic group (mean differences = .16, .13 $p = .01, .03$ respectively). There was no significant difference in Eyes Task accuracy between the euthymic and depressed groups.
Figure 2. Estimated marginal means for Eyes Task accuracy comparing episode groups in patients with bipolar disorder. Measures are controlling for Animal Task accuracy and age of onset. Error bars represent standard error. Patients in the manic group ($n = 14$) had significantly poorer scores than patients in depressed ($n = 25$) or euthymic ($n = 20$) groups. Eyes Task accuracy did not significantly differ between the euthymic and depressed groups.
4.3 Secondary Analysis

4.3.1 Eyes Task Valence

A repeated measures ANCOVA was used to determine if patients in different episode groups had differential Eyes Task accuracy based on the valence of the target expression (Figure 3). As with the investigation of the Eyes Task results, the valence results had Animal Task accuracy and age of onset as covariates. There were no significant main effects for valence or valence by episode group interact ($p = .23, p = .10$ respectively). Within subject effect of valence was not significant ($p = .33$) however, a trend was found for within-subjects valence by group linear contrast, $F(2, 54) = 3.00, p = .06, \eta^2 = .10$.

To further investigate the trend level valence-by-group relationship, post hoc repeated measure ANOVAs were completed for each episode group. Patients in the depressed and manic groups had significant quadratic within-subjects contrasts (depressed: $F(1, 54) = 7.88, p = .01, \eta^2 = .25$; manic: $F(1, 54) = 8.65 p = .01, \eta^2 = .40$). The euthymic group had a significant linear within-subjects contrast, $F(1, 54) = 5.82, p = .03, \eta^2 = .23$. These follow-up tests for a trend level contrast support the pattern observed in Figure 3, with patients in the depressed and manic groups having highest accuracy on negative valence items and the euthymic group having highest accuracy on positive valence items.
Figure 3. Estimated marginal means for Eyes Task accuracy, controlling for Animal Task accuracy and age of onset, comparing target valence to episode type in patients with bipolar disorder. Error bars represent standard error.
4.3.2 Symptom Severity and Eyes Task

The YMRS scores of manic patients were significantly negatively correlated to Animal Task accuracy ($r = -.58$, $p = .03$) but not significantly correlated to Eyes Task accuracy ($r = -.23$, $p = .44$). The Eyes Task or Animal Task accuracies for depressed or euthymic groups were not significantly correlated to YMRS scores. BAI, BDI, and HDRS scores were not significantly correlated to Eyes Task or Animal Task accuracy in manic, depressed, or euthymic groups ($ps > .18$). Combined, these results suggest that Eyes Task accuracy is not related to measures of depressed, anxious, or manic symptom severity.

4.3.3 Speed vs. Accuracy Trade-Off

The ANOVA comparing Eyes Task response times between manic, depressed, and euthymic groups was not significant, $F(2, 56) = 1.02$, $p = .36$. There were no significant differences in response time between the manic, euthymic, and the depressed groups. Response time measures are reported in Table 4. There was also no correlation between Eyes Task accuracy and response time both overall or within groups ($ps > .20$). Furthermore, both Eyes Task and Animal Task accuracy scores were not correlated to response times when considering patients from PC-MHS and HDH separately ($ps > .11$).
Table 4 Eyes and Animal Task Valence and Response Times

<table>
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<th>Euthymic</th>
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<tr>
<td></td>
<td>$M$</td>
<td>$SD$</td>
<td>$M$</td>
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<tr>
<td>Eyes Task</td>
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<td>Animal Task response time (ms)</td>
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Data not standardized
An ANCOVA model with Eyes Task response time was also used to investigate the relationship between episode group and Eyes Task accuracy. Eyes Task response time was not a significant covariate $F(1, 55) = .612, p = .437$. This suggests that the time taken to respond is not related to group differences in Eyes Task performance. There was a significant effect of mood episode on Eyes Task accuracy after controlling for the effects of response time, $F(1, 55) = 3.8, p = .02, \eta^2 = .17$. The significant Eyes Task deficit in the manic group reported in the main analysis was replicated in the response time ANCOVA. Using Bonferroni post hoc tests, the manic group had significantly lower scores than the euthymic group (mean difference = .13, $p = .034$) and the depressed group (mean difference = .16, $p < .01$). There was no significant difference in Eyes Task performance between depressed and euthymic groups when controlling for response time ($p > .05$).


Chapter 5
Discussion

5.1 Main Finding

The ability to decode mental states was significantly poorer in manic patients than in depressed or euthymic patients with bipolar disorder based on accuracy on the Eyes Task. This relationship was maintained when controlling for age of illness onset and the response demands of the Eyes Task with Animal Task accuracy scores. The current study did not find that the emotional valence of the target influenced mental state decoding ability regardless of affective episode. Finally, group differences in Eyes Task accuracy were not found to be associated with the time taken to respond. To the author’s knowledge, this study is the first to compare affective ToM ability between depressed, euthymic, and manic adult patients with bipolar disorder. This study is also the first to investigate affective ToM decoding using the Eyes Task in patients experiencing mania.

The pattern of no observable difference in ToM decoding across depressed and euthymic episodes with significant impairment in manic episodes is unique to this study. Patterns observed in the five main studies of ToM that include both depressed and manic patients with bipolar disorder have some similarities but distinct differences are found.

The results of the current study are most consistent with those reported in pediatric and adolescent patients with bipolar disorder by Schenkel et al. (2008). Schenkel et al. did not compare affective groups explicitly but correlations between
symptom severity and ToM suggest a similar pattern of decreased performance associated with mania found in the current study. They found that higher YMRS scores were associated with poorer performance on the Hinting Task and the negative stories in the Affective Story Task. No significant correlations were observed between YMRS scores and positive or neutral stories. Additionally, no significant correlations between depressive symptoms and ToM tasks were found. Although the pattern of exaggerated deficits with manic but not depressive symptoms is consistent with the differences between episode groups observed in the current study there are limitations to consider. Beyond qualitative differences between adult and pediatric samples, Schenkel et al. included only four depressed patients with the rest of the 26 patients experiencing manic, hypomanic, or mixed episodes. Their overall sample had a mean YMRS score of 20.8 (SD = 9.3) which was comparable to just the manic group in the current study (M = 18, SD = 6). As euthymic patients were not included in the study by Schenkel et al., the inability to report a relationship between overall severity of depression and ToM scores in their study does not directly apply to ToM comparisons between depressed and euthymic groups in the current study.

A decreased ToM ability in the manic phase is somewhat consistent with studies of general ToM in bipolar disorder. Decreased ToM ability in manic patients is consistent with the ToM reasoning scores that Bazin et al. (2009) observed in patients experiencing depressive and manic episodes compared to those with schizophrenia. Although their patients who were depressed were not significantly better at ToM reasoning than patients who were manic, there was enough of a group separation to allow for the depressed group
to significantly differentiate from the schizophrenic group whereas the manic group did not.

In the study by Kerr et al. (2003), depressed and manic patients, but not remitted patients, did significantly worse on false belief tasks than healthy controls. Kerr et al. performed no statistical comparison between patient groups, relying instead on parallel comparisons to the healthy control group. Considering their reported values, the manic group had accuracy scores of at least nine percentage points below the depressed group in both first and second order tasks. Similarities between the current study and the study by Kerr et al. do not extend to include the euthymic group. A large performance gap between depressed and remitted patients contradicts the current study’s inability to differentiate performance scores between depressed and euthymic groups.

On the other side, significantly poorer ToM ability in patients experiencing mania contradicts the results of Wolf et al. (2010). They did not find differences in ToM reasoning between depressed, manic, or euthymic patients with bipolar disorder. Of the four well-known studies that investigate ToM ability in depressed and euthymic patients with bipolar disorder, Wolf et al. are the only ones to report explicit comparisons between affective states. As they found no difference between manic, depressed, and euthymic patients, their findings are only consistent with the current study’s comparison of depressed and euthymic patients. McClure et al. (2005) investigated ToM deficits in pediatric patients experiencing euthymic or affective episodes, however they investigated relationships between ToM and symptom severity instead of comparisons based on episode type. The current literature on general ToM ability across affective episodes in
bipolar disorder is very limited even before taking into consideration the variation in ToM tasks utilized.

Inconsistencies between the pattern of ToM in the current study and those in the literature could be due to added response task demands. Kerr et al. (2003), Bazin et al. (2009), Schenkel et al. (2008) and Wolf et al. (2010) employed tasks that all require memory of social events, especially verbal memory which has been repeatedly shown to be dysfunctional in patients with bipolar disorder (Robinson & Ferrier, 2006; Robinson et al., 2006) and has been argued to be a trait marker of the disorder (Arts, Jabben, Krabbendam, & van Os, 2008; Bora et al., 2009a).

Another concern is the combination of ToM reasoning and ToM decoding in ToM tasks. Bazin et al., Montag et al. and Wolf et al. used tasks that intentionally simulated complex social interactions but ToM deficits moderated by cognitive load in patients with bipolar disorder have been reported. McKinnon et al. (2010) used first and second order questions about complex social interactions such as faux pas to investigate ToM ability in euthymic patients with bipolar disorder. They found a clear moderating effect of cognitive demand with patients having significant deficits in the cognitively taxing second order tasks but not first order tasks. Wolf et al. found a more exaggerated effect of load with no group differences in a comic strip ToM task. Measuring ToM deficits using complex reasoning tasks has merit when applied to social functioning, however, differences in performance related to cognitive load weaken an argument for ToM impairment that is distinct from general social functioning or non-social cognitive deficits.
False belief story tasks and comic tasks have met considerable criticism. False belief tasks were designed to investigate frank ToM dysfunction without being cognitively taxing. The relative ease of false belief tasks is reflected in the study by Kerr et al. with a clear ceiling effect for ToM and control questions in healthy controls and remitted patients. A large concern with first and second order false belief tasks is that some patients with disorders known to have ToM deficits pass them. Baron-Cohen et al. (1997; 2001) found that patients with high functioning autism or AS did not have significant deficits using false belief tasks. The Eyes Task was designed to be sensitive to subtler differences in ToM than story tasks and accurately predicts AS or autism.

It is also important to consider that these studies differed in aspects of mentalization. Kerr et al. (2003) and Schenkel et al. (2008) use false belief tasks whereas Bazin et al. (2009) use questions specific to inferring intentions of others. Differential performance between cognitive and affective ToM has been found within studies of patients with AS, schizophrenia, and PFC damage (Shamay-Tsoory et al., 2002; Shamay-Tsoory et al., 2007; Shamay-Tsoory et al., 2005). Considering that differences in performance are found between ToM tasks within studies (e.g. Schenkel et al; Shamay-Tsoory et al., 2007) a comparison between ToM tasks that are primarily social-perceptual like false belief and the Hinting task to the Eyes Task, a more automatic decoding task, is limited. Reasons for the discrepancy between the current study and some of the literature with respect to overall ToM ability between affective episodes are discussed in the following section.
5.2 Integration of Results into Current Literature

5.2.1 Course of Illness

There were no relationships found between metal state decoding ability and the number of hospitalizations, or number of manic or depressed episodes which does not support the hypothesized negative relationship. This is inconsistent with an investigation of ToM reasoning in euthymic patients with bipolar disorder using video clips by Montag et al. (2010). Montag et al. found that the combined number of hypomanic and manic episodes correlated with poorer performance on the affective but not cognitive ToM questions. The combined number of hypomanic and manic episodes reported by Montag et al. also correlated to errors due to undermentalizing. A relationship between affective ToM and undermentalizing could mean that the affective ToM questions in their study were more sensitive to general cognitive impairment than cognitive ToM questions. An inability to find a relationship between course of illness and ToM in the current study is consistent with Bora et al. (2005) who found no correlation between Eyes Task and number of affective episodes in euthymic patients.

Bora et al. (2009) argue that because ToM deficits are found in patients in the early stages of bipolar disorder (e.g. McClure et al., 2005; Schenkel et al., 2008) or first episode schizophrenia (e.g. Kettle et al., 2008) increased ToM dysfunction associated with number of affective episodes could simply be mediated by general cognitive decline. Both the inability to find a relationship between Eyes Task and number of affective episodes in the current study, and the relationship between number of episodes and undermentalizing reported by Montag et al. (2010) are consistent with the argument
presented by Bora et al. The inability to find a relationship between course of illness measures and Eyes Task lends some support for a specific impairment in mental state decoding associated with experiencing mania instead of group differences in illness progression.

5.2.2 Age of Onset

Lower age of onset was related to poorer Eyes Task performance which was hypothesized and is consistent with false belief ToM studies in pediatric patients (Schenkel et al., 2008) and euthymic adults (Wolf et al., 2010) with bipolar disorder. The relationship between age of onset and ToM ability is of particular concern in the current study. Considered in isolation, an overall correlation between age of onset and Eyes Task is of little meaning as there was a trend for the most severe manic patients to report lower onset age, more severe symptoms, and poorer scores on both Animal and Eyes Task scores. Age of onset is still a relevant covariate as it is not correlated to the Animal Task in this sample. The inability to find a correlation suggests that the impact of a lower age of onset on mental state decoding ability does not extend to the response demands of the Eyes Task. A correlation between age of onset and Eyes Task accuracy approaches significance within the depressed group but not the euthymic or manic groups. This lends support for the role of onset age in mental state attribution instead of the effect being driven by poorer performance and lower age of onset in the manic group.

A specific relationship between ToM and early onset of bipolar disorder is expected as the ability to appreciate mental states of others continues to develop across childhood and adolescence (Wellman & Lagattuta, 2000). Interruption of ToM
development is argued to be exacerbated by the cyclical pattern of poor social skills which further restrict the opportunities to develop ToM ability (Schenkel, Spaulding, & Silverstein, 2005). The relationship between mental state decoding and age of onset in the current study indicates that ToM decoding ability is related to the age and extent to which one’s social development is first interrupted by experiencing symptoms of bipolar disorder. Statistically controlling for the relationship between age of onset and Eyes Task when comparing mental state decoding between affective episodes provides clinically relevant support for exaggerated ToM dysfunction in manic episodes.

5.2.3 Medication

Consistent with the study by Montag et al. (2010) of ToM reasoning in euthymic patients, the medication regimens in the current sample were too heterogeneous to investigate the effect of medications in detail. Still, the current study found no relationships between medication and Eyes Task accuracy, similar to the study by Bora et al. (2005). Although not tested in the current study, Bora et al. also did not find a relationship between ToM performance and serum lithium levels.

Medication effects are of considerable concern as drug classes differentially regulate neurotransmitters such as glutamate. Levels of glutamate in the PFC have been correlated to ToM ability (Montag, Schubert, Heinz, & Gallinat, 2008). In the current study, no effect of being prescribed a mood stabilizer, antidepressant, antipsychotic, or sleep aide on mental state decoding was found. As being prescribed an antidepressant was not related to Eyes Task accuracy, it is expected that between-group differences in
Eyes Task performance, or a lack thereof are not due to higher rates of prescribed antidepressants in the depressed group than the manic or euthymic groups.

Although there are contradictory reports regarding an effect of antipsychotics on ToM ability in controlled studies of medication (e.g. Savina and Beninger, 2007; Sergi et al., 2007), contradictions are also observed in studies of emotion recognition in euthymic patients with bipolar disorder regarding mood stabilizers (Holmes et al., 2008) and medication load (Hassel et al., 2008). It is expected that the effects observed with polypharmacy such as psychomotor slowing (Bora et al., 2009b) and verbal memory deficits (Senturk et al., 2007) would not affect ToM ability specifically so these effects would be controlled for with the Animal Task. The limited investigation of medication effects in the current study suggests that poorer ToM in the manic group is not due to iatrogenic effects.

5.2.4 Comorbidities

This study found no further ToM deficits associated with comorbid Axis I disorders, or a history of substance abuse, suicide attempts or psychosis which did not support the preliminary hypotheses.

5.2.4.1 History of Suicide Attempts

The current study found no relationship between Eyes Task performance and a history of suicide attempts. Jollant et al. (2008), in their fMRI study that found increased response to angry faces in the orbitofrontal cortex in patients with histories of suicide attempts, argue that more studies of social cognition and suicide are required.
They argue that the pattern of activation in patients who have attempted suicide may relate to a hypersensitivity to disapproval and poorer sensitivity to subtle positive social cues. One primary question is if a history of suicide predicts poorer social cognition such as ToM or emotion recognition or if dysfunction lies in the response to accurately assessed social cues. This is of particular concern as suicidality in patients with bipolar disorder peaks with recent psychosocial stress (Leverich et al., 2003).

5.2.4.2 History of Psychosis

No relationship was found between Eyes Task scores and history of psychotic symptoms. This is consistent with studies investigating ToM ability in affective (Lahera et al., 2008; Wolf et al., 2010) and euthymic bipolar disorder (Bora et al., 2005; Olley et al., 2005). It has been suggested that a relationship with ToM exists with current psychotic symptoms instead of past psychotic symptoms (Marjoram et al., 2005). The current study did not investigate measures of psychosis during the patient interview so a distinction between patients with a history of psychosis and those with current symptoms was not made. Nevertheless, as no relationship was found between a history of psychotic symptoms and the Eyes Task nor were there group differences in experiencing psychotic symptoms, it is unlikely that a history of psychosis is related to poorer performance observed in the manic group.

An inability to find a relationship between ToM and comorbidity of Axis I disorders, or a history of suicide attempts or psychotic symptoms combined with reports of a relationship to current psychotic symptoms in depression (Marjoram et al., 2005; Bentall et al., 2009) supports an association between ToM deficits and acute severe
illness. In a recent meta-analytical study, Bora et al. (2009b) reported that patients with schizophrenia who are acutely ill had significant ToM deficits with large effect size compared to remitted patients with schizophrenia. It could be that comorbid disorders such as anxiety may only influence ToM performance in chronically ill patients with bipolar disorder when patients are experiencing acutely severe or episodic symptoms as opposed to continuous symptoms. Research involving acute illness in patients with schizophrenia may help in investigating potential aspects of illness acuity that provokes poorer ToM in patients with bipolar disorder.

5.2.5 Incomplete Remission in Euthymic Patients

An inability to differentiate Eyes Task accuracy between the depressed and euthymic patient groups could be due to maintenance of depressive symptoms. Euthymic patients commonly present with subsyndromal depressive symptoms that do not meet criteria for an affective episode (Judd et al., 2003). The current study required an HDRS rating of 7 or lower and an YMRS rating of 8 or lower. Remitted patients with bipolar or major depressive disorders are reported to maintain significantly higher HDRS score than healthy controls especially with mood subscales (Vieta et al., 2008). The maintenance of subsyndromal symptoms in remission has caused some studies to give more relaxed screening tool restrictions (McKinnon et al. 2010) while also spurring arguments for decreasing the defined remission cutoff of 7 to scores closer to 2 (Zimmerman, Posternak, & Chelminsksi, 2005). Zimmerman et al. found clinically relevant differences in quality of life measures in general psychiatric patients who scored 5-7 from those who scored below 2 on the HDRS. These differences in quality of life may represent a
separation between symptomatic recovery observed in the euthymic group and a functional recovery associated with ToM improvement (see Bora et al., 2006).

Although there are well established differences in neurocognition between depressed and euthymic patients with bipolar disorder such as phonemic verbal fluency (Martinez-Aran et al., 2004), verbal memory, and motor speed (Malhi et al., 2007), Kerr et al. (2003) and Wolf et al. (2010) have conflicting reports regarding ToM. Whereas depressed patients in the study by Kerr et al. performed significantly worse on false belief than euthymic patients, Wolf et al. could not find a difference between depressed and euthymic groups on a battery of ToM reasoning tasks. Severity of depressed symptoms cannot account for these differences as Wolf et al. and Kerr et al. reported similar HDRS group mean scores as the current study. Although similarities were found between the study by Wolf et al. and the current study, Wolf et al. also could not find poorer ToM reasoning scores in patients with mania. Furthermore, Wolf et al. reported a nonsignificant trend for lower scores from remitted patients than the manic and depressed groups but could not elaborate as to why this was the case. These contradictory results may reflect differences in ToM task demands discussed previously so limiting comparison of the current results to studies using the Eyes Task or similar decoding tasks may be necessary.

The current study found mean Eyes Task results in the euthymic and depressed patients comparable to those found by Lee et al. (2005) in female patients with a diagnosis of major depressive disorder with severe or mild/moderate depression (~70%). Lee et al. also recruited patients from PC-MHS and found significant impairment in
depressed patients compared to healthy controls. Their patients had significant ToM deficits compared to non-clinical participants with comparable severity of depressive symptoms reported by Harkness et al. (2005). An inability to differentiate ToM ability in patients with differing severity of unipolar depression reported by Lee et al. and euthymic and depressed patients with bipolar disorder in the current study suggests that ToM deficits may be associated with the diagnosis of clinical unipolar or bipolar depression as opposed to symptom severity.

5.3 Symptom Severity

Symptom Severity is a critical concern in the present study considering that the patients experiencing mania performed significantly worse on both the Eyes and Animal Tasks than depressed and euthymic patients. As the manic group had general performance deficits, a reasonable argument against episode-dependent ToM ability is that the effect is driven by general cognitive deficits in patients who were acutely manic. This argument is weakened, however, by limited relationships between mental state attribution and the severity of symptoms. The only relationship found between severity measures of mania, depression, and anxiety and Eyes and Animal Task accuracy was a negative correlation between symptoms of mania and Animal Task accuracy. If poorer ToM was due to general cognitive deficits it would be expected that a significant relationship between YMRS and Eyes Task would also be found.

A negative relationship between Animal Task and severity of manic symptoms is similar to the study by Wolf et al. (2010) who found that YMRS correlated to preservative errors in a task of executive functioning but did not correlate to any ToM
measures. This could indicate that ToM ability is less sensitive to severity of manic symptoms than some measures of non-social cognition required by ToM tasks. The inability to find a relationship between ToM and manic symptom severity in the current study may conflict with the study by Schenkel et al. who found that manic symptoms in pediatric patients with bipolar disorder was negatively correlated to performance on the Hinting Task and the negative story in the Affective Story Task. Schenkel et al. included patients experiencing depressed and mixed episodes in the correlation between ToM performance and YMRS and did not report episode specific correlations so the relationship between manic symptoms and ToM may reflect between-episode differences in ToM performance similar to the current study.

No relationship was found between Eyes Task accuracy and depressive symptoms as measured using BDI or HDRS. This is consistent with the study by Harkness et al. (2005) of undergraduate students with or without a history of major depressive disorder, the study by Lee et al. (2005) of clinically depressed women, and the study by Bora et al. (2005) of euthymic patients. The inability to find a relationship between depressed symptoms and ToM decoding, however, contradicts the argument by McKinnon et al. (2010) that no relationship between ToM and symptom severity reported by Bora et al. (2003) was due to restricted criteria of depressive symptoms for euthymia. As the current study found no relationship between the severity of depressed symptoms and ToM accuracy, nor was able to differentiate ToM ability between depressed and euthymic groups, it does not provide support for predicting ToM ability through general measures of depression such as the BDI and HDRS.
Measures of anxiety were not correlated to Eyes Task accuracy in the current study which does not support the hypothesized negative relationship. Lee et al. (2005) found that anxiety measures were negatively related to both Animal and Eyes Tasks in clinically depressed women and controls. They found that measures of anxiety did not significantly influence the relationship between clinical depression and mental state decoding. Harkness et al. (2005) found that controlling for anxious symptoms strengthened the relationship between ToM decoding ability and dysphoria in university students. No relationship found between Eyes Task and measures of anxiety in the current study was also reported in a study of outpatients with anxiety disorders or schizophrenia (Morrison & Myhr, 2010) and outpatients with borderline personality disorder (Fertuck et al., 2009). An inability to find a relationship between ToM and the severity of depressive, anxious, and manic symptoms supports the argument that ToM deficits are better predicted by acute illness instead of the combined somatic and affective symptoms used to gauge illness severity.

5.4 Valence Effect

There was no significant difference in Eyes Task accuracy found between positive, negative, or neutral valences, nor was there a significant interaction between valence accuracy and episode type. At the trend level, euthymic patients demonstrated a positive bias and patients who were depressed and manic demonstrated a negative bias. Significant contrasts suggest that the nonsignificant interaction effect could be limited by a lack of statistical power.
Valence trends in the current study contradict traditional mood-congruent emotion recognition patterns reported in patients with bipolar disorder (Lembke & Ketter, 2002; de Almeida Rocca et al., 2009). The current findings also conflict with those of Schenkel et al. (2008) who found poorer accuracy on negative valence stories was associated with manic symptoms in pediatric patients. This pattern in a pediatric sample is still of clinical relevance to adult populations as research involving social cognition in pediatric bipolar disorder has supported a continued pattern of cognitive deficits between pediatric and adult bipolar disorder. Deficits such as working and verbal memory (Pavuluri et al., 2006), attentional set-shifting, and visuospatial memory (Dickstein et al., 2004; McClure et al., 2005) have been reported in both adult and pediatric samples. The contrasting results between Schenkel et al. and the current study could be due to the difference in ToM constructs as well as sensitivity to mood differences. The Eyes Task is an affective ToM task whereas the Affective Story Task is an emotionally valenced cognitive ToM task which may be exclusive to the study by Schenkel et al.

A contrast in the current study from mood-congruent biases reported in emotion recognition tasks could be due to differences in task constructs. In order to differentiate the Eyes Task from typical emotion recognition tasks, Baron-Cohen et al. (1999, 2001) used a combination of target words that describe cognitive processes such as “reflective” and “concerned”. In their study of patients with AS and healthy controls they found Eyes Task correlated positively with the Happés Strange Story Task but not a basic facial emotion recognition task (Ekman, 1992). Studies that have included both the Eyes Task as well as a facial recognition task find that the two are inconsistently correlated. Bora et
al. (2005) found that the Eyes Task but not the Hinting Task was significantly correlated to the Benton Facial Recognition Test (see Levin, Hamsher, & Benton, 1975) and a basic facial emotion recognition task (see Adolphs, Baron-Cohen, & Tranel, 2002). An inability to find a significant correlation between the Eyes Task and an emotion recognition task was also reported in patients with traumatic brain injury although impairments were found in both tasks (Henry, Phillips, Crawford, Ietswaart, & Summers, 2006). As Eyes Task accuracy is not reliably correlated to emotion recognition tasks, an inability to find a significant mood congruent bias in the current study does not hinder an argument for exaggerated deficits associated with mania.

Consistent with differences in ToM task constructs, an inability to find a mood-congruent bias may be an artifact of the Eyes Task. In other studies there were no significant biases in accuracy between negative neutral and positive valence Eyes Task items in undergraduate students who were dysphoric, had a history of a major depressive episode, or were otherwise healthy (Harkness et al., 2005; Harkness et al., 2009), women from the community who were healthy or clinically depressed (Lee et al., 2005) or patients with borderline personality disorder (Fertuck et al., 2009). Because response bias to valence is not generally reported with the Eyes Task, perhaps a trade-off for being challenging and sensitive to more subtle ToM deficits is that the Eyes Task is not as sensitive as other tasks to mood-congruent selective attention.
5.4.1 Speed vs. Accuracy Trade-Off

No significant relationships between response time and Eyes Task accuracy both overall or within groups were found in the current study, which does not support the hypothesized negative relationship. This suggests that a speed vs. accuracy trade-off is not the cause of ToM deficits in manic patients. Although there was a trend for patients who were manic to have faster response times, there were no significant group differences in Eyes or Animal Tasks response times. Of note, are the significantly slower response times in the acutely manic patients from HDH than the manic out-patients from PC-MHS. Slower psychomotor speed is a common feature in patients with bipolar disorder suffering from acute mania and acute depression. For example acute depressed and manic patients needed twice as much time than healthy controls did to complete a task of attention and psychomotor speed called the Trail Making-A task (Mahlberg, Adli, & Bschor, 2008). As response time was not a significant covariate when comparing Eyes Task accuracy between groups, mental state decoding ability was not found to be related to differences in psychomotor speed in the current study. This separation of Eyes Task performance from response time suggests that a deficit in mental state decoding associated with mania may indeed reflect deficits in an automatic social cognitive domain instead of patients hurrying to complete the task.
5.5 Limitations

5.5.1 Illness Classification

Patients in the current study were included based on a diagnosis of bipolar 1 or bipolar 2 disorder considering the criteria discussed in the methods chapter. From there, patients were separated into episode groups based in symptom severity in order to address the primary goal of comparing ToM ability between episodes. All other information regarding condition, such as comorbidity, acuity of the current episode, and specific diagnoses was collected from a post hoc review of patient records in an effort to support the primary findings.

Combining patients who were acutely and chronically ill into more general episode groups could limit an argument for ToM deficits associated with mania in general. Manic patients were recruited from both HDH and PC-MHS. Although not significantly different in many aspects, the five patients from the HDH site, as inpatients experiencing acute mania, arguably represent the most severe patients in the manic group. Still, only two patients in the HDH group had YMRS scores that distinguished them from manic patients from PC-MHS. The patients from HDH performed more poorly on the Animal Task and had overall response times much slower than the manic patients at PC-MHS. Response time, however, was not a significant covariate when comparing Eyes Task accuracy between episode groups. This suggests that psychomotor slowing, although clinically relevant, is not of concern with regards to accuracy on inferring mental states in the current study.
Another nonsignificant trend of interest is the estimated mean age of onset. The estimated mean onset of 16 for the HDH group is younger than the mean estimated age of onsets for the episode groups reported between 24 and 26. Significant psychomotor and cognitive deficits in the Animal Task and a trend for earlier age of onset in the HDH patients are consistent with reports of cognitive deficits associated with earlier age of onset (Jamrozinski, 2010; Taylor & Abrams, 1981). Still, age of onset and Animal Task accuracy are controlled for, both in the investigation of Eyes Task accuracy between groups and when considering valence in the current study.

Importantly, as the HDH patients were identified as a subgroup of particular interest, differences between HDH and PC-MHS patients in the manic group were investigated. There is no equivalent comparison group in the depressed patients although some patients reported high symptom severity, and very poor course of illness. Arguably, it is not the inclusion of acutely manic patients that limits this study but a lack of a comparable, qualitative, clinically relevant distinction for illness acuity in the depressed group.

Both patients with bipolar 1 and bipolar 2 disorders were included in the study but patients in the depressed and euthymic groups were not asked explicitly what type of diagnosis they had been given. Perhaps contrary to expectations, reviewing patient records did not prove informative enough to reliably make this distinction for all patients.

A distinction between bipolar 1 and bipolar 2 disorder is of interest as there have been significant differences in social cognition observed between patients with bipolar 1 and bipolar 2 disorder. In a study of emotion recognition and cognitive impairment
outpatients with bipolar 2 disorder were more impaired in executive functioning, memory, and IQ than out-patients with bipolar 1 disorder (Summers, Papadopoulou, Bruno, Cipolotti, & Ron, 2006). Although diagnosis predicted cognitive function, emotion recognition was relatively unrelated to diagnosis. Summers et al. found that both patient groups were significantly impaired only in surprise recognition, but a significant negative correlation between depressive symptoms (assessed using BDI) and recognition of anger was reported. Contrasting results were found in a similar out-patient study. Those with a diagnosis of bipolar 2 disorder did not significantly differ from healthy controls in an emotion recognition task whereas significant deficits were observed in those with a diagnosis of bipolar 1 disorder (Derntl, Seidel, Kryspin-Exner, Hasmann, & Dobmeier, 2009). Emotion recognition was not correlated to measures of intelligence or residual symptoms. Similarly, Schenkel et al. (2008) reported poorer performance in ToM reasoning (Hinting Task) but not a false belief task (Affective Story Task) in pediatric patients with bipolar 1 compared to bipolar 2 disorder. These three studies, although reporting contradictory results and different measures, provide support for qualitative differences in social cognitive functioning associated with diagnosis.

The patients in the current study had a variety of comorbid disorders which is inconsistent with many of the studies discussed (e.g. Bora et al., 2005; Kerr et al., 2003). Many studies of social and nonsocial cognition exclude patients with substance abuse disorders or a history of psychotic symptoms. As those are very common in patients with bipolar disorder, it could be argued that studies with strict exclusion criteria systematically screen out more severe cases of the disorder, and as such do not
adequately measure the severity of cognitive deficits associated with bipolar disorder. This is also true with regard to including patients experiencing acute symptoms as well as pooling patients with bipolar 1 and bipolar 2 disorder however detailed assessment of patient illness would provide support for episode-dependent differences of ToM in the current study.

5.5.2 Approach to Supportive Data Collection

The current study was a pilot study designed with the initial intention to not compensate participants for their time. Accordingly, time-consuming tasks such as measures of intelligence and executive function were not performed. The patient interviews involving the Eyes Task and measures of symptom severity (YMRS, HDRS, BDI-II, and BAI) included brief open questions for occupation, education, marital status, and number of children. As the questions were open, measurements such as education were condensed into groups in order to appropriately investigate group differences. Using a ratio scale achieved by asking a closed question such as ‘How many years of school did you complete?’ would have allowed for a more reliable, more statistically sound investigation of group differences and relationships of clinical measures to Eyes Task performance.

The current study collected information about course of illness from patient records in an effort to control for potential group differences when investigating effect of episode type on ToM ability. The standardized information in patient records has limited overlap with the measures of interest for this study. For instance, a history, or lack thereof, of suicidality or ideation is consistently and reliably reported regardless of
whether or not the patient was registered at the hospital when they were suicidal. Detailed reports of suicidality are a direct contrast to quantitative reports of illness progression. The number of manic and depressed episodes as well as number of hospitalizations is generally reported only for the time that the patient was registered to a specific hospital group or discussed qualitatively in intake reports. Still, there is a notable trend with reporting. The reported number of previous episodes was generally recorded numerically up to 3, after which qualitative reports distinguished only between “many” and “(rapid) cycling”. The number of hospitalizations was more quantitative due to the ability to combine the patient registration report with the physical number of intake reports and communications for new hospitalizations. Still, no relationship was found between Eyes Task accuracy and hospitalizations or number of episodes.

Age of onset and duration of illness should also be considered carefully. This study used age of first diagnosis from patient records as an indicator of age of illness onset. There are reports of significant gaps between onset of symptoms, treatment seeking, and diagnosis (Lish, Dime-Meenan, Whybrow, Price, & Hirschfeld, 1994). Lish et al. found that 50% of patients with bipolar disorder in the study waited for at least five years after they first experienced symptoms before they sought treatment. Furthermore, this can be exacerbated by misdiagnoses. The number of patients to see three or more health professionals before being diagnosed with bipolar disorder was 32% and an additional 10% of patients saw more than seven professionals before being properly diagnosed (Lish et al). This is comparable to other reports in urban populations although extended time to seek treatment in some rural communities has been reported: in studied
Amish populations a gap between symptoms and treatment seeking averaging 10 years has been observed (Egeland, Blumenthal, Nee, Sharpe, & Endicott, 1987). Egeland et al. reported that despite differences between cultural groups, age of onset for impairment with affective symptoms was the best measure associated with onset age to discriminate bipolar 1 disorder from bipolar 2 disorder and unipolar depression. Further investigation of mental state decoding across affective episodes will benefit from direct patient reports that could include onset of impairment. Patient interviews regarding onset of impairment would reduce the effect of misdiagnosis on age of onset which is common in patients with bipolar disorder, especially with children (Isaac, 1992).

5.5.3 No Test of Neurocognitive Function

The addition of acutely ill patients in the current study may not have been adequately controlled for by the Animal Task alone. In the current study, the HDH subgroup includes the more severe patients in the manic group and had mean Animal and Eyes Task scores that were relatively equal (48% vs. 49% respectively). This is represented by significantly lower Animal Task accuracy but only a trend for lower Eyes Task accuracy when comparing HDH and PC-MHS manic patients. Equivalent Eyes and Animal Task accuracy is at odds with this study’s higher mean group scores for the Animal Task. One interpretation could be that individuals with low scores do not present with differential results on the Animal and Eyes Task. In contrast, preliminary tests for potential outliers highlighted the lack of correlation reported between Animal and Eyes Task accuracy; some patients had very low scores on one task and very high scores on another. To the author’s knowledge, the current study is the first to report such low
numbers on the Animal Task so information regarding the lower limits of the Eyes and Animal Tasks is speculative.

The current study did not include any measure of neurocognitive functioning aside from the Eyes and Animal Tasks. In particular, assessing executive function with tasks validated with patients experiencing mania would have been beneficial. The role of executive function in ToM has been addressed many times in clinical samples such as patients with euthymic bipolar disorder (Olley et al., 2005; Montag et al., 2010) and schizophrenia (Bora, Eryavuz, Kayahan, Sungu, & Veznedaroglu, 2006; Harrington et al., 2005). Aspects of executive function generally correlate with ToM ability assessed through a myriad of tasks. Bora et al. (2005) found significant relationships between Eyes Task accuracy and measures of executive functioning such as psychomotor speed and Stroop interference. Bora et al. also controlled for Eyes Task accuracy with the Rey Auditory Verbal Learning Task which is a measure of attention, verbal learning, and executive function. (AVLT; McMinn, Wiens, & Crossen, 1988).

It could be argued that as significant ToM deficits were maintained when Bora et al. controlled for executive function, these controls might not have been needed. In support of this, a study of healthy individuals investigated the role of executive function on three ToM tasks; the Eyes Task, Strange Stories Test, and the Faux Pas Test. They used a ‘typically-developed’ adult sample in order to better infer the role of executive functioning in ToM ability. Verbal fluency, deductive reasoning and problem solving ability were significant predictors of the Strange Stories and Faux Pas tests whereas no measure of executive function was predictive of Eyes Task performance (Ahmed &
Miller, 2010). Still, the inclusion of tasks of executive function would have supported an argument for poorer Eyes Task accuracy in the manic group as a strong indicator of a deficit in mental state decoding beyond non-social cognitive impairment.

In line with tasks of executive function, estimates of IQ would support an argument for between group differences in ToM. There was no measure of premorbid intelligence in the current study. One study found that patients with severe, chronic bipolar disorder present with intellectual impairments even when considered clinically recovered (Johnstone, Owen, Frith, & Calvert, 1985). Kerr et al. (2003) used the National Adult Reading Test (NART; Nelson, 1982), which is widely used as an indicator of premorbid intelligence based on the premise that the ability to pronounce irregular words is unaffected in many clinical disorders (O'Carroll et al., 1992). Kerr et al. found that manic patients had significantly poorer NART scores than euthymic patients and first and second order false belief accuracy for the whole sample was correlated to NART scores. Ahmed and Miller (2010) recently found that IQ was predictive of the Eyes Task, but this is inconsistent with Baron-Cohen et al. (2001) who did not find a correlation between Eyes Task and IQ. The argument by Baron-Cohen et al. (2001) that Eyes Task accuracy is not related to non-social intelligence has been met with mixed reports of relationships between Eyes Task, IQ, and duration of education.

In an effort to control for the effect of intelligence on ToM ability, the current study collected level of education from patient records. Lee et al. (2005) found that duration of education was not a significant covariate when comparing Eyes Task accuracy between women with major depression and healthy controls. Similarly, Bora et
al. (2005) found that Eyes Task accuracy was correlated to duration of education in euthymic patients but was not a significant covariate in comparing Eyes Task accuracy between euthymic patients and healthy controls. Level of education may be a misleading indicator of intelligence as it has been argued that educational attainment is disrupted in patients with bipolar disorder. When comparing patients with bipolar disorder to demographically matched healthy controls, IQ levels and rate of college entry were comparable but level of completed education was significantly lower in patients with bipolar disorder (Glahn, Bearden, Bowden, & Soares, 2006). The current study did not find that patients with a higher level of completed education performed any better on the Eyes or Animal Tasks than patients with a lower level of education. Although no relationship between mental state attribution using the Eyes Task and level of education was found, future studies would benefit from standardized investigations of education and IQ.

Regardless of the lack of additional neurocognitive measures in the current study, it is unlikely that significant deficits in affective ToM decoding observed in the manic group, or the inability to differentiate the depressed and euthymic groups is due to group differences in general cognition. As discussed with regard to illness severity, the Animal Task controls for the response demands of the Eyes Task by having the same visuospatial template, as well as requiring matching descriptive words to the displayed image. As the Animal Task was not a significant covariate when comparing Eyes Task accuracy between affective groups, it is likely that the response demands of the Eyes Task did not contribute to differences in Eyes Task accuracy between groups.
5.6 Future Directions

5.6.1 Qualitative Measures of Symptom Severity

Lee et al. (2005) found that Eyes Task accuracy in depressed women was significantly correlated to affective measures but not somatic measures of the HDRS scale. Furthermore, Harkness et al. (2009) found that Eyes Task measures were sensitive to mood induction in students with or without a history of depression. Considering these two findings, a question worth investigating is whether or not Eyes Task accuracy is related to measures of severity of mania and depression or just related to current mood. In a study of borderline personality disorder, Fertuck et al. (2009) measured severity of depression using the BDI but also used a measure of current emotional state called The Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1981). POMS is a 65-item scale that measures transient affective mood and is sensitive to acute changes. The POMS-Bipolar Form (Lorr & McNair, 1984) is a 72-item scale that extends the mood profiles to accommodate longitudinal measures across depression, euthymia, and mania. Fertuck et al. reported that valence scores correlated differently to measures of depressive severity and emotional state. For example, the POMS confusion subscale was significantly positively correlated with neutral but not overall, positive, or negative valence items. The current study found no relationship to any measures of symptom severity however, the YMRS, BDI, BAI, and HDRS all include assessment of somatic symptoms experienced over the past week which are included with current mood. A closer consideration of transient affect with measures such as the POMS-Bipolar Form...
may be beneficial in further investigation of the effects of episode on Eyes Task performance.

Another consideration for future studies is the adjustment of sensitivity in the Eyes Task. Domes et al. (2007) separated the Eyes Task into easy and hard measures when investigating the effects of oxytocin in healthy men. They found significant differences in hard items but not easy items. Perhaps investigating both hard and easy Eyes Task measures may highlight more subtle ToM differences between affective groups than the overall Eyes Task score. Additionally, including an easier ToM task such as the Yoni Task may act as a safeguard from floor effects in more acutely ill patients.

5.6.2 Investigation of Longitudinal Changes in ToM Ability between Affective States

A benefit of the Eyes Task is that it has a limited learning effect. No feedback is provided with regard to accuracy so the same person can repeat the task many times. For this reason, the Eyes Task is well suited for longitudinal investigation of ToM decoding ability within patients as they experience changes in affective episodes. One consideration with repeated measures is a loss of interest and associated decrease in task performance. If sustained attention, argued to be a trait-related deficit in bipolar disorder (Clark & Goodwin, 2004), is a covariate of concern, an additional task controlling for a possible vigilance decrement can be included. Continuous performance tests, where participants have to monitor a stream of stimuli and respond to specific targets, are well suited for longitudinal research. CPTs are less sensitive to practice effects than executive functioning tasks and allow for working memory, inhibitory control, and visual processing variables to be manipulated (Elvevag, Weinberger, Suter, & Goldberg, 2000).
5.7 Application

Poorer ToM decoding in manic but not depressed patients as compared to euthymic patients is of particular importance when considering psychosocial disability in the course of bipolar disorder. Eyes Task accuracy was a very strong indicator of social functioning in outpatients with schizophrenia (Bora et al., 2006). This could be the case in the current study as the severity of manic symptoms has been reported to correlate with poorer quality of life (Gazalle et al., 2007). Still, recent longitudinal studies have also reported that severe depressive episodes are associated with poorer psychosocial functioning than corresponding severe manic episodes (Vojta et al., 2001; Judd et al., 2005). With poorer Eyes Task performance associated with mania, the Eyes Task may not be as strong of an indicator of psychosocial function in patients with bipolar disorder as it is in patients with schizophrenia.

A potential cause for why manic patients performed poorly on the Eyes Task may be best explained by the nature of the symptoms associated with mania. Symptoms of illness such as distractibility and agitation interfere with the ability to perform the Eyes Task. This would not be documented through faster response times as patients were likely to disengage from the task as opposed to rush to complete it. An indirect confirmation of manic symptoms interfering with the ability to perform the Eyes Task is that YMRS symptoms were negatively correlated with Animal Task performance and a negative trend was observed for Eyes Task performance. As well, distraction during the task may better explain slower response times in HDH patients than psychomotor slowing.
A reduced ToM in manic patients may provide support for understanding why mania is associated with such destructive interpersonal behaviour. An early study of interpersonal maneuvers of manic patients found that manic patients were more likely than patients with schizophrenia or schizoaffective disorder to manipulate others, detect and exploit social vulnerability in hospital staff, and promote conflict in others (Janowsky, El-Yousef, & Davis, 1974). These behaviours were attenuated when symptoms were reduced. This pattern of behaviour, combined with the current study’s findings, may be an indicator that manic patients are acutely aware of superficial interpersonal interactions but do not appreciate the emotional impact of their actions on others.

Exaggerated ToM deficits in mania but not depression may also reflect the efficacy of different treatments. Perhaps an intact ToM may play a role in why psychotherapy, socialization, and social support are strong predictors of recovery for bipolar depression but not mania (Johnson et al., 2000). Physical symptoms like sleep and agitation are better predictors for severity of mania (Gazalle et al., 2007; Johnson et al., 1999). Between-episode differences in the benefit of socialization as a facet of treatment may be related to the ability to appreciate the mental states of others, however this is only speculative and further research is required.
5.8 Conclusion

This study found a deficit in Eyes Task performance in adult patients with bipolar disorder experiencing mania compared to those experiencing euthymia or depression. This relationship could not be explained by the response demands of the task, differences in response time, or age of illness.

No differentiation in Eyes Task accuracy between the depressed and euthymic groups, when considering the existing research investigating ToM deficits in euthymic patients with bipolar disorder, suggests that a deficit in affective mental state decoding continues into the euthymic phase. As no relationship was found between the severity of symptoms and mental state decoding, it is uncertain if a continued deficit is due to the continuation of subsyndromal symptoms or if it is a trait-related deficit in bipolar disorder that is exacerbated during mania.

No significant relationship was found between Eyes Task accuracy and the severity of depressive, manic, or anxious symptoms. A significant negative relationship between severity of manic symptoms and Animal Task, and the Eyes Task at a trend level may indicate that symptoms of mania such as distractibility and agitation may play a role in poorer scores as opposed to a selective deficit in ToM associated with mania. Further research involving measures of nonsocial cognition and the Eyes Task in subtypes of mania would be of great benefit in understanding ToM in patients with bipolar disorder. If exaggerated ToM deficits are detectable at the onset of mania, regular testing of ToM may be of benefit in the early detection and treatment of mania.
References


transdiagnostic investigation of patients with schizophrenia spectrum disorders and depression. *Arch Gen Psychiatry, 66*(3), 236-247.


bipolar disorder: Evidence for task-specific dysfunction. *Bipolar Disorders, 6*(6), 550-564.


adolescents: International perspective on epidemiology and phenomenology. *Bipolar Disorders, 7*(6), 497-506.


