Abstract

Intellectual functioning (IQ) prior to the onset of illness (premorbid IQ) and the pattern of its trajectory across illness onset can inform us of the early developmental pathology of mental disorders. The goals of this study were to 1) investigate these features in first-episode psychiatric patients with overlapping symptoms including schizophrenia (SZ), schizoaffective disorder (SA) and bipolar disorder (BD), as well as to 2) examine these features and the presence of psychosis, and the influence of mood-incongruent features, in BD patients. To address these objectives, SZ, SA, BD-I, and healthy controls, aged 17-37 years, were pooled from two early-intervention programs. The North American Adult Reading Test was used to estimate premorbid IQ, while the Kaufman Brief Intelligence Test was used to measure current IQ. Group differences in premorbid IQ and IQ trajectories were evaluated with ANOVA and repeated measure ANOVA. Both controls and BD patients had significantly higher premorbid IQ compared to SZ patients, BD patients had scores comparable to control, and there was a strong trend of premorbid IQ deficit in SA patients. Regarding IQ change, only subjects with SA and SZ experienced significant IQ deterioration through illness onset. Regarding psychosis, t-tests deciphered a strong, although insignificant, premorbid IQ difference across BD patients, with deficits seen in psychotic but not non-psychotic patients. Lastly, t-tests revealed a significant decline in IQ across psychotic BD patients with mood-congruent, and not –incongruent, features. Secondary post-hoc analyses revealed that this finding might be attributable to the type of antipsychotic that patients received. Taken together, these results suggest that early neurodevelopmental pathology, which most likely directly affects intellectual functioning, may be different in BD than in SA and SZ. Furthermore, low premorbid IQ could be a potential risk factor for psychosis.
Assessment of IQ before and after illness onset could help facilitate early identification of psychopathology and assist with patient management and care.
Preface

This thesis research was made possible with the collaborations of the Early Psychosis Identification and Intervention study, overseen by Dr. William Honer, and the Systematic Treatment Optimization Program for Early Mania study, overseen by Dr. Lakshmi Yatham, at the University of British Columbia. Participants’ data were all previously collected under Drs. Honer and Yatham’s supervision by fellow psychiatrists and research assistants. Both studies required approval from UBC’s Research Ethics Board: the EPII’s approval number is H01-70454, and STOP-EM’s approval number is H04-70169.

With the help of my supervisor Dr. Ivan Torres, I designed this thesis project and identified the research questions. I contributed to the scoring and data entry of subjects’ neurocognitive testing (including their IQ scores), I reviewed individual patient charts to collect and confirm information about their scores on clinical measures, as well as their medication history, in order to enter them in large databases. Using converging sources, I combined and recoded the data from both studies into a cohesive database to prepare them for analyses. I performed the totality of the statistical analyses, as well as the interpretation of the results with the mentoring of Dr. Torres.

While this thesis research has yet to be published, some of the participants’ data (e.g., premorbid IQ) have been used in other publications by Drs. Honer and Yatham’s respective teams.
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List of Abbreviations

Antipsychotic (AP)
Bipolar disorder (BD)
Clinical Global Impression scale (CGI)
Early Psychosis Identification and Intervention study (EPII)
Executive Functioning (EFs)
Full-scale IQ (FS-IQ)
Global Assessment of Functioning (GAF)
Gray matter density (GMD)
Hamilton Rating Scale for Depression (HAM-D)
Kaufman’s Brief Intelligence Test (K-BIT)
Mood stabilizer (MS)
National Adult Reading Test (NART)
North-American Adult Reading Test (NAART)
Positive And Negative Syndrome Scale (PANSS)
Prefrontal Cortex (PFC)
Schizoaffective disorder (SA)
Schizophrenia (SZ)
Systematic Treatment Optimization Program for Early Mania (STOP-EM)
The University of British Columbia (UBC)
Wechsler Adult Intelligence Scale (WAIS)
Wechsler Intelligence Scale for Children (WISC)
Acknowledgements

It is with immense gratitude that I acknowledge the support of my supervisor and mentor Dr. Ivan Torres. This thesis would not have been possible without his limitless patience and kind guidance. Thank you for rejuvenating my passion for research and neuropsychology, and for equipping me with the tools I need to embark on the next stage of my academic life.

I also extend my deepest appreciation to Drs. William Honer and Tim O’Connor for their incredible support through the transitory phase of my master’s degree, and for offering me the privilege of working with Dr. Torres and the Mood Disorder Unit.

I would like to thank my research committee members, Drs. Todd Woodward, Colleen Brenner, Lakshmi Yatham, and Noah Silverberg for their invaluable constructive criticism and insightful advice throughout this process. I am also incredibly indebted to Drs. Geoff Smith, Honer and Yatham, as well as the EPII and STOP-EM research teams (H. Baitz, T. Chakrabarty, J. Basivireddy, and T. Dhanoa), for sharing their databases, knowledge, and irreplaceable input.

To the remarkable individuals I met at UBC, through the Neuroscience program, and the Torres lab, I cannot thank you enough for your boundless love – your friendship means the world to me.

Last, but definitely not least, I would like to express my enduring gratitude to my family: my mother Mahnaz, my brothers Anousha and Arsham, and my rock, Charlie. Thank you for believing in me, every step of the way.
Dedication

This thesis is dedicated to my mother and best friend, Mahnaz.
Chapter 1: Introduction

1.1 Overlap among psychopathologies

For over a century, psychotic and major mood disorders have been conceptualized as two separate distinct illnesses. This approach to diagnosis stems from the Kraepelinian house of thought (Kraepelin, 1899, 1921). Popularized by the omnipresent Diagnostic and Statistical Manual of Mental Disorders (DSM), this categorization system continues to influence how patients are labelled and treated, and how research is conducted in mental health (Angst, 2007; Craddock & Owen, 2005; Häfner, Sedvall, & Angst, 1993; Weber & Engstrom, 1997). However, even Kraepelin, the renowned father of modern psychiatry, eventually admitted to the difficulties in distinguishing certain psychopathologies from one another, particularly schizophrenia and bipolar disorder (Kraepelin, 1920).

A substantial portion of research funds, time, and interest has been invested in uncovering the epidemiological, environmental, biological, and developmental etiologies of schizophrenia (SZ). Other schizophrenic-spectrum disorders, such as schizoaffective disorder (SA), or mood disorders, such as bipolar disorder (BD), have been far less studied. An essential contributing factor to the dearth of information is in the difficulty of correctly identifying SA and BD, partially due to the similarities they share with each other and SZ. The overlap between these three illnesses is discernable at symptomatic, genetic, structural brain imaging, and cognitive levels.
1.1.1 Symptomatic overlap

Clinical similarities between SZ, SA, and BD patients are evident even when patients present with an initial psychotic or manic episode. At this stage of the illness, diagnostic labels and treatment options tend to change frequently, as the nature of patients’ symptoms evolves. In individuals with BD, this fluctuation is particularly problematic as patients can only be diagnosed with this illness after the occurrence of a manic, hypomanic, or mixed episode. In the majority of cases, this occurs after an extensive history of depressive episodes, leading to many years of misdiagnosis. To further complicate things, over half of BD patients experience psychotic symptoms in their lifetime (Goodwin & Jamison, 1990), while about a quarter of SZ patients experience depression (Siris, 2000). As for SA, patients are often mistaken for SZ or BD with psychosis (Poulton et al., 2000; Sprock, 1988) until they experience two weeks of psychotic symptoms in the absence of prominent mood symptoms, as per the DSM’s definition (American Psychological Association [APA], 1994). Moreover, the predictive power of diagnostic symptoms has been questioned. Based solely on DSM-III symptoms, researchers successfully dissociated SZ from affective patients, although they misclassified about 14% of each group (Taylor & Amir, 1994). This percentage is however much bigger for SA patients, which appear to be in the range of 44% misclassification (Jahn, 2010). This is probably due to the fact that approximately 41% of their diagnostic symptom characteristics overlap with those of affective disorders and 71% with those of SZ patients (Whaley, 2002).

1.1.2 Genetic overlap

Family, twin, and individual gene studies are powerful ways to tap into the heritability and the genetic predisposition of an illness. The risks of developing either BD, SA or SZ appear to be
quite intertwined. Compared to the rest of the healthy population, BD presents more frequently amongst relatives of SZ or SA patients (Gershon et al., 1982; Lichtenstein et al., 2009; Vallès et al., 2000), SZ occurs more frequently amongst relatives of SA or BD patients (Lichtenstein et al., 2009; Vallès et al., 2000), and SA occurs more frequently amongst relatives of SZ or BD patients (Laursen et al., 2005). Evidence from twin studies further demonstrates that SA has a particularly high concordance rate with mania, the fundamental feature of BD, as well as SZ (Cardno, Rijsdijk, Sham, Murray, & McGuffin, 2002). An interesting case study of genetically identical triplets found two of the triplets to be diagnosed with SZ and one with SA-bipolar type (McGuffin, Reveley, & Holland, 1982). This phenomenon highlights the overlap that is present across these disorders. The emerging findings from individual gene studies also show similarities across these illnesses (Shao & Vawter, 2008). Genes involved in the nervous and immune systems’ development, such as neuroregulin-1 (Georgieva et al., 2008; Green et al., 2005; Li et al., 2007; Mei & Xiong, 2008; Thomson et al., 2007), BDNF (Lencz et al., 2009; Neves-Pereira et al., 2002; Post, 2007), DAOA/G30 (Bass et al., 2009; Corvin et al., 2007; Prata et al., 2008), and DISC1/2 (Hamshere et al., 2005; Hennah, Thomson, Peltonen, & Porteous, 2006; Hodgkinson et al., 2004; Thomson et al., 2005), appear to play a role in the neurodevelopment of SZ, SA and BD. Where these illnesses differ may be more evident in the various mutations of these overlapping genes, but this needs to be further investigated (Georgieva et al., 2008). Taken together, the genetic literature seems to generally support the theory that the transference of psychiatric symptoms, particularly psychosis, may not be disorder-specific.
1.1.3 Structural brain imaging overlap

In recent decades, the study of structural brain abnormalities has been of particular interest in mental illness as it helps to shed some light on the cerebral structures and systems that are involved in psychopathology. Studies generally find similar abnormalities across BD, SA and SZ, with a few distinctions that appear unique to each disorder. For instance, enlarged ventricles, sulci, and cerebellar atrophy have been noted in neuroimaging studies across all three diagnostic entities (Rieder, Mann, Weinberger, van Kammen, & Post, 1983).

A number of investigators have compared the structural brain differences between BD and SZ patients. A meta-analysis that reviewed 56 magnetic resonance imaging (MRI) studies found common gray matter deficits (GMD) in SZ and BD patients in the areas of the insula (bilaterally), and the subgenual anterior cingulate, areas involved in many cognitive tasks (e.g., Wang, Metzak, Honer, & Woodward, 2010). However, deficits in a region of the perigenual anterior cingulate (anterior Brodmann area 24), thought to underline the regulation of the amygdala and emotions (Wang et al., 2009), seemed specific to the BD population (Ellison-Wright & Bullmore, 2010). A recent study also found similar GMD reductions in frontal, parietal, insular, and cerebella cortices in both SZ and psychotic affective groups, with the latter having a particularly enlarged right posterior cingulate, and reduced cerebellar and insular volumes compared to SZ and healthy subjects (de Castro-Manglano et al., 2011). Moreover, researchers have observed amygdala enlargement in BD patients, but amygdala reduction in SZ patients; and, hippocampi reductions in SZ, which appear preserved in BD patients (Altshuler, Bartzokis, Grieder, Curran, & Mintz, 1998; Strakowski et al., 1999).
With respect to SA patients, the pattern of results shows that SA exhibits similar mediodorsal and ventrolateral abnormalities in the thalamus to SZ patients, with specific deformations in the anterior and posterior thalamus for the SZ subjects, and in the medial and lateral regions of the thalamus for SA subjects (Smith et al., 2011). Individuals with SA also seem to share similar enlargements of striatal volumes with BD patients, who have additional irregularities in the palladium (Getz et al., 2002).

Commonalities in structural anomalies are not only present in chronic patients, but they can also be detected at illness onset. Results from a first-episode psychosis/mania meta-analysis of 45 studies supported a substantial overlap across SZ and BD (De Peri et al., 2012). Intracranial, whole brain, total gray and white matter volumes were all reduced in these subjects, while lateral ventricular volume was enhanced in their MRI scans. However, total GMD deficits and ventricular enlargement were more recurrent in the SZ population, and white matter volume reduction was more frequent in BD. Taken together, these various imaging studies demonstrate a large amount of overlapping abnormalities in the brain of SZ, SA and BD patients, with a few unique features to each disorder. It is of note that most of the shared irregularities are occurring in cortical regions that are critical for executive functions (EFs), information processing, learning and memory, and affect regulation (Bearden, Hoffman, & Cannon, 2001; Ellison-Wright & Bullmore, 2009; Lu, Zhou, Keedy, Reilly, & Sweeney, 2011).

1.1.4 Cognitive overlap

A number of studies have compared the neurocognitive profiles of SZ, SA and BD individuals in specific neuropsychological functions to see if they share common findings. All three of these
entities show deficits in attention, processing speed, memory, and executive functions that differ mostly in severity rather than pattern (Amann et al., 2012; Beatty, Jocic, Monson, & Katzung, 1994; Heinrichs, Ammari, McDermid Vaz, & Miles, 2008; Reichenberg et al., 2009; Schretlen et al., 2007; Seidman et al., 2002; Selva et al., 2007; Varga, Magnusson, Flekkøy, Rønneberg, & Opjordsmoen, 2006; Zanelli et al., 2010). It is typically found that SZ patients have the worst neurocognitive functioning, BD patients show better functioning than SZ patients, and SA patients fall in between SZ and BD patients, thus following a severity continuum (Amann et al., 2012; Hill et al., 2013; Zanelli et al., 2010). The predictive power of neurocognitive measures has also been evaluated. Based on cognitive variables alone, approximately 73-91% of SZ (Dickerson, Sommerville, Origoni, Ringel, & Parente, 2001; Heinrichs et al., 2008; Tam & Liu, 2004), 74% of BD (Tam & Liu, 2004), and only 35% of SA (Heinrichs et al., 2008) patients seem to be correctly classifiable. Therefore, although variable in degree, there is a clear overlap in neurocognitive deficits across these three illnesses, and even more so with SA and SZ, than SA and BD (Cheniaux et al., 2008; Manschreck, Maher, Beaudette, & Redmond, 1997; Pagel, Baldessarini, Franklin, & Baethge, 2013).

Whereas the cognitive deficits alluded to in this section primarily pertain to specific neuropsychological deficits, the next section concentrates on more global aspects of cognitive functioning, namely intellectual functioning.

1.2 Intellectual functioning

Given the significant amount of overlap that is present in SZ, SA, and BD patients, it is increasingly difficult to continue to perceive these illnesses in a Kraepleinian fashion, as having
distinct etiologies. Nevertheless, one way to further capture a potential distinction (or similarity) between these disorders is to assess their early developmental patterns through the study of their general intellectual functioning. As the psychologist David Wechsler defined it, “intelligence is the aggregate or global capacity of the individual to act purposefully, to think rationally and to deal effectively with his environment” (Wechsler, 1944, p. 3). The intelligence quotient (IQ) represents “a score determined by one’s performance on a standardized intelligence test relative to the average performance of others of the same age” (Neisser et al., 1996). Scores on these standardized tests are then typically converted to a scale with a mean of 100 and a standard deviation of 15 (Neisser et al., 1996).

At the neuroanatomy level, IQ is closely associated with the brain’s architecture, such as GMD (Ramsden, Richardson, Josse, & Thomas, 2011), brain volume (Willerman, Schultz, Neal Rutledge, & Bigler, 1991), and cortical thickness (Burgaleta, Johnson, Waber, Colom, & Karama, 2014). At the level of illness expression, IQ levels are good indicators of the severity of an illness, and patients’ social and occupational functioning (Kremen, Seidman, Faraone, & Tsuang, 2008; Leeson et al., 2011). Furthermore, levels of pre-illness IQ (or IQ before the presentation of psychotic or manic symptoms, premorbid IQ) and change in IQ through illness onset can provide etiological clues into a disorder’s developmental abnormalities. On one hand, illness-related genetic predispositions or early brain pathology may result in lowering of IQ scores even prior to illness onset by affecting the neurochemical balance or cognitive potential of a person during brain maturation (Goldstein et al., 2000; Randall, 1983; Thompson et al., 2001; Toga & Thompson, 2005). On the other hand, neurodevelopmental progression of brain dysfunction may lead to further or faster decline in IQ from premorbid to post-illness onset.
states, as is the case in some congenital disorders (Levine, Kraus, Alexander, Suriyakham, & Huttenlocher, 2005). For all the above reasons, the study of IQ and psychopathology has been a main interest in psychiatry.

1.2.1 Current intellectual functioning across disorders

The expansive schizophrenic-spectrum literature has consistently demonstrated patients to have low IQ levels and poor performance on a vast number of neurocognitive tests, both in symptomatic and stable states, when compared to healthy controls and to mood disorder patients (Altshuler et al., 2004; Barrett, Mulholland, Cooper, & Rushe, 2009; Bildner et al., 2000; Hill et al., 2009; Meier et al., 2014; Zanelli et al., 2010). Most prior studies have treated SZ and SA as the same subject group in their analyses (Anderson et al., 2013; Bildner et al., 2000; Faber et al., 2011; Faerden et al., 2009; Shad, Muddasani, Prasad, Sweeney, & Keshavan, 2004; Zhang et al., 2013), but the few studies that have examine SA’s profile, separately, found that, symptomatically and cognitively, these individuals fall somewhere in between SZ and BD patients (Benabarre et al., 2001; Conus et al., 2010; Cotton et al., 2013; Pagel et al., 2013). However, contradictory findings have emerged in regards to SA’s intellectual profile: while one study found their IQ to be lower than those of psychotic BD and healthy controls (DeRosse, Burdick, Lencz, Siris, & Malhotra, 2013), another found current IQ scores to be higher in SA than BD (Pagel et al., 2013). Similarly in BD, some studies show that patients’ current IQ scores do not deviate far from those of healthy individuals (Robinson et al., 2006; Torres et al., 2010; Zanelli et al., 2010), while others find BD individuals to have slightly lower IQ scores compared to healthy controls (Barrett et al., 2009; Bora, Yucel, & Pantelis, 2009; Bourne et al., 2013).
1.2.2 Premorbid intellectual functioning

1.2.2.1 Cohort studies

Conscript cohorts can provide useful information on individuals’ intellectual and physical profiles at the peak of their health. Findings from Finnish (Tiihonen et al., 2005), Swedish (David, Malmberg, Brandt, Allebeck, & Lewis, 1997; Zammit et al., 2004), and Israeli (Reichenberg et al., 2002; Reichenberg et al., 2008) cohorts have all found that IQ and neurocognitive functioning levels of adolescents who later develop SZ are significantly lower than those who do not develop a mental illness, even after adjusting for social, behavioral, and demographical confounders. Moreover, before and after the onset of illness, both SZ and SA patients show impairments on certain intellectual measures (e.g., executive functions, verbal ability and mathematical reasoning tasks) compared to psychotic and non-psychotic BD patients, and healthy controls (Reichenberg et al., 2002, 2009). The adolescent profiles of BD patients are less clear as some researchers found above-average IQ and cognitive premorbid levels (Reichenberg et al., 2008; Tiihonen et al., 2005), while others did not find any differences from controls (Reichenberg et al., 2002; Zammit et al., 2004). Conscript cohorts can thus inform us about the potential cognitive features that are present in teenagers who later develop psychopathologies. These studies are however limited by their shortage of female subjects, and their exclusion of individuals with physical and learning disabilities.

Birth cohort studies can make up for some of conscripts’ shortcomings by tracing the development of a representative sample of the population from an earlier age. Similar to military cohorts, results from the New Zealand (Koenan et al., 2009; Meier et al., 2014), New England (Seidman et al., 2013; Seidman, Buka, Goldstein, & Tsuang, 2006), and British (Schulz, Sundin,
Leask, & Done, 2014) birth cohort studies showed that low childhood IQ, as measured by the Wechsler Intelligence Scale for Children (WISC), is associated with an increased risk of developing adult SZ. This finding may also hold true for SA adults, as both bipolar and depressed subtypes of SA show a trend for lower childhood IQ than healthy individuals (Seidman et al., 2013). As for the BD population, contradictory information emerged once again, with one study finding that high IQ increased the risk for mania in adulthood (Koenan et al., 2009), while another found a trend for low childhood IQ in psychotic and non-psychotic BD patients compared to controls (Seidman et al., 2013).

Together, these studies demonstrate that individuals with low pre-illness IQ might be at risk of developing SZ or SA. However, the question of what happens to premorbid intellectual functioning at the onset of illness cannot be answered by cohort studies.

1.2.2.2 First-episode studies

First-episode studies can help with cohort studies’ main limitation. They offer a window into the cognitive profiles of patients at illness onset, prior to the effects of treatment and recurrent episodes. Although first-episode datasets do not typically have pre-illness IQ scores of patients available before the onset of their psychosis or mania, they can rely on measures such as the National Adult Reading Test (NART) to estimate premorbid IQ (discussed in Section 3.2.1). The results of these studies generally show that premorbid IQ is relatively low in SZ subjects compared to controls and mood disorder patients (Anderson et al., 2013; Barrett et al., 2009; Bildner et al., 2000; Zanelli et al., 2010), and comparable to controls in BD patients (e.g., Torres et al., 2010). To date, none of the first-episode studies have teased apart IQ in SA specifically.
In sum, the integrated literature on premorbid intellectual functioning indicates that individuals who later develop SZ (or possibly SA) typically show deficits in premorbid IQ levels, while those who develop BD show small or no deficits. This pattern of premorbid intellectual functioning suggests that patients who consistently show low pre-illness IQ may have more early developmental pathology than mood disorder patients.

1.2.3 Trajectory of intellectual functioning in psychopathology

As was pointed out in Section 1.1, all three illnesses show neuroanatomical, genetic and cognitive abnormalities that generally overlap. What is less clear is whether these overlapping features predate the onset of psychotic and/or manic symptoms or whether they develop in conjunction with the onset of the illnesses. Thus, tracing the trajectory of IQ change could be helpful in deciphering potential etiological differences between BD, SA and SZ.

The comparison of post-illness IQ scores to IQ scores taken premorbidly, as measured by common instruments such as the Wechsler Adult Intelligence Scale (WAIS) and the WISC for instance, is the ideal way to examine change in IQ across illness development. However, pre- and post- onset IQ data are rarely available. Two birth cohort studies (Meier et al., 2014; Seidman et al., 2006) that utilized this approach illustrated that those individuals who developed SZ as adults experienced a decline in IQ from their childhood level. A more common method of determining intellectual patterns is by means of premorbid IQ estimates. For example, datasets from first-episode programs have investigated IQ change by comparing scores obtained on a current IQ measure such as the WAIS to premorbid estimates of IQ such as the NART. Similar
to cohort studies, their results generally demonstrate IQ decline in SZ, psychotic-BD, and other psychotic disorders at illness onset (Barrett et al., 2009; Leeson et al., 2011; Townsend, Malla, & Norman, 2001; Zanelli et al., 2010). However, IQ change has not been investigated in other psychiatric illnesses, such as non-psychotic BD and SA individuals.

Up until now, our discussion has been about the potential for diverging IQ patterns to distinguish amongst different diagnostic entities. Findings of unique IQ patterns among different groups can thus serve to validate the grouping of patients into diagnostic categories, and to provide some etiological clues into the illnesses. Another possibility is that individual symptom dimensions or characteristics may better separate patients into etiologically meaningful groups. For example, presence of psychosis, rather than diagnostic category, may be a better way to identify subsets of patients, and this could be revealed by differential patterns of IQ across these subtests of patients. The following section describes psychosis and the association with IQ.

1.3 Psychosis in psychopathology

A main issue in psychiatry is the level of heterogeneity that is present between and within each diagnostic category. Individuals with SA, for example, can have little in common with each other since the range of diagnostic criteria is very broad. In fact, the symptomatic and cognitive profiles, as well as treatment response, of one patient can be notably different from those of another patient. One core clinical feature that is influential to patients’ overall functioning is psychosis. The DSM defines psychosis as “delusions, hallucinations, disorganized speech, or disorganized or catatonic behavior” (APA, 1994), all of which can be found in SZ, SA and BD. Importantly, across all three patient groups, a prominent theme that emerges is that overlap
occurs most when psychosis is present in these pathologies. For instance, mood disorder patients who experience psychosis share a lot more structural abnormalities with SZ and SA patients than their non-psychotic counterparts (McDonald et al., 2004; Pearlson et al., 1995; Salokangas et al., 2002). Frontal and temporo-parietal white matter volume reduction (McDonald et al., 2004) and enhanced dopamine receptor density levels (Pearlson et al., 1995) occur at similar levels in both psychotic BD and SZ patients, but not non-psychotic BD subjects. Enlarged cerebral ventricles have been observed in the MRIs of patients with SZ and psychotic depression, but not in those depressed patients without psychotic features (Salokangas et al., 2002). These findings exemplify the overlap that emerges with the presence of psychotic symptoms.

### 1.3.1 Psychosis and intellectual functioning

In addition to being a core clinical feature of SZ, SA, and most BD individuals, psychosis appears to be associated with preferential brain dysfunction (Chan, Di, McAlonan, & Gong, 2011) and possible IQ deterioration (Townsend et al., 2001; Woodberry, Giuliano, & Seidman, 2008). In SZ, a significant decline in intellectual functioning is recognized at the onset of psychosis (Townsend et al., 2001). Although, this relationship remains unclear in SA and BD patients, the literature has found psychosis to considerably affect individuals’ overall functioning. Age of onset, length and severity of illness, and neurocognitive performance are all variables that appear to be associated with the presence of psychotic symptoms (Bora, Yücel, & Pantelis, 2010; Martínez-Arán et al., 2004; Simonsen et al., 2010, 2011; Wigman et al., 2012). In a general fashion, a longitudinal study demonstrated that non-clinical psychotic symptoms experienced at age 12 years correlated with low but not high IQ at age 8 years (Horwood et al., 2008).
The influence of psychosis can be particularly informative when evaluated in a disorder such as BD, in which patients can present with or without psychotic symptoms. Amongst BD specifically, patients with a history of psychosis tend to have worse social functioning (Rosen, Rosenthal, Dunner, & Fieve, 1983) and poorer performance on neurocognitive measures, such as verbal memory (Bora et al., 2010; Martínez-Arán et al., 2004; Simonsen et al., 2010, 2011), verbal fluency (Simonsen et al., 2010, 2011); working memory (Bora et al., 2010; Simonsen et al., 2010, 2011), inhibition (Simonsen et al., 2010, 2011), planning and reasoning (Bora et al., 2010), and cognitive flexibility (Bora et al., 2007, 2010). In fact, certain researchers have found the neurocognitive and intellectual profiles of psychotic BD patients to resemble that of SZ and SA patients, showing deficits in current IQ scores (Reichenberg et al., 2009; Simonsen et al., 2010), and the profile of non-psychotic BD patients to resemble that of healthy controls, both showing average premorbid and current IQ levels (Reichenberg et al., 2002; Simonsen et al., 2010, 2011). Since these skills are important to everyday functioning, psychosis is an important characteristic to identify in the early stage of affective disorders.

One study that compared psychotic and non-psychotic chronic BD patients on current IQ measures found a trend for higher IQ in non-psychotic patients than in psychotic patients (Simonsen et al., 2011). No study, however, has compared these BD subgroups directly on premorbid IQ measures, nor has any study examined IQ change across the two groups.

1.3.2 Mood congruency of psychosis

The significance of the presence of psychotic symptoms can be further scrutinized by investigating the concept of congruence. In affective disorders such as BD, patients who
experience psychosis can have one of two types of psychotic features: mood-congruent, where there is a correspondence between their psychosis and the type of mood episode they are experiencing (manic or depressive), or mood-incongruent, where the psychotic experience is not consistent with the subject’s mood episode. Although understudied, individuals with mood-incongruent psychosis have been shown to have worse functional outcome (Harrow, Grossman, Herbener, & Davies, 2000; Strakowski et al., 2000; Tohen, Tsuang, & Goodwin, 1992), shorter remission time (Azorin, Akiskal, & Hantouche, 2006; Strakowski et al., 2000; Tohen et al., 1992) and more hospitalizations (Goes, 2007; Mazzarini et al., 2010) than patients with mood-congruent features and those without any psychosis. As more studies on mood congruency emerge, it is becoming evident that it may be an important factor to take into account when considering the full clinical profile of patients for diagnosis and treatment options (Gonzalez-Pinto et al., 1998). None of the studies that have examined mood congruency in SA or BD populations have investigated its relation to intellectual or other cognitive functioning.

1.4 Unresolved research questions

1.4.1 Premorbid IQ across diagnoses

Although deficits in premorbid intellectual functioning in SZ patients have been corroborated across a number of cohort and first-episode studies (Anderson et al., 2013; Barrett et al., 2009; Bildner et al., 2000; David et al., 1997; Koenan et al., 2009; Meier et al., 2014; Reichenberg et al., 2002; Schulz et al., 2014; Seidman et al., 2006; Tiihonen et al., 2005; Zammit et al., 2004; Zanelli et al., 2010), pre-illness IQ levels of SA and BD patients have yet to be firmly established. While research hints at low levels of IQ in SA (Seidman et al., 2013; Wilson, Nian, & Heckers, 2014), findings for BD are more variable; some have noted high premorbid IQ
(Koenan et al., 2009; Reichenberg et al., 2008), others low (Seidman et al., 2013), and still others average IQ scores (Torres et al., 2010). Thus, some clarification, particularly with respect to SA and BD patients, needs to be made about premorbid IQ in psychopathology.

1.4.2 IQ trajectories across diagnoses

Multiple studies have shown that patients with SZ have a low premorbid IQ that typically continues to deteriorate at the first psychotic episode (see Section 1.2). The trajectory of IQ across illness onset is however unclear in SA and BD patients. As previously mentioned, most studies fail to untangle the differences between SZ and SA in their analyses and results (Anderson et al., 2013; Bildner et al., 2000; Faber et al., 2011; Faerden et al., 2009; Shad et al., 2004; Zhang et al., 2013), despite the fact that there are certain symptomatic and cognitive discrepancies between the two diagnostic groups (Conus et al., 2010; Cotton et al., 2013; DeRosse et al., 2013; Pagel et al., 2013). With respect to BD, none of the existing first-episode mania studies have investigated IQ change across illness onset.

1.4.3 The role of psychosis in intellectual functioning

In order to examine the association between psychosis and intellectual functioning, a comparison between psychotic and non-psychotic individuals must take place. The only patient group for which this is possible is BD. Although a few studies have deciphered the neurocognitive differences between psychotic and non-psychotic BD patients (Bora et al., 2007; Martínez-Arán et al., 2004; Simonsen et al., 2010, 2011), only one has compared chronic patients on current IQ scores (Simonsen et al., 2011), no valid study has compared them on premorbid IQ scores, and none have reported on how these groups differed on trajectories of IQ change across illness.
onset. Furthermore, there has not been a single study that has teased apart the relationship between premorbid IQ or IQ trajectories and mood congruency.

1.5 Goal of the study

Given the significant cognitive, structural, genetic, and symptomatic overlap that is present in SZ, SA and BD individuals, I proposed to use the objective and stable measure of IQ to help determine if any of the neurodevelopmental mechanisms of these illnesses is truly distinct. To accomplish this, I used naturalistic datasets from first-episode psychosis and first-episode mania programs to capture the early cognitive decrements of psychopathology at illness onset, a stage that is deprived of the complex effects of chronic treatment and recurrent episodes.

In sum, with this thesis, I proposed to 1) investigate premorbid intellectual functioning (IQ) and estimated change in IQ from the premorbid to illness onset periods in first-episode patients with SZ, SA and BD, as well as to 2) examine the relationship between psychosis (and mood incongruence) and premorbid IQ and IQ change in BD patients.
Chapter 2: Aims of the study

2.1 Aim 1: intellectual functioning across illness onset

The first aim of this study was to examine premorbid IQ and estimated change in IQ across illness onset in first-episode SZ, SA and BD patients.

2.1.1 Aim 1, hypothesis 1: premorbid IQ across diagnostic groups

Considering the direction of the current evidence on the cognitive, genetic, symptomatic and structural overlap that exist across these three illnesses, I proposed that patients with SZ, SA, and BD might share some developmental problems, but that the intellectual pattern of SA and SZ patients would be more similar to each other than to individuals with BD. Therefore my first hypothesis was that SZ and SA patients had lower premorbid IQ scores compared to individuals with BD and healthy controls. To test my hypothesis, I used the North American Adult Reading Test (NAART) to compare estimated premorbid IQ scores of patients with SZ, SA, and BD to those of healthy controls.

2.1.2 Aim 1, hypothesis 2: IQ change across diagnostic groups

The second step to determining if SZ, SA, and BD share a similar developmental course was to explore their trajectories of intellectual functioning. Most studies report a substantial worsening in functional and occupational outcome at the onset of psychosis for individuals with SZ and other psychoses (such as SA), but less so in mood disorders (DeRosse et al., 2013; Meier et al., 2014; Seidman et al., 2006). Hence, based on the existing literature, my second hypothesis for this first aim was that a) the IQ of all patient groups decline compared to healthy controls, and
that b) SZ patients experience the largest decline in IQ and BD patients the smallest decline in IQ. To measure the change in intellectual functioning across illness onset, I examined the change from premorbid IQ estimates, provided by the NAART, to current IQ levels, as measured by the Kaufman Brief Intelligence Test (K-BIT), in controls, and each patient group.

2.2 Aim 2: psychosis and intellectual function

Differences in premorbid IQ deficits or IQ declines at the illness onset period may not be tied to different diagnoses, but rather to the presence or absence of psychosis. Thus, the second aim of this thesis was to explore this latter model, and to untangle the relationship between intellectual functioning and psychosis.

2.2.1 Aim 2, hypothesis 1: premorbid IQ and psychosis

The current evidence from the literature supports the idea that psychotic BD patients might have more cognitive dysfunction than non-psychotic BD patients. Given the reported similarities between SZ and psychotic BD patients, I proposed that low premorbid IQ and the manifestation of psychosis are correlated. I hypothesized that patients with psychosis have lower premorbid IQ (suggesting more neurodevelopmental pathology) than those without psychosis. To test this, I measured the association between the occurrence of psychosis and premorbid NAART IQ in BD patients, the only subject group containing both patients with and without psychosis.

2.2.2 Aim 2, hypothesis 2: the effect of psychosis on IQ change

Given the strong evidence for psychosis’ negative impact on patients’ overall functioning, I proposed that IQ deteriorates more at the onset of psychosis then at the onset of mania alone.
Thus, **my second hypothesis for this second aim** was that BD patients who experience psychotic symptoms have a steeper decline in IQ levels, from premorbid to current scores, compared to their non-psychotic counterparts. **To test this,** I examined the trajectory of IQ change in psychotic and non-psychotic BD patients using K-BIT and NAART scores.

### 2.2.3 Aim 2, hypothesis 3: mood congruency and IQ

Information about the mood congruency features of a psychotic episode can add a layer of precision to the overall knowledge of a mental patient’s schema. In BD, patients with mood-incongruent psychosis typically have earlier illness onset, shorter remission times and worse prognosis than patients experiencing mood-congruent psychosis (Harrow et al., 2000; Strakowski et al., 2000; Tohen et al., 1992). Therefore, I proposed that mood-incongruent psychotic features affect IQ more negatively than mood-congruent features, both premorbidly and at the onset of illness. In other words, **my third hypothesis for this second aim** was that **a)** BD patients with mood-congruent psychosis had higher NAART-predicted IQ scores than those with mood-incongruent psychosis, and that **b)** mood-incongruent BD patients had steeper IQ decline than those with mood-congruent psychosis. **To test this,** I examined the difference in NAART scores across both subgroups of psychotic BD patients, and the trajectory of IQ change using K-BIT and NAART scores.
Chapter 3: Methods

3.1 Participants

Subjects, aged 17-37, were pooled from two early-interventions programs: the Early Psychosis Identification and Intervention (EPII) study (Smith et al., 2009), and the Systematic Treatment Optimization Program for Early Mania (STOP-EM) program (Yatham, Kauer-Sant’Anna, Bond, Lam, & Torres, 2009). The EPII was conducted in the South Fraser Health Region, which comprises Surrey, White Rock, Delta, and Langley in British Columbia. Its primary goal was to investigate risk factors and predictors for recovery from a first episode of psychosis. The study involved following patients’ overall functioning for a period of time of 9-12 months, and was conducted from 2002 until 2009. The prospective naturalistic STOP-EM program is conducted at the University of British Columbia (UBC) and it prioritizes the study of clinical and functional outcomes and cognition in patients experiencing their first manic episode over a 20-year follow-up. It started in 2004 and has been actively recruiting since then. For both the EPII and the STOP-EM studies, subjects were recruited through UBC and Vancouver General Hospital and affiliated sites, as well as through physician and psychiatrist referrals. Both the EPII and the STOP-EM program were approved by the University of British Columbia Clinical Research Ethics Board, and written informed consent was obtained from each participating subject.

Baseline assessments of physical and mental abilities were conducted at the earliest point after the diagnosis of a psychotic or manic episode. This included socio-demographic interview, clinical (mood) scales, psychiatric diagnosis, physical examination, medical investigations, neurocognitive testing, neuroimaging (i.e., MRI scan) and blood sampling for genetic material.
Patients were tested on neurocognitive measures when they were stable/euthymic enough to concentrate and attend to the tasks at hand.

Information from both the EPII and the STOP-EM programs were maintained in separate, locked facilities. Participants from both studies were assigned a random subject number, and their name, initials, date of birth, and other personal identifiers were kept separate from their data, blood samples and results.

3.1.1 Diagnosis

Patients experiencing their first-episode of psychosis and/or mania typically show symptoms that tend to fluctuate in nature and severity. For this reason, diagnosis was established at enrollment and revised, as deemed necessary, during follow-up visits. Diagnoses of patients in the EPII study were determined during multi-disciplinary conferences as more information about each patient’s symptoms became available throughout the study. This integrated diagnostic decision was made based on the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 2012). In the STOP-EM study, a psychiatrist confirmed their diagnosis using their clinical expertise and the DSM-IV, as well as the Mini International Neuropsychiatric Interview (Sheehan et al., 1997) during the initial appointment. Across both studies, diagnostic decisions were reinforced with comprehensive assessments of both personal and family history of physical, neurological and psychiatric disorders. When possible, this assessment was complemented with an interview with a family member for information on patients’ birth, development, and onset of illness.
3.1.2 Psychosis

In each dataset, the presence of psychosis, and whether psychotic symptoms were mood-congruent or incongruent, was coded for each BD patient. Subjects were classified as psychotic if they demonstrated symptoms of delusion, hallucination or formal thought disorder based on clinical presentation, chart review and multidisciplinary conference notes. All subjects, bar one, who had a thought disorder also had either delusions or hallucinations. Furthermore, across both STOP-EM and EPII studies, if psychosis was present in BD patients, symptoms were classified as congruent if they met the following DSM-IV criteria: “delusions or hallucinations whose content is consistent with the typical manic themes of inflated worth, power, knowledge, identity, or special relationship to a deity (e.g., God's voice may be heard explaining that the person has a special mission) or famous person” (APA, 1994). BD patients were classified as incongruent if they met the following DSM-IV criteria: delusions or hallucinations whose content do not involve typical manic themes, rather included are symptoms such as “persecutory delusions (not directly related to grandiose themes), delusions of thought insertion/broadcasting (e.g., others can hear one's thoughts), and delusions of being controlled” (APA, 1994).

Individuals who presented with a thought disorder (e.g., pressure of speech or flight of ideas) were classified as mood-congruent. Patients who presented with both congruent and incongruent psychotic features (n = 4 from STOP-EM, n = 2 from EPII) were categorized as having incongruent features. In the EPII dataset, the final decision of BD patients’ psychotic features was made by the principal investigator psychiatrist based on a symptom checklist that was completed at the end of each case conference, after all of the available information had been presented. In the STOP-EM dataset, classifications were based on a psychiatrist’s review of each patient’s full symptom profile, chart notes and discharge summaries.
3.1.3 Inclusion and exclusion criteria

3.1.3.1 Inclusion criteria in the first-episode programs

For both first-episode programs, only subjects who could comprehend and comply with the protocol, and who could give written informed consent, were admitted into the studies. The EPII program included male and female patients and healthy controls who were under the age of 45 years. Patients were eligible to participate in the study if they had experienced a first unresolved psychotic episode, whether they were in- or outpatients, with or without any comorbidities. Participants received $5 for completing baseline neurocognitive testing, $20 for the MRI scan, and were refunded their transportation fee (parking/public transit) to the research facility. The STOP-EM program included male and female patients and healthy controls between the ages of 14 and 35 years. Patients who were currently experiencing or had experienced a first DSM-IV defined manic or mixed episode within the past 3 months were eligible to participate in the study. All in-and outpatients were included, whether or not they had experienced any psychotic features or if they had any comorbidities. Participants were compensated with $25 for completing their baseline neurocognitive assessment, $25 for the MRI scan, and $10 for their transportation, for a total of $60, or $50 if they were inpatients. The liberal inclusion criteria in these first-episode programs allowed for a better representation of the full scope of patients who are routinely seen in clinical practice.

3.1.3.2 Exclusion criteria in the first-episode programs

The STOP-EM study excluded individuals who had a previous manic or mixed episode over three months before the baseline assessment. The EPII program did not exclude patients based on the length of their first psychotic episode, but rather on the extent of treatment received prior
to their entry to the study. At the time of referral, all patients were in their first episode of illness but the duration of that first episode varied depending on the time needed to obtain a patient’s approval for psychiatric treatment and to acquire a referral. The variability in psychosis length is not surprising as it is representative of actual patient profiles in regular clinical settings. To date, no significant correlation has been found between duration of untreated psychosis and IQ or change in IQ (Barnes, 2000). In most cases, patients from the EPII database either had no previous antipsychotic trial or there was an ongoing trial that, based on the chart records, was estimated to have lasted less than 8 weeks. However, this is an approximation as for some patients there was not enough data to confidently evaluate the length of treatment each patient had before the start of the study.

Across both first-episode programs, controls were excluded if they, or their first-degree relative, had a history of mental illness.

3.1.3.3 Inclusion and exclusion for this study

The EPII and STOP-EM projects included a variety of individuals who presented with psychotic and/or manic symptoms. The inclusion criteria that were enforced for this thesis were the following: male and female subjects aged 17-37 years, who were fluent in the English language. Both in- and outpatients with verified diagnoses of SZ, SA and BD-I were included, whether or not they had psychosis or any comorbidities. Excluded were subjects who were not primary users of the English language and those with a history of identified reading disability (e.g., dyslexia), as these problems can affect NAART and K-BIT scores. I also excluded subjects with significant head injuries, neurological disorders, or mental retardation. The initial pool of potential subjects
from the STOP-EM study was of 83 BD-I, 1 SA and 45 controls. Of those, 14 BD-I and 5 controls were removed due to one or more of the exclusion criteria (i.e., age, non-English speakers, reading disability, neurological disorders, controls’ first-degree relatives with psychiatry diagnoses), leaving 69 BD-I patients, 1 SA and 40 controls. The initial pool of potential subjects from the EPII study was of 57 SZ patients, 18 SA patients, 16 BD-I patients and 78 controls. Of those, 14 SZ, 1 SA, 2 BD-I and 31 controls were removed due to one or more of the exclusion criteria, leaving 43 SZ, 17 SA, 14 BD-I and 47 controls. The final number of participants included for this thesis was \( N = 231 \), of which 87 were healthy controls, 83 BD-I, 43 were patients with SZ and 18 were patients with SA. From the EPII study, 14 BD with psychosis were included and from the STOP-EM study 69 BD patients were included, of which 53 had a history of psychosis, for a total of 83 BD-I across both programs. Of the patients with BD-I with psychosis, a total of 34 had mood-congruent psychosis (11 from the EPII program, 23 from the STOP-EM program), and 33 had mood-incongruent psychosis (3 from the EPII program, 30 from the STOP-EM program).

### 3.1.3.4 Matching of controls

Healthy control subjects were selected to match first-episode mania patients on factors of age and sex in the STOP-EM program. In the EPII study however, controls were not matched to first-episode psychosis patients at recruitment; they simply had to meet the inclusion and exclusion criteria. For this study, I included 40 controls from the STOP-EM program and 47 from the EPII program, for a total of 87 controls.
3.2 Data collection

The EPII and the STOP-EM programs collected extensive demographic, clinical, and cognitive data that were transferred into computerized databases. All relevant information from the amalgam of paper and digital files were corroborated, and then organized into a cohesive database that included key variables from both studies. All variables were recoded to facilitate statistical analyses. Data entry and calculations for the neurocognitive measures (and IQs) were scored and double-checked by at least two different trained raters. The data of all subjects were anonymized from the start of each study by using randomly assigned identification numbers. Moreover, subject’s names were kept separate from their data at all times. Documentation on all subjects was maintained in locked facilities for each study.

3.2.1 IQ assessments

3.2.1.1 Estimate of premorbid IQ

For this study, we used a version of the original British National Adult Reading Test (NART) (Nelson, 1982) to estimate premorbid IQ in North-American patient and controls subjects (Blair & Spreen, 1989). The North American Adult Reading Test (NAART) requires subjects to read, out-loud, 61 short irregular words that are scored for accuracy based on Canadian and American pronunciation rules. During test administration, subjects were asked to read the list of words at a slow pace. They were encouraged to attempt every word even if they did not know them; no time limit was imposed. Success on this task calls for prior familiarity with the written form of the words, such that they cannot be deduced by grapheme-phoneme correspondence. This rule prevents subjects from phonetically decoding the pronunciation of the words using guesswork alone. Moreover, the short length of the words makes this test convenient to use in
psychopathology as it does not overload individuals’ capacity of processing information. The complete list of NAART words administered to subjects can be found in Appendix A, Section A.1.

Single word reading tasks appear to be resistant to cortical atrophy (Nelson & O’Connell, 1978) and brain injury (Green et al., 2008). In healthy subjects, both NART and NAART have high internal consistencies of $r > .90$ (Blair & Spreen, 1989; Crawford, Stewart, Cochrane, Parker, & Besson, 1989) and very high test-retest reliabilities of $r = .98$ (Crawford et al., 1989) and $r = .99$ (Blair & Spreen, 1989), respectively. Importantly, NART scores at 77 years of age correlate well with IQ levels obtained at age 11 in healthy individuals ($r = .73, p < .001$; Crawford, Deary, Starr, & Whalley, 2001).

The clinical utility of this reading test for assessing premorbid IQ has been investigated in a variety of illnesses. In demented, depressed, and chronic SZ patients, NART scores remain stable while other cognitive measures fluctuate with illness progression (Crawford, Besson, Parker, Sutherland, & Keen, 1987; Kondel, Mortimer, Leeson, Laws, & Hirsch, 2003; Morrison, Sharkey, Allardyce, Kelly, & McCreadie, 2000; Smith, Roberts, Brewer, & Pantelis, 1998). Moreover, NART scores appear to be unaffected by acute SZ symptoms (O’Carroll et al., 1992).

Estimating premorbid IQ in SZ is a complex issue that has not been fully explored. Despite the fact that many researchers have utilized the NART in psychopathology, there has not been a definitive validation study that has examined the correlation between current single-word reading abilities (e.g., via the NAART) and IQ measures obtained before the onset of SZ (or SA or BD).
One study that has come the closest to investigating this question did find that current reading scores predicted premorbid IQ in SZ patients \((r = .50, p < .05;\) Russell et al., 2000). The nature of this study’s pre-illness IQ measure is questionable, however, as most of their participants had a childhood diagnosis of psychosis or emotional disorder. Therefore, it is possible that the presumed measure of premorbid IQ in these early onset patients may have actually represented a measure of post-illness onset IQ. It is thus possible that the correlation between reading ability and IQ would have been even higher had the premorbid measure of IQ been obtained prior to illness onset. In sum, although the utility of the NA(A)RT has not been widely researched in the context of psychopathology compared to other disorders and controls, it has nevertheless been used widely to estimate full-scale premorbid IQ in psychopathology.

### 3.2.1.1 Concerns about the validity of the NART

A number of debates have risen about the validity of the NART as a measure of premorbid IQ (Ebmeier et al., 1993; Griffin, Mindt, Rankin, Ritchie, & Scott, 2002; Russell et al., 2000). Some researchers have suggested combining reading scores with demographic variables, such as education, occupation and age, to increase the NART’s precision. The majority of studies that investigated this possibility failed to find any clear benefit in this addition, hence supporting the NART as a standalone test of premorbid IQ (Bright, Jaldow, & Kopelman, 2002; O’Carroll et al., 1992; Sharpe, 1990; Tracy, McGrory, Josiassen, & Monaco, 1996).

There has also been a concern about the use of the NART in conjunction with a measure of current IQ, and in particular the possibility that they may be measuring the exact same construct. However, past findings argue against this. Specifically, multiple studies have employed both
premorbid and current IQ measures concurrently in the SZ population (Barrett et al., 2009; Joyce, Hutton, Mutsatsa, & Barnes, 2005; Kremen et al., 2008; Leeson et al., 2011; Townsend et al., 2001; van Winkel et al., 2006; Zanelli et al., 2010). Most of these studies found significant differences between reading scores and current IQ scores, with the latter being generally lower than the former. Thus, deficits seem to be more pronounced in current IQ scores than in reading scores. If these tests were measuring the same construct, it would be expected that the magnitude of impairment would be the same for both. While no study has reported on the correlation between the NART and a current measure of IQ in SZ, the overall findings illustrate that these tests are distinct enough to be used concurrently when attempting to estimate IQ change.

In sum, although not perfect, the NART has proven to be a reasonable choice when it comes to estimating full-scale premorbid IQ in psychopathology

3.2.1.1.2 Obtaining WAIS IQ estimates with the use of NAART raw scores

The WAIS is considered the gold-standard for measuring IQ by most researchers (e.g., Kaufman, 2006; Meyer & Weaver, 2006; Strauss, Sherman, & Spreen, 2006; Wechsler, 1981). Since this test provides robust results and is widely used, reading based premorbid IQ scores are usually used to predict WAIS scores. For this study, error scores on the NAART (number of mispronounced words) were used to derive a WAIS-R full-scale IQ score. The following formula, which was standardized on male and female Canadian and American subjects, allowed us to make this estimate (Blair & Spreen, 1989):

\[
\text{WAIS-R full-scale IQ} = 100 - \left( \frac{\text{NAART error score} \times 10}{\text{alpha coefficient}} \right)
\]
Estimated FS-IQ = 127.8 – 0.78(NAART errors) (S. E. = 7.63)

, where S. E. represents the standard error of the estimate.

### 3.2.1.2 Current IQ measure

For this study, the Kaufman Brief Intelligence Test (K-BIT) was completed by all subjects during their baseline neurocognitive assessment. The K-BIT is an easy to administer, short, and highly reliable test, consisting of two main subscales, a verbal and a non-verbal scale (Kaufman & Kaufman, 1990). The verbal portion of the test is made up of an expressive vocabulary subsection, which requires subjects to provide the name of 45 pictured objects, as well as a 37-item definition subsection, which requires subjects to provide the word that best fits 2 clues (a description and a partial spelling of the word). The non-verbal portion of the test consists of 48 matrix completions, where subjects must find the relationship between different visual stimuli in a multiple choice format. Examples of these tasks can be found in Appendix A, Section A.2. The verbal and non-verbal IQ scores can be used to derive a composite IQ score (Kaufman & Kaufman, 1990; Hildman, Friedberg, & Wright, 1993). In this thesis, I mainly made use of the composite K-BIT IQ score during my analyses.

### 3.2.2 Clinical measures

Mood and functioning levels were evaluated in all first-episode patients at baseline and various other time points. The Clinical Global Impression scale (CGI), the Global Assessment of Functioning (GAF) and the positive scale of the Positive And Negative Syndrome Scale (PANSS) were administered to all patients. Depressive symptoms were assessed with the
Hamilton Rating Scale for Depression (HAM-D) in the STOP-EM study. Further detail about these clinical measures can be found in Appendix B.

3.2.2.1 Medication

Data regarding medication history and medication at time of testing were gathered from the EPII and the STOP-EM programs. Using converging sources, the most accurate medication information was retrieved from the EPII datasets. In cases where some inconsistencies were noted, data files were cross-checked with individual chart notes and the best and most consistent data was retained. When discrepancies between the two were found, I used comments that were written by the investigators at the time of baseline assessment to understand why data was omitted or unclear. In the STOP-EM study, the medication information was more readily accessible and consistent throughout paper and electronic formats. Although information about medication dosage was difficult to discern, the type of medication received was defined for most patients. Thus, I coded patients from both the EPII and the STOP-EM on the general type of medication they received during the baseline testing session, either antipsychotics [AP] (e.g., olanzapine, risperidone, quetiapine), mood stabilizers [MS] (e.g., lithium, epival, lamotrigine, topamax), combination therapy (antipsychotic and mood stabilizer), antidepressants or anxiolytics.

3.3 Statistical analyses

All statistical analyses were conducted using the statistics software package IBM SPSS Statistics, version 22.0 (International Business Machines [IBM] Corporation, 2013). Given the
specific and directed hypotheses that were put forth, a significance value of $p < .05$ was used for the main analyses.

3.3.1 Normality of distribution

Before conducting the main analyses, I checked if the IQ data was parametric. To do so, I first verified the normality of the data’s distribution using histograms, P-P plots, skewness and kurtosis levels, and the Shapiro-Wilk test (Shapiro & Wilk, 1965). The $z$-score of the skewness and kurtosis of the IQ tests were calculated using the following formulas:

$$Z_{\text{Skewness}} = \frac{S - 0}{SE_{\text{Skewness}}}$$

$$Z_{\text{Kurtosis}} = \frac{K - 0}{SE_{\text{Kurtosis}}}$$

where $S$ stands for skewness and $K$ stands for the value of Kurtosis, and $SE$ represents the standard error of the skewness and kurtosis values. These analyses were carried both within and between the four subject groups (controls, BD, SA and SZ).

3.3.2 Demographics between controls, BD patients, SA patients and SZ patients

I evaluated group differences of various variables: gender, age at testing, age of onset, education, ethnicity, symptom ratings, and medication. A one-way analysis of variance (ANOVA) was used to assess differences between continuous variables (e.g., number of education years and age), while a Pearson’s chi-square test was used to assess group differences in categorical variables (e.g., gender and ethnicity). Post-hoc analyses of significant chi-square tests were performed similarly to those proposed by Beasley & Schumacker (1995). Adjusted $z$-scores (adjusted residuals in SPSS) were first transformed into chi-square scores. Then, calculated chi-square scores were transformed into $p$-values that were compared to an adjusted $p$-value, which was
based on the number of tests (n) performed (Beasley & Schumacker, 1995; García-pérez & Núñez-antón, 2003): adjusted p-value = \frac{0.05}{n} .

3.3.3 IQ and diagnosis

3.3.3.1 Premorbid IQ across diagnostic groups

The first hypothesis of my first Aim (AIM-I) was that SZ and SA patients had lower premorbid IQ scores compared to individuals with BD and healthy controls. To address this hypothesis, I used a one-way analysis of variance (ANOVA) to assess premorbid IQ differences across all four subject groups (healthy controls, BD patients, SA patients, SZ patients). These tests were followed-up with post-hoc Bonferroni comparisons to determine how premorbid IQ scores differed between groups. The magnitude of difference between groups was calculated using Cohen’s effect size:

\[
d = \frac{\text{Mean Premorbid IQ} - \text{Mean Current IQ}}{\sqrt{\frac{(SD \text{ Premorbid IQ})^2 + (SD \text{ Current IQ})^2}{2}}}
\]

, where SD represents the standard deviation of the mean.

3.3.3.2 Trajectories of IQ change across four subject groups

The second hypothesis of AIM-I was that a) the IQ of all patient groups decline compared to healthy controls, and that b) SZ patients experience the largest decline in IQ and BD patients the smallest decline in IQ. A repeated measures analysis was used to evaluate main effects of the repeated measure (IQ change: NAART vs K-BIT) and the between-subjects measure (group), and their interaction (IQ Change x Group). Follow-up paired simple t-tests were used to explore
trajectories in change in mean IQ scores (premorbid to current IQ) across each subject group. The magnitude of the change for each group was further evaluated using Cohen’s effect size based on the obtained t-value (Rosenthal, 1991): \[ d = \frac{t\text{-value}}{\sqrt{n}} \]

### 3.3.4 IQ and psychosis

#### 3.3.4.1 Demographics between BD subgroups

To obtain a better understanding of how psychotic and non-psychotic BD patients differed, I first compared these two groups on basic demographic as well as clinical variables. Independent samples T-tests were used to evaluate group differences in continuous variables (i.e., education, age, age of onset, GAF, PANSS, HAM-D, CGI). Pearson’s chi-square test was used to investigate group differences in categorical variables (i.e., gender, ethnicity, treatment type). Post-hoc chi-square analyses were conducted as described above in Section 3.3.2.

#### 3.3.4.2 Premorbid IQ in psychotic and non-psychotic BD patients

The first hypothesis of my second aim (AIM-II) was that patients with psychosis would show lower premorbid IQ than those without psychosis. To address this hypothesis, a t-test was used to determine whether NAART scores differed between BD patients who experienced psychosis and those who did not. The magnitude of difference between groups was calculated using Cohen’s effect size.
3.3.4.3 Trajectories of IQ change in psychotic and non-psychotic BD patients

My second hypothesis for AIM-II was that BD patients who experience psychotic symptoms have a steeper decline in IQ levels, from premorbid to current scores, compared to their non-psychotic counterparts. For this second hypothesis, a repeated measures ANOVA, with (IQ change) as the repeated measure and (psychosis: yes, no) as the between-subjects factor, was used. Follow-up paired simple t-tests were used to explore any significant interaction (IQ Change x Psychosis), and to see whether these two subgroups of BD differed in their IQ trajectory (premorbid to current IQ). The magnitude of the change found was further evaluated using Cohen’s effect size.

3.3.5 Mood congruency and IQ in BD patients

3.3.5.1 Demographics between mood-congruent and -incongruent psychotic BD patients

I compared mood-congruent and mood-incongruent psychotic BD patients on basic demographic as well as clinical variables using independent samples t-tests for continuous variables (i.e., education, age, age of onset, GAF, PANSS, CGI) and chi-square tests for categorical variables (i.e., gender, ethnicity, treatment type). Post-hoc chi-square analyses were conducted as described above in Section 3.3.2.

3.3.5.2 Premorbid IQ and mood congruency in BD patients

The third hypothesis of AIM-II was that a) BD patients with mood-congruent psychosis had higher premorbid IQ scores than those with mood-incongruent psychosis, and that b) mood-incongruent BD patients had steeper IQ decline than those with mood-congruent psychosis. To address the first portion of the last hypothesis, I used a t-test to determine how NAART levels
differed between BD patients who experienced mood-congruent psychosis and those who had mood-incongruent psychosis. The magnitude of difference between groups was calculated using Cohen’s effect size.

3.3.5.3 Trajectories of IQ change across congruency in psychotic features in BD

For the second part of this hypothesis, I used a repeated measures ANOVA to look at main effects of the repeated measure (IQ change) and the between-subjects factor (congruency: congruent, incongruent), and their interaction effect (IQ Change x Congruency). Follow-up paired simple t-tests were used to explore any significant result, and to see whether these two subgroups of psychotic BD patients differed in their IQ trajectory (premorbid to current IQ). Moreover, the magnitude of the change found was further evaluated using Cohen’s effect sizes.
Chapter 4: Results

4.1 Normality of distribution of premorbid and current IQ scores

The first set of analyses that were carried out aimed to verify if the IQ data was parametric. Across (and within) all four subject groups, histograms and P-P plots demonstrated generally normal curves and linear lines for both premorbid and current IQ scores, the core variables of this study. Levene’s test of homogeneity found the variances to be equal across all groups for NAART scores, $F_{\text{NAART}}(3, 227) = 1.10, p = .35$, and K-BIT scores $F_{\text{KBIT}}(3, 227) = .74, p = .53$. The kurtosis and skewness of the NAART and K-BIT scores were calculated for each group (see Table 1). Both IQ measures were normally distributed within each group, with the exception of the control group’s K-BIT scores, which had a leptokurtic kurtosis of $z = 2.97, p < .01$. The Shapiro-Wilk (S-W) normality test confirmed this finding, $t(87) = .97, p = .03$. A boxplot of IQ distribution within each subject group is shown (Figures 1 and 2). Because of the near-normal distribution of the IQ measures, they were deemed appropriate for parametric statistics.

<table>
<thead>
<tr>
<th></th>
<th>Full-Scale NAART IQ scores</th>
<th>Composite K-BIT IQ scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Skewness z-score (p-value)</td>
<td>Kurtosis z-score (p-value)</td>
</tr>
<tr>
<td>Controls</td>
<td>-1.74 (p &gt; .05)</td>
<td>-0.08 (p &gt; .05)</td>
</tr>
<tr>
<td>Bipolar</td>
<td>-1.14 (p &gt; .05)</td>
<td>-1.30 (p &gt; .05)</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>0.20 (p &gt; .05)</td>
<td>-0.50 (p &gt; .05)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>0.96 (p &gt; .05)</td>
<td>-0.89 (p &gt; .05)</td>
</tr>
</tbody>
</table>

Table 1 Z-scores and p-values of normality tests on the IQ distribution of healthy controls and patient groups. An (*) indicates a significant finding.
Figure 1 Boxplot distributions of full-scale NAART IQ scores of all subject groups. Error bars reflect standard deviations.

Figure 2 Boxplot distributions of composite K-BIT IQ scores of all subject groups. Error bars reflect standard deviations.
4.2 Demographics between groups

Table 2 provides a comparison of demographic and clinical variables between groups, along with the statistical values. Across controls and all three patient groups, there were no group differences in age or ethnicity. There were differences in gender distribution between the groups, with the SA group having significantly more male than female subjects compared to the control group ($z = 3.05, p_{\text{adjusted}} = .01$), which had slightly more female than male subjects. There were significant differences in education across the four subject groups. Specifically, both control and BD subjects had significantly higher education levels than SA and SZ patients ($p < .001$). Across the three diagnostic groups, there were no differences in age of onset of illness. However, there were significant differences in treatment, with more BD patients treated with mood stabilizers, either alone ($z = 4.34, p_{\text{adjusted}} < .001$), or in combination with antipsychotics ($z = 9.17, p_{\text{adjusted}} < .001$), than SA and SZ patients. In contrast, the proportion of patients treated with antipsychotics were comparable across the three patient groups ($p = .16$). There were also significant differences in three of the clinical scales across the patient groups. BD patients had significantly higher scores on the GAF than SA and SZ patients, indicating better global functioning. Moreover, BD patients scored lower than SA and SZ patients on the CGI, indicating a more positive global clinical impression of these patients. Lastly, BD patients had significantly lower scores on the PANSS positive scale than SA and SZ patients, indicating minimal positive symptoms compared to the other patient groups.
Table 2 Average demographic and clinical variables of all the subject groups.

Numbers in parenthesis represent the standard deviations. Certain variables were not available for the full set of data: Age of onset: BD (n = 80); Ethnicity: Controls (n = 80), BD (n = 78); Education: SZ (n = 42); Medication: BD (n = 80); Global assessment of functioning scale (GAF): BD (n = 80), SA (n = 17); Clinical global impression scale (CGI): BD (n = 81), SZ (n = 42); Positive and negative symptoms scale (PANSS): BD (n = 81), SZ (n = 42); Hamilton rating scale for depression (HAM-D): BD (n = 69). An (*) indicates a significant result.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 87)</th>
<th>Bipolar (n = 83)</th>
<th>Schizoaffective (n = 18)</th>
<th>Schizophrenia (n = 43)</th>
<th>F-test/Chi-square test (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at testing</td>
<td>22.7 (5.2)</td>
<td>22.9 (4.4)</td>
<td>21.9 (5.9)</td>
<td>21.5 (4.6)</td>
<td>$F(3, 227) = .89, p = .45$</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>42.5%</td>
<td>51.8%</td>
<td>88.9%</td>
<td>69.8%</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>66.3%</td>
<td>82.1%</td>
<td>83.3%</td>
<td>76.7%</td>
<td>$\chi^2(6) = 7.82, p = .25$</td>
</tr>
<tr>
<td>Education years</td>
<td>13.4 (2.1)</td>
<td>13.5 (2.2)</td>
<td>11.3 (1.6)</td>
<td>11.8 (1.4)</td>
<td>$F(3, 226) = 12.61, p &lt; .001$</td>
</tr>
<tr>
<td>Age of onset</td>
<td>n/a</td>
<td>20.4 (5.3)</td>
<td>19.8 (6.1)</td>
<td>18.7 (5.4)</td>
<td>$F(2, 138) = 1.30, p = .26$</td>
</tr>
<tr>
<td>% on Antipsychotic (alone or with MS)</td>
<td>n/a</td>
<td>66.3%</td>
<td>88.9%</td>
<td>72.1%</td>
<td>$\chi^2(2) = 3.69, p = .16$</td>
</tr>
<tr>
<td>% on Mood Stabilizer (alone or with AP)</td>
<td>n/a</td>
<td>87.5%</td>
<td>22.2%</td>
<td>4.7%</td>
<td>$\chi^2(2) = 85.59, p &lt; .001$</td>
</tr>
<tr>
<td>% on Combination of MS and AP</td>
<td>n/a</td>
<td>61.3%</td>
<td>22.2%</td>
<td>4.7%</td>
<td>$\chi^2(2) = 40.10, p &lt; .001$</td>
</tr>
<tr>
<td>% on Antidepressant</td>
<td>n/a</td>
<td>7.5%</td>
<td>35.3%</td>
<td>14.3%</td>
<td>$\chi^2(2) = 9.70, p = .01$</td>
</tr>
<tr>
<td>% on Anxiolytics</td>
<td>n/a</td>
<td>11.3%</td>
<td>27.8%</td>
<td>19.1%</td>
<td>$\chi^2(2) = 3.53, p = .17$</td>
</tr>
<tr>
<td>% on No medication</td>
<td>n/a</td>
<td>7.5%</td>
<td>11.1%</td>
<td>27.9%</td>
<td>$\chi^2(2) = 9.73, p = .01$</td>
</tr>
<tr>
<td>GAF score</td>
<td>n/a</td>
<td>62.9 (17.2)</td>
<td>36.9 (13.8)</td>
<td>37.7 (11.0)</td>
<td>$F(2, 137) = 48.34, p &lt; .001$</td>
</tr>
<tr>
<td>CGI score</td>
<td>n/a</td>
<td>2.3 (1.4)</td>
<td>4.0 (0.8)</td>
<td>4.1 (0.8)</td>
<td>$F(2, 138) = 35.40, p &lt; .001$</td>
</tr>
<tr>
<td>PANSS positive scale score</td>
<td>n/a</td>
<td>9.48 (5.2)</td>
<td>15.6 (4.2)</td>
<td>18.4 (6.3)</td>
<td>$F(2, 138) = 39.63, p &lt; .001$</td>
</tr>
<tr>
<td>HAMD score</td>
<td>n/a</td>
<td>6.1 (6.8)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
4.3 IQ and diagnosis

4.3.1 Premorbid IQ across four subject groups

The first hypothesis of AIM-I was that SZ and SA patients had lower premorbid IQ scores compared to individuals with BD and healthy controls. The one-way ANOVA revealed significant differences between the groups, $F(3,227) = 11.38, p < .001$, and follow-up Bonferroni post-hoc comparisons demonstrated that controls and BD patients had significantly higher full-scale NAART IQ scores than SZ patients ($p < .001, d = 1.00$). BD patients did not significantly differ from controls or SA patients. Patients with SA did not significantly differ from controls, BD or SZ patients on the measure of premorbid IQ. However, unlike BD patients ($d = .14$), a strong trend for NAART deficits appeared for patients with SA compared to controls (Cohen’s $d = .59$). The first hypothesis of AIM-I was thus mostly confirmed by these analyses (see Figure 3).

![Mean premorbid IQ scores](image)

**Figure 3** Mean premorbid (NAART) IQ scores across all subject groups.
Error bars are based on standard error values.
4.3.2 Change in IQ across four subject groups

The second hypothesis of AIM-I was that a) the IQ of all patient groups decline compared to healthy controls, and that b) SZ patients experience the largest decline in IQ and BD patients the smallest decline in IQ. Repeated measures analysis of variance revealed all effects to be significant. There was significant main effect of the repeated measure (IQ change), $F(1, 227) = 34.75$, $p < .001$, indicating that NAART IQ scores were significantly higher than K-BIT IQ scores across all subject groups ($p < .001$). There was also a significant main effect of the between-subjects factor (group), $F(3, 227) = 22.35$, $p < .001$. Pairwise comparisons revealed controls and BD patients to have significantly higher performance compared to SA ($p = .001$ and $p = .008$, respectfully) and SZ patients ($p < .001$ for both). No significant difference was found between the overall performance of controls and BD, and that of SZ and SA patients. Importantly, there was a significant (IQ Change x Group) interaction, $F(3, 227) = 7.71$, $p < .001$. Paired-samples t-tests demonstrated significant IQ decline in SA patients, $t(17)= 2.83$, $p = .01$, and SZ patients, $t(42)= 5.21$, $p < .001$, but not in BD patients, nor controls (see Figure 4). Cohen’s effect sizes (see Table 3) revealed high deterioration in IQ in the SA group and the SZ group, but minimal IQ change in the BD group and the controls. Participants with BD also showed a slight, although non-significant, decline in IQ. These results support parts a) and b) of the hypothesis partially, as the IQ of all groups except BD showed significant decline compared to controls, and the steepest IQ declines were for the SA and the SZ groups.
Table 3 Mean premorbid IQ scores and current IQ scores for all patient groups, and the results of their IQ change.

Premorbid IQ was quantified by mean FS-IQ NAART scores and current IQ by mean composite IQ KBIT scores. S.D stands for the standard deviation. An (*) indicates a significant finding.

<table>
<thead>
<tr>
<th></th>
<th>Mean NAART IQ (S.D)</th>
<th>Mean K-BIT IQ (S.D)</th>
<th>Significance: T-test, p-value</th>
<th>Cohen’s effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>107.21 (7.33)</td>
<td>106.62 (10.19)</td>
<td>t(86) = 0.67, p = .51</td>
<td>d = .07</td>
</tr>
<tr>
<td>Bipolar</td>
<td>106.14 (7.91)</td>
<td>104.39 (9.77)</td>
<td>t(82) = 1.92, p = .06</td>
<td>d = .21</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>102.78 (7.74)</td>
<td>96.44 (10.04)</td>
<td>t(17) = 2.83, p = .01*</td>
<td>d = .67</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>99.09 (8.91)</td>
<td>91.53 (11.74)</td>
<td>t(42) = 5.21, p &lt; .001*</td>
<td>d = .79</td>
</tr>
</tbody>
</table>

Figure 4 Trajectories of IQ change (premorbid to current) across all subject groups.

Premorbid IQ was quantified by mean FS-IQ NAART scores and current IQ by mean composite IQ KBIT scores. Errors bars are based on standard error values.
4.3.3 IQ and diagnosis, by gender

Given the significant gender differences across the groups, premorbid IQ and estimated change in IQ were examined in males separately in an effort to remove this potential confound. Since the SA group had a particularly low number of female subjects, the same analysis could not be conducted in females. With males, Levene’s test was not violated and the variances for NAART IQ scores were found to be equal across the diagnostic categories, $F(3, 122) = 1.46, p = .23$. A one-way ANOVA on NAART scores yielded significant differences between the groups, $F(3,122) = 8.14, p < .001$, and follow-up Bonferroni post-hoc comparisons showed male controls to have significantly higher premorbid IQ than male SZ patients ($p < .001$), and male BD patients to have significantly higher premorbid IQ than male SZ patients ($p = .01$), confirming the results found in the analyses above. Although not significant, male SA patients did appear to show lower premorbid IQ than both male controls and male BD patients. The result of these analyses on the male subgroup of participants brings further support to the first hypothesis of AIM-I.

When a repeated measure analysis of variance was conducted in male subjects, all effects were once again revealed to be significant. There was a significant main effect of the repeated measure (IQ change), $F(1, 122) = 16.39, p < .001$, the between-subjects factor (group), $F(3, 122) = 15.23, p < .001$, and a significant (IQ Change x Group) interaction, $F(3, 122) = 5.85, p = .001$. Follow-up paired-samples $t$-tests on male subjects revealed a significant decline in IQ in SA and SZ male patients, but not in male BD patients or male controls (see Figure 5). Effect size calculations revealed moderate-to-severe deterioration in IQ in the SA and SZ groups, minimal IQ change in BD patients, and none in the control group (see Table 4). Overall, the pattern of findings in males
was comparable to the pattern observed in the full sample, which suggests that gender does not likely play a major role in associating with premorbid IQ or IQ trajectory.

<table>
<thead>
<tr>
<th></th>
<th>Mean NAART IQ (S.D)</th>
<th>Mean K-BIT IQ (S.D)</th>
<th>Significance: T-test, p-value</th>
<th>Cohen’s effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>108.41 (7.10)</td>
<td>109.03 (11.59)</td>
<td>(t(36) = -.46, p = .65)</td>
<td>(d = -.08)</td>
</tr>
<tr>
<td>Bipolar</td>
<td>105.33 (7.14)</td>
<td>104.33 (9.98)</td>
<td>(t(42) = .75, p = .46)</td>
<td>(d = .11)</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>102.81 (8.18)</td>
<td>97.13 (9.67)</td>
<td>(t(15) = 2.42, p = .03^*)</td>
<td>(d = .61)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>99.27 (8.97)</td>
<td>91.97 (11.06)</td>
<td>(t(29) = 4.72, p &lt; .001^*)</td>
<td>(d = .86)</td>
</tr>
</tbody>
</table>

Table 4 Mean premorbid IQ scores and current IQ scores across all male subjects, and the results of their IQ change.
Premorbid IQ was quantified by mean FS-IQ NAART scores and current IQ by mean composite IQ KBIT scores. S.D stands for the standard deviation. An (*) indicates a significant finding.

![Figure 5 Trajectories of IQ change in male subjects](image)

Figure 5 Trajectories of IQ change (premorbid to current) across the male subset of all subject groups.
Premorbid IQ was quantified by mean FS-IQ NAART scores and current IQ by mean composite IQ KBIT scores. Error bars are based on standard error values.
4.3.4 Trajectories of IQ change, covarying for education

During the initial analysis on demographic variables (Section 4.2), a significant difference in education years across the four groups demonstrated that control and BD subjects had higher education levels than SZ and SA subjects. Thus, to evaluate the potential confounding effect of education on IQ patterns, I re-evaluated premorbid IQ with a univariate analysis on NAART scores while using education as a covariate. The results revealed a significant difference between the groups, $F(3,224) = 9.54, p < .001$, and follow-up Bonferroni post-hoc comparisons illustrated once again that control and BD subjects had significantly higher premorbid IQ levels than SZ patients ($p < .001$ and $p = .002$, respectively). With respect to SA, the trend for low premorbid IQ disappeared with estimated marginal means that became similar to those of BD subjects (Table 5).

When a repeated measure analysis of variance was conducted with education years as a covariate, there were significant main effects of the between-subjects factor (group), $F(3, 224) = 21.17, p < .001$, as well as the factor of education, $F(1, 224) = 20.60, p < .001$, a significant (IQ Change x Group) interaction, $F(3, 224) = 9.60, p < .001$, and a significant (IQ Change x Education) interaction, $F(1, 224) = 4.18, p = .04$. The repeated measure (IQ change) was not significant, $F(1, 224) = .45, p = .50$. The results revealed significant IQ decline in both SA and SZ patients, and only minimal IQ change in BD subjects (Figure 6). Overall, the pattern of findings using education as a covariate was comparable to the trajectories of IQ change found initially in Section 4.3.2. However, the results suggest that the variance in IQ is partially shared with variance in education years.
It should be noted that the analyses covarying for education are likely over-controlling for a variable that is intimately tied to the different groups, so they should be viewed as secondary and as efforts to test limits. It could be argued that these analyses may not be appropriate.

<table>
<thead>
<tr>
<th></th>
<th>Estimated marginal NAART IQ mean (S.E)</th>
<th>Estimated marginal K-BIT IQ mean (S.E)</th>
<th>Significance: T-test, p-value</th>
<th>Cohen’s effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>108.32 (.77)</td>
<td>108.52 (1.10)</td>
<td>( t(86) = .27, p = .79 )</td>
<td>( d = .03 )</td>
</tr>
<tr>
<td>Bipolar</td>
<td>105.37 (.79)</td>
<td>103.91 (1.12)</td>
<td>( t(82) = 1.06, p = .29 )</td>
<td>( d = .12 )</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>105.18 (1.72)</td>
<td>97.89 (2.44)</td>
<td>( t(17) = 2.38, p = .02^* )</td>
<td>( d = .56 )</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>100.98 (1.13)</td>
<td>92.78 (1.60)</td>
<td>( t(42) = 4.10, p &lt; .001^* )</td>
<td>( d = .63 )</td>
</tr>
</tbody>
</table>

Table 5 Estimated marginal mean premorbid IQ and current IQ scores, with education as a covariate, and the results of their IQ change. S.E stands for the standard error of the marginal means. An (*) indicates a significant finding.

Figure 6 Trajectories of IQ change (premorbid to current) using education as a covariate factor. Premorbid IQ was quantified by mean FS-IQ NAART scores and current IQ by mean composite IQ KBIT scores. Error bars are based on standard error values.
4.4 Potential confounding factor of NAART

A number of researchers have expressed their apprehension over the use of the NART to estimate premorbid IQ in groups whose scores approach ceiling or basal levels (Griffin et al., 2002; Nelson & Willison, 1991; Russell et al., 2000). This concern about the validity of our premorbid IQ estimate raised the possibility that the apparent decline observed in SA and SZ might be due to the NAART’s overestimation of premorbid IQ in individuals with below average IQ, rather than to true decline in IQ. Hence, it might be that, instead of IQ decline across illness onset, patients with SA or SZ consistently have low intellectual functioning even before the onset of illness, and that this does not change significantly after illness onset. To evaluate this possibility, I repeated the analyses on premorbid IQ and trajectories of IQ change using control subjects who displayed low current IQ scores, below 100 points (n = 14).

4.4.1 Patterns of intellectual functioning when compared to control subjects with low IQ

A one-way ANOVA on NAART scores yielded significant differences between the groups, \( F(3,154) = 7.25, p < .001 \), and follow-up Bonferroni post-hoc comparisons found BD patients to have higher premorbid IQ scores than SZ patients (\( p < .001 \)). Control subjects did not have significantly different premorbid IQ scores than any of the patient groups. Moreover, SA patients did not significantly differ from any of the other groups.

A repeated measure analysis of variance conducted with low-IQ controls revealed a significant main effect of the repeated measure (IQ change), \( F(1, 154) = 47.47, p < .001 \), the between-subjects factor (group), \( F(3, 154) = 15.45, p < .001 \), and a significant (IQ Change x Group) interaction, \( F(3, 154) = 5.77, p = .001 \). Follow-up paired-samples \( t \)-tests showed a significant
difference between NAART and K-BIT IQ scores in control subjects with low-IQ, as well as in
SA and SZ patients, but not in BD patients (see Figure 7). Effect size calculations demonstrated
moderate-to-severe deterioration in IQ in the SA and SZ groups, as well in the low-IQ control
group, and minimal IQ change in BD patients (see Table 6).

Considering that the control subjects in this study did not have any serious physical, mental or
neurological disorder, and that IQ is not expected to decline in healthy populations, this analysis
demonstrates that NAART may overestimates IQ in individuals with low IQ by about 8 points,
but not in subjects with average IQ scores.

<table>
<thead>
<tr>
<th></th>
<th>Mean NAART IQ (S.D)</th>
<th>Mean K-BIT IQ (S.D)</th>
<th>Significance: T-test, p-value</th>
<th>Cohen’s effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>102.86 (7.07)</td>
<td>94.21 (5.51)</td>
<td>$t(13) = 4.22, p = .001$</td>
<td>$d = 1.13$</td>
</tr>
<tr>
<td>Bipolar</td>
<td>106.14 (7.91)</td>
<td>104.39 (9.77)</td>
<td>$t(82) = 1.92, p = .06$</td>
<td>$d = .21$</td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>102.78 (7.74)</td>
<td>96.44 (10.04)</td>
<td>$t(17) = 2.83, p = .01$</td>
<td>$d = .67$</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>99.09 (8.91)</td>
<td>91.53 (11.74)</td>
<td>$t(42) = 5.21, p &lt; .001$</td>
<td>$d = .79$</td>
</tr>
</tbody>
</table>

Table 6 Mean premorbid IQ scores and current IQ scores across all groups, using low-IQ controls, and the results of their IQ change.
Premorbid IQ was quantified by mean FS-IQ NAART scores and current IQ by mean composite IQ KBIT scores.
S.D stands for the standard deviation. An (*) indicates a significant finding.
Figure 7 Trajectories of IQ change (premorbid to current) across all subject groups, using low-IQ controls.
Premorbid IQ was quantified by mean FS-IQ NAART scores and current IQ by mean composite IQ KBIT scores. Error bars are based on standard error values.

4.4.2 Correlation between obtained IQ and accuracy of estimated premorbid IQ scores in healthy subjects

As a final step in the investigation of the predictability value of the NAART as an estimate of premorbid IQ, I calculated the correlation between obtained IQ (composite K-BIT IQ score) and the difference between estimated premorbid IQ and actual IQ scores (NAART minus K-BIT) in healthy control subjects. Overall, the correlation was strong ($r = -.74$), indicating that the accuracy of predicted premorbid IQ was highly dependent on the overall IQ level. Inspection of Figure 8 reveals that the most accurate predictions occurred at an average IQ level. Moreover, whereas at high IQ levels the NAART underestimates IQ, at low IQ levels the NAART overestimates IQ scores.
Given that the second aim of this thesis was conducted in the BD subset of participants, who displayed average levels of intellectual functioning, I proceeded with the analyses on IQ and psychosis and mood congruency.

![Correlation between actual IQ score and the difference between actual and estimated IQ scores in healthy controls](image)

Figure 8 Relationship between K-BIT IQ scores and the difference between NAART-estimated and K-BIT IQ scores in healthy controls.

4.5 IQ and psychosis

4.5.1 Demographics between groups: psychotic BD vs. non-psychotic BD

Psychotic and non-psychotic BD patients were compared on demographic and clinical variables (Table 5). There were no significant group differences, except for gender distribution, $\chi^2(1) = 6.55$, $p = .01$, which found most BD patient without psychosis to be females and most BD patients with psychosis to be males ($z = 2.56$, $p = .01$).
<table>
<thead>
<tr>
<th></th>
<th>Non-Psychotic BD ( (n = 11) )</th>
<th>Psychotic BD ( (n = 67) )</th>
<th>( T )-test/Chi-square test ( (p )-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>18.1 (3.5)</td>
<td>20.8 (5.4)</td>
<td>( t(74) = 1.53, \ p = .13 )</td>
</tr>
<tr>
<td><strong>Age at testing</strong></td>
<td>21.7 (3.6)</td>
<td>23.1 (4.6)</td>
<td>( t(76) = .96, \ p = .34 )</td>
</tr>
<tr>
<td><strong>Sex (% male)</strong></td>
<td>18.2%</td>
<td>59.7%</td>
<td>( \chi^2(1) = 6.55, \ p = .01^* )</td>
</tr>
<tr>
<td><strong>Ethnicity (% Caucasian)</strong></td>
<td>90.0%</td>
<td>81.3%</td>
<td>( \chi^2(2) = .87, \ p = .65 )</td>
</tr>
<tr>
<td><strong>Education years</strong></td>
<td>13.6 (2.2)</td>
<td>13.5 (2.3)</td>
<td>( t(76) = .09, \ p = .93 )</td>
</tr>
<tr>
<td><strong>% on Antipsychotic</strong></td>
<td>70.0%</td>
<td>65.2%</td>
<td>( \chi^2(1) = .09, \ p = .76 )</td>
</tr>
<tr>
<td><strong>% on Mood Stabilizer</strong></td>
<td>70.0%</td>
<td>89.4%</td>
<td>( \chi^2(1) = 2.86, \ p = .09 )</td>
</tr>
<tr>
<td><strong>% on Combination of both</strong></td>
<td>50%</td>
<td>62.1%</td>
<td>( \chi^2(1) = .53, \ p = .47 )</td>
</tr>
<tr>
<td><strong>% on Antidepressant</strong></td>
<td>10.0%</td>
<td>6.1%</td>
<td>( \chi^2(1) = .22, \ p = .64 )</td>
</tr>
<tr>
<td><strong>% on Anxiolytic</strong></td>
<td>10.0%</td>
<td>10.6%</td>
<td>( \chi^2(1) = .003, \ p = .95 )</td>
</tr>
<tr>
<td><strong>% on no medication</strong></td>
<td>10.0%</td>
<td>7.6%</td>
<td>( \chi^2(1) = .07, \ p = .79 )</td>
</tr>
<tr>
<td><strong>GAF score</strong></td>
<td>67.0 (14.2)</td>
<td>62.3 (17.9)</td>
<td>( t(75) = .80, \ p = .43 )</td>
</tr>
<tr>
<td><strong>CGI score</strong></td>
<td>3.1 (1.5)</td>
<td>2.2 (1.4)</td>
<td>( t(75) = 1.78, \ p = .08 )</td>
</tr>
<tr>
<td><strong>PANSS positive scale score</strong></td>
<td>7.6 (1.9)</td>
<td>9.9 (5.6)</td>
<td>( t(75) = 1.29, \ p = .20 )</td>
</tr>
<tr>
<td><strong>HAMD score</strong></td>
<td>7.5 (6.3)</td>
<td>6.2 (7.1)</td>
<td>( t(62) = .55, \ p = .59 )</td>
</tr>
</tbody>
</table>

Table 7 Average demographic and clinical variables of psychotic and non-psychotic BD patients. Numbers in parenthesis represent the standard deviations.

Certain variables were not available for the full set of data: Age of onset: BD without psychosis \((n = 10)\), BD with psychosis \((n = 66)\); Ethnicity: BD without psychosis \((n = 10)\), BD with psychosis \((n = 64)\); Medication: BD without psychosis \((n = 10)\), BD with psychosis \((n = 66)\); Global assessment of functioning scale (GAF): BD without psychosis \((n = 10)\); Clinical global impression scale (CGI): BD without psychosis \((n = 10)\); Positive and negative symptoms scale (PANSS): BD without psychosis \((n = 10)\); Hamilton rating scale for depression (HAMD-D): BD with psychosis \((n = 57)\). An \(^*\) indicates a significant result.
4.5.2 Premorbid IQ and psychosis in BD patients

The first hypothesis of my second aim (AIM-II) was that patients with psychosis would show lower premorbid IQ than those without psychosis. There was no significant group difference in premorbid IQ, $t(76) = 1.56, p = .12$. However, a plot of these data shows a trend for patients with psychosis to show lower premorbid IQ than those without psychosis (see Figure 9). Cohen’s effect size demonstrated that the magnitude of difference in premorbid IQ levels between BD patients with and without psychosis was moderately high ($d = .54$). An effect size of this caliber suggests that the lack of significant result might be partially attributable to the reduced sample size (i.e., there were $n = 11$ BD patients without psychosis).

Given the findings in Section 4.4, it is possible that NAART was overestimated in psychotic BD patients and that, in actuality, their premorbid IQ was substantially lower than BD patients without psychosis. However, this is unlikely as both groups displayed average levels of current IQ as measured by the K-BIT (107.09 for non-psychotic BD and 104.00 for psychotic BD, $p = .36$). In sum, the trend for BD patients with psychosis to have lower NAART-estimated IQ scores provides partial support to my first hypothesis of AIM-II.
4.5.3 Change in IQ and psychosis in BD

My second hypothesis for AIM-II was that BD patients who experience psychotic symptoms have a steeper decline in IQ levels, from premorbid to current scores, compared to their non-psychotic counterparts. Repeated measures analysis of variance did not yield any significant main effects, $F_{\text{AIQ}}(1, 76) = 2.69, p = .11$; $F_{\text{Psychosis}}(1, 76) = 1.89, p = .17$, or interaction (IQ change x Psychosis), $F(1, 76) = .13, p = .73$. Hence, the analysis of my data failed to support my hypothesis that BD patients experiencing psychosis had a steeper decline of their IQ at the onset of psychotic symptoms, compared to their non-psychotic counterparts (see Table 8 and Figure 10).
Table 8 Mean premorbid IQ scores and current IQ scores for psychotic and non-psychotic BD patients, along with the result of their IQ change.
Premorbid IQ was quantified by mean FS-IQ NAART scores and current IQ by mean composite IQ KBIT scores. S.D stands for the standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Mean NAART IQ (S.D)</th>
<th>Mean K-BIT IQ (S.D)</th>
<th>Significance: T-test, p-value</th>
<th>Cohen’s effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-psychotic BD</td>
<td>109.73 (6.90)</td>
<td>107.09 (5.82)</td>
<td>( t(10) = 1.25, p = .24 )</td>
<td>( d = .38 )</td>
</tr>
<tr>
<td>Psychotic BD</td>
<td>105.70 (8.09)</td>
<td>104.00 (10.30)</td>
<td>( t(66) = 1.68, p = .10 )</td>
<td>( d = .21 )</td>
</tr>
</tbody>
</table>

Figure 10 Trajectories of IQ change across psychotic and non-psychotic BD patients.
Premorbid IQ was quantified by mean FS-IQ NAART scores and current IQ by mean composite IQ KBIT scores. Error bars are based on standard error values of the means.

4.6 Mood-congruency and IQ

4.6.1 Demographics between subgroups of psychotic BD patients: mood-in/congruent
Mood-congruent and mood-incongruent psychotic BD patients were compared on demographic and clinical variables (see Table 9). There were no significant group differences.
<table>
<thead>
<tr>
<th></th>
<th>Mood-congruent psychotic BD</th>
<th>Mood-incongruent psychotic BD</th>
<th>T-test/Chi-square test (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>20.7 (6.0)</td>
<td>20.9 (4.9)</td>
<td>$t(64) = .12$, $p = .91$</td>
</tr>
<tr>
<td>Age at testing</td>
<td>23.2 (4.8)</td>
<td>23.0 (4.5)</td>
<td>$t(65) = .18$, $p = .86$</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>64.7%</td>
<td>54.5%</td>
<td>$\chi^2(1) = .72$, $p = .40$</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>81.3%</td>
<td>81.3%</td>
<td>$\chi^2(2) = .34$, $p = .84$</td>
</tr>
<tr>
<td>Education years</td>
<td>13.6 (2.0)</td>
<td>13.4 (2.5)</td>
<td>$t(65) = .30$, $p = .77$</td>
</tr>
<tr>
<td>% on Antipsychotic</td>
<td>60.6%</td>
<td>69.7%</td>
<td>$\chi^2(1) = .60$, $p = .44$</td>
</tr>
<tr>
<td>% on Mood Stabilizer</td>
<td>87.9%</td>
<td>90.9%</td>
<td>$\chi^2(1) = .16$, $p = .69$</td>
</tr>
<tr>
<td>% on Combination of both</td>
<td>57.6%</td>
<td>66.7%</td>
<td>$\chi^2(1) = .58$, $p = .45$</td>
</tr>
<tr>
<td>% on Antidepressant</td>
<td>9.1%</td>
<td>3.0%</td>
<td>$\chi^2(1) = 1.07$, $p = .30$</td>
</tr>
<tr>
<td>% on Anxiolytic</td>
<td>15.2%</td>
<td>6.1%</td>
<td>$\chi^2(1) = 1.44$, $p = .23$</td>
</tr>
<tr>
<td>% on no medication</td>
<td>9.1%</td>
<td>6.1%</td>
<td>$\chi^2(1) = .22$, $p = .64$</td>
</tr>
<tr>
<td>GAF score</td>
<td>59.9 (16.9)</td>
<td>64.7 (18.9)</td>
<td>$t(65) = 1.09$, $p = .28$</td>
</tr>
<tr>
<td>CGI score</td>
<td>2.4 (1.4)</td>
<td>2.1 (1.4)</td>
<td>$t(65) = .67$, $p = .51$</td>
</tr>
<tr>
<td>PANSS positive scale score</td>
<td>10.6 (5.9)</td>
<td>9.2 (5.2)</td>
<td>$t(65) = 1.03$, $p = .31$</td>
</tr>
<tr>
<td>HAMD score</td>
<td>7.0 (8.6)</td>
<td>5.5 (5.8)</td>
<td>$t(36.6) = .73$, $p = .47$</td>
</tr>
</tbody>
</table>

Table 9 Average demographic and clinical variable across mood-congruent and -incongruent psychotic BD patients.
Numbers in parenthesis represent the standard deviations. Certain variables were not available for the full set of data: Age of onset: Mood-congruent ($n = 33$); Ethnicity: Mood-congruent ($n = 32$), Mood-incongruent ($n = 32$); Medication: Mood-congruent ($n = 33$); Hamilton rating scale for depression (HAM-D): Mood-congruent ($n = 23$); Mood-incongruent ($n = 30$).
4.6.2 Premorbid IQ and mood-congruency

The third hypothesis of AIM-II was that a) BD patients with mood-congruent psychosis had higher premorbid IQ scores than those with mood-incongruent psychosis, and that b) mood-incongruent BD patients had steeper IQ decline than those with mood-congruent psychosis. A t-test failed to reveal a significant group difference in premorbid IQ, \( t(65) = .66, p = .51 \). A weak Cohen’s effect size of \( d = .16 \) was found between the two congruency subtypes. Thus, the analyses failed to support the hypothesis that mood-incongruent psychotic BD patients had lower premorbid IQ than their mood-congruent counterparts.

4.6.3 Change in IQ and mood congruency

Lastly, I examined the relationship between change in IQ and mood congruency in BD patients. The repeated measures analysis revealed a trend for the repeated measure (IQ change), \( F(1, 65) = 2.84, p = .10 \), and the between-subjects factor (congruency), \( F(1, 65) = 2.49, p = .12 \), as well as their interaction (IQ Change x Congruency), \( F(1, 65) = 3.48, p = .07 \). Given this near-significant interaction, paired-samples t-tests were conducted to examine IQ change across each group. T-tests revealed a significant decline in IQ for BD patients with mood-congruent psychotic features, \( t(33) = 2.19, p = .04 \), but not for mood-incongruent patients, \( t(32) = .16, p = .88 \) (see Table 10 and Figure 11). This result goes in the opposite direction to the original hypothesis.
<table>
<thead>
<tr>
<th></th>
<th>Mean NAART IQ (S.D)</th>
<th>Mean K-BIT IQ (S.D)</th>
<th>Significance: T-test, (p)-value</th>
<th>Cohen’s effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood-congruent</td>
<td>105.06 (8.69)</td>
<td>101.53 (10.21)</td>
<td>(t(33) = 2.19, p = .04^*)</td>
<td>(d = .38)</td>
</tr>
<tr>
<td>Mood-incongruent</td>
<td>106.36 (7.50)</td>
<td>106.55 (9.91)</td>
<td>(t(32) = -.16, p = .88)</td>
<td>(d = -.03)</td>
</tr>
</tbody>
</table>

Table 10 Mean premorbid IQ scores and current IQ scores of mood-congruent and –incongruent BD patients, along with the result of their IQ change.
Premorbid IQ was quantified by mean FS-IQ NAART scores and current IQ by mean composite IQ KBIT scores. S.D stands for the standard deviation. An (*) indicates a significant result.

Figure 11 Trajectory of IQ change in psychotic BD
Premorbid IQ was quantified by mean FS-IQ NAART scores and current IQ by mean composite IQ KBIT scores. Error bars are based on standard error values of mean.

4.6.4 Current IQ and mood-congruency
As no data has been published on current IQ differences between mood-congruent and incongruent psychotic BD patients, here I report the results on IQ based on the EPII and STOP-EM datasets. A \(t\)-test revealed group differences in composite K-BIT IQ scores, \(t(65) = 2.04, p =\)
.045, indicating that BD patients with mood-incongruent features had significantly higher IQ scores than mood-congruent patients, $M_{\text{incongruent}} = 106.55$, $SD_{\text{incongruent}} = 9.91$; $M_{\text{congruent}} = 101.53$, $SD_{\text{congruent}}= 10.21$. The effect size of the magnitude of the difference in current IQ scores between the two subgroups was moderately-high, $d = .50$. Although no predictions were made for the current IQ levels of mood-congruent and incongruent BD patients, this result is somewhat opposite to what the literature suggests about individuals with mood-incongruent symptoms (i.e., they typically have worse overall functioning).

Given the significant difference in current IQ scores between the two psychotic BD groups, it is possible that premorbid IQ scores were overestimated in mood-congruent patients and underestimated in mood-incongruent patients. If this were to hold true, then it is possible that, rather than a decline in IQ, mood-congruent patients experienced deficits in IQ premorbidly that were maintained, and not worsened, after the onset of illness. In this scenario, mood-incongruent patient might be the ones experiencing a decline from their underestimated premorbid IQ across illness onset. However, this is unlikely as both patient groups displayed average overall IQ scores.

### 4.6.5 IQ and mood-congruency: STOP-EM program alone

There was an imbalance in the distribution of mood congruency features across the two first-episode programs. While the STOP-EM study had a sample of $n = 23$ BD patients with mood-congruent psychotic features, compared to $n = 30$ with mood-incongruent features, the EPIII study had a sample of $n = 11$ BD patients with mood-congruent psychotic features, compared to $n = 3$ with mood-incongruent features. This disparity was somewhat atypical as most studies on
mood congruency report a ratio that is close to 50:50 (Harrow et al., 2000; Stephen M Strakowski et al., 2000; Tohen et al., 1992). Therefore, I re-examined the relationship between IQ and mood congruency in the data that came from the most balanced source, the STOP-EM program.

A t-test did not reveal a significant group differences in premorbid IQ across the BD patients with psychosis from the STOP-EM study, $t(51) = .41, p = .69$. This result failed once again to support part a) of my hypothesis about premorbid IQ and congruency. The repeated measures analysis of variance resulted in a significant main effect of IQ change, $F_{\text{AQ}} (1, 51) = 5.04, p = .03$, as well as a significant (IQ Change x Congruency) interaction, $F(1, 51) = 7.09, p = .01$. The between-subjects factor (congruency) was not significant, $F_{\text{Congruency}} (1, 51) = 2.51, p = .12$.

Paired-samples t-tests were conducted to further examine the trajectory of IQ change in each sub-group of psychotic BD patients. Like the results from the full set of psychotic BD patients in Section 4.5.3, these analyses demonstrated significant IQ decline in mood-congruent patients, but not mood-incongruent patients. This significant interaction does not support the original hypothesis that patients with mood-incongruent psychotic symptoms show worse decline than mood-congruent patients. In fact, this outcome demonstrates an opposite trend.

4.6.6 IQ and antipsychotic treatment

Given the unexpected IQ findings amongst mood-congruent and –incongruent psychotic BD patients, I conducted a post-hoc examination of whether any satellite clinical factors could have affected these outcomes. While there was no significant difference between the overall treatment that patients received (i.e. antipsychotic vs mood stabilizer vs combination therapy – see Table
the type of antipsychotic, specifically, was unevenly distributed. Specifically, chi-square analysis demonstrated that more mood-incongruent patients were treated with quetiapine than mood-congruent patients ($\chi^2(1) = 8.84, p = .003$, see Table 9).

To further explore the potential influence of specific antipsychotic treatments, I divided psychotic BD patients into groups of antipsychotic treatment (risperidone, olanzapine, quetiapine, other antipsychotic, no antipsychotic) and I examined their trajectory of IQ change. Repeated measures analysis found significant main effects of the repeated measure (IQ change), $F(1, 60) = 4.91, p = .03$, and the between-subjects variable (antipsychotic type), $F(4, 60) = 2.45, p = .04$, but not of the (IQ change x Antipsychotic) interaction, $F(4, 60) = 1.52, p = .20$. Despite the lack of significant interaction (which may have been due to reduced power associated with small sample sizes in some groups), follow-up paired-samples $t$-tests were nevertheless conducted to further explore IQ change across each group. $T$-tests revealed a near-significant decline in IQ in patients treated with olanzapine ($p = .058$). As can be seen in Figure 12 and in Table 12, subjects treated with olanzapine or risperidone experienced a notable decline in IQ ($d = .71$ and $d = .28$, respectfully). However, psychotic BD patients treated with quetiapine did not experience a decline in IQ. In fact, they seemed to experience a subtle increase in IQ ($d = -.39$).

Thus, the type of antipsychotic treatment that patients received might have influenced their trajectories of IQ change across illness onset.
<table>
<thead>
<tr>
<th>% on Risperidone</th>
<th>Mood-congruent (n = 33)</th>
<th>Mood-incongruent (n = 33)</th>
<th>Chi-square Test (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>39.4%</td>
<td>36.4%</td>
<td>$\chi^2(1) = .06, \ p = .80$</td>
</tr>
<tr>
<td>% on Quetiapine</td>
<td>3.0%</td>
<td>30.3%</td>
<td>$\chi^2(1) = 8.84, \ p = .003^*$</td>
</tr>
<tr>
<td>% on Olanzapine</td>
<td>12.1%</td>
<td>3.0%</td>
<td>$\chi^2(1) = 1.95, \ p = .16$</td>
</tr>
<tr>
<td>% other antipsychotic (typical or atypical)</td>
<td>6.0%</td>
<td>0.0%</td>
<td>$\chi^2(1) = 2.06, \ p = .15$</td>
</tr>
<tr>
<td>% no antipsychotic</td>
<td>39.4%</td>
<td>30.3%</td>
<td>$\chi^2(1) = .60, \ p = .44$</td>
</tr>
</tbody>
</table>

Table 11 Distribution of antipsychotic treatment across mood-congruent and -incongruent psychotic BD patients.
An (*) indicates a significant result.

<table>
<thead>
<tr>
<th>Mean NAART IQ (S.D)</th>
<th>Mean K-BIT IQ (S.D)</th>
<th>Significance: $T$-test, $p$-value</th>
<th>Cohen’s effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>104.08 (8.10)</td>
<td>$t(24) = 1.70, \ p = .10$</td>
<td>$d = .28$</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>108.82 (5.79)</td>
<td>$t(10) = -1.11, \ p = .29$</td>
<td>$d = -.39$</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>102.00 (8.86)</td>
<td>$t(4) = 2.63, \ p = .06$</td>
<td>$d = .71$</td>
</tr>
<tr>
<td>No antipsychotic</td>
<td>106.65 (8.79)</td>
<td>$t(22) = .42, \ p = .68$</td>
<td>$d = .18$</td>
</tr>
</tbody>
</table>

Table 12 Mean premorbid IQ scores and current IQ scores across various antipsychotics in psychotic BD patients, along with the result of their IQ change.
Premorbid IQ was quantified by mean FS-IQ NAART scores and current IQ by mean composite IQ KBIT scores. Std dev stands for the standard deviation.
Figure 12 Trajectories of IQ change in psychotic BD patients across different antipsychotics.
Premorbid IQ was quantified by mean FS-IQ NAART scores and current IQ by mean composite IQ KBIT scores. Error bars are based on standard error values of mean.
Chapter 5: Discussion

The premise of this thesis was to examine estimated premorbid IQ and estimated developmental trajectories of IQ change in psychopathology from the perspective of two models. The first assessed the degree to which potential differences in these variables might exist between various clinical diagnostic entities, a finding that would support the idea that developmental differences exist among DSM disorders. The second model addressed whether developmental differences in IQ might more closely be associated with a shared clinical feature, the presence of psychosis and whether psychosis had congruent or incongruent features.

5.1 IQ across diagnostic categories

5.1.1 Premorbid IQ and IQ change across subject groups

The first objective was to examine premorbid IQ and estimated change in IQ across illness onset in SZ, SA and BD-I patient groups. The first set of analyses confirmed the hypothesis that only the SA and SZ groups had significantly lower scores than controls. SZ patients had the lowest premorbid IQ scores, followed closely by SA patients, with whom they did not significantly differ. Moreover, premorbid IQ scores of BD patients and controls did not significantly differ either. The second hypothesis of AIM-I was mostly supported. Results revealed steep declines in IQ for the SZ and SA groups, and minimal decline in BD patients. It should be noted that significant changes in IQ were solely present across the SA and SZ groups, not BD patients.
Taken together, these results demonstrate that premorbid IQ and trajectories of IQ change are different between mood-disorders and primarily-psychotic disorders. Thus, although BD, SA and SZ patients share a vast array of similarities in cognitive, genetic, structural and symptomatic patterns, their intellectual profiles are not identical. BD patients show premorbid IQ levels that are comparable to those of controls, with minimal IQ decline across illness onset, and SA and SZ patients share similar low premorbid IQ levels and have further marked declines in IQ at illness onset. These findings offer support to the classification of psychiatric patients into diagnostic categories and, also, to previous research studies that have grouped SA patients with SZ patients in their analyses.

Furthermore, the similarity in the trajectories of IQ change in SZ and SA might suggest that these two illnesses share early brain pathologies and neurodevelopmental progression of brain dysfunction, which may be distinct from, or not be present, in BD. This is supported by evidence from childhood reports, which have often catalogued deficits in cognition and language, as well as social, emotional and behavioural development in individuals who develop SZ in the future (e.g., Cannon et al., 1997; David et al., 1997; Jones, Murray, Jones, Rodgers, & Marmot, 1994; Murray et al., 2004; Reichenberg et al., 2002; Reichenberg et al., 2008; Trotta, Murray, & MacCabe, 2014). Disturbances found in children who later develop BD, however, are primarily associated with social-emotional development and less with IQ or other cognitive deficits (e.g., Stringaris et al., 2014; Trotta et al., 2014; Whitney et al., 2013). A possible explanation for this could be the differential expression of genes that impair neurodevelopment and neural networking differently in SZ and BD (Jones & Murray, 1991). Linkage studies have shown that SZ patients and their unaffected relatives have reduced GMD in the fronto-striato-thalamic and
the lateral temporal regions, while BD patients and their unaffected relatives have reduced GMD in the anterior cingulate gyrus and the ventral striatum (McDonald et al., 2004). Moreover, although a direct comparison has yet to be made, it appears that patients at ultra-high risk of developing SZ share similar brain structure anomalies with chronic SZ patients, which are different from the anomalies that ultra-high risk BD patients share with their chronic counterparts (Kempton et al., 2009; Morey et al., 2005; Pantelis et al., 2003; Whalley et al., 2012). Likewise, SZ and BD patients seem to recruit differential neural networks during certain cognitive tasks (e.g., memory, verbal fluency, emotional processing, face-name learning task) (Costafreda et al., 2011; Hall et al., 2010; McIntosh et al., 2008; Whalley et al., 2012). These differences in loci activation could pertain to compensation patterns for areas affected in SZ/SAD and not BD, and vice versa.

The neuroimaging literature also supports my findings of IQ decline in SAD and SZ across illness onset, but not BD. Anomalies of the anterior cingulate and the prefrontal cortices have been seen in individuals at risk of developing psychosis who transitioned into SZ (and other psychoses), but not BD (Fornito et al., 2008; Sun et al., 2009). Thus, the findings of this thesis are consistent with previous studies that demonstrate preferential brain disturbances in SZ compared to BD.

5.1.2 The influence of gender and education differences on IQ

Although intelligence tests are standardized across healthy male and female individuals, as well as a wide age group, a small number of studies have found gender differences in premorbid IQ in psychopathology. For instance, some studies found male patients to have lower premorbid IQ than their female counterparts in both SA (McGlashan & Bardenstein, 1990) and SZ (Aylward,
Walker, & Bettes, 1984) populations, while others have found either no differences between the sexes (McGlashan & Bardenstein, 1990), or have found female SZ patients to have lower premorbid functioning than males (Bildner et al., 2000). In light of these findings, I conducted the series of analyses for AIM-I in males separately due to the inequality of gender distribution in the SA subject group.

Similar to the results reported above, the male subgroups of controls and BD patients had considerably higher premorbid IQ than SZ and SA patients, although only significantly different than male SZ. Moreover, a steep decline in IQ was seen in male SA and SZ patients, which was largest for the SZ group, closely followed by the SA group, and smallest for the BD group. In sum, these findings demonstrated that gender was not a major contributor to the (premorbid and trajectory) IQ differences found in the first two analyses.

With respect to education level, it is difficult to dissociate its impact on IQ as it is an inherent part of how intellectual functioning is measured and how demographic regression equations of estimates of premorbid IQ are built. Moreover, educational level is intimately tied to different disorders. Nevertheless, the influence of education on IQ patterns across all subject groups was evaluated. The results demonstrated that, while variance in education accounted for some of the variance observed in premorbid IQ scores, with the SA group no longer showing a deficit in NAART scores, IQ decline was maintained in both SA and SZ groups.
5.2 IQ and psychosis in BD patients

The second aim of this study was to examine whether differences in IQ patterns were tied to the presence or absence of psychosis in BD patients. Given the dearth of research on the relationship between developmental IQ patterns and the occurrence of psychosis, the novel findings of these analyses were highly anticipated.

5.2.1 Premorbid IQ across psychotic and non-psychotic patients

The first hypothesis of AIM-II was that BD patients with psychosis would show lower premorbid IQ than those without psychosis. Although the results did not reach statistical significance, a trend did appear to be present, corroborating the theory that individuals with psychosis have more premorbid IQ deficit than their non-psychotic counterparts. Given that the effect size difference was moderately-large in magnitude, it is likely that the lack of significance is attributable to diminished power due to the small sample size in this analysis.

5.2.2 Trajectory of IQ change across psychotic and non-psychotic patients

My second hypothesis for AIM-II was that BD patients who experience psychotic symptoms have a steeper decline in IQ levels compared to their non-psychotic counterparts. However, this hypothesis was not supported. While BD patients with psychosis show lower premorbid IQ than BD patients without psychosis, these two groups show comparable IQ trajectories across the illness onset period.

Given that the two BD subgroups differed primarily on the basis of whether their manic symptoms where characterized with psychosis or not, any discrepancy seen at the IQ level is
attributable to their main differentiating trait. Based on my findings, since no significant difference in IQ change was found across illness-onset, it appears unlikely that the sole presence of psychosis is a critical factor in IQ decline in psychopathologies. Rather, it might be low premorbid IQ, resulting from early neurodevelopmental disturbances, that predisposes patients to psychotic features. This hypothesis is supported by the slew of evidence that has emerged over the last decade about the resemblance of psychotic mood-disorder patients’ to SZ patients’ neurocognitive and neurodevelopmental profiles (e.g., genetically, intellectually, etc., see Sections 1.1 and 1.3), as well as the number of longitudinal studies that find that deficits in childhood/teenage IQ correlate with psychotic symptoms later-on in life (e.g., Horwood et al., 2008).

5.3 IQ and mood congruency

The last set of analyses was designed to evaluate the influence of mood congruency type on IQ deficits across illness onset in BD patients with psychotic symptoms.

5.3.1 Premorbid IQ in mood-congruent and –incongruent psychosis

Part a) of the third hypothesis of AIM-II was that BD patients with mood-congruent psychosis would have higher premorbid IQ scores than those with mood-incongruent psychosis. No significant result was however found between the two subgroups of psychotic BD patients.

One possible explanation for the lack of finding might be attributable to the inequality in the distribution of congruency-type across the two original datasets (EPII and STOP-EM). However, supplementary analyses conducted on the STOP-EM study alone did not change the results
obtained by the full set of psychotic BD patients. Such findings might imply that mood congruency is not a vital component to premorbid IQ deficits in BD-I patients who experience psychosis.

5.3.2 Trajectory of IQ change across mood-congruent and –incongruent psychosis

Part b) of the third hypothesis of AIM-II was that mood-incongruent BD patients would have steeper IQ decline than those with mood-congruent psychosis. Although no significant relationship was found between IQ change and mood congruency, a trend did appear: psychotic patients with mood-congruent, but not –incongruent, features experienced some IQ decline across illness onset. This novel finding was unexpected as the literature on mood congruency generally demonstrates that individuals with mood-incongruent symptoms experience worse overall functioning (see Section 1.3.2).

Follow-up analyses conducted on STOP-EM subjects alone confirmed a significant interaction between congruency-type and IQ change, such that BD subjects with mood-congruent psychotic features had a worsening of IQ levels across illness onset, while those with mood-incongruent features did not show a decline in IQ.

5.3.3 Current IQ and mood congruency

To further our knowledge of the impact of mood congruency on IQ, I investigated the relationship between composite K-BIT IQ levels and congruency type. This analysis found mood-incongruent psychotic patients to have significantly higher current IQ scores compared to their congruent counterparts. Again, this was an interesting and unexpected outcome, as one
would predict patients with mood-incongruent features to have worse intellectual functioning than those with congruent features, due to their severe clinical symptoms.

Together with the above findings on premorbid IQ and IQ trajectory, these results imply that, while psychotic BD patients generally have lower premorbid IQ scores than their non-psychotic counterparts, no such distinction can be made between patients with congruent and incongruent features. Stated differently, although the expression of psychosis could be tied to early brain pathology and correlates with deficits in premorbid IQ, the distinction in congruency-type might only affect IQ at illness onset (and in the opposite direction). Furthermore, while there exist some indications that mood-congruent patients have better functional outcomes than mood-incongruent patients (see Section 1.3.2), this is the first study to compare these two psychotic subgroups of BD on any aspect of cognitive or intellectual functioning. It is thus possible that despite their overall worse disposition, mood-incongruent BD patients maintain intact IQ levels, and another feature of their clinical presentation may associate with poorer functioning. However, an alternative post-hoc explanation might be that the preservation of IQ in mood-incongruent patients is a consequence of the type of antipsychotic treatment they received at illness onset. This idea is further explored in the next sub-section.

5.3.4 IQ and medication

Amongst the demographic and clinical variables compared, the sole factor that differed across congruent and incongruent patients was the type of antipsychotics that BD individuals were taking at the time of testing. Mood-incongruent patients, who had the least amount of IQ decline
across illness onset, were also treated more frequently with quetiapine compared to mood-congruent patients.

Supplementary exploratory analyses on the relationship between IQ change and the type of antipsychotic that psychotic BD patients received revealed that, across both subgroups, those treated with quetiapine maintained a high IQ, while the IQ of those treated with risperidone or olanzapine were more likely to decline after illness onset, suggesting a potentially protective effect on cognitive functioning for quetiapine. Interestingly, a number of studies support this idea. Findings from recent studies on euthymic BD patients have illustrated that those treated with quetiapine (either alone, Torrent et al., 2011, or in conjunction with a mood stabilizer, Kozicky et al., 2013; Kozicky, Torres, Bond, Lam, & Yatham, 2012), had superior cognitive performance on learning, memory and verbal fluency tasks (Torrent et al., 2011), as well as executive function tasks (Kozicky et al., 2013, 2012), compared to those treated with risperidone (either alone, Torrent et al., 2011, or in conjunction with a mood stabilizer, Kozicky et al., 2013, 2012). Moreover, the clinical benefits of quetiapine on patients’ symptomology and overall functioning have been corroborated by the guidelines of the Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders (Yatham et al., 2009).

The mechanics of the effects of quetiapine on neural transmission have been explored in the SZ population, where differences found on measures of cognition across various antipsychotics have been attributed to quetiapine’s relative strong affinity to serotonin 5-HT2 receptors and its low binding affinity to dopamine receptors (Arnt & Skarsfeldt, 1998; Dev & Raniwalla, 2000; Riedel et al., 2007; Seeman, 2002). During tonic dopaminergic transmission, risperidone and
quetiapine seem to bind the same proportion of receptors. However, during phasic transmission (activity-dependent), while quetiapine dissociates rapidly to allow some of the dopaminergic signaling through, risperidone minimally dissociates with the receptors, hindering the inherent physiological dopaminergic signaling (Dev & Raniwalla, 2000; McIntyre, Soczynska, Woldeyohannes, Alsuwaidan, & Konarski, 2007).

Furthermore, quetiapine’s main metabolite, N-desalkyl quetiapine, is also an efficient noradrenergic transporter inhibitor, which leaves more noradrenaline at the synapse of neurons in the prefrontal cortex and helps relieve depression-like, as well as negative, symptoms (Calabrese et al., 2005; Dev & Raniwalla, 2000; McIntyre et al., 2007; Pira, Mongeau, & Pani, 2004; Sokolski & Denson, 2003). Therefore, in the patients participating in this study, it is possible that quetiapine may have been offered more commonly to patients who presented with psychotic symptoms that were incongruent in nature. In this light, the potentially protective cognitive effect of quetiapine in mood-incongruent patients might have simply been a propitious by-product of the antipsychotic. Clearly, more work is needed to follow up on this idea.

5.4 Clinical implications

Given the pattern of information in the literature and the findings of this thesis, one could infer that deficits in estimated premorbid IQ scores are suggestive of intellectual deficits before the onset of the illness, perhaps as a consequence of early neurodevelopmental pathology. Ideally, it would be best to obtain premorbid IQ levels in young individuals to help predict the onset of subsequent psychopathologies. Unfortunately, this information is rarely available in clinic and, instead, measures that can estimate pre-illness IQ are used. However, one must take caution in
applying the NAART predicted premorbid IQ method in practice, as there is a large variation in NAART-predicted IQ scores across and within all the patients groups (see Figure 1), which reflects the heterogeneity of intellectual functioning across these psychopathologies and healthy controls. The post-hoc analyses conducted in Section 4.4 on the predictability value of the NAART as an estimate of premorbid IQ demonstrated that researchers and clinicians must take caution when using this tool in populations who have below-average IQ scores, as it may reveal misleading IQ declines by overestimating premorbid IQ.

Finally, the specific features of the symptoms that BD patients present with (psychosis, congruency type) should be followed meticulously as they could also provide insight on the trajectory and etiology of their illness.

5.5 Limitations

Although a rigorous method was applied to the analyses of this thesis, a number of limitations exist; I address these below.

5.5.1 Validity of the NAART as a measure of premorbid IQ

The post-hoc analyses conducted in Section 4.4 found a discrepancy of about 8 points between obtained and estimated IQ in healthy controls with low-IQ scores, which is comparable to the standard error of the mean dictated by the full-scale WAIS formula based on NAART errors (i.e., S.E. = 7.63).
The findings indicate that the NAART may overestimate premorbid IQ in individuals with below-average IQ and may underestimate premorbid IQ in those with above-average IQ. This finding could imply that the premorbid IQ scores of SA and SZ patients are in reality lower than those estimated by the NAART. Thus, the reported decline in IQ in SA and SZ might be to some degree artifactual, such that SA and SZ individuals might have large deficits in intellectual functioning before the onset of their illness that is maintained, and not worsened, across illness onset. However, longitudinal cohort studies that used actual pre- and post-onset illness IQ scores have shown that IQ does indeed decline in the SZ population (Meier et al., 2014; Seidman et al., 2006). While, no such comparison has been performed in SA, the SZ findings give some indication that the findings from this thesis study are still valuable.

Moreover, the results on the NAART do not invalidate the findings of this study as the distribution of the low-IQ control group selected was biased given that subjects were not randomly selected from the population to compare them to the patient sample. Hence, while the results do draw our attention towards the need for a better premorbid IQ measure in low-IQ populations, they do not affect the analyses between and within the control and BD groups.

It is improbable that the NAART’s predictability issues substantially affected the psychosis analyses as there were no significant differences in current IQ scores between the two groups, and both psychotic and non-psychotic BD patients displayed average IQ levels. In the congruency analyses, it is possible that premorbid IQ was underestimated in mood-incongruent patients, and that they may have experienced some decline in IQ across illness onset. Moreover, it is possible that premorbid IQ was overestimated in mood-congruent psychotic patients, such
that they may have had deficits before the onset of their illness that was maintained, and not worsened, across illness onset. However, as previously mentioned, given that the BD group generally showed average IQ levels, it is unlikely that these subjects’ premorbid IQ scores were influenced by the NAART’s imperfect predictability power.

5.5.2 Comparability of the K-BIT as a measure of current IQ to the standard WAIS

While most studies use the WAIS as a measure of current IQ levels, both of the first-episode studies (STOP-EM and EPII) used the K-BIT. Therefore, the measure of IQ change was based on premorbid IQ (from NAART scores transformed into full-scale WAIS scores) and current IQ (based on composite K-BIT scores). As a consequence, the comparability of these non-identical scores might be called into question, along with their influence on the overall results.

A number of studies have investigated the strength of the correlation between composite K-BIT and full-scale WAIS scores. They have unanimously found a very strong association (r = .88-.89) between the two tests across healthy adults (Kaufman & Kaufman, 1990; Walters & Weaver, 2003), as well as psychiatric (Hays, Reas, & Shaw, 2002) and clinical populations (Naugle, Chelune, & Tucker, 1993). The association between these IQ tests and education level, an important variable in most standardized IQ tests, is also comparable (Kaufman, Kaufman, Liu, & Johnson, 2009; Naugle et al., 1993). While most researchers accept the K-BIT as robust measure of intellectual functioning, one study found that the K-BIT overestimated IQ scores in clinical patients by about 5 points compared to the WAIS-R (Naugle et al., 1993). Moreover, in our sample, the correlation between estimated full-scale WAIS (e.g., NAART score) and composite IQ K-BIT was of $r = .54$, which is lower than those typically reported between NAART and WAIS.
If we were to consider the implications of this difference on my current results, it would imply that any IQ change detected across the patients groups might be even larger than what was found to be significant, as current IQ scores might in reality be lower than those observed. In other words, the groups of SA, SZ, and mood-congruent psychotic BD patients might have even more IQ decline at illness onset than expected.

5.5.3 Study design issues

By combing two large datasets of participants from two first-episode programs, it is inevitable to run into a few methodological issues. While mostly comparable, the STOP-EM and EPII studies differed to some extent on their sampling of participants. For instance, the STOP-EM study matched controls to patients’ age and gender, but the EPII did not. Thus, it might seem inappropriate to compare (or combine) subjects from one study to the other. However, considering that participants from both datasets did not significantly differ on critical demographic and clinical variables (see Sections 4.1 and 4.2), it would be safe to assume that the amalgamation of the STOP-EM and EPII studies did not have a substantial effect on the results that were derived from them.

Moreover, since patients were followed for different lengths of time before being categorized under a DSM-IV label, it is important to consider the possibility that some patients might have experienced a change in their diagnostic label as a consequence of future symptoms. For example, a BD patient who starts experiencing psychotic symptoms outside of a mood episode for an extended amount of time might later obtain a SA diagnosis. Caution should thus be taken
when applying the IQ patterns drawn from the average scores of each group to individual psychiatric patients.

Lastly, the naturalistic design of this study implied that patients were not randomized into specific treatment groups, rather medication was given on an individual response-based approach. Therefore, any examination of medication effects needs to be considered as a post-hoc exploratory analysis.

Despite these limitations, this study succeeded in capturing a glimpse of the intellectual functioning of a representative sample of BD, SA and SZ patients across their illness-onset.
Chapter 6: Conclusion

Although the commonalities that psychiatric disorders, such as BD, SA and SZ, share are indubitably prominent, the findings of this study espouse the notion that primary-psychotic disorders and mood-disorders might have differential early brain pathologies that results in low premorbid IQ and large deficits in IQ change across illness onset in SZ and SA, and somewhat normal premorbid IQ, along with minimal IQ change, in BD. These patterns of IQ support the findings of previous researchers about the deficits found in SZ patients, and provide more clear evidence for deficits in SA patients and IQ preservation in the BD population.

This thesis research is the first to elucidate a number of unresolved questions about the influence of psychosis and mood-congruency on intellectual functioning. This unique examination of trajectories of IQ change in BD patients revealed that low premorbid IQ might contribute to the risk of psychosis later in life, while mood-congruency may affect IQ after illness-onset, but not in the hypothesized direction. BD patients experiencing mood-incongruent psychotic symptoms maintain IQ levels, while patients with mood-congruent features show a decline in IQ across illness onset. One possible post-hoc explanation for this surprising finding might be that certain atypical antipsychotic (i.e., quetiapine) help preserve IQ, although this needs to be investigated further.

While a future longitudinal study with a larger sample size of at-risk individuals could help reinforce the findings obtained here, the significance of the current results should not be underestimated. In the future, estimations of trajectories of IQ change could have the potential to
be a useful tool for clinicians to improve their diagnostic decision, as well as the symptom management options for their patients.
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Appendices

Appendix A  IQ measures

A.1  NAART word list

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A.2 K-BIT examples

Example of the expressive vocabulary portion of the K-BIT’s verbal IQ section:

“Name this”

Example of the Definitions portion of the K-BIT’s verbal IQ section:

“What word fits?”

Lights the room
L  M

Example of the matrix portion of the K-BIT’s non-verbal IQ section:

“With which object does the teapot fit?”
Appendix B  Clinical variables

B.1  Clinical global impression scale
The CGI (Guy, 1976) is widely used in psychiatry to assess patients’ global functioning prior to and after initiating treatment. This brief rating provides a clinician’s view on how well an individual is functioning clinically based on psychosocial history and reported and observed symptoms in the past week. Although there are two main portions to this test, the severity and the improvement scale, only the baseline severity scores were included for the purpose of my research questions. The CGI-Severity asks clinicians to answer a single question: “Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?” The answer is rated on a 7-point scale, where 1 = normal; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients. Its validity and reliability have been verified in individuals with SZ (Haro et al., 2003; Leucht et al., 2006; Rabinowitz, Mehnert, & Eerdekens, 2006) and mood disorders (Leon et al., 1993; Spearing, Post, Leverich, Brandt, & Nolen, 1997) amongst others.

B.2  Global assessment of functioning scale
The GAF is a simple rating scale that was first included as Axis V in the DSM-III-R and was retained in DSM-IV and DSM-IV-R (APA, 1994). It assesses individuals’ psychological, social and occupational functioning on a continuum scale of 1 to 100, separated by 10-point intervals. The validity and reliability of this measure has been illustrated in mentally ill individuals (Jones, Thornicroft, Coffey, & Dunn, 1995) and SZ patients specifically (Schwartz, 2007; Startup, Jackson, & Startup, 2010).
B.3 Positive and negative symptoms scale

The PANSS (Kay, Fiszbein, & Opler, 1987) is a 30-item instrument that assesses psychiatric patients’ positive and negative symptoms as well as global psychopathology on a 7-point rating scale, where (1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate severe, 6 = severe, and 7 = extreme). Out of all the listed items, 7 are aimed at evaluating positive symptoms, 7 for negative symptoms, and 16 for global psychopathology. Each item is precisely defined and anchor points are given for the rating of each item. For this study, only the positive subscale was used to examine symptoms of delusion, conceptual disorganization, hallucinatory behaviour, excitement, grandiosity, suspiciousness/persecution and hostility. Thus, the range of possible PANSS positive subscale was 7-49. The literature supports the reliability, validity and stability of this measure in SZ patients, with positive and negative scores emerging as independent constructs with normal distributions (Kay et al., 1987; Peralta & Cuesta, 1994).

B.4 Hamilton rating scale for depression

The HAM-D is a popular instrument for the assessment of depression severity in mentally ill patients (Hamilton, 1986). In the FEM study’s version, 29 items were rated for increasing intensity and frequency of patients’ symptoms by a trained clinician. Eight items are scored on a 5-point scale, ranging from 0 = not present to 4 = severe, and 9 are scored from 0-2 (0 = not present, 1 = mild, 2 = severe). Based on the sum of the first 17 items, a total of 0-7 is representative of a normal mental state, 8-13 reflects mild depression, 14-18 moderate depression, 19-22 severe depression, and a score of 23 or more reflects very severe depression. The utility, reliability and validity of this scale in psychopathology have been reaffirmed multiple times (Hedlund & Vieweg, 1979; Rehm & O’Hara, 1985).