COGNITIVE FUNCTIONING IN BIPOLAR DISORDER: THE INFLUENCE OF SEX

by

Swetha Popuri

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Abstract

Following a wave of similar research conducted in samples with schizophrenia, there has been a recent surge of studies investigating sex differences in the phenomenology of bipolar disorder (BD). These studies have almost exclusively focused on sex differences in course and clinical presentation. As compared with male BD patients, women with BD have increased likelihood of experiencing rapid cycling, mixed mania, suicidal ideation, and a medical or psychiatric comorbidity. However, in addition to its characteristic affective disturbance, the phenomenology of BD is associated with significant and persistent cognitive impairment. There is evidence to support that sexual dimorphisms, the basis of sex differences in cognitive functioning, are altered in BD. Additionally, it has been found that healthy patterns of cognitive sex differences are disrupted in schizophrenia, a closely related illness to BD. Despite this evidence, there have been few studies that have investigated the influence of sex on cognitive functioning in BD; the results that are available are both scant and contradictory.

In order to clarify whether sex influences cognitive functioning in BD, 66 patients with BD-I disorder and 105 matched healthy controls were tested on a broad battery of neuropychological tests. As patients used in this sample were tested immediately proceeding symptomatic remission from their first-manic episode, this experimental design is poised to assess sex differences in cognitive functioning early in the course of BD. Overall, unlike in schizophrenia, healthy patterns of cognitive sex differences are intact early in the course of BD.

To supplement and contextualize the study presented above, a large portion of this thesis is dedicated to providing literature reviews of the following topics: sex differences in the clinical phenomenology of BD, cognitive impairment in BD, sex differences in cognitive impairment and their neurobiological underpinnings in healthy samples.

Preface

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To my parents, Padma and Murli Krishna

1. Introduction: literature overview and thesis objectives

The goal of this thesis is to better understand how sex influences cognitive impairment in bipolar disorder; this chapter serves as an introduction to the thesis materials to follow. A clinical description of bipolar disorder will first be provided followed by a literature review regarding sex differences found in the clinical phenomenology of this illness. These data will contextualize and justify the thesis objectives that will be delineated in the final section of this chapter.

1.1 Clinical description of bipolar disorder

Acute affective episodes: manic, depressive and mixed states. Bipolar disorder (BD) is a chronic, recurrent affective disorder characterized by cyclic episodes of mania/hypomania and depression, with intervening periods of clinical remission or euthymia. In addition to this affective disturbance, the phenomenology of BD commonly involves cognitive deficits, disturbances to the sleep/wake cycle, and high rates of medical and psychiatric comorbidity (Balanza-Martinez et al., 2010). Despite the prevalence of these associated impairments, the diagnostic criteria for BD in the American and international diagnostic systems primarily center on recognizing and delineating symptoms associated with acute mood episodes and their course of presentation (Goodwin and Lieberman, 2010). Mania is seen as the defining feature of BD. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), a manic episode involves an abnormally and persistently elevated, expansive, or irritable mood lasting for at least one week or until hospitalization is required. In addition to these core features, several other symptoms are commonly present during a manic

episode; these include: inflated self-esteem or grandiosity, decreased need for sleep, pressure of speech, distractibility, flight of ideas, and psychomotor agitation. However, this list of symptoms is not exhaustive and the expression of mania is highly heterogeneous across patients (Goodwin and Lieberman, 2010). Though each individual patient may experience some degree of consistency across their manic episodes, this consistency is not a given, and the symptom profile may change considerably over the course of this illness; treatment factors such as medication may increase the chance of this variance (Cassidy et al., 2002). Patients may also present with psychotic symptoms during mania and several studies have associated the presence of these symptoms with a less favorable long-term course (MacQueen et al., 1997; Tohen et al., 2003). Withstanding the considerable variability that can be expressed during mania, these episodes frequently impose marked social or occupational impairment for individuals (Goodwin and Lieberman, 2010).

Significant functional impairment is also associated with depressive states. In fact, the functional impact of syndromal and subsyndromal depression is higher than mania both to the individual and, from an economic standpoint, to society at large (Gitlin et al., 1995; Bryant-Comstock et al., 2002). To be characterized as a depressive episode, a patient must exhibit a depressed mood or a loss of interest or pleasure in most activities for at least two weeks. Again, depressive episodes are marked by significant heterogeneity, and a constellation of other symptoms may accompany these core features: changes in appetite, weight, or sleep; decreased energy; difficulty thinking and making decisions; feelings of worthlessness or guilt (Goodwin and

Lieberman, 2010). Some symptoms, such as irritability and psychomotor speed, are expressed commonly during both mania and depression, and these overlaps may work to blur the distinction between the two polarities (Deckersbach et al., 2004; Goodwin and Lieberman, 2010).

Indeed, many symptoms associated with depression and mania can be simultaneously expressed. During a mixed episode, a patient expresses a range of symptoms so as to qualify for the DSM-IV-TR criteria of both a manic and depressive episode (Goodwin and Lieberman, 2010). Mixed episodes occur frequently in BD, with one estimate citing that 40% of BD-I hospital admissions were for mixed states (Kruger et al., 2005). Mixed symptoms may emerge simultaneously, or manic symptoms may build on preexisting depressive symptoms. It is common for a mixed episode to evolve into a major depressive episode (Goodwin and Lieberman, 2010). More so than in manic episodes, mixed episodes accompany comorbid obsessive compulsive disorder, feelings of helplessness, and suicidal ideation (Dilsaver et al., 1994; McElroy et al., 1995). Patients who frequently experience mixed episodes are often excluded from research studies, and for this reason relatively little is known about this subset of individuals (Goodwin and Lieberman, 2010). Given their prevalence and contribution to the mortality rate associated with BD, BD samples with mixed states warrant further research.

Bipolar subtypes. BD is often construed as a spectrum with three major subgroups: bipolar I (BD-I), bipolar II (BD-II), and cyclothymia (Goodwin and Lieberman, 2010). BD-I is characterized by the presence of recurrent manic or mixed episodes;

psychotic symptoms are experienced by 75% of BD-I patients (Tohen et al., 1990). BD-II is characterized by hypomanic rather than manic or mixed episodes. Although hypomania has a similar symptom profile to mania, these symptoms are experienced at a decreased severity (Goodwin and Lieberman, 2010). However, due to the increased chronicity and time spent in depression that is associated with BD-II, both subtypes have an equally severe impact on functioning (Suppes and Dennehy, 2002; Vieta and Suppes, 2008). In addition, the lifetime prevalence of BD-I and BD-II are a similar 1% and 1.1%, respectively (Merikangas et al., 2007). Cyclothymia is considered more benign than either BD-I or BD-II and is associated with hypomanic features and symptoms that fall short of qualifying for a major depressive disorder. Milder affective, motoric, and cognitive symptoms are seen in this sample (Goodwin and Lieberman, 2010). The taxonomy of a psychiatric illness profoundly affects both researchers and clinicians as it determines research samples and treatment strategies. The diagnostic definition of BD and the subtype classification system described above is continually evolving as more is understood about the genetic and neurobiological abnormalities that underlie this illness.

Cognitive impairment. Beyond the affective disturbance that classifies patients as having BD, this illness accompanies significant cognitive deficits in the domains of verbal learning and memory, attention/processing, and executive dysfunction (Robinson et al., 2006; Torres et al., 2007). Presumably, these cognitive aberrations are the product of gross anatomical and neurochemical irregularities; indeed, evidence of such pathology is continually amassing (Post and Kaur-Sant'Anna, 2010). Many of these cognitive

impairments are present in BD patients after their very first manic episode, although the severity of these impairments is less than that observed later in the course (Nehra et al. 2006). As such, cognitive impairment in BD is most likely generated by both neurodevelopmental and neurodegenerative factors (Goodwin et al., 2008). Clinical management of cognitive symptoms is made difficult as the pharmacological agents used to treat affective symptoms sometimes adversely affect cognition (Balanza-Martinez et al., 2010). Currently no established cognitive remediation programs address these impairments from a nonpharmacological angle. In part, this delay in generating cognitive behavioural intervention strategies is caused by the complicated nature of discerning iatrogenic from illness-related cognitive impairment in BD (Goldberg and Chengappa, 2009); polypharmacy treatment regimes and comorbid conditions, both of which are highly common in BD, may also contribute to overall cognitive impairment (Balanza-Martinez et al., 2010).

Cognitive deficits represent an important target for future therapeutic intervention as these impairments carry a significant functional burden. Psychosocial dysfunction in BD was once thought to be completely resolved by periods of euthymia; it is now known that there is a gap between the syndromal recovery associated with this phase and functional recovery (Bonnin et al., 2010). A two-year longitudinal study following patients after their first manic episode reported that 73% of their sample failed to achieve functional recovery even after their affective symptoms had remitted (Tohen et al., 2000). Many factors are associated with poor functional outcome such as history of psychosis, greater chronicity of illness, and comorbid substance abuse;

cognitive impairment is an especially impactful member of this list (Bonnin et al., 2010). In fact, cognitive impairment is thought to be a better indicator of functional outcome than many clinical indices (Wingo et al. 2009). In part, the strength of this association with functional outcome can be explained by the pervasive nature of cognitive impairment throughout the course of BD. While clinical symptoms completely or partially resolve during euthymia, cognitive dysfunction in many domains persists during this phase (Torres and Malhi, 2010).

As full affective and functional remission is not yet possible with the treatment strategies available, neurobiologists and psychiatrists alike are searching for ways in which to minimize heterogeneity and gain a clearer picture of the etiology of this complex disorder. For example, there has been a recent push to consider BD-I patients with a history of psychotic symptoms as a separate subtype (Goodwin and Lieberman, 2010). Affective and functional disturbance is more severe in these individuals and it is thought that "psychotic BD" is more closely related to schizophrenia (SZ) than other subtypes (Tohen et al., 2003). Considering bipolar patients with a history of psychosis as a separate subtype may be an etiologically revealing avenue of thought in that it a) may construct a subgroup with reduced heterogeneity and b) comparing differences across subgroups may lead to insight as to their mechanisms of pathogenesis. Additionally, identifying a subgroup with less heterogeneity can lead to the development of more targeted therapeutic interventions that may be needed to maximize recovery in these individuals. An analogous approach is currently being considered with sex and its influence on BD. Following a similar wave of research conducted in SZ samples, many

studies have revealed that that there are distinct differences in the clinical phenomenology of men and women with BD (Abel et al., 2010; Diflorio and Jones, 2010). As this is a nascent area of research, several questions remain to be answered: What is the neurobiological contribution to these sex differences? Are the pathophysiological mechanisms that produce the symptoms of BD the same in both men and women? Are these sex differences a reflection of the disease itself, or do treatment factors play a role? Of primary concern to this thesis are the following two questions:

1. Are sex differences in the cognitive impairment observed in BD?
2. If so, are these sex differences in cognitive impairment present at the onset of the illness or do they emerge over the course of several episodes?

In beginning to answer these two questions, it would be prudent to first review the literature regarding phenomenological sex differences observed in BD. This review is presented in the next section.

1.2 Sex differences in the clinical phenomenology bipolar disorder

There are numerous sex differences found in the course and clinical presentation of BD. Both epidemiological and phenomenological considerations will be reviewed.

1.2.1 Epidemiological considerations

The lifetime prevalence rate for bipolar disorder I (BD-I) has traditionally been quoted as 1-1.3% (Diflorio and Jones, 2010). More recent large-scale epidemiological surveys have resulted in a wider range of reported statistics. The National Epidemiological Survey on Alcohol and Related Conditions (N = 43,093) conducted out of

the United States received a lifetime prevalence rate for DSM-IV BD-I of 3.3% (Morgan et al., 2010). As a follow-up, the National Comorbidity Survey Replication, again conducted out of the United States (N = 9,282), found the lifetime prevalence rate of 1% for BD-I using DSM-IV criteria (Nierenberg et al., 2010). Furthermore, the Psychosis in Finland Study (PIF) found a DSM-IV BD-I lifetime prevalence rate of only 0.24% using a representative sample of 8,028 persons (Jonna et al., 2008).

Multiple factors seem to underlie the variance found in these figures, including geographic location, choice of diagnostic instrument, and differing assessment guidelines. Age inclusion criteria seem to vary drastically among national surveys, with some including persons 15 years or older and others using participants 30 years or older. This may play an especially important role in determining the lifetime prevalence rate of bipolar disorder as this condition is known to have an age of onset during the adolescent years (Kawa et al., 2005). Another major concern is that many national surveys fail to discriminate between the various subtypes of BD and statistically group BD-I, bipolar disorder II (BD-II), and occasionally subsyndromal versions of bipolar disorder all into one category. A recent Canadian survey (N = 36,984) reported a lifetime prevalence rate of 2.2% using this unstratified definition of bipolar disorder (Schaffer et al., 2006). Two other national surveys from Germany and the U.S. have utilized a grouped BD-I and BD-II definition of BD and have received a lifetime prevalence rate of 1% and 3.4%, respectively (Kawa et al., 2005). It should be noted, however, that this definitional ambiguity is intrinsic to the study of BD itself as there continues to be a lack of consensus regarding the boundaries between the various subtypes of BD.

Though the figures reported by these studies have considerably varied, they have been consistent in reporting no significant sex differences in the lifetime prevalence of BD-I (Diflorio and Jones, 2010). However, several papers have found that BD-II is more common in women. BDII has a reported lifetime prevalence rate of 1.1% (Merikangas et al., 2007) and as its diagnosis does not require symptoms of full mania, BD-II seems to be more consistent with "depressive diathesis" exhibited by women who show signs of BD (Diflorio and Jones, 2010). Despite the multitude of papers that claim that BD-II is more common amongst women, this finding is weakened by the fact that BD-II is difficult to diagnose and easy to misdiagnose. In addition to being consistently underdiagnosed, attention deficit disorder and major depressive disorder are both commonly misdiagnosed as BD-II (Baldassano et al. 2005). Potential sex differences in these misdiagnosed groups would be an interesting line of inquiry that has yet to be addressed by the literature. Moreover, Benazzi et al., a research group that produced two seminal papers that first proposed the increased preponderance of BD-II amongst women, have recently published a paper that states that when age is accounted for in the analysis, women are no more likely to be diagnosed with BD-II than men (Benazzi 1999, 2001, 2004). As such, the heightened prevalence of BD-II amongst women is still a disputed issue in the literature.

1.2.2 Sex differences in the clinical presentation of bipolar disorder

The clinical presentation of bipolar disorder in women seems to be distinct from that of men. Previous reviews regarding sex differences in BD have described the unique clinical presentation displayed by women with BD as having a 'depressive diathesis'; it

was traditionally held that women tend towards more depressive episodes than men who tend towards more manic episodes (Diflorio and Jones, 2010). However, the current survey of the literature presented much more balanced findings. This review will also present findings regarding mixed mania, suicidality, and co-morbidity.

Depression. Depression is characterized by a minimum of two weeks of low mood, diminished enthusiasm, or anhedonia with accompanying neurovegetative symptoms and cognitive changes. A robust finding within the literature is that women are more likely to present with and initial episode of depression and are more likely to have a depressive/mixed episode precede a manic/hypomanic episode (Kawa et al. 2005; Kessing, 2004). Women are also considered unipolar depressed longer than men. Older studies utilizing inpatient samples have reported that women tend to experience more depressive episodes than manic episodes. Studies using hospital admission rates as an index have corroborated this finding (Angst, 1978; Roy-Byrne et al., 1985).

However, there is still much debate regarding whether women experience more depressive episodes than men. Though older studies have reported that, in comparison with men, women experience depressive episodes that are lengthier and occur more frequently, newer studies have largely overturned these findings. In a study that investigated sex differences in BD using a 48-week prospective design that is free from a recall bias, no sex differences in total number of any mood episode using both BD-I and BD-II samples was found (Benadetti, 2007). Recent studies have also found no sex differences in percentage of time spent in any mood episode (Baldassano et al., 2005; Morgan et al. 2005). Reasons for the discrepancy between older and newer studies may

be due to several methodological differences and variations in inclusion/exclusion criteria.

However, there is evidence to suggest that the depressive episodes experienced by women exhibit sex specific characteristics. As compared to men, women tend to experience depressive episodes marked by more atypical symptoms, which include: weight gain, hypersomnia, and leaden paralysis (Kawa et al., 2005). A limited number of studies have also reported that women experience depression in a more seasonal pattern than men. In terms of hospitalizations for depression, women with BD displayed a bimodal peak in admissions during the spring and fall (Diflorio and Jones, 2010). Finally, there is some evidence that suggests that women suffer from depressive episodes that are more treatment refractory than men (Kawa et al., 2005). Whether this is due to the unique etiology of BD in women or simply an artifact of the delay in properly diagnosing women with BD is an issue unexplored by the literature.

Mania. Mania is defined as a consistent abnormally elevated or irritable mood for at least 1 week. Overall, an episode of mania often accompanies marked increased energy level, poor judgment, and inappropriate social behavior. Older studies often implicated men as having more manic episodes of greater severity than women (Kessing et al., 2004). Again, newer literature has found that in terms of these clinical variables, men and women are equal. Studies have found that men and women have the same time to remission from a manic episode and time spent with any subsyndromal manic symptoms (Diflorio and Jones, 2010).

Some studies have also claimed that men and women show difference in their symptomatological presentation of mania. Men are more likely to present with mania that includes hyperactivity, risk-taking behavior, and grandiosity, while women more often present with symptoms of racing thoughts and distractibility (Taylor and Abrams, 1981; Young et al., 2007). Some studies have found that women experience less psychotic symptoms than men (Diflorio and Jones, 2010). Additionally, there is evidence to suggest that there are sex differences in clinical features of psychosis during a manic episode. In one recent study involving 137 women and 109 men admitted to the hospital with mania, found that as compared to men, women experience more hallucinations, delusions of reference, and paranoid delusions (Kruger, 2009). The source of these sex differences in the clinical presentation of mania is currently uncharacterized.

Mixed episodes / mixed mania. The current diagnostic criteria for mixed episode, or mixed mania, is the co-occurrence of a full depressive episode and a full manic episode. However, this strict definition is often replaced by 'intermediate' and 'broad' definitions that seem to be more useful in both research and clinical settings. When using the 'intermediate' definition, the diagnosis of mixed mania can be made when acute mania is accompanied by several depressive symptoms whereas the 'broad' definition requires only the presence of symptoms that seem to oppose the manic state (Goodwin and Lieberman, 2010). Despite the definition for mixed mania that is used, an overwhelming amount of evidence suggests that mixed mania occurs more often in women (Arnold et al., 2000; Kessing, 2004). Unfortunately, the wide array of

employable definitions for mixed mania make it difficult to compare studies from a quantitative perspective. Although ratio of diagnosed women to men varies according to the definition employed during research, one study, which pooled 13 others, found an average female to male ratio of 1.9: 1 (Diflorio and Jones, 2010). The mechanism underlying women's increased succeptibility to mixed mania is still not fully established. The majority of studies point to a mechanism that involves the hypothalamic-pituitary-axis (Diflorio and Jones, 2010). The propensity of women towards mixed mania remains an important clinical issue as this mixed state is associated with increased suicidality and greater chronicity (Goodwin and Lieberman, 2010).

Suicidality. The suicide rate within BD samples is 15 times higher than the general population with 10-19% of BD patients completing the act (Rihmer and Fawcett, 2010). However, when type I and type II of BD are statistically considered together, the rate may be even higher with one study placing the lifetime risk of suicide at 26% (Kawa et al., 2005). In fact, the suicide risk is greater in BD than in unipolar depression (Rihmer and Fawcett, 2010). Studies have found that women are more likely to report a history of suicidal gestures and attempts (Morgan et al., 2005). Yet, this finding has not been completely consistent. One recent longitudinal study reported that men are at greater risk (Marangell et al., 2008). In terms of completed suicides, however, there seem to be no sex differences. This latter finding is interesting as the women in the general population are more likely than men to complete suicide (Kawa et al., 2005).
Though the rate of completed acts is equivocal, there are specific concerns regarding suicidality that may be especially important for women. There has been some literature

to suggest that the female sex is at increased risk for mixed mania, rapid cycling, and BDII (Diflorio and Jones, 2010). Rapid cycling and BDII are both associated for increased risk of suicidality (Goodwin and Lieberman, 2010). Although there is a lack of consensus on the issue, there is some literature to suggest that mixed mania is also associated with greater risk of suicide (Kessing, 2004). Particularly pertinent to women is the finding that female patients with BD are more likely to have suffered from childhood sexual abuse than men. Additionally, female psychiatric patients are more likely to be sexually and physically abused than male psychiatric patients. Early stressors such as childhood sexual abuse has been strongly linked to increased risk of suicide (Bonnin et al., 2010).

Comorbidity. BD is often accompanied by a constellation of comorbidities with 65% of patients suffering from other psychiatric or physical ailments (Belanza-Martinez et al., 2009). Comorbidity is an exceedingly important clinical consideration as it is connected with poorer outcomes. Several studies have reported that medical and psychiatric comorbidity is more common amongst women (Diflorio and Jones, 2010). One study that analyzed comorbidity rates in hospitalizations for a first episode of mania found that women were 2.7 times more likely than men to present with a comorbid diagnosis (Tuhen et al., 2003). The medical illnesses that have been found to be more prevalent amongst women with BD are: thyroid disease, migraine headaches, and obesity (Kawa et al., 2005). However, there seems to be some dispute amongst the literature regarding this last factor with some studies reporting null or opposite findings (Suominen et al., 2009). These variations may be due to treatment effects as various first-line medications are known to affect weight gain and may do this differentially

between the sexes. In general, women with BD seem to incur greater impairments to physical health and more pain disorders than men (Kawa et al., 2005).

There is a lengthy list of axis I psychiatric comorbidities that have found to be common in BD including: agoraphobia, post traumatic stress disorder, panic disorder, social phobia, alcohol abuse, substance abuse, and bulimia nervosa. Several of these illnesses have been reported to be more common in women including: post traumatic stress disorder, panic disorder, social phobia, and bulimia (Suominen et al., 2009). One study placed women with BD at a ten times greater risk of developing eating disorders than men (Kawa et al., 2005). Men with BD have been associated with greater risk of developing: alcohol abuse, substance abuse, obsessive-compulsive disorder, and gambling problems. Studies have placed conduct disorder as being four times as common in male than female patients with BD (Hendrick et al., 2000). One study also placed alcohol and substance abuse/dependence at two times greater in men than in women. Several other studies have corroborated this finding of a greater incidence of alcoholism and substance abuse amongst men. However, studies have also shown that women with BD have a four times greater risk of developing alcoholism than men and that this relative risk is greater than in men with BD. This increased risk of alcoholism may be especially problematic for women as first-pass metabolism and alcohol dehydrogenase activity is lower in women than in men, thus lending to a greater degree of alcohol toxicity (Diflorio and Jones, 2010).

1.2.3 Sex differences in the course of bipolar disorder

This review will attempt to summarize known data regarding sex differences in age of onset, diagnosis, rapid cycling, and prognosis and outcome. The discussion of sex differences in course will not be assessed from a lifetime perspective in this review. As such, the exploration of special considerations needed in treatment and management of BD women in pregnancy, perimenopause, and menopause is beyond the scope of this review.

Age of onset. The average age of onset for bipolar disorder is 21 years. The last three decades have witnessed papers consistently reporting a lower age of onset for BDI versus BDII (Goodwin and Lieberman, 2010). However, there is much less consensus regarding potential sex differences in age of onset. Many papers have reported that women have an earlier age of onset of bipolar disorder than men (Kawa et al., 2005). Several more studies have indicated that women with BDII tend to have lower age of onset than men with the same diagnosis (Diflorio and Jones, 2010). However, this last decade has produced studies that have been inconsistent in corroborating this claim. One study, which included 360 outpatients diagnosed with bipolar disorder, found that women had an age of onset of illness 3.2 years later than men (Kennedy et al. 2005). However, another recent study having 211 outpatients found no such difference (Nagash et al., 2005). A general criticism has been cast on studies that attempt to evaluate age of onset through assessing a clinical sample asserting that such a sample may include an overrepresentation of the very ill. This issue has been addressed by a recent Canadian community survey having 36,984 participants. This study also failed to

observe any significant differences in age of onset between men and women (Schaffer et al., 2006).

Diagnosis. Several studies have pointed to a greater delay in diagnosis for women with bipolar disorder versus men. One study placed this delay at 11 years for women versus an average of 6 years for men (Kennedy et al., 2005). Clinical practice biases towards diagnosing women with unipolar depression may account for some of this delay. However, the more likely source of this diagnostic lag may be the unique clinical presentation of bipolar disorder in women. Women are more likely to experience their first bipolar episode in the depressive polarity. Studies have also shown that, when compared to men, women experience a longer interim between this first episode and their first manic episode (Kawa et al., 2005). As a first manic episode must precede a diagnosis of BD, this extended interim would certainly be one factor accounting for the delay in an accurate diagnosis for women. As several papers demonstrate, diagnosis of women with BDII also shows this same pattern of delayed diagnosis (Kawa et al., 2005).

These delays in diagnosis result in delays to treatment that may adversely affect functional outcome. Failure to diagnose BD has been associated with a more persistent and treatment resistant course of illness (Diflorio and Jones, 2010). These findings certainly highlight the importance of early intervention for women and stress the importance of continually refining diagnostic tools. Two recent papers have suggested using early age of onset as a characteristic to distinguish bipolar disorder from unipolar disorder (Alba et al., 2006; Benazzi, 2003). Unipolar disorder has a later average age of

onset than both BDI and BDII. In one study, an analysis of 3,014 Sardinian adults diagnosed with BDI, BDII, or major depressive disorder found an average age of onset of 24, 29, 32, respectively. Further research needs to be conducted in a clinical setting to determine the utility of age of onset as a discriminating diagnostic feature of BD. As there are only poor biological markers and no laboratory tests to diagnose BD, the search for unique and readily identifiable clinical features remains a pressing goal for BD research.

Rapid cycling. Rapid cycling is defined by the DSM-IV as the occurrence of a minimum of four mood episodes during a 12-month period. The major depressive, manic, hypomanic, or mixed episodes must also be separated by full or partial remission that is maintained for at least two months or must switch in affective polarity. This affective lability is associated with much social and functional impairment. Indeed, rapid cycling has been linked to increased rates of depression, suicidality, substance abuse, and anxiety (Goldberg and Berk, 2010). Several studies have found rapid cycling to be significantly more common amongst women than men with some studies quoting a 2:1 female to male ratio (Kupka et al., 2003; Tondo and Baldessarnini, 1998; Coryell et al., 1992). One study involved 456 individuals diagnosed with either BDI or BDII; out of their sample, 91 participants in their study met the criteria for rapid cycling and 61 of these participants were women. From these data, they concluded that rapid cyclers are more likely to be women (Coryell et al., 1992).

However, there are several recent studies that have found no sex differences in rapid cycling. Retrospective data from 481 patients enrolled in the STEP-BD project

found that men and women had equal rates of rapid cycling (Baldassano et al., 2005). The same result was concluded from the 18-month prospective Jorvi Bipolar Study of 160 patients diagnosed with bipolar disorder (Suominen et al. 2009). Another study conducted from the STEP-BD data stated that although BDII and the female sex are both linked to rapid cycling, they could neither be used as statistical predictors nor are of much clinical utility in predicting future mood episodes (Schneck et al., 2008). Clearly the literature is mixed regarding rapid cycling and its particular frequency amongst women. This may be partially attributable to the difficulty in recruiting a large sample of rapid cyclers. Additionally, the preponderance of substance abuse and psychiatric comorbidities amongst samples of rapid cycling patients make it difficult to conduct statistical analysis that is free of confounds (Goldberg and Berk, 2010).

Of greater concern than the prevalence of rapid cycling amongst women, is the growing body of evidence implicating antidepressants in triggering an increase rate of mood cycling (Suominen et al., 2009). These data have a two-fold consequence for women. First, some studies have shown that women are more susceptible to this antidepressant-induced rapid cycling. Second, studies have shown that there is a longer delay in accurate diagnosis for women as compared to men. Initially, women with bipolar symptoms are often misdiagnosed with unipolar depression for which antidepressants are usually prescribed (Kawa et al., 2005). Some studies even go so far as to imply that the increased risk of women towards rapid cycling is simply an artifact of women's tendency to be prescribed anitdepressants (Schneck et al., 2008)

Prognosis and outcome. Many factors need to be considered when discussing functional outcome for bipolar disorder patients including: the natural course, the impact of the first episode, the impact of the depressive phase, cycle length, age of onset, age, sex, type of illness, personality traits and temperament, co-morbidity, family history, and life events (Baur et al., 2001). This list of variables is not exhaustive by any means and though they all seem intuitively related to functional recovery, one review of 15 studies found that not all of these variables impact functional outcomes consistently across studies (Martinez-Aran et al., 2007). Predominant methods for assessing functional impairment include the Global Assessment of Functioning scale (GAF) as well as the consideration of socially relevant variables such as employment status, marriages status, and ability to live independently (Tabares-Seisdedos et al., 2008). Assessments using the latter variables have recently led many to believe that functional impairment in BD is much greater than previously considered. Independent living, personal relationships, and vocational success are all greatly stunted in BD patients. While 6% of the general population is unemployed, 50-65% of BD patients are jobless; 19-23% of BP-I Patients were married (versus 60% of adults in the general population); and as compared to 6% of the general population, 19-58% of BD patients were not living independently (Martinez-Aran et al., 2007). In the McLean-Harvard First Episode Mania Study, it was found that two years after an initial hospitalization for mania or mixed-mania depression, only 43% of BPI patients regained their premorbid occupational and residential status (Tuhen et al., 2003).

Although there is a growing interest in investigating functional recovery of BD patients within the literature, there are no studies that specifically consider sex in the context of assessing outcomes. It is known that both rapid cycling and mixed mania are associated with poorer outcomes (Suominen et al., 2005). As was presented, there is some research to suggest that both states are more frequent amongst women (Arnold et al., 2000). Men and women also display a unique profile of comorbidities (Diflorio and Jones, 2010). The health hazards associated with each comorbidity also drastically affects functional outcome. The psychosocial outcome for women is additionally affected by their tendency towards a depressive affective polarity in BD (Kawa et al. 2005). Women with bipolar disorder report a lower perception of their overall health and well-being when compared to men (Bonnin et al., 2010). The efficacy of treatment protocols may also be attenuated by the delay in diagnosis for women and any conflicting therapies provided when women are misdiagnosed. Although there are some sex differences reported in the literature, there are also studies that have shown no significant differences between men and women in terms of time spent in remission and time spent in any syndromal or sub-syndromal episode (Diflorio and Jones, 2010). However, the McLean-Harvard First Episode Mania Study found that the female sex is associated with shorter time to syndromal recovery (Tuhen et al., 2003). Unfortunately, a confound that is present in these multitudinous studies which investigate clinical variables is the presence of differing treatment strategies.

Summary. Although there is considerable heterogeneity in the literature, the overall picture nevertheless conveys that there are sex differences in the phenomenology of BD. The most consistent findings include the increased prevalence of rapid cycling, mixed episodes, suicidality, and a psychiatric or medical comorbidity in women with BD. These differences are most likely the product of a complex combination of neurobiological and psychosocial factors; the relative contribution of neurobiology versus psychosocial characteristics to these sex differences in the phenomenology of BD is still unknown. Understanding the basis of these sex differences in the course and clinical presentation of BD may lead to increased etiological understanding and more targeted and effective treatment strategies.

1.3 Thesis objectives

The body of literature presented in the previous section focused exclusively on sex differences found in the sectors of BD phenomenology that concern affective disturbance. Beyond affective irregularities, the pathology of BD includes significant deficits to cognitive functioning. Despite the functional impact of these cognitive deficits, sex differences in the cognitive impairment associated with BD is a topic that has been minimally broached. This thesis intends to explore how sex influences cognition in BD by assessing whether there are sex differences in the cognitive impairment profiles of men and women with BD early in their course of illness.

The crux of the thesis is presented in Chapter 4, which contains original work that investigates cognitive impairment in the domains of verbal learning /memory, sustained attention/processing speed, and executive function in a first-episode sample

of BD patients. Chapters 2 and 3 encompass relevant literature reviews that will enable a better understanding of the material that is presented in Chapter 4. Chapter 2 summarized what is known about cognitive impairment across both symptomatic and euthymic mood states in BD. The cognitive impact of various comorbidities and medications used to treat BD will also be presented. Overall, the goal of this chapter will be to underscore the importance of cognitive impairment in BD and to present relevant research that identifies the cognitive domains that are the most impacted by the disease. This research was used to inform the decision making process that chose the cognitive domains to be assessed for sex differences in Chapter 4. Chapter 3 similarly informed the experimental design of the work presented in Chapter 4. Chapter 3 concerns morphological, physiological, and cognitive sex differences found in healthy populations. A better understanding of how sex influences cognition in healthy samples is an informative step towards understanding how sex influences cognition in abnormal sample such as BD. Together, Chapters 2 and 3 prepare the reader for the arguments presented in Chapter 4.

Again, the ultimate goal of this thesis is to better understand whether sex influences cognitive impairment in BD early in its course. To this end, the content of this thesis explores the following concepts:

- Cognitive impairment in BD:
    - Dysfunction associated with mood states and euthymia
    - Confounding effects of common comorbidities and treatment strategies
    - The neurobiological basis of cognitive impairment in BD

    - The functional impact of cognitive impairment in BD

- Sex differences in cognition in healthy samples:
    - The neurobiological origin of sex differences in cognition
    - Morphological and physiological sex dimorphisms
    - Sex differences in cognition

In exploring these concepts, it is hoped that the necessity of understanding how sex impacts psychiatric conditions -- including BD -- is conveyed.

2. Cognitive Impairment in bipolar disorder

This chapter will begin by underscoring the importance of cognitive research in BD to researchers, clinicians, and patients. With this discussion in place, the next section of the chapter will summarize the cognitive dysfunction that is associated with BD during manic and depressive acute mood states as well as during euthymia. What is currently known about the neurobiology of the cognitive dysfunction in BD and the steps that are being taken to better understand the etiology of this impairment is then considered. Finally, the cognitive impact of medications used to treat affective symptoms in BD will be presented followed by a brief overview of the novel pharmacological agents that may be used to treat cognitive impairment in BD in the future.

2.1 Cognitive research in bipolar disorder: relevance for researchers, clinicians, and patients

Research investigating cognitive functioning in BD has grown extensively over the past decade. This illuminating body of work has significantly contributed to a drastic reconceptualization of the illness. BD was originally characterized as a chronic, recurrent affective disorder with patients experiencing cyclic episodes of mood instability – mania/hypomania and depression – followed by periods of complete clinical remission or euthymia. Initially, neurocognitive dysfunction in these samples was thought to be mild, transient, and restricted to acute symptomatic episodes (Goodwin and Lieberman, 2010). However, an abundance of evidence has now established that lasting and stable cognitive impairment is present in all phases of bipolar disorder including the remission

phase (Torres and Malhi, 2010). Recent meta-analyses and reviews of studies investigating euthymic BD patients, have found marked impairment across the cognitive domains of attention/processing speed, verbal learning/memory, and executive functioning (Torres et al., 2007). As cognitive dysfunction persists during euthymia, this phase is no longer considered a period of complete functional recovery. Indeed, there is now broad consensus that cognitive impairment is state-independent and represents a core clinical feature of BD (Torres and Malhi, 2010); this addition to the clinical picture is of potentially great etiological and therapeutic importance.

The finding that full cognitive functionality is not recovered even when affective symptoms have remitted, has led to a conceptual reframing of BD. It was largely on the basis of these intermittent phases of complete recovery that the traditional Kraepelinian model distinguished BD from schizophrenia (SZ; Jamrozinski, 2010). Evidence regarding cognitive impairment during euthymia has contributed to challenging the notion of BD and SZ as separate clinical illnesses with distinct pathophysiologies (Hill et al., 2008). Converging evidence from several fields, most notably genetic psychiatry and cognitive neuropsychology, has prompted some researchers to suggest that BD and SZ are better characterized along a continuum rather than as separate disorders (Latalova et al., 2011). Researchers adopting this perspective began searching for neurocognitive allied phenotypes, or endophenocognitypes, shared by BD and SZ in order to better understand the etiopathophysiology of both disorders (Hill et al., 2008). These efforts have led to some promising results with deficits in verbal memory and some aspects of executive functioning being targeted as putative endophenotypes (Balanza-Martinez et

al., 2008). With further research, these same cognitive deficits may prove to be of considerable diagnostic utility to clinicians by serving as illness-trait markers.

In addition to its relevance for researchers and clinicians, studies investigating cognitive impairment in BD may have salient implications for patients. Although affective and psychotic symptom management are currently the primary targets of psychiatric intervention, cognitive impairment in BD is far from benign. Persistent cognitive disability, especially in the domains of verbal/learning and memory and executive function, has been associated with poor functional outcome and psychosocial adjustment in BD patients as measured by both subjective reports and objective, performance-based indices such as vocational, education, and marital status (Wingo et al., 2009). In fact, a global index of cognition was found to predict functional outcome better than clinical factors in both BD and SZ (Bonnin et al., 2010). Subjectively, nearly two-thirds of BD patients complain of awareness of cognitive dysfunction even during periods of affective regularity (Martinez-Aran et al., 2005). Overall, cognitive impairment seems to adversely affect the quality of life of patients by establishing significant social and occupational barriers to their successful reintegration into community settings. As BD affects nearly 4.4.% of the population, suboptimal functional recovery in these patients carries with it a significant societal burden (Merikangas et al., 2007).

Given its functional impact, cognitive impairment is a likely therapeutic target. However, it is often difficult for a clinician to assess whether these cognitive disturbances arise from the pathophysiology of BD or are secondary due to the adverse

effects of the treatment medication (Goldberg and Chengappa, 2009). The picture is further complicated by the frequent use of polypharmacy and the presence of comorbid conditions such as ADHD and substance abuse that are themselves associated with cognitive dysfunction (Balanza-Martinez et al., 2010). These difficulties have contributed to the lag in generating effective behavioral and pharmacological intervention strategies for cognitive dysfunction in BD. Nevertheless, the field is moving towards this direction and knowledge of the cognitive impact of medications and comorbidities associated with BD is continually increasing. There have also been some preliminary attempts to generate pharmacological cognitive enhancement agents to be used as adjunctive therapy in BD (Balanza-Martinez et al., 2010).

To summarize, research investigating cognitive impairment in BD is of crucial relevance to researchers, clinicians, and patients alike. For researchers, this field has contributed significantly to understanding the etiology of BD by clarifying the relationship between BD and SZ and by identifying potential endophenotypes for both illnesses. By recognizing that cognitive impairment is a core clinical feature of BD that persists across moods states and considerably contributes to patient disability, this body of research has better equipped clinicians to generate long-term pharmacological and behavioral treatment strategies for their patients. There is also the potential that the identification of cognitive disruption in specific domains will serve as illness-trait markers that may aid clinicians in diagnosing patients earlier and with more prognostic power and accuracy. These improvements to clinical practice may ultimately result better illness management and increased quality of life for patients with BD. Given the

importance of this vein of research, this chapter will continue by reviewing what is currently known about cognitive impairment in BD. Before discussing the dysfunction that is involved in both symptomatic and remitted states of the illness, cognitive domains consistently impacted by BD and their psychiatric assessment will be discussed.

2.1.1 Cognitive domains impacted in bipolar disorder

As cognitive impairment is a core clinical feature of BD, evaluation of neuropsychological functioning is an important part of the clinical examination. Neuropsychological assessment usually involves the administration of a battery of psychometrically validated cognitive tests (Torres and Malhi, 2010). These tests will have been previously administered to large numbers of healthy individuals that vary in demographic characteristics such as age and educational attainment. The patient's performance on any given test can then be compared to the normative scores achieved by healthy individuals that share their demographic profile (Torres and Malhi, 2010). The choice to administer any particular test should rely on that test's reliability, validity, specificity, and sensitivity. An ideal neuropsychological test consistently assesses functioning in one cognitive construct or domain; in psychiatric settings, this test must be sufficiently sensitive to detect the cognitive impairment imparted by that specific illness pathology. A patient's performance on such a test would be highly informative to the clinician as cognitive domains may be associated with specific neural regions or brain systems (Latlova et al., 2011); poor performance on a cognitive task would allow a clinician to infer that the task's associated neural substrate may be impacted by that illness. However, such inferences should be made with caution as the cognitive tasks

currently employed in research all fall short of the ideal especially in the areas of test validity and specificity (Torres and Malhi, 2010). In reality, cognitive tests often tap into multiple domains and it still remains unclear how most of these cognitive domains (e.g. attention) are neurally generated and organized (Burdick et al., 2007). In response to this dilemma, newer experimental paradigms borrowing techniques from both cognitive neuropsychology and neuroscience have been generated. For example, there has been a recent wave of studies employing experimental designs in which a participant's brain is imaged using structural or functional magnetic resonance imaging while they are simultaneously engaged in a cognitive task (Cahill, 2006). These studies have been particularly revealing in the effort to understand the biological underpinnings of cognitive constructs. Deciphering the biological processes that underlie healthy cognitive functioning is an important step towards understanding the pathophysiological mechanisms that result in cognitive dysfunction in BD and other mental illnesses.

The first step in this process, however, must be to characterize the cognitive domains that are most consistently impaired in patients with BD. Only a subset of all existing cognitive domains is adversely impacted in BD and general intellectual functioning is largely preserved in these patients (Goldberg and Chegappa, 2009; McDonough-Ryan et al., 2002). Recently, the International Society for Bipolar Disorder (ISBD) identified the domains that have repeatedly been found to be impaired in BD (Yatham et al., 2009). Broadly, these domains are attention/vigilance, verbal

learning/memory, and executive function. These domains and their respective cognitive tests will be discussed in detail bellow.

Attention/processing speed. Attention is a multidimensional cognitive process; in its active form, attention allows the individual to focus on important stimuli by filtering out irrelevant information and inhibiting competing actions or thoughts. Vigilance, or sustained attention, is the ability to maintain this attentional focus over time. Failure to maintain attention to the relevant stimuli will negatively impact task processing speed (Filley and Cullum, 1994). Attentional impairment can be especially impactful as an intact attentional capacity is essential to all higher cognitive skills (Burdick et al., 2007). Neuropsychologists have yet to fully understand attention in a mechanistic fashion. However, the frontal and parietal lobes are thought to be essential to this cognitive process (Balanza-Martinez et al., 2008). Attention and sustained attention have been assessed in BD using many varying cognitive tests: Continuous Performance Task, Trail Making Test – Part A, and WAIS Digit Symbol task. In each task, the participant's ability to focus on relevant stimuli and ignore competing stimuli is challenged; several attentional tasks test psychomotor processing speed, which is defined as the time it takes to process a signal, prepare a response, and execute that response (Sobin and Sackeim, 1997). Both attention and vigilance have been found to be in impaired in BD patients regardless of mood state (Najt et al., 2005; Clark et al., 2002). There are also reports of impaired selective attention, psychomotor speed, and sustained attention in relatives and first-degree relatives of patients with BD (Antila et al., 2007; Kilmes-Dougan, 2006).

Verbal learning/memory. Learning and memory refer to the cognitive processes of acquiring and retaining symbolically represented information. In verbal learning and memory, the symbolic system used to represent information is language (Ditmann and Abel, 2010). Items to be acquired and recalled in this research domain include: letters, letter combinations, digits, numbers, sentences, etc. The participant may be told to either pay attention to, or disregard the spatio-temporal relationship between items (Healy and McNamara, 1996). These cognitive processes have been broadly associated with the left-hemisphere and the Peri-Sylvian region (Ojemann, 2002). Verbal learning and memory has been assessed in BD samples using specific subtests of the California Verbal Learning Test (CVLT) and Rey Auditory Verbal Learning Test (RAVLT) (Andreano and Cahill, 2009). In these tasks, participants are read a list of words and are asked to remember and repeat them immediately and after a brief delay. Verbal learning and memory is impaired in BD patients during both symptomatic and remission phases (Burdick et al., 2007). Verbal learning and memory was also impaired in first-, and second-degree relatives with BD (Balanza-Martinez et al., 2008).

Executive function. Executive function is an overarching term relating to several cognitive processes including: working memory, planning, task-monitoring, response inhibition, attentional set-shifting, and preservation (Alfredo, 2008). These diverse cognitive processes come into play during: novel or unfamiliar situations, activities that involve planning and decision making, and tasks that involve error monitoring and correction. The neural regions thought to be involved in executive function include the prefrontal and parietal cortices, as well as several subcortical structures (Friedman,

2008). Many cognitive tests have been used to assess executive function in BD samples: Trail Making Test-part B, Stroop Test, Wisconsin Card Sorting Test, Digit Span Backwards, and Tower of London (Yatham, 2009). Executive dysfunction is experienced across mood states with recent studies indicating that impairment in this domain is the most commonly reported cognitive deficit in patients with BD during euthymia (Burdick et al., 2007). Impairment in executive function, specifically abstraction, cognitive flexibility, planning, and working memory, has been found in first-degree relatives in BD (Balanza-Martinez et al., 2008).

2.2. Cognitive functioning across illness phases in bipolar disorder

Bipolar disorder is characterized by both symptomatic and euthymic phases. The affective irregularity during the symptomatic phase can be of a depressive or manic polarity and can vary in severity (e.g. mania vs. hypomania). Although cognitive impairment in BD is present during both symptomatic and remitted phases, the research indicates that the extent of cognitive impairment experienced may be influenced to some degree by state (Torres and Malhi, 2010). The section will proceed with a discussion of the cognitive impairment that is associated with the various states of BD: depression, mania and euthymia. Finally, as BD patients commonly present with one or more comorbid illnesses, the impact of these comorbidities to overall cognitive impairment will be discussed (Balanza-Martinez et al., 2009).

2.2.1 Cognitive dysfunction associated with symptomatic states

There is a general worsening of cognitive dysfunction during a manic or depressive mood state as compared to an affectively stabilized state (Torres and Malhi,

2010). Mania is associated with globalized neuropsychological impairment with deficits being seen in the domains of sustained attention, verbal and visual learning/memory, and executive function (Latalova et al., 2011). A depressive state is also associated with deficits in these cognitive domains in addition to impairment being seen in psychomotor speed (Torres and Malhi, 2010). In cross-sectional studies comparing manic, hypomanic and depressed BD patients to healthy controls, all patient groups show deficits in verbal memory and executive function when compared to healthy controls; however, few significant differences are seen in cognitive performance across patient groups (Martinez-Aran et al., 2004). Collectively, these studies indicate that there are no substantial differences to the severity of cognitive dysfunction experienced across depressive, manic, and hypomanic mood states. After the resolution of a symptomatic mood state, some cognitive impairments improve while other deficits remain (Latalova et al., 2011). The etiology of cognitive impairment during states of affective disturbance remains unclear and is most likely multifaceted. It is possible that during symptomatic remission, patients put in more effort into achieving the highest possible score when completing cognitive tasks; the poorer cognitive performance seen in hypomanic, manic, and depressed patients could partially be a function of willingness rather than exacerbated pathology per se (Torres and Malhi, 2010).

2.2.2 Cognitive dysfunction during euthymia

Research regarding cognitive dysfunction during the euthymic phase in BD is growing rapidly; a recent review found that 45 original articles, nine review articles, and 4 meta-analyses have been written on the subject between 2008 and 2009 alone

(Jamrozinski, 2010). The most consistently reported cognitive domains that are impaired during euthymia are verbal learning/memory, attention (including sustained attention and psychomotor speed), and executive function (including preservation and response inhibition) (Torres et al., 2007). Beyond qualifying for statistical relevance, one recent study concluded that 43% of euthymic bipolar patients show clinically significant cognitive impairment, with clinically significant impairment being defined as scoring two standard deviations below the normative mean in at least one cognitive domain (Gualtieri and Morgan, 2008). However, there is a significant degree of heterogeneity in this literature (Jamrozkinski, 2011). There are several reasons that account for this heterogeneity: the definition for euthymia varies considerably between studies; data that describe the type of psychotic symptoms experienced by the sample are usually lacking, various neuropsychological tests are used to assess the same cognitive domain, and neuropsychological tests are sometimes assigned to different cognitive domains. Finally, mediating and moderating variables may further obscure the picture; these include: residual symptoms, medication and polypharmacy, alcohol/substance abuse, and smoking (Torres and Malhi, 2010). Some heterogeneity may also result from studies accounting for comorbidities differently. The neurocognitive impact of common comorbidities is described below.

2.2.3 Cognitive dysfunction associated with comorbid conditions

Most patients with BD present with a medical or psychiatric comorbidity (Krishnan, 2005). Many of these comorbid diseases have been associated with cognitive dysfunction and it is difficult to understand the cognitive impairment that is due to BD

disease processes versus the pahtophysiology of these other illnesses (Goldberg and Chengappa, 2009). The medical comorbidities that are commonly seen in BD patients include: cardiovascular/cerebrovascular diseases, neurological disorders (e.g. migraine, epilepsy), and metabolic abnormalities (e.g. obesity, diabetes mellitus type-II). These disorders all accompany cognitive impairment; pharmacological agents used to manage these illnesses may also have a cognitive impact (Balanza-Martinez, 2010). Studies that investigate the contribution of cognitive impairment imparted by these medical comorbidities in patients with BD are currently unavailable.

The most well researched psychiatric comorbidites in BD samples are substance abuse and attention deficit hyperactivity disorder (ADHD); several studies have investigated neurocognitive functioning in BD patients with either substance abuse or ADHD. Among all Axis I disorders, BD has the highest lifetime prevalence of alcohol and substance abuse (Sbrana et al., 2005). In a recent study that compared euthymic BD patients with and without alcohol dependence and abuse, to control groups found that the patient group with comorbid substance abuse had increased dysfunction than both the control and substance abuse-free patient group in certain measures of executive control (Levy et al., 2008). Although there is some contention as to the degree to which comorbid alcohol abuse affects neurocognitive function in BD patients, collectively the literature suggests that alcohol abuse either adds to the neurocognitive dysfunction by the way of its own independent mechanisms or that it lends to an exacerbation of BD-associated pathological processes that impact cognition (Balanza-Martinez et al., 2010; Levy et al., 2008). There is also limited evidence to support that other addictive substances (e.g.

cocaine) also contribute to cognitive dysfunction in BD (Cahill et al., 2006). With regards to ADHD, this comorbidity is seen more often in children and adolescents with BD (Balanza-Martinez et al., 2010). Consequently, much of the literature that investigates the cognitive effects of ADHD in patients with BD are conducted in younger samples. There is evidence to support that young BD patients with comorbid ADHD perform worse on verbal memory than young BD patients without ADHD (McClure et al., 2005; Pavuluri et al., 2006); although, whether ADHD confers additional cognitive impairment is still disputed in the literature (Balanza-Martinez et al., 2010).

2.3 Neurobiological basis of cognitive impairment in bipolar disorder

The exact etiology of cognitive dysfunction in BD is currently unknown. BD is extremely heterogeneous and it is likely that multiple factors feed into the cognitive pathogenesis from which cognitive impairments arise. Efforts to understand the contribution of genetics, environmental factors, and clinical factors will be discussed.

With regard to genetics, the specific susceptibility genes for developing BD are still unknown as this illness is complex and multidimensional. However, there have been several studies in recent years that have attempted to find endophenotypes for BD; endophenotypes have the potential to be etiologically revealing as they provide intermediate disease related phenotypes for which it is easier to susceptibility genes (Balanza-Martinez et al., 2008). The criteria for a characteristic to qualify as an endophenotype state that the characteristic is: a) associated with the illness, b) is hereditable, c) state-independent, d) co-segregated with illness within families, and e) also found in unaffected relatives at a higher rate than in the general population (Hasler

et al., 2006). Neurocognitive studies investigating cognitive impairment in the relatives of BD patients – discordant twins, first-, and second-degree relatives – have identified measures of verbal learning and memory, attention, and some aspects of executive function as suitable endophenotypes (Balanza-Martinez, 2010).

The field is still waiting to see whether these putative characteristics will help find susceptibility genes that explain the etiopathogenic mechanism that leads to cognitive impairment in BD. However, some genetic abnormalities have already been suggested as contributing to cognitive impairment in BD. Brain-derived neurotrophic factor (BDNF) and cathecol O-methlytransferase (COMT) polymorphisms have been associated with impaired performance on executive function tasks in BD samples (Rybakowski et al., 2006; Burdick et al., 2007). Mutations in genes governing the neuronal migration process have been found to predict prefrontal cognitive deficits in a mixed sample of BD-I and SZ patients (Tabares-Seisdedos et al., 2008). Overall, there is evidence to suggest that genetics contribute to cognitive disability in BD patients.

Recent studies have investigated the potential of environmental factors to influence cognitive dysfunction in BD patients. There is limited evidence to support that obstetric complications and early traumatic adversity (e.g. sexual and emotional abuse) is associated with poorer performance on verbal and executive tasks in BD samples (Martino et al., 2008; Strejilivich and Martino, 2008). However, it is understood that these factors do not wholly account for the cognitive deficits seen in BD and that other factors must contribute to produce the entire pathological phenotype as it relates to cognition (Balanza-Martinez et al., 2009).

Clinical factors have also been associated with worsening cognitive dysfunction in BD; these include: lifetime number of acute episodes, illness duration, and number of hospital admissions (Robinson and Ferrier, 2006). Increases in these factors have all been associated with greater cognitive impairment. However, the direction of causality between a more aggressive course of illness and greater cognitive impairment cannot yet be concluded. Several reports have also found that a history of psychosis is also associated with more severe cognitive impairment especially in the domains of verbal memory and executive function (Bora et al., 2007), although some have failed to replicate this finding (Lahera et al., 2008). A confound in any study that attempts to associate clinical factors to cognitive impairment is medication effects. For example, it is unclear whether a history of psychosis or the use of antipsychotics is the main underlying factor contributing to cognitive dysfunction. It is clear that certain medications add to the cognitive burden found in BD, but the exact mechanism by which this exacerbation is produced is still largely unknown (Balanza-Martinez et al., 2009). What is known about the cognitive impact of major pharmacological agents used to treat BD is summarized below.

2.4 Cognitive impact of medication used in BD and future directions

It is now understood that several medications that are commonly used to treat BD have a significant cognitive impact. The cognitive profile of a medication should be carefully considered when constructing long-term prophylactic treatment strategies. In many cases, optimally managing affective and psychotic symptoms with medication leads to a trade-off in cognitive impact. Knowledge of how a drug positively or

negatively impacts cognition can aid clinicians in teasing out iatrogenic from illness-related cognitive complaints and help them in creating pharmacological strategies with the most favorable functional outcome. However, understanding how medications contribute to cognitive dysfunction remains a complex issue (Goldberg and Chegappa, 2009). As there are ethical concerns to keeping patients medication-naïve, very few studies have investigated cognitive impairment in unmedicated patients. In patients who are medicated, given the heterogeneity of the illness, there is great variability in the type of medication and dose that are prescribed (Balanza-Martinez et al., 2010). Additionally, polypharmacy is very commonly practiced in BD treatment management. It can be difficult to predict the contribution of each drug to overall cognitive dysfunction when a patient is managed using polypharmacy as the cognitive impact is not simply an additive function of the impairment experienced by patients receiving monotherapy (Goldberg and Chengappa, 2009). Nevertheless, understanding how commonly prescribed drugs affect cognition is a useful first step. What is known about the cognitive impact of lithium, anticonvulsants, antipsychotics, and antidepressants used to treat BD will be summarized below.

Lithium. Lithium remains the first-line treatment option for long-term prophylaxis of BD. Overall, the cognitive impact of lithium is weak (Pachet and Wisniewski, 2003). Studies investigating cognitive dysfunction in euthymic BD patients found that cognitive impairments are similar across patients who are treated with lithium and those treated without lithium (Clark et al., 2002). In another study, plasma lithium levels were not related to performance on a broad neuropsychological battery

(van Gorp et al., 1998). However, there is some contention as to the domains that are affected and those that are spared. Two early reviews of the literature concluded that lithium exerts mild negative effects in tasks of verbal memory and psychomotor speed, while sparing visuo-spatial, attentional, and executive function capability (Honig et al., 1999; Pachet and Wisniewski, 2003). While more recently a two-year longitudinal study found that euthymic BD patients on lithium monotherapy display stable deficits in attention/processing speed and executive function, but not verbal memory (Mur et al., 2008). Further studies are needed to resolve these discrepancies. With regards to the reversibility of the cognitive effects of lithium, most studies point to lithium-associated deficits reverting upon discontinuation (Kocsis et al., 1993). However, there is a study that reported lasting negative effects after lithium use has ceased as well (Tsaltas et al., 2009).

There have also been several neuroimaging studies investigating the effect of lithium on the brain of patients with BD. Overall, lithium has been associated with increases in total grey matter, and grey matter of the hippocampus and prefrontal cortex in these patients (Bearden et al., 2007; Yucel et al., 2007). In one report, lithium was found to counteract the long-term gray matter deterioration associated with BD (van der Schot et al., 2009). Taken together, these findings seem to suggest a neurotrophic/neuroprotective nature to lithium. This viewpoint meshes well with preclinical data that has also shown the neurotrophic/neuroprotective effects of lithium in animal models of Alzheimer's, Huntington's, and Parkinson's diseases (Balanza-Martinez et al., 2010). On a clinical level, however, there is question as to how this grey

matter growth translates to cognitive improvement. There are currently no-reports of lithium-associated neurocognitive improvement in BD. The discrepancy between what is clinically observed with lithium use – mild neurocognitive deficits – and what is observed in neuroimaging and preclinical studies – neurotrophic/neuroprotective effects - needs to be resolved with further investigation.

Anticonvulsants. Several anticonvulsants, or antiepileptic drugs, have been found to be beneficial to symptom management in BD; these include valproic acid (valproate), carbamazepine, and lamotragine. Topiramate is also an anticonvulsant that is used to treat BD but it is not a front-line treatment and is often used in conjunction with mood stabilizers (Balanza-Martinez et al., 2010). The cognitive effects of anticonvulsants have been minimally investigated in BD. However, the literature investigating the cognitive impact of these drugs in samples with epilepsy is abundant. In epileptic samples, valproate and carbamazapine has been associated with attention and memory tasks (Senturk et al., 2007). Lamotrigine, a newer generation of anticonvulsant, is thought to have a better cognitive profile than either valproate or carbamazapine in samples with epilepsy (Gualtieri and Johnson, 2006). In the few studies that have been conducted in patients with BD, valproate was found to have a similar cognitive profile to lithium (Senturk et al., 2007); patients prescribed monotherapy with either valproate or lithium experience mild impairments to verbal learning and memory. Promisingly, lamotrigine was found to have some cognitive benefits in samples with BD. Two studies investigating cognition in BD-I patients reported that lamotrigine therapy was associated with significant improvement in self-reported cognitive ability (Kaye et al., 2007; Khan et

al., 2004). In another study investigating euthymic BD patients using lamotrigine found that these patients perform better on cognitive tasks assessing verbal learning and memory than do patients receiving carbamazapine or valproate (Daban et al., 2006). In a recent study that compared the cognitive profile of several anticonvulsants in samples with BD found that valproate, topiramate, and carbamazapine all have poorer cognitive profiles that lamotrigine (Gualtieri and Johnson, 2006).

Antipsychotics. Antipsychotics are prescribed to the subset of BD patients that experience psychotic symptoms during a manic episode. There are several reports of the adverse cognitive impact of antipsychotics (Balanza-Martinez et al., 2009). Compared to euthymic patients not taking antipsychotics, euthymic BD patients taking antipsychotics complete significantly fewer categories of the Wisconsin Card Sorting Task (WCST), an indication of impaired abstraction and concept formation; duration of therapy with antipsychotic medication has been negatively correlated with completed categories on the WCST (Zubieta et al., 2001). Atypical antipsychotic use has also been linked to deficits in psychomotor speed and verbal learning and memory measures in pediatric and adult BD samples (Bearden et al., 2007; Savitz et al., 2008). However, it is not often easy to interpret these findings. A history of psychosis in BD is itself associated with a more severe cognitive impairment profile as compared to BD patients without psychosis (Goodwin and Lieberman, 2010). As patients with a history of psychosis are those who are prescribed antipsychotics, it is difficult to know whether the additional cognitive impairments are due to the disease process or are secondary due medication use. Of all the cognitive impairments associated with antipsychotic use in BD samples, deficits in

psychomotor speed seem to be the most likely to be iatrogenically induced (Bora et al., 2009). Overall, there is a need for further investigation as to detrimental cognitive effects of antipsychotics. It would be beneficial to compare groups of BD patients using different atypical antipsychotics with and without concomitant medication use.

*Antidepressants.*Antidepressants are frequently used to manage depression in BD patients in addition to therapy with mood stabilizers. The cognitive effects of antidepressants in BD are not currently known. However, in unipolar depression, tricyclic antidepressants have been linked to impairments in verbal learning and memory (Amado-Boccara et al., 1995). Conversely, selective serotonin reuptake inhibitors (SSRIs) and other non-tricyclic agents are know to spare cognition in unipolar samples. In fact, some animal studies have found that some antidepressants have neuroprotective effects (Zobel et al. 2004). Given the frequency of prescribing antidepressants in BD, studies investigating the cognitive effects of antidepressant use in these samples are urgently needed.

Studies investigating drug naïve-patients are both few in number and contradictory in results. Some reports conclude that cognitive impairment in is independent of medication use (Taylor-Tavares et al., 2007) and other report that some medications exacerbate impairment in certain cognitive domains (Holmes et al., 2008). These reports usually compare drug naïve groups to their medicated counterparts. Several confounds have been attributed to the type of experimental design that has been employed in these types of studies; drug-naïve patients are usually symptomatic to some degree and severity of symptoms across medicated and unmedicated groups

may be difficult to match; the unmedicated group contains a disproportionately large number of BD-II patients, a group that is thought to have more cognitive domains spared than BD-I patients; comorbid illnesses are not well matched across medicated and medication-free groups (Balanza-Martinez et al., 2009). Due to these confounds, the proportion of cognitive impairment conferred by medications is still unknown.

2.4.1 Pharmacological therapy for cognitive dysfunction

In addition to investigating the cognitive impact of medications currently indicated to treat BD, researchers have attempted to find pharmacological agents that enhance cognitive function and can eventually be used as adjunctive therapy in these samples. However, this is a nascent field and many of the putative agents have yet to be rigorously tested using randomized and placebo-controlled trials with BD samples. The agents that have been considered can be grouped into the procholinergics, antiglutamatergics, and stimulants. Procholinergic agents, such as donepezil and galantamine, have been hypothesized to correct the muscarinic and nicotinic cholinergic receptor function that is aberrant in BD and is thought to be associated with deficits in attention and working memory. These agents have met with limited success in small, uncontrolled, trials. Antiglutamatergic agents have been proposed to combat cognitive dysfunction through their action on the N-methyl-D-aspartate (NMDA) glutamate receptor; hypofunction of NMDA receptors is associated with pathogenesis of psychosis in schizophrenia (Goldberg and Chengappa, 2009). However, there are no trials that investigate the efficacy of antiglutamatergic agents in BD samples and those that have been investigated in SZ samples have failed to improve cognitive scores (Lieberman et

al., 2009). Stimulants such as amphetamine and mixed amphetamine salts, methylphenidate, and modafinil, have been suggested to improve cognition in BD but have not been tested in these samples yet; drug trials with these agents have shown improvement in executive function in ADHD and SZ samples (Goldberg and Chengappa, 2009). While novel approaches for improving cognition in BD samples are continually emerging (e.g. agents that enhance dopaminergic activity), there needs to be more effort to systematically test the agents that have been mentioned above in a clinical trial format (Burdick et al., 2007).

There is a great paucity of research investigating nonpharmacological, behavioral interventions for cognitive improvement in BD samples as compared to similar research in SZ. In SZ, cognitive remediation strategies have been shown to be effective in improving neurocognitive functioning on specific cognitive measures (Penades et al., 2006). Given that psychosocial approaches have been shown to be effective in BD for affective symptom management, there is great potential for cognitive remediation to be beneficial to these patients (Balanza-Martinez et al., 2009). Although such programs are currently unavailable, several groups are working towards developing such cognitive remediation strategies for BD.

3. Sex differences in Cognitive Domains Impaired in bipolar disorder

This chapter centers on summarizing sex differences found in the cognitive domains of attention/processing speed, verbal learning/memory, and executive function in healthy samples. As discussed in Chapter 2, these are the cognitive domains that are the most consistently impaired in BD. Before these impairments are delineated, however, the neurobiological origin of sex differences in cognitive functioning will be explained; studies concerning the morphological and physiological sexual dimorphisms of the brain in healthy populations will be presented.

3.1 Sexual dimorphisms of the whole brain in healthy populations

The diverse and impactful actions of gonadal hormones during brain development, along with contributions from sex chromosomes and experience, accurately predict the existence of structural and functional brain differences between sexes. Male and female tissues differ at every level of organization from histological to morphological and physiological (Cahill, 2006). In humans, the liver and kidneys display noted sex differences that ultimately influence organ functionality in healthy and disease states (Lenroot and Giedd, 2010). But without doubt, the most influential sexually dimorphic organ in humans is the brain. Again the reverberations of these sexual dimorphisms can be seen in the healthy (cognitive sex differences) and the diseased (phenomenological differences on mental disorders). Literature in area of human sexual dimorphisms of the brain is vast. Here, a review of sex differences in gross brain morphology and physiology will be presented that is restricted to features of the

whole brain and individual lobes. These data were derived from humans in healthy populations.

Morphology. Brain structure was historically investigated with postmortem studies and then later *in vivo* with computerized tomography and magnetic resonance imaging (MRI). Converging evidence from studies conducted with various protocols in children and adults has reliably shown that males have larger brain volumes than females, even after accounting for body size (Witelson, 2006; Allen et al., 2003; Nopoulos, 2000). It has been estimated that male brain volumes exceeding female brain volumes by approximately 9-12% with the average male brain measureing 1260cc and the average female brain measuring 1130cc when excluding CSF and non-neural tissues (Witelson et al., 2006). Males also show greater ventricular and CSF volumes than females. These robust data regarding total brain volume (TBV), though interesting when considered alone, become increasingly important when investigating volumetric sex differences in any subsection of the brain (Lenroot and Giedd, 2010). TBV must be accounted for when measuring sex differences in grey matter (GM) content, white matter (WM) content, and volumes of individual lobes and substructures. The sometimes-discrepant findings in literature investigating volumetric sex differences arise, in part, due to different statistical strategies taken in accounting for TBV. The two major statistical strategies employed are normalization, where the target volumes are each divided by the TBV measure, and covariance, where the TBV measure is used as a covariate in all parametric analysis. In addition, the measure of TBV can include or discount the skull.

At times, employing different strategies in statically accounting for TBV can nullify, moderate, or reverse findings of volumetric sex differences. This is well demonstrated in literature investigating sex differences in GM content. In a study where data were covaried for intracranial volume, height, and weight, total GM percentage was found to be higher in females (Luders et al. 2004). In another study that investigated GM as a percentage of total intracranial volume, men were found to have a higher percentage of GM (Good et al., 2001). Many more studies have investigated GM/WM ratios rather than GM or WM volumes alone. In these studies, many but not all reported higher GM/WM ratios in females in the whole brain as well as several brain regions (Peters et al., 1998; Gur et al., 1999). In addition to sex differences in GM and WM content, studies have found differing developmental trajectories of GM and WM volumes in males versus females. For example, multiple studies have found that WM volumes increase more rapidly in males (Lenroot and Giedd, 2010; Perrin et al., 2008). These changes are, in part, attributable to gonadal steroids. There is evidence to support that total GM volume and GM volumes of specific regions positively correlate with estradiol in developing females. Volumetric changes in GM and WM can also be induced by age in a sex-dependent manner (Sowell et al., 2004). Studies in the realm of sex differences in GM/WM content continue to be clarified.

There have also been consistent reports of sex differences in cortical morphometry. Post-mortem studies in adults have found higher neuronal densities in granular layers of the cortex in females, while higher overall neuronal density and number is observed in males, regardless of body size. Higher synaptic density

throughout the cortex is also found in males. Some studies have found greater overall surface area, cortical gyrification, and cortical complexity in females (Luders et al., 2004). Post-mortem and neuroimaging studies have been inconclusive in determining sex-differences in cortical thickness. Some studies have found greater cortical thickness in females and other studies have found greater cortical thickness in males, with TBV being accounted for in all cases (Lenroot and Giedd, 2010). The discrepancies found in these results have been attributed to the compounding effects of varying imaging and statistical techniques.

Physiology. In addition to sex differences found in brain morphology, sex differences in brain function have also been reported. These data were acquired from neuroimaging studies employing functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). Some imaging studies have been conducted while the participant is at rest (Devous et al., 1986); however, many are conducted while the participant is engaged in some cognitive activity (Jones, et al. 1998; Esposito et al., 1996). A majority of studies have found that females exhibit greater total cerebral blood flow (CBF) than males during both rest and cognitive activity. In alignment with these finding, several studies have found higher cerebral metabolic rate of glucose utilization (CMRglu) in females, though not all studies have replicated this claim. It has also been suggested that the CMRglu found in females is an artifact of their own average smaller brain size as compared to men as CMRglu inversely correlates to brain size (Hatazawa et al., 1987). CMRglu is known to vary across the menstrual cycle suggesting that brain metabolism

may be modified by hormonal action (Reiman et al., 1998). Brain activation levels have also reported sex differences, even in studies controlling for cognitive ability. One study reported increased bilateral activation, as opposed to regional activation, in females versus males in response to a cognitive task (Cosgrove et al., 2007); although, the concept of increased bilaterality in females versus males remains a highly disputed issue. Like CMRglu, brain activation during cognitive tasks fluctuates across the menstrual cycle. The sex steroid mechanisms that allow for this modulation in activation are still under question (Cosgrove et al., 2007). Nevertheless, the acknowledgment that sex steroids impact brain physiology during the menstrual cycle should be accounted for in the methodology of future studies in this area. Widespread sex differences are also abundant in the serotonergic and glutamatergic function (Cosgrove et al., 2007). These differences may have profound affects in both healthy and abnormal (psychiatric) states.

3.2 Sex differences in cognitive domains impaired in bipolar disorder

With the ubiquitous influence of sex at the neural level, it is unsurprising that these are sex differences at the behavioral level. With regards to sex differences in cognition, the classic dichotomy holds that men are better at spatial abilities while women are better at verbal abilities; however, even as an overarching summary describing patterns of cognitive strengths, this may be an oversimplification (Andreano and Cahill, 2009). Men are not better at all spatial abilities, and the cognitive tactics that lend to the female advantage in the verbal domain confer similar advantage into realms that are not explicitly verbal. In addition, the notion of a performance-based advantage

as the key metric for assessing sex differences in cognition is now being widely challenged. With the advent of experimental paradigms that marry human-brain imaging techniques with cognitive testing, it is now being understood that on many cognitive tasks, males and females use differing neural strategies to perform at a similar level (De Vries, 2004). Rather than searching for performance-based differences on psychometric tasks, many researchers investigating the influence of sex on cognition have now shifted their focus to unraveling these distinctions in cognitive strategy.

Over four-decades of literature concerning cognitive sex differences has amassed. Given the sheer volume of literature that is available, a thorough review is inappropriate for this thesis. Briefly, the most robust and widely reported cognitive sex difference is the male advantage seen in mental spatial rotation (Andreano and Cahill, 2009; Silverman et al., 2007). However, it is thought that this advantage is restricted to the visuo-spatial component of this task. Studies investigating sex differences in spatial working memory, a cognitive domain also tested by mental rotation, have found equivocal results (Andreano and Cahill, 2009). A large and consistent male advantage is also seen in tests of navigation, with men completing tasks more quickly and with greater accuracy (Galea and Kimura, 1993; Silverman, 2000). Interestingly, a significant body of research has established that men and women use distinct cognitive strategies when partaking in visuo-spatial tasks; women have increased neural activation in right frontal regions, while significant activation is restricted to parietal regions in men (Andreano and Cahill, 2009). Several more studies indicate that in tasks involving remembering objects in an array, women have an advantage; again, men and women

are thought to employ different cognitive strategies when completing object location memory task (Levy et al., 2005; Silverman et al., 2007). A female advantage is also observed in tasks of verbal memory, episodic and autobiographical memory, some tasks involve processing speed, and emotional memory (Andreano and Cahill, 2009). However, effect sizes for these differences are less large than those consistently observed in mental rotation and there is much heterogeneity in the literature.

For the purposes of this thesis, literature regarding sex differences in the cognitive domains that are consistently found to be impaired in BD will be discussed. The domains of focus include attention/processing speed, verbal learning and memory, and executive function:

3.2.1 Attention/processing speed

Attention is complex cognitive domain that has not been traditionally associated with sex differences (Maccoby and Jacklin, 1974). However, there have been several standardized tests of attention and processing speed that have found sex differences in their normative data. Studies have found that women perform more poorly than men on the Continuous Performance Test (CPT) (Chen et al., 1998). The CPT is a strenuous and sometimes lengthy test of sustained attention. In these types of tasks, the participant must pay attention to a continuous stream of stimuli while responding to a sporadically presented preset target stimulus. In one study with 816 participants, women were found to have longer reaction times to responding the targets stimulus and were found to have decreased accuracy (Conners et al., 2003).

As the CPT requires a motor reaction (e.g. such as clicking a mouse) in response to target sequences, an important aspect to consider on these tests is psychomotor speed. Several studies have shown that psychomotor speed is faster in men. In one study of 7979 individuals 30 years or older, reaction time was shown to be shorter in men across all age groups, where an age group width was 10 years (Era et al., 2011). This male advantage is seen throughout the lifetime; a study of 1799 older adults found poorer attention and psychomotor performance in women (Mazaux et al., 1995). However, it has been suggested that the male advantage in psychomotor speed is conferred solely by way of the motor component. In processing speed, women may have a slight advantage. In a task where participants were asked to simply name colors and forms, rather than press a button in response to the forms, females performed better (Kimura et al., 1996). Conversely, men were found to have better reaction times on a Stroop Test; the Stroop test is a test of selective attention and processing speed (Alansari, 2006).

Several other cognitive tests of attention have shown sex differences. The Trail Making Test (Part A and Part B; TMT) is another test of attention in which sex differences have been found. In Part A of this paper and pencil test, the participant is presented with an array of digits from 1 to 24 that are placed randomly throughout the test sheet. The participant is requested to connect the numbers in sequential order by drawing lines between them. In Part B, the test sheet contains a random array of letters and numbers. The participant is asked to draw lines between the numbers and letters such that letter and number is alternated with the letter in alphabetical order and the

numbers in numerical order (e.g. A-1-B-2, etc.). Studies with larger sample sizes have found a sex difference in the TMT favoring men (Wiederhold et al., 1993); some studies have reported separate data for men and women (Elias et al., 1993). However, studies with smaller samples sizes stratified by age group have failed to consistently replicate this result (Soukup et al., 1998). The Paced Auditory Serial Addition Test (PASAT) is a test of information processing requiring the participant to add digits as they are presented in a continuous manner. This task requires the participant to attend to the next stimulus while maintain the current total in short term memory. Normative data for the PASAT report sex differences in performance. Interestingly, the direction of the difference is dependent on ethnicity, with male advantage seen in some ethnicities and a female advantage being seen in others (Diehr et al., 1998).

While the sex differences reported in adult samples have been highly heterogeneous, there seems to be a consistent female advantage in attention in children and adolescents. In a study that tested 1,100 girls and 1,100 boys with the Cognitive Assessment System (CAS) battery, girls were found to be better than boys in the attention subtest (Naglieri and Johannes, 2001). The CAS is a battery informed by A.R. Luria's Planning, Attention-Arousal, Simultaneous, and Successive theory of intelligence and the CAS battery has been found to successfully detect frontal lobe deficits. In another study, 400 Finnish children were tested on a broad array of cognitive tasks, including tasks of attention. Tasks were constructed to be age appropriate to the participant, however, all attention task required the participant to find targets in an

array of distracters. In this study, girls of all age groups performed better than boys in both speed and accuracy (Klenberg et al., 2001).

Overall, there is much variation in the reports of sex differences in attention and processing speed. Partly in response to this variation, studies have attempted to understand whether attention is produced via the same neural pathways in women and men. There is some evidence that women and men employ different cognitive strategies in response to a task require attention. In an event-related potential (ERP) study employing the Attentional Network Test, a test of selective attention, alerting and orienting, increased prefrontal activity was seen in women but not in men event though both sexes performed equally well on the task (Neuhaus et al., 2009).

3.2.2 Verbal learning and memory

The female advantage in verbal abilities was well documented by Maccoby and Jacklin's (1974) influential review of sex differences in cognition. The body of literature developed since that time has robustly corroborated their findings. Though this literature has investigated a variety of verbal abilities, only a subset of these findings pertains to verbal learning and memory. The cognitive tests of verbal learning and memory include the: Controlled oral Word Association Test (COWAT), Rey Auditory Verbal Learning Test (RAVLT), and California Verbal Learning Test (CVLT) (Andreano and Cahill, 2009). The COWAT is a measure of verbal fluency; in this test the participant is given a letter or a semantic category and is asked to generate as many words as possible with that letter/category. Studies of verbal learning can be thought to be measuring vocabulary and semantic verbal memory. On the other hand, the CVLT and the RAVLT

are thought to more concretely measure episodic recall. In these tasks, the participant is asked to recall word lists before and after a delay of several minutes (Andreano and Cahill, 2009).

Tasks of verbal memory and fluency show a distinct advantage for women. Females have performed better on studies of phonological and semantic fluency (Thilers et al., 2007). Superior recall of word lists is observed in women in several more studies (Kimura and Seal, 2003). In addition to standardized measures such as the CVLT, RAVLT, and Weschler Adult Intelligence test, better episodic recall in females is also seen in studies that measured paired-associates learning, story recall, and verbal recognition (Andreano and Cahill, 2009). Furthermore, the female advantage in broad verbal capabilities including verbal memory, are seen even before puberty (Kramer et al, 1997). Therefore, it is likely that organizational rather than activational effects produce this wide-ranging female verbal advantage. In one study that matched male and female groups by estradiol level, women nonetheless performed better on a verbal recall task. There is also evidence to support that this female verbal advantage is seen across the lifetime; in studies controlling for differences in education level, women were found to perform better than men in all age groups. Decline of verbal abilities is also thought to occur at a significantly earlier age in men (Andreano and Cahill, 2009).

Given these lifetime differences seen in verbal abilities, researchers have proposed that there is a fundamental difference in the way that men and women neurobioloigcally process languages. It has been suggested that women process language more bilaterally than men who process language in a left-lateralized manner.

In support of this is theory is a study finding that language capability is spared after left temporal lobectomy in women but not in men (Trenery et al., 1995). Additionally, in neuroimaging studies where participants brains are imaged during the learning for foreign words, left-lateralized fusiform activity is seen in men while bi-lateral fusiform activity is seen in women (Chen et al., 2007). These neural distinctions between men and women may also be expressed in terms of differences in cognitive strategy. It is thought that women show a higher degree of semantic and phonological clustering in verbal recall than men (Andreano and Cahill, 2009).

3.2.3 Executive function

Like attention, executive function is a cognitive domain that has not traditionally been associated with sex differences (Maccoby and Jacklin, 1974). Generally, a performance-based difference is not noticed in these higher cognitive tasks of working memory, planning, mental flexibility, attentional set-shifting, and problem solving. However, the lack of a performance-based difference does not necessitate that men and women perform these mental functions in the exact same manner (Cahill, 2006). For example, there are several studies that indicate that working memory is processed differentially in men and women (Speck et al., 2000). Working memory is defined as the ability to temporarily maintain and manipulate information in short-term memory. The brain regions that are implicated in working memory include the dorsolateral prefrontal cortex (DLPFC), inferior prefrontal cortex, areas of the parietal lobe, and the anterior cingulate. Sex differences in terms of both volume and neuronal density have been

found in several regions thought to be involved in working memory (Janowsky et al., 2000).

These neuroanatomical differences between men and women seem to influence how working memory is processed in the brain. Neuroimaging studies have found differing activational patterns between men and women when participating in working memory tasks. In two studies employing positron emission tomography (PET), sex differences in signal intensity was found in somatosensory cortex and anterior cingulate gyrus (Esposito et al., 1996; Speck et al., 2000). Functional MRI studies have found that, while the same brain regions were activated in response to a working memory task (DLPFC, parietal cortex, and the caudate), men had bilateral or right-lateralized activation in these regions while women showed left-lateralized activity. Another fMRI study found that women had more signal intensity in the middle, inferior, and orbital prefrontal cortices (Goldstein et al., 2005). A review of fMRI studies investigating working memory found that studies in which men and women are analyzed separately differ from studies employing mixed-sex samples in terms of activational patterns. Therefore, it was concluded that combining men and women on fMRI studies of cognition may obscure or bias results (Goldstein et al., 2005). Studies finding sex differences in activational patterns of working memory processing have been more consistent than those that report performance-based differences in working memory; some studies of visuo-spatial working memory have found sex differences favoring males, although studies finding the null effect are equivocal (Andreano and Cahill, 2009).

It is thought that these differences in activational patterns between men and women on working memory tasks reflect distinct problem solving strategies, neurodevelopmental differences, or a combination of both. Supporting the neurodevelopmental theory is evidence that suggests that working memory is modulated by hormones. In studies of postmenopausal women, those who received the estrogen-based hormone replacement therapy fared better on a task of working memory than those who did not receive hormone replacement therapy; in a with-in subjects test-retest design, women fared better on a working memory task after having received hormone replacement therapy (Janowsky et al., 2000). Preclincal evidence has also shown that extradiol affects working memory in rats. Another study found that increasing the testosterone/estrogen ratio by way of testosterone replacement, improves working memory in men. Sex-steroids and menstrual cycle phase have also shown to affect patterns of activation in an fMRI study in which participants perform a visuo-spatial working memory task (Janowski et al., 2000).

In addition to working memory, there is limited evidence to report that there may be sex differences in the planning component of executive function. The Tower of London task is a task of planning that requires the participant to rearrange colored beads on a series of three pegs so that they match an arrangement provided by the experimenter. Difficulty of the task can increase by increasing the number of beads and increasing the number of pegs. This task is thought to assess frontal lobe function. Studies have found a male advantage on a computerized Tower of London task and an analogous Tower of Hanoi task (De Luca et al., 2003; Bishop et al., 2001). One fMRI

study also found different activation pattern between men and women while they were participating in a Tower of London task, although others have failed to replicate the finding (Boghi et al., 2006). There is some indication that planning is sexually differentiated during childhood and preadolescence as well. In a study testing 1100 boys and 1100 girls found a female advantage on the planning component of the CAS (described above; (Naglieri and Johannes, 2001).).

Several other components of executive function do not show appreciable sex differences; among others, these include set-shifting, mental flexibility, problem-solving capacity. Though there are studies that have found sex-differences in multi-tasking and risk-assessment/inhibition, these constructs have been studied through unstandardized or observational means in healthy samples. Overall, men and women perform similarly on tasks of executive function. However, they may take different neural strategies to receive the same behavioral outcome (Goldstein et al., 2005).

4. The influence of sex on cognitive functioning in first-episode bipolar disorder I patients

As outlined in Chapter 3, decades of research have revealed that the human brain is sexually dimorphic at every level of neural organization from cytoarchitecture to gross morphology (Cahill, 2006). However, the manner in which this sexual differentiation extends to the behavioral and cognitive levels is not easy to predict. Previously, the widespread misconception was held that if no sex difference exists for a particular behavior, the neural substrates that are responsible for that behavior function identically in both sexes (De Vries, 2004). Yet, sex differences in the human brain are far more ubiquitous than are the behavioral differences observed between men and women. The advent of neuroimaging studies has helped to resolve this apparent discrepancy. From these studies, it was found that men and women often employ different neural strategies to reach the same behavioural endpoint (De Vries, 2004). That is, performance-based indices on tests of cognition are not sufficient in detecting sex differences in neural mechanisms. For example, while visuo-spatial and verbal cognitive tasks often show sex differences in performance, men and women perform equally well on most tasks of executive function; nevertheless, it has been found that men and women activate distinctly different brain areas when performing these tasks (Goldstein et al., 2005).

These neurobiological distinctions between men and women have consequences in the psychiatric realm. There are often pronounced sex differences in the prevalence rates of both neurological and neurophyciatric disorders. Illnesses that are over 75%

more common in women than in men include: Rett syndrome, lymphocytic hypophysitis, anorexia nervosa, and bulimia; Illnessess that are over 75% more common in men include: Tourette's syndrome, autism, ADHD, and dyslexia (Bao and Swaab, 2010). Moreover, in several neuropsychiatric disorders, sex differences are seen in the signs, symptoms, and course of the illness. SZ is 2.7 times more common in men than in women. In addition, males with SZ are prone to a more severe form of the illness, have poorer pre-morbid functioning, earlier onset, more negative symptoms and cognitive deficits, and exhibit a greater number of structural brain abnormalities. Studies have also shown that males with SZ experience more severe relapses and are more treatment resistant to neuroleptic medication (Abel et al, 2010). Cognitive deficits also feature largely in the pathophysiology of SZ; recent studies suggest that healthy patterns in cognitive functioning are disrupted in SZ patients such that male and female patients perform more similarly than to healthy men and women (Mendrek, 2007; Vaskinn et al., 2011).

Similar to SZ, sex differences have been observed in the phenomenology of BD. These differences in clinical presentation and course were summarized in Chapter 3. Far fewer studies have investigated whether healthy patterns of cognitive functioning are maintained in BD. The finding that sex differences in cognitive functioning are attenuated in SZ is of relevance to BD research as SZ and BD share aspects of their psychopathology, neurobiology, and treatment efficacy. Genetic studies have also shown that BD and SZ share some degree of genetic susceptibility (Hill et al., 2008). Given the close relationship between SZ and BD, sex differences in cognitive functioning

in BD samples warrants some investigation. Assessing sex difference in cognitive functioning can have both etiological and therapeutic value. For example, the finding that sex differences in cognitive functioning are attenuated in SZ led researchers to the understanding that the factors that produce sexual dimorphisms, which in turn are the factor that result in sex differences in cognitive functioning, may be associated with the insults that produce SZ (Bao and Swaab, 2010). Similarly, the finding of altered patterns of sex differences in BD is potentially important because it suggests that the biological mechanisms underlying normal sex differences may also be implicated in the etiology of BD. A greater understanding of the neural mechanisms that produce this illness in both men and women may lead to better therapeutic strategies and greater functional recovery for both sexes.

4.1 Introduction

To date, only three studies have directly investigated sex differences in cognitive functioning within a BD sample. The first study, conducted by Barrett *et al.* (2008), examined 26 patients diagnosed with BD and matched healthy control subjects on measures of spatial working memory (SWM), planning and attentional set-shifting using the Cambridge Automated Neuropsychological Testing Battery (CANTAB), as well as verbal fluency using the Controlled Oral Word Association Task (COWAT). They found a significant diagnosis by sex interaction in their SWM strategy scores such that their male patients performed worse than their female patients while their male controls outperformed their female controls. In the second study by Carrus *et al.* (2010), 86 BDI patients and matched healthy controls were tested on various tasks of general

intellectual ability and declarative memory using the Wechsler Memory Scale-III, Wechsler Adult Intelligence Test-Revised, Hayling Sentence Completion Task, and the Wisconsin Card Sorting Test. They found a significant diagnosis by sex interaction on measures of immediate memory, where male patients performed worse than female patients and healthy controls. In the largest and most recent study conducted by Vaskinn et al. (2011), 106 patients with BD-I and matched healthy controls were tested with various subtests of the Wechsler Adult Intelligence Scale. Results from this study failed to reveal a diagnosis by sex interaction across the full sample of patients with bipolar disorder. However, there was a suggestion that males with BD-I and a history of psychosis showed preferentially diminished delayed verbal recall. In sum, compared to healthy individuals, the existing literature suggests that males with BD may show a relative disadvantage in spatial working memory and memory functioning.

However, a clear interpretation of these results is obscured by heterogeneity present in the patient cohort of existing studies. For example, male patients in the Barrett et al. (2008) were older, more symptomatic, and had experienced a greater number of mood episodes than their female patients. These factors when paired with the small sample size of this study may have biased the results. Similarly, in the Carrus et al. study (2010) a significantly greater number of female patients had a history of psychosis than male patients. Due to this heterogeneity, potential confounding clinical variables, and lack of cognitive test overlap between studies, the literature in this area is unclear with regard to the extent that cognitive impairment in BD is influenced by sex.

The present study tested 66 BDI euthymic patients and 90 matched healthy control subjects on a broad battery of neurocognitive tasks. This study attempted to address some of the methodological issues plaguing previous studies by recruiting a more homogeneous group of bipolar I patients and testing them immediately after remission from their first manic or mixed episode. In utilizing a first-episode sample, the influence of variables such as chronicity of illness and cumulative treatment effects on cognition is likely minimized. Additionally, the patient sample used is homogeneous in terms of age and clinical characteristics. Sex differences were assessed in healthy controls and BDI patients using tasks that have been shown to be sensitive to cognitive impairments seen in BD as well as in unipolar depression, and schizophrenia (De Luca et al., 2003; Yatham et al., 2010). Additionally, the cognitive domains assessed by this battery – verbal memory, verbal fluency, executive function, working memory – are those in which sex differences have been repeatedly observed in healthy populations as has been summarized in previous chapters. As such, the assessment of a first-episode patient population with this testing battery allows for a methodologically stringent evaluation of whether sex influences cognitive impairment in BDI early in its course.

4.2 Materials and methods

Participants. The 60 patients and 90 healthy controls enrolled in this study were participants of the Systematic Treatment Optimization for Early Mania (STOP-EM) project. STOP-EM is a comprehensive prospective study assessing patients who have recently experienced their first bipolar manic or mixed episode according to *DSM-IV-TR* criteria. A complete description of the study protocol has been provided in previous

papers (Yatham et al., 2009). Briefly, patients aged between 18 and 35 years who had experienced a first manic or mixed episode within the last 3 months were recruited from the University of British Columbia affiliated Hospitals and Clinics via referrals from local physicians and psychiatrists. Particpants were required to be clinically stable during the initial study assessment. All diagnostic assessments were conducted by fully qualified psychiatrists utilizing both comprehensive clinical interviews and the Mini International Neuropsychiatric Interview.

For comparison purposes, healthy control subjects free of personal or familial psychiatric illness in first degree relatives were recruited into the study from the community and matched on the basis of sex, age, premorbid IQ, and educational attainment. Patients and controls were assessed at least every six-months or as clinically indicated. Only baseline visit data are used in the present study.

Psychiatric assessment. Clinical variables were collected following the protocol of the STOP-EM program in which patients were provided with clinically indicated treatment based on evidence based treatment guidelines (Yatham et al, 2009) and clinically accepted standards. Psychiatric status at baseline and at each 6 monthly visit was assessed using several clinical rating scales including the: Young Mania Rating Scale (YMRS), Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Rating Scale for Depression (HAM-D), Clinical Global Impression Scale for Bipolar Disorder (CGI-BP), and Global Assessment of Functioning Scale (GAF). Information regarding the patient's psychiatric history including number and type of prior mood episodes, history of psychotic symptoms during a mood episode, duration of illness, age of onset of illness,

number of hospitalizations, and lifetime substance abuse or dependence was also recorded as was information regarding the dose and duration of their pharmacological treatments.

Neurocognitive assessment. A 2-3 hour neurocognitive battery was administered to participants in a quiet environment following standardized testing procedures. Premorbid IQ was assessed using the North American Adult Reading Test Full Scale IQ (NAART FSIQ) and the Kaufman Brief Intelligence Test (KBIT) IQ composite score was used to evaluate current intelligence. The touch screen CANTAB V2 System was used to administer the cognitive tests of attention, planning, and executive function. These tests were Stockings of Cambridge, Spatial Working Memory, Paired Associates Learning, Intra/Extra Dimensional Set Shift, and Rapid Visual Processing. In addition to the CANTAB tests, the CVLT-II and COWAT were administrated to participants using traditional paper and pencil methods. The details of these tasks have been described in other papers (De Luca et al., 2003). However, brief descriptions will be provided.

Stockings of Cambridge (SOC): In this computer-based task, the subject is presented with two arrangements of coloured balls hanging from stockings attached to a beam. The participant is instructed to move one ball at a time to make the arrangements identical within a recommended number of moves. SOC is a computerized Tower of London Task and is a test of spatial planning ability and is a measure of frontal lobe function. The inhibitory control component required in such tasks of strategy and planning has shown moderate effects in bipolar disorder versus controls (Yatham, 2010). In healthy samples, several studies across multiple testing

paradigms have found that males outperform females in tasks requiring planning (De Luca et al., 2003; Bishop et al., 2001). Raw scores for the SOC variable 'number of problems solved in the minimum number of moves' was used in analysis.

Spatial Working Memory (SWM): In this task, the participant is presented with a number of boxes on a computer screen. A blue token is hidden beneath one box. When found, the token is hidden in another box where a token has not been hidden before. The participant is required to find as many blue tokens as there are boxes, eliminating the number of boxes that need to be searched by process of elimination. SWM is a task that tests the participant's ability to manipulate spatial information in working memory. This test has been shown to detect frontal lobe and executive dysfunction. Working memory, both spatial and verbal, has been heavily implicated as being impaired in BD (Yatham et al., 2010). In healthy populations, the spatial component of this task likely confers a performance advantage to men (Andreano and Cahill, 2009). Additionally, CANTAB normative data found a significant effect of sex in the SWM task across the lifespan (De Luca et al., 2003). There are some data to indicate that healthy sex differences SWM task performance seems to be altered in BD and in schizophrenia (Kurtz and Garrety, 2009). Raw scores for SWM variables 'between search errors' and 'strategy' was used in analysis.

Intra/Extra Dimensional Set Shift (IED). IED is a modified computerized version of the Wisconsin Card Sorting task. The stimuli presented to the participants are solid color-filled novel shapes, white-line drawings, or the combination of the two. The rules are based on the color-filled shapes or the white-line drawings. Once the participant has

acquired the rule and is consistently choosing the right pattern, the rule is then changed. IED is a test of rule acquisition and rule reversal. It is a complex task that assesses the participant's visual discrimination skills as well as their attentional maintenance, flexibility, and set-shifting ability. Performance on this type of task has been shown to be impaired in BD (Yatham et al., 2010). While sex differences in performance is not always found in this domain, there are numerous sexual dimorphisms found in the frontal lobe in healthy populations and activation in these regions in response to various cognitive tasks associated with executive functioning seems to vary between sexes (Cahill, 2006). There is also limited evidence to show that cognitive tasks involving the prefrontal cortex display sex differences in performance in people with schizophrenia. IED 'EDS errors' and 'total errors' raw scores were used for analysis.

Rapid Visual Processing (RVP): In this task, the numbers 2-9 flash one at time in a box in the center of the computer screen. The participants are asked to look for target sequences of three numbers (e.g. 2-4-6) and are instructed to press a response pad when the third digit of the target sequence appears. RVP is a test of sustained attention. It is thought to be sensitive to dysfunction in the frontal and parietal lobe areas. Sustained attention and processing speed have been found to be impaired in BD (Torres and Malhi, 2010). Studies assessing attention and processing speed have been found to show distinctions between men and women in healthy populations using both ERP and fMRI paradigms (Raja and Yang, 2012). Studies in healthy populations have shown that females outperform males on tests of selective attention; however, males may show

greater visuo-spatial processing speed than females (Andreano and Cahill, 2009). Both processes are utilized during this task. RVP raw scores for the variable 'discriminability' and 'mean latency' were used in analysis.

CVLT-II: This task is thought to test verbal memory and ability to use semantic strategies to aid in verbal memory. In this task, a subject is read 16 words aloud over 18-20 seconds. The words can be grouped into four semantic categories (e.g. ways of traveling, furniture, animals, etc.) although this is initially unapparent to the participant as the words in each semantic category are distributed randomly. The participant is then required to repeat as many of the words that they can remember in any order. This sequence is repeated until the participant has heard the list read aloud 5 times. Verbal learning and memory is robustly impaired in bipolar disorder (Torres and Malhi, 2010). Additionally, females outperform males on verbal memory tasks in healthy populations (Andreano and Cahill, 2009). Raw scores for the CVLT-II variables 'Trial 1', 'Trial 1-5', and 'long delay free recall' were used in analysis.

COWAT: This is a test of phonemic verbal fluency. The participant is given one minute to say as many words that begin with a specific letter as fast as they can. The participant is told to avoid proper nouns and words that are the same with a different ending such as 'eat' and 'eating'. Two sets of three letters, FAS and CFL, are counterbalanced across testing sessions. Verbal fluency is impaired in BD samples (Kurtz and Gerraty, 2009). In healthy samples, females have been frequently found to outperform males (Andreano and Cahill, 2009). The COWAT raw 'total score' variable was used in analysis.

Statistical analysis. Statistical analysis was conducted to examine whether the pattern of sex differences in cognitive functioning observed in healthy controls is maintained within BD patients. All statistical analysis was conducted using PASW version 18 for Windows. Clinical, demographic, and neurocognitive data were assessed for normality using histograms and the Shapiro-Wilk test. For those variables that did not meet the criteria for normality, several transformations (including logarithmic, natural log (ln), square root, and inverse) were attempted in order to adjust the data so that the skew and kurtosis lay between 1 and -1. Where transformations could not normalize the data, Mann-Whitney *U*-tests were performed to assess whether mean rank differences lay across group and sex. Sex differences in clinical and demographic variables were assessed through univariate analysis of variance (ANOVA), using group and sex as between-subject factors. Frequency data regarding patient medication use, patient history of psychosis, and hospitalization was assessed using chi-squared tests. In order to determine whether there were significant sex differences on any of the neurocognitive variables across diagnostic groups, normally distributed data and transformed data were analyzed using ANOVA.

4.3 Results

Group and sex differences in demographic variables. Table 1 presents the means and standard deviations (SD) for the demographic variables: age, years of education, NAART and KBIT IQ. The p-value presented in the last column of Table one represents the p-value for the interaction. As indicated by the '—', no interaction was tested for handedness measures as these data did not display normality.

Table 1. Demographic characteristics of study participants

	Patients				Controls				
	Males (N = 29)		Females (N = 31)		Males (N = 42)		Females (N = 63)		
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p*-value*
Age	22.41	3.93	24.42	4.43	20.89	2.83	23.62	4.81	0.65
Years of education	13.28	1.92	14.06	2.31	13.83	4.81	14.44	2.18	0.91
NAART	107.45	6.13	106.74	8.33	107.74	6.65	108.82	6.79	0.45
KBIT IQ	104.83	10.12	103.87	10.09	109.83	10.53	106.51	10.11	0.48
Handedness	12.62	5.47	14.77	7.54	12.20	8.38	13.00	6.89	--

*these figures represent the *p*-value for the interaction

Interactions and main effects for each variable are presented below:

Age: Male and female age data for both patients and controls failed the Shapiro-Wilk test of normality ($p < 0.05$). However, female patient and female control data had a kurtosis and skew that lay between 1 and -1. Male data from both controls and patients had a skew and kurtosis that lay between 2 and -2. Transformations failed to increase the normality of this sample. The data was judged to be sufficiently normal to allow for ANOVA analysis. Histograms of age data are provided in Appendix A. There was no significant interaction between patients and controls in age [$F(1,150) = 0.20$, $p = 0.65$]; however, there was a main effect of sex with women being older [$F(1,150) = 11.84$, $p = 0.001$] and a trend level effect of group with patients being older [$F(1,150) = 2.98$, $p = 0.09$]. Although there was a significant main effect of sex and group for age, this was likely an artifact of the small standard deviation values due to the homogeneity of age in study participants. Females were on average only three years older than males, and patients were on average only 1 year older than controls. These are differences that are not likely to be clinically meaningful with regard to their influence on cognitive testing.

Total Years of Education: Male patient data and male and female control data for years of educations met the Shapiro-Wilk test of normality ($p > 0.05$). Male patient data were both skewed and kurtotic. However, transformations only decreased the overall normality of this sample. As most of the data was normally distributed and as non-parametric tests involve a substantial drop in power, years of education data was analyzed using ANOVA. Histograms for these data are provided in Appendix A. The sex x group interaction [$F(1,150) = 0.01$, $p = 0.91$] and group main effect [$F(1,150) = 1.49$, $p = 0.23$] were both nonsignificant. There was a trend level effect of sex favoring more years of education for females [$F(1,150) = 3.61$, $p = 0.06$]. However, females only had one more year of education than males.

NAART and KBIT: male and female data from patients and controls were normally distributed with skew and kurtosis lying between 1 and -1. In NAART data, group [$F(1,150) = 1.02$, $p = 0.32$], sex [$F(1,150) = 0.03$, $p = 0.88$], and interaction [$F(1,150) = 0.57$, $p = 0.45$] effects were all nonsignificant. Additionally, in KBIT data, sex [$F(1,150) = 1.49$, $p = 0.23$], and interaction [$F(1,150) = 0.52$, $p = 0.48$] effects were nonsignificant. Controls did score on average 3 points higher than patients and this effect was significant [$F(1,150) = 4.82$, $p = 0.03$].

Handedness: These data were significantly skewed and were not improved by transformations; they were analyzed through nonparametric measures. Handedness scores were matched across patients and controls [$U = 2{,}216.50$, $p = 0.06$] and males and females [$U = 3{,}049.00$, $p = 0.26$].

Group and sex differences in clinical variables. Means and standard deviations for clinical variables are given in Table 2.

Table 2. Clinical characteristics of study patients

	Males N = 29		Females N = 31		
Measure	Mean	SD	Mean	SD	*p*-value*
Scale:					
HAM-D	5.90	6.67	7.81	8.60	0.34
YMRS	0.83	1.54	2.13	4.01	0.18
MDRS	5.38	6.30	6.71	8.36	0.49
CGI	2.13	1.30	2.19	1.36	0.81
GAF	68.86	15.08	66.32	11.41	0.46
Age of Onset	19.85	4.80	20.35	5.68	0.72
Previous Episodes (Depression)	1.07	1.41	1.22	1.80	0.88
Previous Episodes (Hypomania)	0.14	0.49	0.74	2.11	0.14
	Males		Females		
	Raw	%	Raw	%	
Hospitalized for 1st Mania:					0.83
Yes	25	86.21	27	87.10	
No	4	13.79	4	12.90	
Past History of Psychosis:					0.76
Yes	21	72.41	24	77.42	
No	8	27.58	7	22.58	
Mood Stabilizer:					0.10
No Medications	7	24.14	1	3.23	
Divalproex	12	41.38	16	51.61	
Lithium	10	34.48	14	45.16	
					0.11
Antipsychotics:					
No Medications	10	34.48	6	19.35	
Risperidone	7	24.14	13	41.94	
Olanzapine	8	27.59	3	9.68	
Seroquel	3	10.34	9	29.03	
Loxapine	1	3.44	0	0.00	

*p-value result from either an Independent Samples t-test, Mann-Whitney U-test, or chi-squared test.

Clinical Scales: GAF data were normally distributed as assessed by the non-significant Shapiro-Wilk test statistic ($p > 0.05$). The CGI data failed the Shapiro-Wilk test of normality but was judged to be sufficiently normal to conduct parametric analysis,

the skew and kurtosis for male patients were within 1 and -1 as was the skew for female patients, while the kurtosis for female patients was 1.26. Histograms for CGI data will be provided in Appendix A. The MADRS and HAM-D data were transformed using a square-root function. The GAF, CGI, MADRS, and HAM-D data were analyzed using the independent-samples t-test. As the normality of YMRS data were not improved with transformations, and as the skew and kurtosis for the male and female data were well out of bounds, the nonparametric Mann-Whitney *U* test was used to analyze this data. From these analyses, male and female patients were found to be well-matched on all of the psychiatric scales used in assessment: HAM-D [$t(52) = -1.16$, $p = 0.25$], YMRS [$t(52) = -1.71$, $p = 0.09$], MADRS [$t(52) = -0.58$, $p = 0.56$], CGI [$t(55) = -0.04$, $p = 0.97$], and GAF [$t(55) = -0.24$, $p = 0.81$].

Additional Clinical Variables: Age of onset data for male and female patients failed the Shapiro-Wilk test for normality ($p < 0.05$), however, the data was judged to be sufficiently normal as their skew and kurtosis were all within 1.5. Histograms for this data are provided in Appendix A. Data for number of past episodes (both depression and hypomania) were not normally distributed. These data were not improved by transformations; as such, nonparametric measures were used to analyze these variables. Male and female patients were well matched for age of onset of illness [$t(56) = -0.36$, $p = 0.72$], , and number of previous mood episodes (depressive, [$U = 424.25$, $p = 0.88$] and hypomanic [$U = 499.50$, $p = 0.14$]).There were no significant sex differences in the number of patients having been hospitalized for their first mania [$\chi^2 = 0.04$, p =

0.83], having a past history of psychosis [$\chi^2 = 0.09$, p = 0.77], taking any particular mood stabilizer [$\chi^2 = 4.67$, p = 0.10], or any particular antipsychotic [$\chi^2 = 9.06$, p = 0.11].

Group and sex differences in cognitive function. Mean scores for the cognitive measures of patients and controls are presented in Table 3.

Table 3: Descriptive statistics for neurocognitive variables

	Patients				Controls				
	Males n = 29		Females n = 31		Males n = 35		Females n = 55		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p-value*
COWAT									
Total Score	39.69	8.56	35.48	9.03	43.03	8.11	41.58	12.08	0.41
CVLT:									
Trial 1	6.38	1.72	6.97	2.09	7.09	2.17	7.60	2.38	0.92
Trial 1-5	49.93	8.90	53.45	12.15	58.18	9.04	60.18	8.12	0.64
Free Recall (long delay)	10.69	2.97	11.33	2.96	13.15	2.41	13.62	2.36	0.85
IED:									
EDS Errors*	4.65	5.62	10.93	10.45	10.20	10.00	12.76	10.68	0.27
Total Errors	26.64	41.37	29.97	25.52	17.23	15.93	19.28	16.73	0.88
SOC:									
Number of problems solved in min moves	8.79	2.22	8.87	2.09	9.90	1.79	9.23	1.89	0.15
RVP:									
Discriminability	0.89	0.06	0.89	0.04	0.93	0.03	0.91	0.04	0.12
Mean Latency	437.39	64.74	480.94	79.19	416.14	52.25	489.04	95.49	0.27
SWM:									
Between Errors	19.17	16.92	21.42	20.57	6.51	6.55	14.93	18.16	0.23
Strategy	31.39	6.37	32.10	6.08	27.37	5.30	29.54	6.07	0.47

*p-values reported are for the interaction effect

All cognitive variables were normally distributed as assessed by a nonsignificant p-value on the Shapiro-Wilk test and/or skew and kurtosis values of one or less. Histograms for patient and control data for cognitive variables are provided in Appendix B. All cognitive variables were assessed by ANOVA.

Significant group effects, favoring controls, were observed for COWAT Total Score [$F(1,150) = 7.84$, $p = 0.006$], CVLT Trials 1-5 [$F(1,149) = 22.05$, $p < 0.001$], CVLT Long

Delay Free Recall [$F(1,148) = 28.23$, $p < 0.001$], IED EDS Errors [$F(1,145) = 4.81$, $p = 0.03$], IED Total Errors [$F(1,148) = 5.67$, $p = 0.019$], SOC Number of Problems Solved in Minimum moves [$F(1,148) = 7.83$, $p = 0.006$], and RVP discriminability [$F(1,149) = 20.27$, $p < 0.001$]. Trend level significance for the group effect was observed for CVLT Trial 1 [$F(1,149) = 3.39$, $p = 0.068$]. The group effect for RVP mean latency was nonsignificant [$F(1,149) = 0.25$, $p = 0.62$].

A significant main effect of sex favoring males was observed for EDS Errors [$F(1,145) = 6.91$, $p = 0.01$], RVP discriminability [$F(1,149) = 4.10$, $p = 0.045$], and RVP mean latency [$F(1,149) = 19.33$, $p < 0.001$]. A trend level of significance for the main effect of sex was observed for COWAT Total Score [$F(1,150) = 2.81$, $p = 0.096$; favoring males – surprising males were favored – double check data for this], CVLT Trials 1-5 [$F(1,149) = 3.00$, $p = 0.085$; favoring females], and SWM Between Errors [$F(1,148) = 1.43$, $p = 0.23$; favoring males]. Nonsignificant main effects of sex were found for CVLT Trial 1 [$F(1,149) = 2.28$, $p = 0.13$], CVLT Long Delay Free Recall [$F(1,148) = 1.56$, $p = 0.21$], IED Total Errors [$F(1,148) = 0.405$, $p = 0.53$], SOC number of problems solve in minimum moves [$F(1,148) = 1.39$, $p = 0.24$], and SWM strategy [$F(1,148) = 2.02$, $p = 0.16$]

There were no significant interaction effects observed for any of the cognitive variables. The p-values of the interactions are provided above in Table 3.

4.4 Discussion

The main findings of this study are: 1. Bipolar patients as a group showed poorer cognitive performance than age and sex matched healthy controls, 2. Sex was an important determinant of neurocognitive function in that males performed better than

females on measures of sustained attention and set shifting, whereas there was a trend for females to perform better than males in verbal learning. Most importantly, however, there were no group x sex interactions indicating that sex had the same impact on neurocognitive function in bipolar I patients as in healthy controls. These results are in line with those found by Vaskinn et al. (2011), but disagree somewhat with the results found by Barrett et al. (2008) and Carrus et al. (2010). While Barrett et al. (2009), and Carrus et al. (2010) found preservation of healthy sex differences for a majority of the tasks included in their cognitive batteries, in contrast with the present findings, these previous papers also reported that sex differences in cognitive performance in bipolar patients differed from healthy controls on measures of SWM and immediate memory. Several underlying factors, including the use of varying testing materials, may contribute to this discrepancy.

The methodological limitations of the previous studies have already been mentioned and it is possible that their findings were an artifact of small sample size and large sample heterogeneity. The patients and healthy controls enrolled in the present study were statistically comparable in terms of intellectual capacity. Additionally male and female patients in this study were statistically homogenous in terms of psychiatric status. Although patients were significantly older than controls, the clinical relevance of this difference is minimal as the mean age of the patient group was only two years above that of the control group. The control of these relevant demographic clinical and variables may account for the lack of group x sex interactions found on any cognitive variable including SWM in this study.

Another possible interpretation of the present findings in the context of earlier studies might be that sex-differences in cognitive functioning remains intact early in the course of BDI but may be altered later in the illness. That is, cognitive impairment may take differential trajectories in men and women with BDI as the illness progresses. Furthermore, differential trajectories between sexes may be more apparent for certain cognitive domains such as SWM or immediate memory. This hypothesis helps explain why the results of this study align with those found by Vaskinn et al. (2011); compared to the samples utilized in both the Barrett et al. (2008) and Carrus et al. (2010) studies, the sample studied by Vaskinn et al. (2011) was younger and had been symptomatic for fewer years. It is possible that a significant cognitive insult must first occur before sex differences in cognitive functioning veers away from healthy patterns in BD. The next wave of questions that arise from this finding will necessarily concern the mechanisms that protect women with BD from greater cognitive deterioration, or alternatively, the mechanisms that exacerbate cognitive deterioration in men with BD. These mechanisms may encompass both illness-related and iatrogenic processes as medications may have different effects in men and women. As many these medications act on the sexually dimorphic dopaminergic and glutamatergic neurochemical systems, the notion that medication will have different effects in men and women seems probable.

This hypothesis that the alteration of healthy patterns of cognitive sex differences emerge over the course of the illness also aligns with recent neuroanatomical evidence that suggests that sexual dimorphisms that are present in healthy controls are altered in BD patient samples that have experienced multiple mood episodes. In voxel-based MRI

studies conducted with BD patients and healthy controls, significant diagnostic group x sex interactions have been found in the left frontal, left temporal, right parietal, right occipital lobe, and the cerebellar vermis (Mackay et al., 2010; Womer et al., 2009). Similar findings of altered sexual dimorphisms have been found in subregions of the prefrontal cortex in both adult and pediatric bipolar populations (Dickstein et al., 2005; Najt et al. 2007). Sexual dimorphisms are phenotypically impactful and are thought to be the basis of sex-differences in cognitive functioning in healthy populations (Adreano and Cahill, 2009). If these sexual dimorphisms are altered in BD, it stands to reason that sex differences in cognitive functioning may be altered as well.

There is parallel evidence of altered sexual dimorphisms co-occurring with altered sex differences in cognitive performance in samples with schizophrenia in tasks involving the prefrontal cortex (Roesch-Ely et al., 2009). These results are particularly telling as, in terms of cognitive impairment, BD and SZ are considered by many to be on the same spectrum, with SZ representing the more severe condition (Hill et al, 2008). However, until the present study, there had yet to be an investigation of sexual dimorphisms in first-episode BD patients. The results from this study would suggest that as healthy sex differences in cognitive performance are maintained in first-episode patients, healthy sexual dimorphisms may be maintained as well. Again, however, similar performance on cognitive tasks between men and women does not guarantee that the neural substrate functions equally between sexes. Another consideration must be the effect of compensation; neural processing in men and women with BD may be abnormal even early in the course of the illness. However, compensatory mechanisms

may prevent this abnormality from registering on a behavioural level. For example, studies have demonstrated that in response to tasks of planning and spatial memory, women show more activation in the prefrontal lobe especially on the right side while men show more bilateral activation in the parietal lobe despite performing equivocally (Andreano and Cahill, 2009). Further studies testing first-episode BD samples using cognitive batteries paired with various imaging techniques are needed in order to ascertain whether these healthy sexually dimorphic patterns of brain activation are maintained in psychiatric populations.

The results presented in this study need to be considered within a framework of several limitations. Although the cognitive battery employed in this study effectively detected group differences in cognitive functioning, it may not have been optimally sensitive in detecting sex differences. While group effects were found in nearly all measures with healthy controls performing significantly better than the patients sample, sex differences were only found in a subset of the tasks tested. In accordance with previous literature, significant sex differences were found on measures of sustained attention (RVP discriminablity and mean latency), executive function (IED EDS errors), and verbal declarative memory (CVLT Trial 1 there was no sex difference for CVLT Trial 1, CVLT Trial 1-5- this was a trend). Measures of planning (SOC), spatial working memory (SWM), and verbal fluency (COWAT) did not show any significant sex differences.

However, the finding of comparable performance between sexes in these tasks is not without precedent. While some tests of planning using Tower of London and the Tower of Hanoi designs have shown that males outperform females, several studies

have failed to replicate these findings (De Luca et al., 2003). Similarly, while many studies have shown that verbal fluency is increased in women, several studies including COWAT normative data have found equivocal performance between sexes (Ruff et al., 1996). Literature regarding visuospatial working memory is also not without its ambiguities. Spatial working memory seems to be a multidimensional construct that assesses several distinct cognitive abilities (Andreano and Cahill, 2009). Over the years, several tasks have been designed that assess spatial working memory including: CANTAB SWM, spatial span on the Corsi-Block Tapping Task, Delayed Response Task, Mental Rotation, and the N-back working memory task. The most robust sex difference in cognitive performance is seen in Mental Rotation, with men outperforming women. However, lack of sex differences in spatial working memory have been found using several of these paradigms, while other measures have found that women outperform men (Andreano and Cahill, 2009). Overall, it seems that the complexity of these cognitive domains produces a high degree of sensitivity to operationalization, with variable results being received from different tasks and test environments. Again, it should be emphasized that equivocal performance on cognitive tasks does not necessarily indicate that sex differences do not exist in terms of cognitive processing.

Future studies investigating cognitive sex differences in psychiatric populations would also benefit from controlling for menstrual cycle in their designs. Studies in healthy populations have shown that performance on various cognitive tasks as well as the detection of sex differences varies according to phase of menstrual cycle (Kimura, 1996; Postma et al., 1999). Failure to account for phase of menstrual cycle represents a

major limitation of this study, as is the case with prior studies in BD. While this overall picture remains unclear, there have been some strong suggestions made that left/mixed handedness predicts better cognitive flexibility while strong right-handedness predicts better time estimation skills (Andreano and Cahill, 2009). Handedness has not been previously associated with the specific tasks used in this study and has not been associated with sex. Nevertheless handedness may have mediated or moderated some of these results.

Despite its limitations, this study remains the first in addressing the issue of cognitive sex differences in BD early in its course; whether these sex differences remain healthy throughout the course of the illness represents a future line of inquiry that may yield informative results. Additionally, too few studies have addressed whether healthy sexual dimorphisms and patterns of neural activation are conserved in these patient samples. Longitudinal studies following patients from their first-episode assessing neurocognition, brain morphology, brain function are needed to better understand the basis of sex differences observed in the clinical phenomenology of BD. Recognizing distinctions between the pattern of impairment seen in men and women with BD may help to generate more targeted therapeutic strategies. For example, in regards to the novel pharmacological cognitive-enhancement agents that are currently in development to ease cognitive dysfunction in BD, some agents may be more indicated for one sex than the other dependent on the agent's cognitive profile.

Summary. Sex influences cognitive functioning in BD. However, early in the course of the illness, the influence of sex in BD samples is equivalent to that observed in healthy samples. That is, healthy patterns of cognitive functioning as measured by performance-based cognitive tests, are maintained early in the course BD. This pattern may not persist over the course of the illness. As the repeated insult of mood episodes further impacts cognition, sex differences that veer away from healthy patterns may be observed. A promising avenue of future research involves investigating sex differences in cognitive functioning in a longitudinal manner. Recognizing the distinctions between the profile of cognitive impairment seen in men and women with BD as they emerge over the course of their illness may help in designing treatment strategies that will more effectively remedy the functional burden in both sexes.

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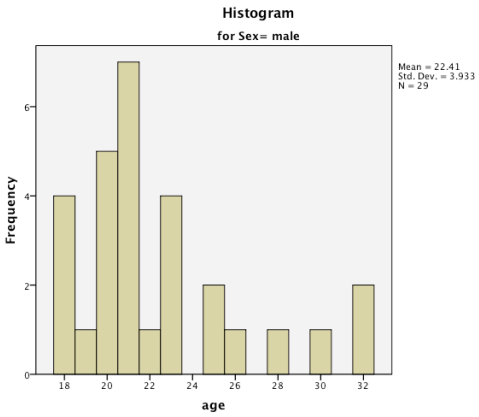
Appendices

Appendix A: Demographic and clinical variable histograms

Age: Male Patient Data



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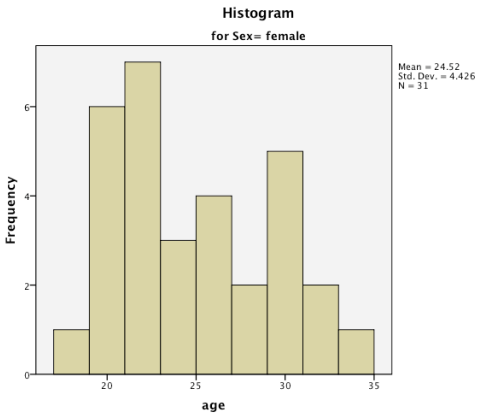
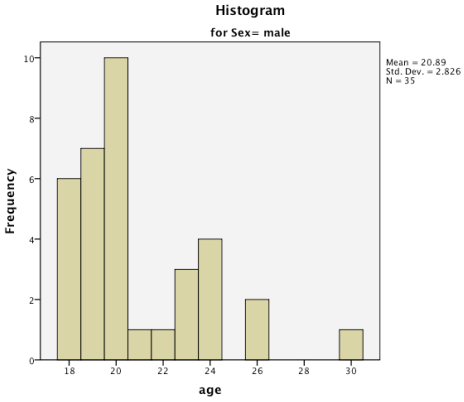


Age: Male Control Data



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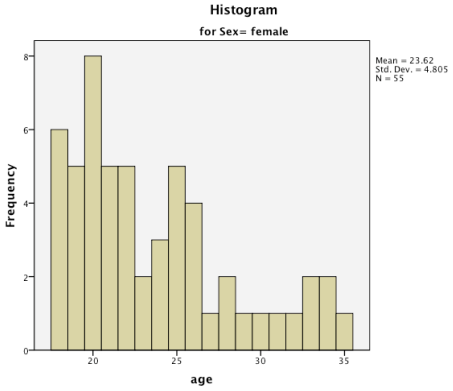
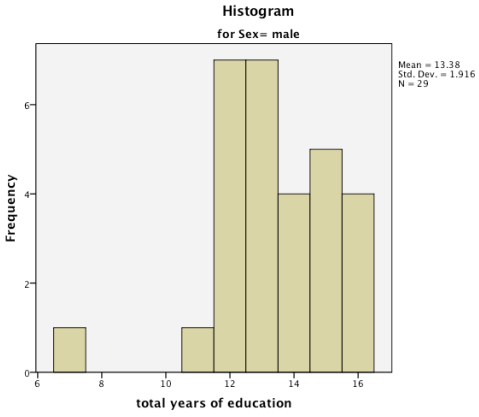


Years of Education: Male Patients



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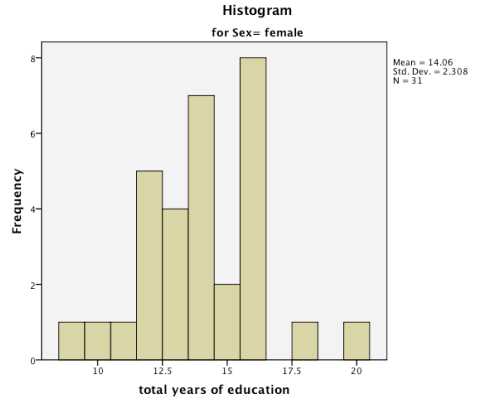
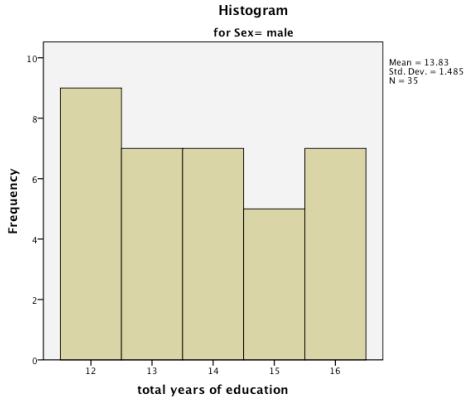


Years of Education: Male Controls



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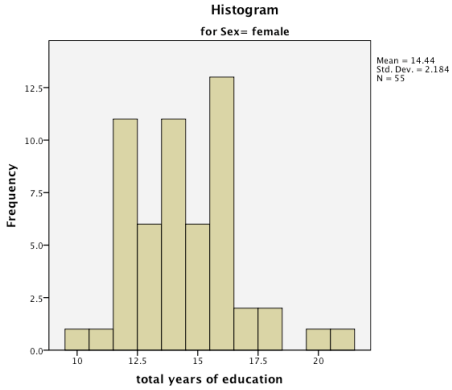
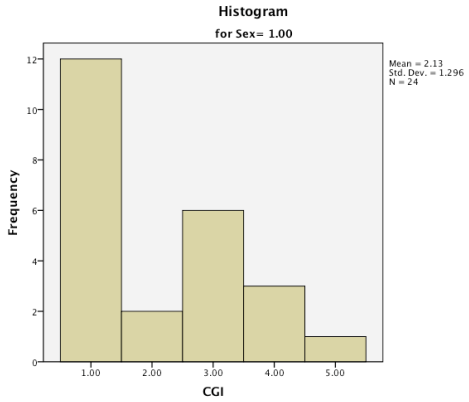


CGI: Male Patients



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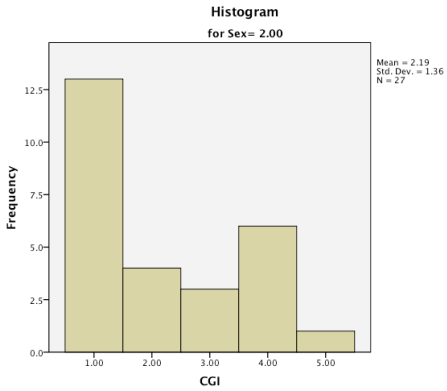
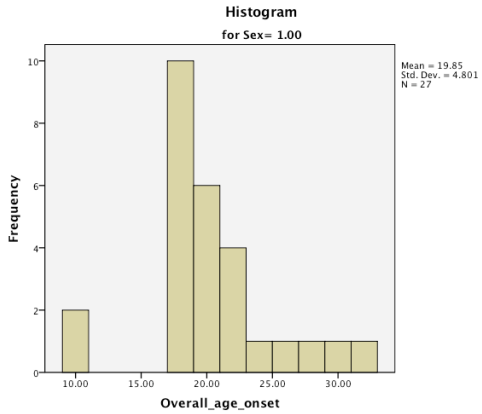
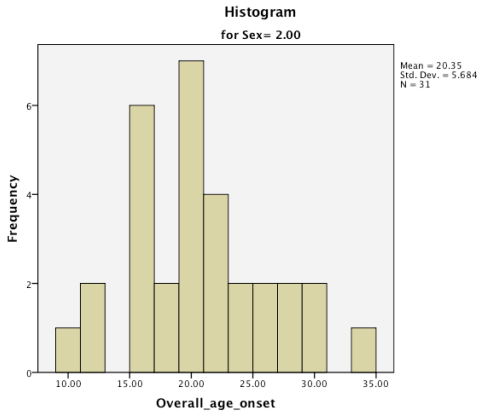


Age of Onset: Male Patients

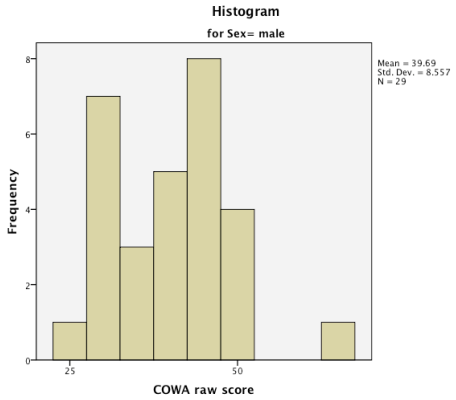


Age of Onset: Female Patients



Appendix B: Cognitive variable histograms

COWAT Total Score: Male Patients



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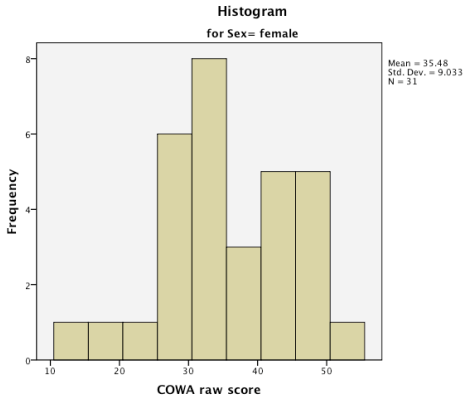
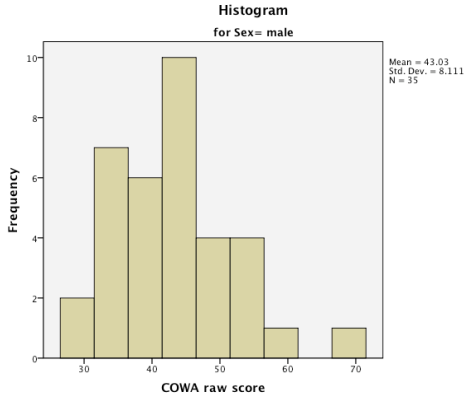
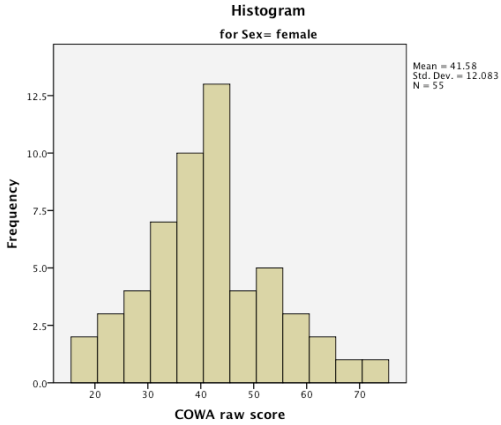


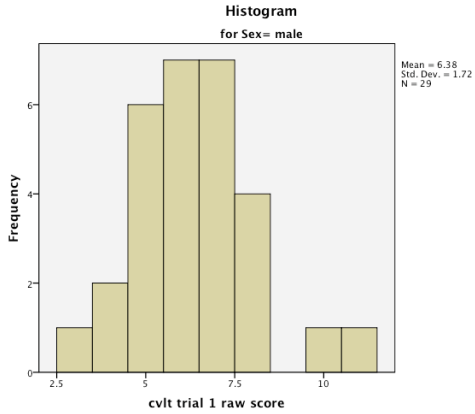
COWAT Total Score: Male Controls



COWAT Total Score: Female Controls



CVLT Trial 1: Male Patients



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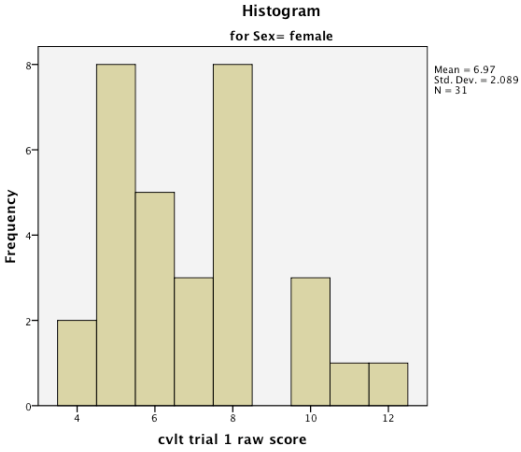

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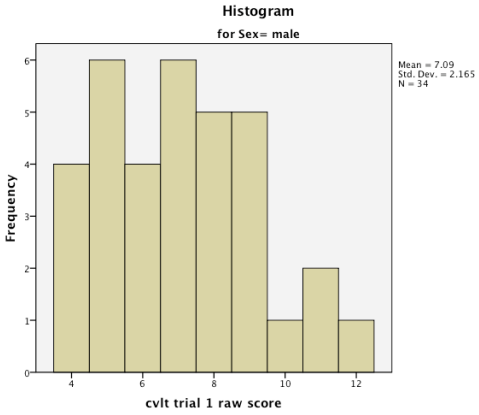
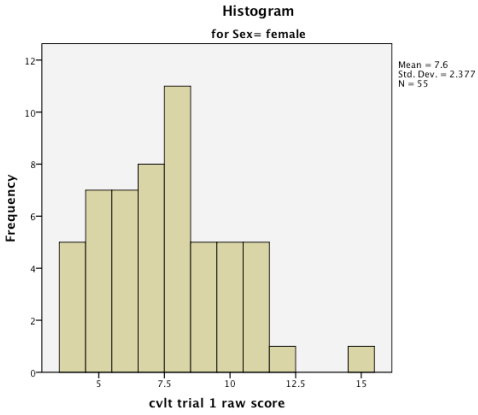
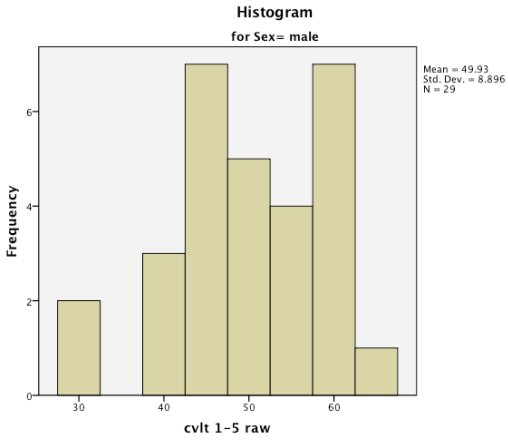


CVLT Trial 1: Female Controls



CVLT Trial 1-5: Male Patients



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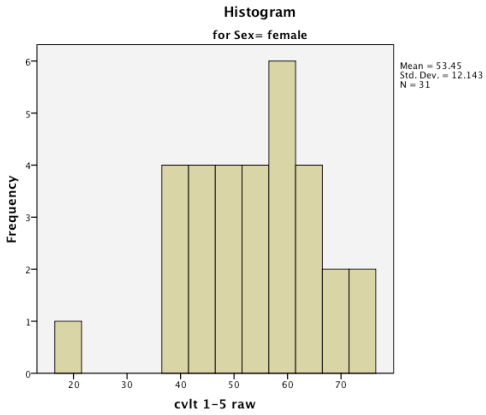
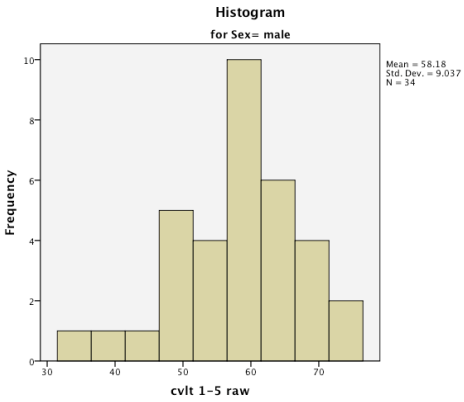
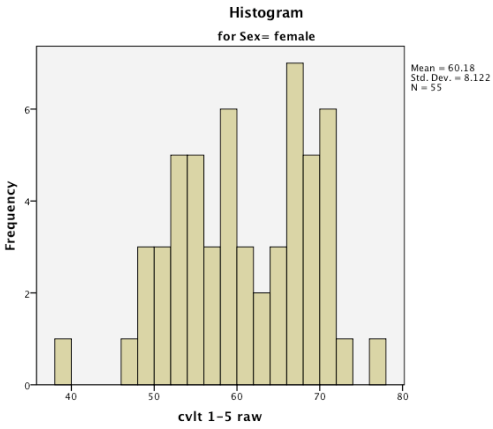


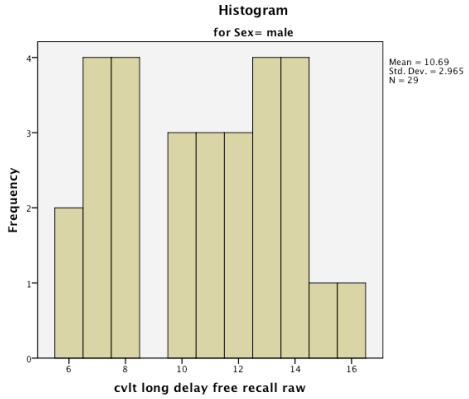
CVLT Trial 1-5: Male Controls



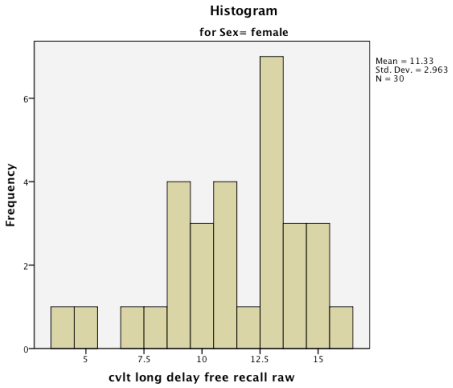
CVLT Trial 1-5: Female Controls



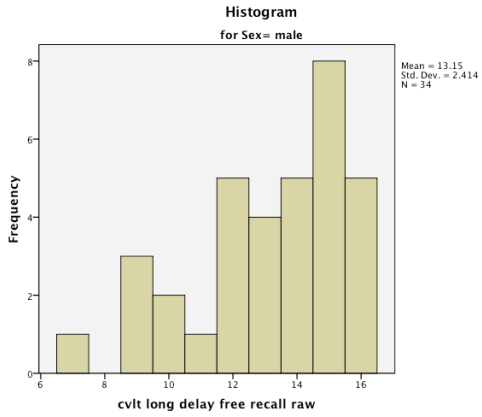
CVLT Long Delay Free Recall: Male Patients



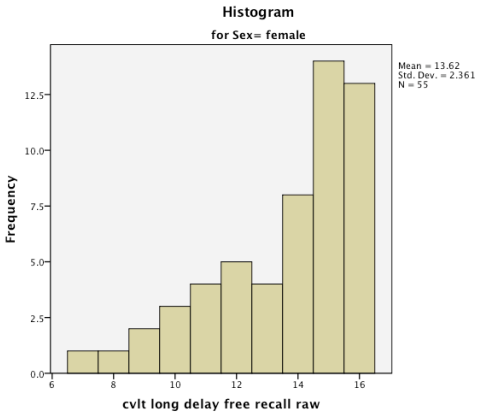
CVLT Long Delay Free Recall: Female Patients



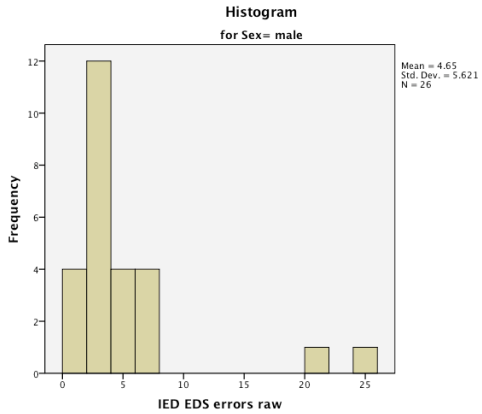
CVLT Long Delay Free Recall: Male Controls



CVLT Long Delay Free Recall: Female Controls



IED EDS Errors: Male Patients



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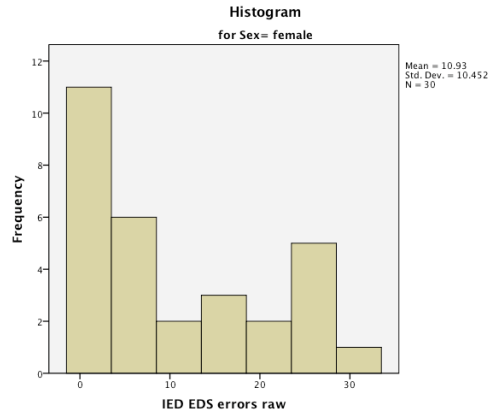

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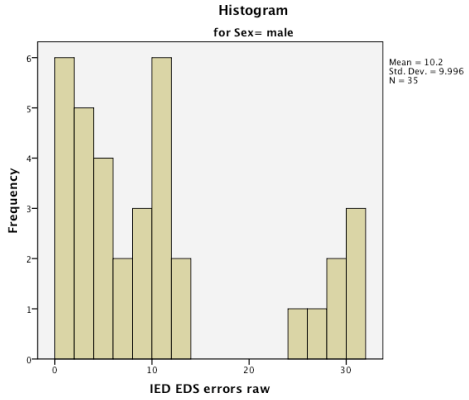
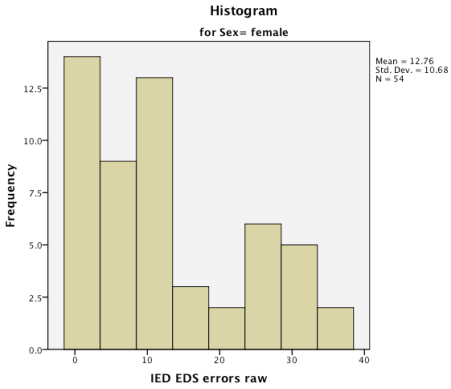
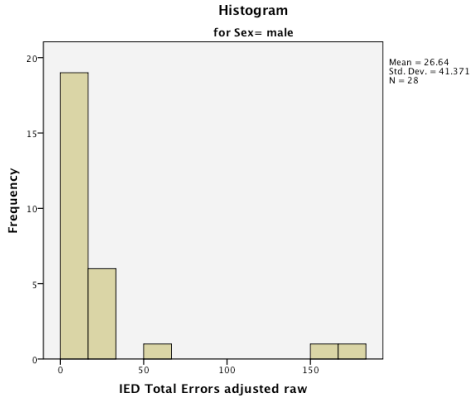


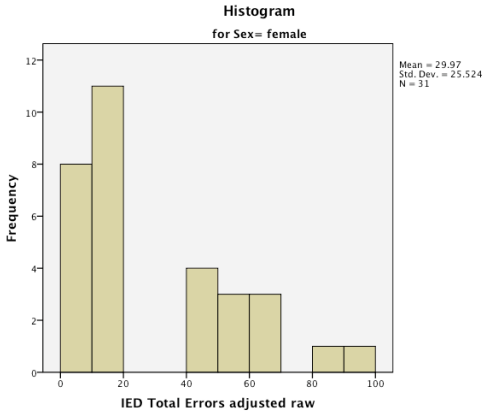
IED EDS Errors: Female Controls



IED Total Errors: Male Patients



IED Total Errors: Female Patients



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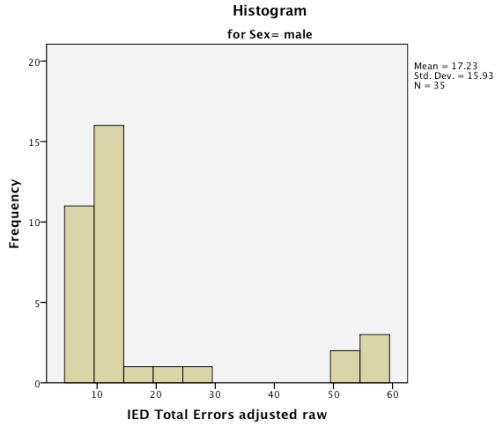
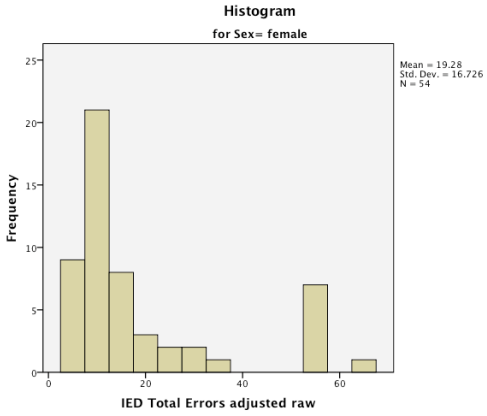
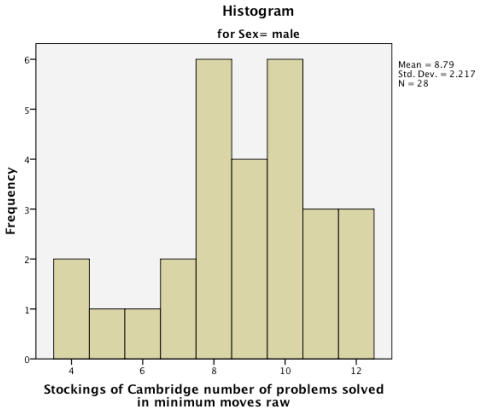


IED Total Errors: Female Controls



SOC # of Problems Solved in Min. Moves: Male Patients



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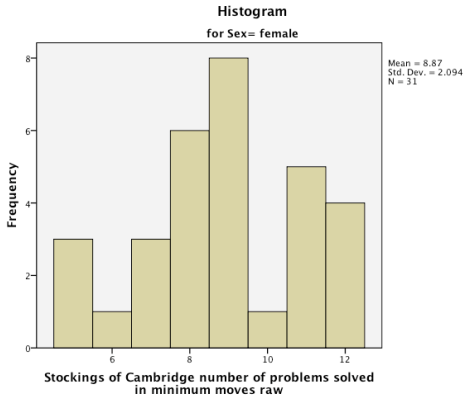

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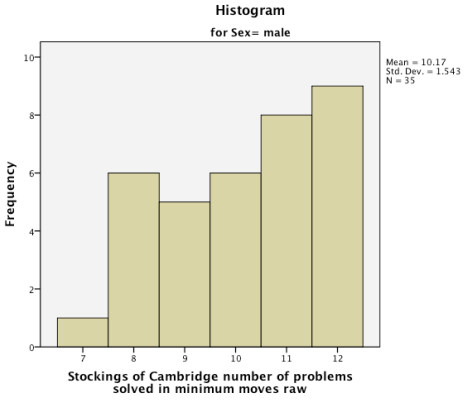
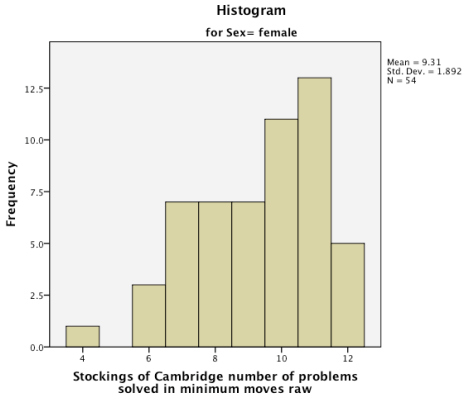
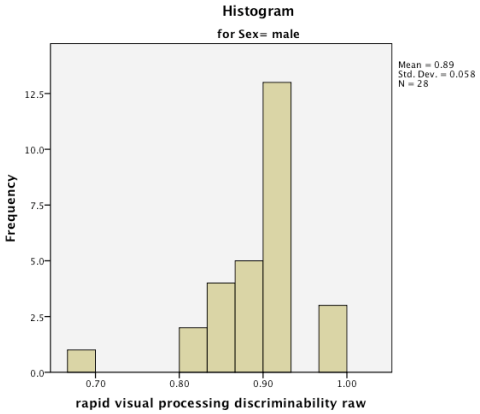


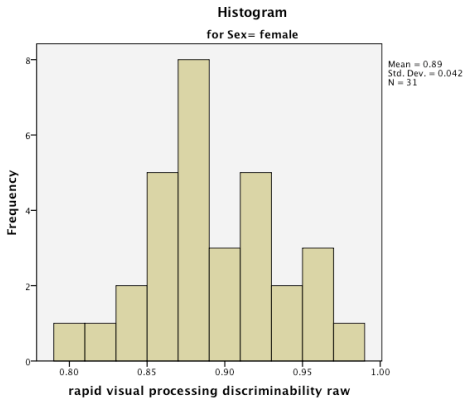
SOC # of Problems Solved in Min. Moves: Female Controls



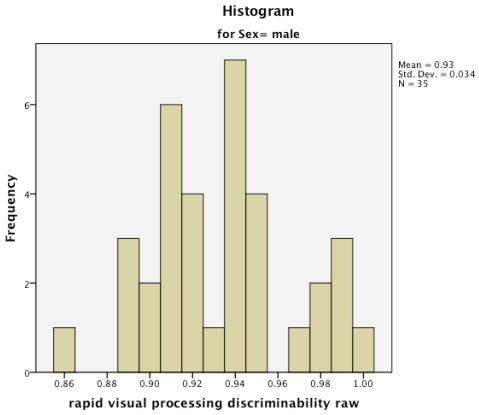
RVP Discriminability: Male Patients



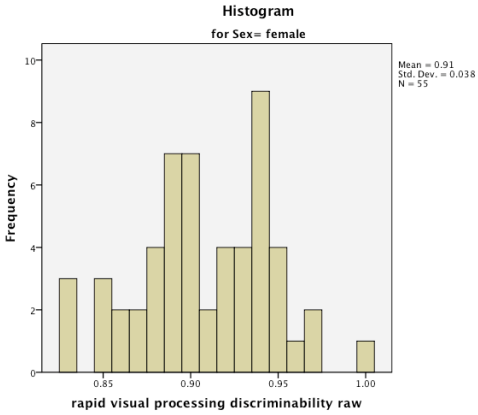
RVP Discriminability: Female Patients



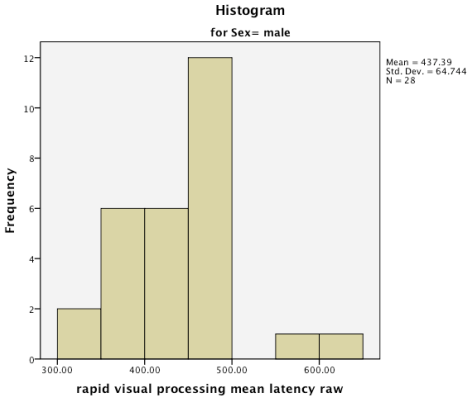
RVP Discriminability: Male Controls



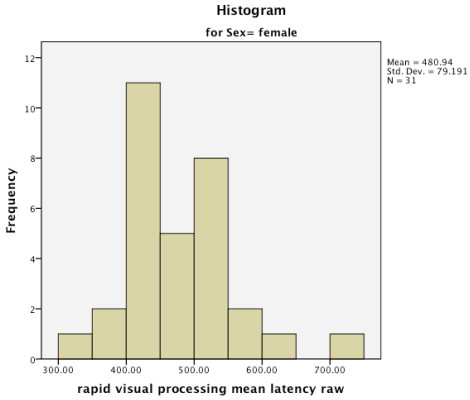
RVP Discriminability: Female Controls



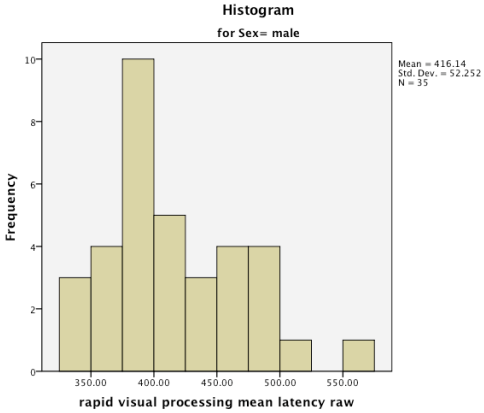
RVP Mean Latency: Male Patients



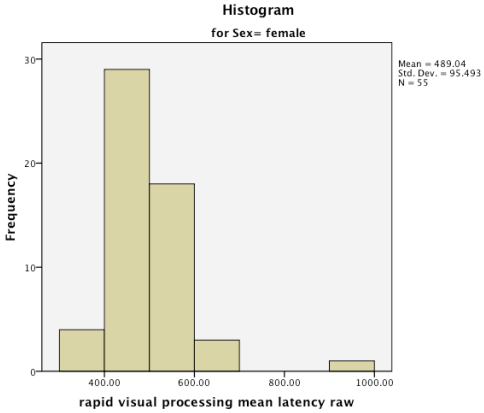
RVP Mean Latency: Female Patients



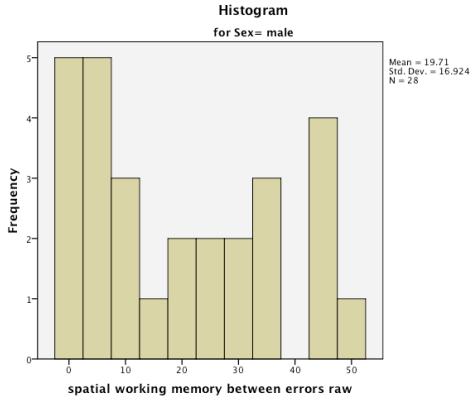
RVP Mean Latency: Male Controls



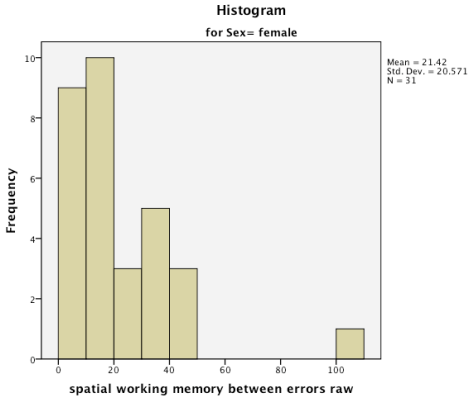
RVP Mean Latency: Female Controls



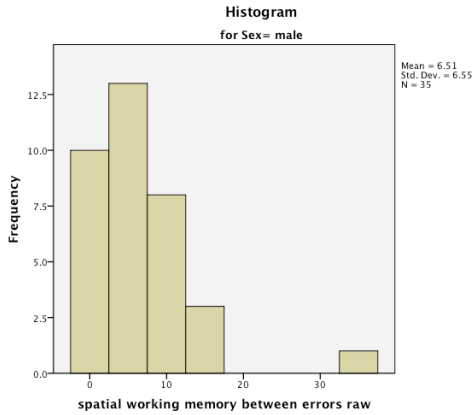
SWM Between Errors: Male Patients



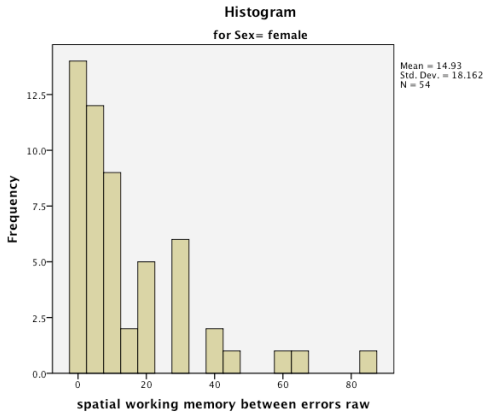
SWM Between Errors: Female Patients



SWM Between Errors: Male Controls

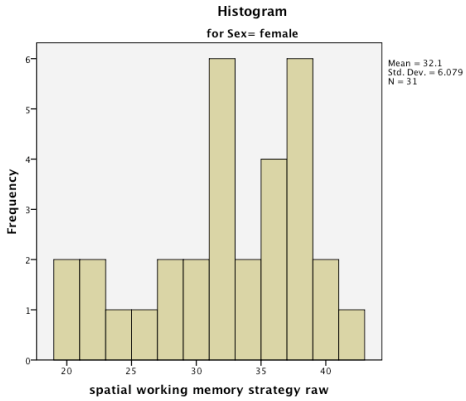


SWM Between Errors: Female Controls



SWM Strategy: Male Patients

SWM Strategy: Female Patients



SWM Strategy: Male Controls

SWM Strategy: Female Controls