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Assessing the potential to use neurocognition to predict who is at risk for developing bipolar disorder: a review of the literature

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Abstract

Introduction—The importance of early intervention strategies has recently been recognized in the field of psychiatry. Although early intervention strategies in schizophrenia have been extensively studied, recent efforts to identify individuals who are at increased risk for other disorders, such as bipolar disorder, have gained significant interest. There is some available data to suggest that cognitive deficits may precede the onset of mania, therefore it would be beneficial to identify cognitive predictors of bipolar disorder in an effort to facilitate early intervention.

Methods—We conducted a literature review of conscript, cohort, high-risk, family based and first-episode mania studies that assessed neurocognition in order to ascertain potential cognitive predictors of bipolar disorder. Results: There is little evidence that individuals at risk for bipolar disorder exhibit deficits in global measures of neurocognition, such as IQ. However, deficits in specific neurocognitive domains, including verbal memory and executive function, appear to represent potential predictors of bipolar disorder.

Conclusions—These conclusions are preliminary; however they provide a starting point for future work. Additional efforts toward understanding both the clinical and cognitive prodrome will be important in elucidating the pathophysiology of bipolar disorder.

Keywords

bipolar disorder; cognition; predictors; verbal memory; executive function; prodrome

Introduction

In keeping with other areas of chronic mental and physical illness, the importance of prevention in bipolar disorder has been increasingly recognized throughout the field. The advancement of early intervention in schizophrenia can serve as a useful template in early bipolar prevention studies, especially given the similarity of major clinical symptoms (Berrettini, 2003), neurocognitive deficits (Krabbendam, Arts, van Os, & Aleman, 2005) and the significant genetic overlap between the two disorders (Purcell, Wray, Stone, Visscher, O'Donovan, Sullivan et al., 2009). Early intervention studies in schizophrenia have been

actively investigating predictors of schizophrenia with a major goal to prevent the onset of psychosis. Similarly, identifying predictors of bipolar disorder will be essential in determining who should receive early intervention and which features of the disorder should be targeted. Preventing the onset of mania would preempt the lifelong, devastating effects that are associated with the disorder (Post, Denicoff, Leverich, Altshuler, Frye, Suppes et al., 2003).

Researchers are just beginning to scratch the surface of identifying clinical predictors of mania (e.g., Correll, Penzner, Frederickson, Richter, Auther, Smith et al., 2007), however it has become increasingly evident that multiple predictors should be used in order to develop models that more accurately identify who is at greatest risk (e.g., Cannon, Cadenhead, Cornblatt, Woods, Addington, Walker et al., 2008). Investigating clinical and cognitive predictors of bipolar disorder would significantly enhance our ability to accurately predict risk. The purpose of this review is to identify potential cognitive predictors of bipolar disorder that could be used to identify individuals who are at increased risk for the disorder. Specifically, we investigate if there is evidence that neurocognitive measures are sensitive to differentiate the at-risk subjects for bipolar disease from healthy controls and specific to differentiate between subsequent converters and non-converters to bipolar disorder as well as distinguish converters to bipolar disorder from converters to schizophrenia or unipolar affective disorders. Complications with this line of research will be discussed, as well as suggestions for future directions.

IQ as a predictive measure of bipolar disorder

Conscript studies—There has been an abundance of research on the utility of using premorbid IQ as a measure to predict future psychiatric illness (Burdick, Gunawardane, Woodberry, & Malhotra, 2009). Different methodologies can contribute to our knowledge of how IQ may be used as a risk factor. Conscript studies take advantage of large, young adult male populations that are enlisted in military service by requiring certain neurocognitive tests, such as IQ, prior to enlisting in service. Several conscript studies have evaluated whether measures of IQ in healthy males could be used to predict a later diagnosis of bipolar disorder. Overall, studies do not find a relationship between IQ at baseline and a later diagnosis of bipolar disorder (Mortensen, Sorensen, Jensen, Reinisch, & Mednick, 2005; Reichenberg, Weiser, Rabinowitz, Caspi, Schmeidler, Mark et al., 2002; Zammit, Allebeck, David, Dalman, Hemmingsson, Lundberg et al., 2004). However, one early study reported that individuals who later became manic (i.e. pre-bipolar subjects) had higher intelligence scores compared to controls, whereas individuals who later became schizophrenic (i.e. pre-schizophrenia subjects) had lower intelligence scores compared to controls (Mason, 1956). Another study showed that the risk for bipolar disorder increased as a function of decreased performance on a visuospatial reasoning subtest and increased performance on an arithmetic subtest (Tiihonen, Haukka, Henriksson, Cannon, Kieseppa, Laaksonen et al., 2005). Therefore, although data are mixed, there is little evidence to suggest that lower premorbid IQ is predictive of bipolar disorder, with some findings to indicate that an increased IQ may be predictive. This is contrary to the overwhelming literature that has shown a relationship between low premorbid IQ and the development of schizophrenia (David, Malmberg, Brandt, Allebeck, & Lewis, 1997; Davidson, Reichenberg, Rabinowitz, Weiser, Kaplan, & Mark, 1999; Gunnell, Harrison, Rasmussen, Fouskakis, & Tynelius, 2002); a finding that is conserved when directly comparing pre-schizophrenia and pre-bipolar subjects (Reichenberg et al., 2002).

Cohort studies—Another method that has been utilized to identify predictors of future psychiatric risk is to study large birth cohorts longitudinally. Only a few cohort studies have reported predictors of mania, primarily due to the small sample of pre-bipolar subjects in

these populations (less than 1%). Results from the Dunedin birth cohort initially suggested pre-bipolar subjects (N=20) did not differ from controls on IQ measures (Cannon, Caspi, Moffitt, Harrington, Taylor, Murray et al., 2002). However, at a later follow-up, higher IQ increased risk for mania in a smaller sample (N=8) of subjects (Koenen, Moffitt, Roberts, Martin, Kubzansky, Harrington et al., 2009). A more recent study in a large sample of pre-bipolar subjects (N=280) revealed that individuals with either low or high grades in school had a 2-fold and 4-fold risk for mania, respectively (MacCabe, Lambe, Cnattingius, Sham, David, Reichenberg et al., 2010). These studies also confirmed that a low IQ is predictive of schizophrenia spectrum disorders (Cannon et al., 2002; Koenen et al., 2009).

Longitudinal studies in high-risk samples—Only two studies have provided prospective data on pre-bipolar subjects. In one study of individuals at clinical high-risk (CHR) for schizophrenia, 8 subjects eventually developed bipolar disorder (Olvet, Stearns, McLaughlin, Auther, Correll, & Cornblatt, 2010). Neither premorbid nor current IQ differed between the pre-bipolar subjects and the non-converter control subjects. In another study, 9 individuals at genetic high-risk (GHR) for bipolar disorder (i.e. offspring of a bipolar parent) who developed a manic episode in early adulthood were compared to GHR subjects without a mood disorder diagnosis in early adulthood (Meyer, Carlson, Wiggs, Martinez, Ronsaville, Klimes-Dougan et al., 2004). The pre-bipolar group had a significantly lower performance IQ than the healthy GHR subjects, but comparable verbal and full-scale IQ scores. However, it is important to note that, although different from controls, the performance IQ scores for the pre-bipolar individuals were well within the normal range when compared with normative data.

Family-based studies—Bipolar family studies provide data on an enriched sample of individuals with elevated genetic loading for bipolar disorder by virtue of shared DNA with the affected proband. With prevalence estimates of 7–22% (Merikangas, Chakravarti, Moldin, Araj, Blangero, Burmeister et al., 2002), the risk for bipolar in first degree relatives is approximately 10-fold that in the general population (1.5%; Kessler, McGonagle, Zhao, Nelson, Hughes, Eshleman et al., 1994), and monozygotic concordance (40–43%) is significantly higher than that noted in dizygotic twins (5–6%; Kieseppa, Partonen, Haukka, Kaprio, & Lonnqvist, 2004; McGuffin, Rijdsdijk, Andrew, Sham, Katz, & Cardno, 2003) suggesting a substantial genetic contribution to the etiology of the illness. Although most individuals with a family history of bipolar won't develop the disorder, data from this sample could provide insight into which cognitive deficits are linked to the underlying genetic risk.

Twin studies consistently report normal IQ in both affected and unaffected twins when compared with healthy controls (Gourovitch, Torrey, Gold, Randolph, Weinberger, & Goldberg, 1999; Kieseppa, Tuulio-Henriksson, Haukka, Van Erp, Glahn, Cannon et al., 2005; Pirkola, Tuulio-Henriksson, Glahn, Kieseppa, Haukka, Kaprio et al., 2005). There is also no difference when comparing unaffected siblings (non-twins) and healthy controls on measures of IQ (Keri, Kelemen, Benedek, & Janka, 2001). Some studies report that unaffected offspring of bipolar parents have a lower IQ compared to healthy controls (Klimes-Dougan, Ronsaville, Wiggs, & Martinez, 2006; Maziade, Rouleau, Gingras, Boutin, Paradis, Jomphe et al., 2009), whereas one study reported comparable IQ but lower scores on academic achievement measures in unaffected bipolar offspring (McDonough-Ryan, DelBello, Shear, Ris, Soutullo, & Strakowski, 2002). One limitation to the interpretation of these data is that several of these studies included offspring who were unaffected with regard to bipolar disorder but who carried various other comorbid diagnoses (Klimes-Dougan et al., 2006; Maziade et al., 2009); therefore, it is possible that the reduced IQ can be accounted for by the presence of other psychiatric symptoms/syndromes. One study that included offspring who were unaffected by any Axis I disorder reported no differences on

current IQ when comparing unaffected bipolar offspring and controls (Frangou, Haldane, Roddy, & Kumari, 2005).

First-episode mania studies—Data from first-episode mania studies are also informative towards understanding potential IQ deficits in this population. Although these patients have already been diagnosed with the disorder, factors contributing to the deterioration of cognition, such as chronic medication use and repeated affective episodes (Martinez-Aran, Vieta, Reinares, Colom, Torrent, Sanchez-Moreno et al., 2004), are minimized in this population. Measures of premorbid and current IQ have been consistently found to be comparable in first-episode bipolar patients and healthy controls (Hill, Reilly, Harris, Rosen, Marvin, Deleon et al., 2009; Torres, DeFreitas, DeFreitas, Kauer-Sant'Anna, Bond, Honer et al., 2010; Zanelli, Reichenberg, Morgan, Fearon, Kravariti, Dazzan et al., 2010), with a single exception (Barrett, Mulholland, Cooper, & Rushe, 2009). When directly comparing first-episode bipolar patients with first-episode schizophrenia subjects, schizophrenia patients typically had lower current (Barrett et al., 2009; Zanelli et al., 2010) and premorbid IQ (Zanelli et al., 2010) than bipolar subjects, although this finding was not consistent across all studies (Hill et al., 2009).

Summary of IQ findings—Overall, there is no compelling evidence to suggest that IQ deficits are predictive of bipolar disorder. In fact, there are a few studies that find the opposite pattern, with higher IQ predicting a subsequent onset of bipolar disorder. Moreover, even when significant group differences are reported, IQ values are typically within the normal range, representing a non-specific predictor which could be explained by the ascertainment of “supernormal” control subjects. Therefore, it appears that general measures of cognition are not viable as a predictor of bipolar disorder. This may not be surprising based on the profile of impairment in patients with bipolar illness, with more domain-specific deficits representing the most persistent cognitive traits (Burdick et al. 2009). Perhaps the identification of more specific cognitive deficits will be beneficial in the search for such cognitive predictors.

Deficits in specific cognitive domains as a predictive measure of bipolar disorder

IQ findings are informative in assessing global neurocognitive functioning; however, IQ does not provide a fine grained analysis of the neurocognitive deficits that may be more directly related to the pathophysiology of a specific disorder. By administering a neurocognitive battery that utilizes measures that tap into different domains, such as attention, verbal memory, and executive function, we can begin to understand specific deficits that characterize the disorder. Unfortunately, conscript and birth cohort studies typically focus on IQ, limiting the type of available data in individuals prior to the onset of bipolar disorder. Complicating matters further, high risk, family-based and first-episode studies have not administered the same neurocognitive tests, thus it is difficult to directly compare results across studies. Regardless, some consistent findings have been reported and may provide some insight into which deficits exemplify bipolar disorder.

Longitudinal studies in high-risk samples—There is a paucity of prospective data on specific cognitive deficits in individuals who will later develop bipolar disorder. Meyer and colleagues (2004) found that 67% of pre-bipolar subjects were impaired on the Wisconsin Card Sorting Task (WCST), a measure of executive functioning. Moreover, the combination of WCST impairment and patient reports of early attentional problems predicted the subsequent onset of bipolar disorder, but not unipolar depression. In work by our group, a neurocognitive composite score did not differ when comparing pre-bipolar and pre-schizophrenia subjects; however, there was a large degree of heterogeneity in the pre-bipolar subject scores (Olvet et al., 2010).

Family-based studies—Twin and sibling studies reliably report that unaffected siblings of bipolar patients have deficits in memory-related tests when compared to healthy controls. Verbal memory (Gourovitch et al., 1999; Keri et al., 2001; Kieseppa et al., 2005) and tests of declarative and working memory (Christensen, Kyvik, & Kessing, 2006) are especially impaired in unaffected siblings. Likewise, unaffected offspring of bipolar parents have deficits in verbal and visual memory (Klimes-Dougan et al., 2006; Maziade et al., 2009), and executive functions (Klimes-Dougan et al., 2006; Maziade et al., 2009). Response inhibition is also impaired in unaffected offspring (Frangou et al., 2005) and there were trends that suggest attention may be impaired (Klimes-Dougan et al., 2006; Maziade et al., 2009). Limited data also point toward a possible resilience or compensatory factor in unaffected relatives of patients with bipolar disorder, with unaffected relatives outperforming healthy controls on certain measures of attention (Pirkola et al., 2005) and executive function tasks (Frangou et al., 2005).

Few studies directly compared unaffected siblings or offspring of individuals with bipolar disorder and schizophrenia. Studies tend to support more impairment in unaffected first-degree relatives of individuals with schizophrenia on attention (Pirkola et al., 2005), working memory (Keri et al., 2001) and visual backward masking tasks (Keri et al., 2001). One study found that unaffected first-degree relatives of individuals with bipolar disorder made more errors on an executive function task compared to unaffected first-degree relatives of individuals with schizophrenia (Maziade et al., 2009); however, this study included offspring with a high genetic loading for both bipolar disorder and schizophrenia, making the group vulnerable to both disorders.

First-episode mania studies—Similar to data from GHR studies in bipolar disorder, first-episode mania studies consistently show deficits in visual, verbal, and working memory compared to healthy controls (Barrett et al., 2009; Hill et al., 2009; Torres et al., 2010; Zanelli et al., 2010). Other domains in which first-episode mania patients performed significantly worse than healthy controls included attention (Torres et al., 2010), language (Barrett et al., 2009; Zanelli et al., 2010), spatial reasoning (Torres et al., 2010), response inhibition (Barrett et al., 2009) and executive functioning (Barrett et al., 2009; Torres et al., 2010). It is important to note that in many cases patients were assessed before symptoms had fully remitted; therefore, the effects of acute mania on neurocognitive functioning cannot be ruled out in these studies.

Consistent with the literature that suggests that individuals with schizophrenia have more severe neurocognitive deficits than individuals with bipolar disorder (Krabbendam et al., 2005), first-episode studies that directly compared the two groups reported more impairment in individuals with schizophrenia globally (Hill et al., 2009) and across multiple domains (Zanelli et al., 2010).

Summary of domain findings—In general, executive function and memory (both verbal and visual) appear to be affected in individuals at risk for bipolar disorder, as well as those in the early phase of the disorder. Thus, these domains represent the most promising avenue for identifying cognitive predictors. It is perhaps surprising that deficits on tests of attention were not more robustly associated with the risk for the illness given the fact that difficulties concentrating and overactivity are clinical characteristics of bipolar disorder alongside the high comorbidity noted with ADHD in both children and adults (Kim & Miklowitz, 2002; Kowatch, Youngstrom, Danielyan, & Findling, 2005; Wingo & Ghaemi, 2007). Additional studies will be necessary to disentangle the effects of comorbid diagnoses and to further elucidate the overlap between clinical and cognitive aspects of attention in bipolar patients.

Discussion

Summary of findings

The challenge in identifying cognitive predictors of bipolar disorder begins with the relative paucity of research on the topic. The schizophrenia prodrome has been well characterized and has been researched for decades, yielding significant findings that point towards clinical and cognitive predictors (Cannon et al., 2008; Lencz, Smith, McLaughlin, Auther, Nakayama, Hovey et al., 2006; Seidman, Giuliano, Meyer, Addington, Cadenhead, Cannon et al., 2010). However, the field of bipolar disorder has yet to firmly establish the presence of a prodrome or to identify clear, replicated clinical/cognitive predictors for the disorder. Through this review, some potential cognitive predictors have been identified, which may serve as a starting point to guide future studies.

In general, IQ does not appear to be a viable cognitive predictor of bipolar disorder. Most studies agree that there is no significant IQ deficit in individuals before they develop bipolar disorder (Cannon et al., 2002; Meyer et al., 2004; Mortensen et al., 2005; Olvet et al., 2010; Reichenberg et al., 2002; Zammit et al., 2004), if they are at high-risk for the disorder based on family history (Frangou et al., 2005; Gourovitch et al., 1999; Kieseppa et al., 2005; Pirkola et al., 2005), or if they are in the early stages of the disorder (Hill et al., 2009; Torres et al., 2010; Zanelli et al., 2010). There is even some evidence to suggest that an increased IQ may be predictive of bipolar disorder (Koenen et al., 2009; MacCabe et al., 2010; Mason, 1956). This is in stark contrast with the schizophrenia literature which consistently finds IQ deficits in those at increased risk (David et al., 1997; Davidson et al., 1999; Gunnell et al., 2002) and in the early stages of the disorder (Barrett et al., 2009; Zanelli et al., 2010). Therefore, schizophrenia is characterized by a generalized cognitive impairment, whereas bipolar disorder may be characterized by more specific cognitive deficits.

Specific neurocognitive domains that show promise as cognitive predictors of bipolar disorder include memory and executive function. Deficits in these domains were detected in unaffected siblings (Christensen et al., 2006; Gourovitch et al., 1999; Keri et al., 2001; Kieseppa et al., 2005) and offspring (Klimes-Dougan et al., 2006; Maziade et al., 2009), as well as first-episode patients (Barrett et al., 2009; Hill et al., 2009; Torres et al., 2010; Zanelli et al., 2010). These findings are in line with what has been reported in chronic patients with bipolar disorder. Cognitive deficits in memory and executive function have been reported during acute episodes, as well as during euthymic periods (Fleck, Shear, Zimmerman, Getz, Corey, Jak et al., 2003; Martinez-Aran et al., 2004). In fact, convergent and meta-analytic data suggest that verbal memory, in particular, may be the most valuable endophenotype for bipolar disorder (Balanza-Martinez, Rubio, Selva-Vera, Martinez-Aran, Sanchez-Moreno, Salazar-Fraile et al., 2008; Glahn, Bearden, Niendam, & Escamilla, 2004). More research is needed before a prospective predictive model can be developed for bipolar disorder, but it is encouraging that there is a strong foundation in place for the field to progress in this direction.

Overall, the literature seems to suggest that memory and executive function deficits are sensitive to distinguishing at-risk subjects for bipolar disorder from healthy controls. However, it is unclear if there are domains that are specific for identifying at-risk subjects for bipolar disorder from those at risk for other psychiatric disorders. Performance on an executive function task differentiated pre-bipolar and pre-unipolar subjects (Meyer et al., 2004), and performance on working memory and visual backward masking tasks differentiated siblings of bipolar patients and siblings of schizophrenia patients (Keri et al., 2001). Clinical high-risk studies could focus on these domains as an initial effort to distinguish those who convert to bipolar disorder or schizophrenia, which would then be useful in prospective studies.

Potential problems with identifying cognitive predictors of bipolar disorder

Overlap with schizophrenia—Identifying cognitive processes that are impaired in bipolar disorder is just the first step towards pinpointing cognitive predictors. Such predictors must be specific to bipolar disorder in order for them to be optimally predictive. A great deal of genetic overlap between bipolar disorder and schizophrenia has been reported (Craddock, O'Donovan, & Owen, 2006; Purcell et al., 2009), as well as a significant similarity in neurocognitive profiles (Schretlen, Cascella, Meyer, Kingery, Testa, Munro et al., 2007). Similar deficits have also been observed in the unaffected relatives of both patient groups (e.g., Maziade et al., 2009).

Although verbal memory and executive function deficits are the two most promising cognitive predictors of bipolar disorder, they are not specific to bipolar illness, as deficits in these domains are common in individuals with schizophrenia (Zanelli et al., 2010) and in individuals at CHR for psychosis in general (Carrion, Goldberg, McLaughlin, Auther, Correll, & Cornblatt, 2011; Lencz et al., 2006; Seidman et al., 2010). Therefore, the lack of specificity of verbal memory as a cognitive predictor will impede its effectiveness in bipolar prediction models. A primary challenge is to identify any cognitive abnormality that is noted in bipolar patients that is not also seen in schizophrenia given the very broad and profound impairments seen in schizophrenia. Early work in the area of affective processing (utilizing measures such as affective go/no-go tasks) has provided some promising data on specificity when comparing bipolar patients with schizophrenics (Gopin, Burdick, Derosse, Goldberg, & Malhotra, 2011). Perhaps examining tasks that are specific to one disorder and not the other (e.g. affective processing) or combinations of specific deficits (e.g. executive dysfunction and attention problems) may be the next step towards identifying independent predictors of bipolar disorder. Heterogeneity of cognitive deficits in bipolar subjects

Finally, it may be difficult to identify cognitive predictors of bipolar disorder due to the variability in neurocognitive performance exhibited by individuals with the disorder. It has been consistently reported that individuals with bipolar disorder display less severe neurocognitive deficits than individuals with schizophrenia (Gourovitch et al., 1999; Pirkola et al., 2005). However, it is possible that this diminished signal is a result of averaging scores across individuals with a wide range of performance deficits, thus masking the identification of certain subgroups that have pronounced cognitive dysfunction. For example, Altshuler and colleagues (2004) reported a bimodal pattern for executive functioning, with one group of bipolar patients performing comparably to controls and another performing comparably to individuals with schizophrenia. More recently, Martino and colleagues (2008) found that 38% of their bipolar sample was not impaired on any cognitive domain, whereas 40% had some impairment and 22% had significant impairment. Reichenberg and colleagues (Reichenberg, Harvey, Bowie, Mojtabai, Rabinowitz, Heaton et al., 2009) carried out similar analyses in psychotic bipolar patients and found 60% of the sample had deficits at least 1 standard deviation below average, while the remaining 40% of the sample was not substantially impaired. Our own data highlight the difficulty in identifying a cognitive predictor of bipolar disorder due to the large variability in neurocognitive performance among pre-bipolar subjects (Olvet et al., 2010). Therefore, until there is a better understanding of why there is such heterogeneity in neurocognitive performance in individuals with bipolar disorder, it will be difficult to use neurocognition as a predictor.

The role of psychosis—Approximately 50–60% of patients with bipolar I disorder experience psychosis during acute episodes, while a substantial proportion never become psychotic (American Psychiatric Association, 2000). Several studies support the notion that the presence of psychotic symptoms in the course of the illness negatively affects cognitive

performance in individuals with bipolar disorder, even during periods of euthymia. Not only does performance, in general, appear to be affected by psychosis (Albus, Hubmann, Wahlheim, Sobizack, Franz, & Mohr, 1996), but some specific cognitive domains, such as verbal memory (e.g., Martinez-Aran, Torrent, Tabares-Seisdedos, Salamero, Daban, Balanza-Martinez et al., 2008), spatial working memory (Glahn, Bearden, Barguil, Barrett, Reichenberg, Bowden et al., 2007; Glahn, Bearden, Cakir, Barrett, Najt, Serap Monkul et al., 2006), and executive function (Glahn et al., 2007), are also influenced by psychosis history. These data suggest that a clinical presentation that is more similar to the schizophrenia syndrome is associated with greater frequency and severity of cognitive impairment in patients with bipolar disorder. Prediction models will require consideration of these findings when evaluating risk factors that might be specific for psychotic bipolar disorder as opposed the full bipolar spectrum.

Future directions

There is a great deal of work yet to be done in the effort to identify possible cognitive predictors of bipolar disorder. Although it is unclear if the bipolar and schizophrenia prodromes can be differentiated due to the significant overlap in neurocognitive deficits, it will ultimately be advantageous to differentiate these two populations before the onset of the disorder. The CHR approach in schizophrenia has led to a number of clinically important findings, including the identification of endophenotypic markers that enhance the prediction of psychosis (Cannon et al., 2008; Lencz et al., 2006) and treatment strategies that may reduce the risk for developing psychosis (Cornblatt, Lencz, Smith, Olsen, Ather, Nakayama et al., 2007). Researchers can take advantage of the progress made in the field of psychosis in order to expedite the development of identifying predictors for bipolar disorder, with the ultimate goal of preventing the onset of the disorder.

Identifying clinical predictors is an important first step towards understanding the pathophysiology of bipolar disorder that would allow us, in turn, to investigate cognitive predictors. Including mania-specific measures in a prospective assessment will be essential in establishing these predictors. Recently, investigators have attempted to use the CHR model in order to investigate the potential prodrome to bipolar disorder (Bechdolf, Nelson, Cotton, Chanen, Thompson, Kettle et al., 2010; Conus, Ward, Lucas, Cotton, Yung, Berk et al., 2010; Correll et al., 2007; Olvet et al., 2010; Skjelstad, Malt, & Holte, 2009). According to retrospective reports, between 45 and 96% of bipolar disorder patients reported prodromal symptoms at least one month prior to the full onset of bipolar disorder (Conus et al., 2010; Correll et al., 2007; Jackson, Cavanagh, & Scott, 2003; Mantere, Suominen, Valtonen, Arvilommi, & Isometsa, 2008). Other clinical features, such as temperament, have provided some evidence for predictability. For example, the Cyclothymic-Hypersensitive Temperament (CHT) questionnaire is the only measure that has been used to predict conversion to the bipolar spectrum (broadly defined) disorder in children and adolescents with depression (Kochman, Hantouche, Ferrari, Lancrenon, Bayart, & Akiskal, 2005). Perhaps focusing on specific mania symptoms, such as sleep disturbances and temperament, will allow for the differentiation between risk for bipolar disorder and schizophrenia.

Another fundamental step toward improving the potential for identifying cognitive predictors of bipolar disorder would be to establish a standard neurocognitive battery that specifically focuses on measures that tap into deficits exhibited by individuals with bipolar disorder. A committee was commissioned by the International Society for Bipolar Disorders to begin to evaluate the potential for a consensus battery. One of the recommendations made by the committee was to consider the use of a battery that might cross diagnostic boundaries and still serve the purpose of adequately tapping into the major domains of impairment in bipolar disorders. (Yatham, Torres, Malhi, Frangou, Glahn, Bearden et al., 2011). A recent study has provided evidence that the MATRICS Consensus Cognitive Battery (MCCB),

established for cognitive trials in schizophrenia (Green & Nuechterlein, 2004), might serve as a feasible platform for a similar battery specific to bipolar disorder (Burdick, Goldberg, Cornblatt, Keefe, Gopin, Derosse et al., 2011). Additional work and collaborative efforts will be necessary to optimize a battery that will serve to cross traditional diagnostic boundaries while simultaneously highlighting the more illness-specific impairments in bipolar disorder.

Once basic clinical and neurocognitive predictors have been explored, more complex models will allow for increased accuracy in identifying individuals who are truly at risk for developing bipolar disorder. Studies of the prodrome to psychosis have reported increased predictability and specificity when using a combination of factors, including clinical symptoms, functional capacity and neurocognitive performance (Cannon et al., 2008; Koutsouleris, Davatzikos, Bottlender, Patschurek-Kliche, Scheuerecker, Decker et al., 2011). Ultimately, a combination of clinical and cognitive factors may be the key to maximizing our ability to predict who will develop bipolar disorder. Meyer and colleagues (2004) reported that the combination of executive function deficits and problems with attention based on informant ratings were specific to pre-bipolar subjects, and not to pre-unipolar depression subjects. Comprehensive multivariate models are much more powerful than utilizing single predictors and may be the key to differentiating pre-bipolar subjects from healthy controls and from subjects who convert to other disorders (i.e. schizophrenia and unipolar depression).

Taking advantage of the methodology set in place for CHR research in psychosis may be a practical starting point. Prospective studies of individuals at CHR for psychosis have already identified pre-bipolar subjects (Olvet et al., 2010; Thompson, Conus, Ward, Phillips, Koutsogiannis, Leicester et al., 2003) and retrospective studies find that psychotic symptoms are present during the prodrome for bipolar disorder (Correll et al., 2007; Jackson et al., 2003). Thus, the CHR method has already established sensitivity in differentiating pre-bipolar subjects and healthy individuals. Moving forward, researchers should concentrate on differentiating pre-bipolar and pre-schizophrenia subjects by using measures that tap into mania-specific symptoms, temperament (i.e. the CHT), and neurocognitive markers (i.e. verbal memory, executive function).

As has been seen in other fields of medicine, an understanding of the correlates and predictors of an illness can serve to effectively identify early intervention strategies, with the ultimate goal of complete prevention. Although work in the field of bipolar disorders to this end is in its infancy, it will be critical moving forward. This review has served as a summary of where the field stands with the hope to motivate researchers to pursue this line of research and to inform future studies.

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Table 1

IQ as a predictive measure of bipolar disorder.

Study	Subjects	Main Findings ¹	Statistic Reported	Results	p-values
Conscript Studies					
Mortensen et al., 2005	Pre-Mood (N=15)	Pre-Mood = HC BPP scores	t-test	nr	0.46
	Pre-SZ (N=50)	Pre-SZ < HC BPP scores		nr	0.0003
Reichenberg et al., 2002	Pre-BP (N=68)	Pre-BP = HC IQ	Cohen's d	< 0.20	ns
	Pre-SZ (N=536)	Pre-SZ < HC IQ		0.32–0.60	< 0.0005
		Pre-SZ < Pre-BP IQ		-	< 0.05
Zammit et al., 2004	Pre-BP (N=108)	IQ did not predict BP	Adjusted Odds Ratio	0.99	0.78
	Pre-SZ (N=362)	Low IQ predicted SZ		1.26	< 0.001
Mason, 1956	Pre-BP (N=25)	Pre-BP had high AGCT scores	Chi square	17.65	0.001
	Pre-SZ (N=368)	Pre-SZ had low AGCT scores		32.60	0.02
Tiihonen et al., 2005	Pre-BP (N=100)	Low VR predicted BP	Adjusted Odds Ratio	1.41	< 0.0001
	Pre-SZ (N=621)	High ARTT predicted BP		0.81	< 0.008
		Low VR predicted SZ		1.35	< 0.0001
Cohort Studies					
Cannon et al., 2002	Pre-BP (N=20)	IQ did not predict BP	β	0.11	0.30
	Pre-SZF (N=36)	Low IQ predicted SZ		-0.33	0.01
Koenen et al., 2009	Pre-BP (N=8)	High IQ predicted BP	Adjusted odds ratio	3.10	0.03
	Pre-SZ (N=35)	Low IQ trend predicted SZ		0.69	0.07
MacCabe et al., 2010	Pre-BP (N=280)	Low school performance predicted BP	Adjusted hazard ratio	1.96	nr
		High school performance predicted BP		3.34	nr
High-risk Studies					
Olvet et al., 2010	Pre-BP (N=8)	Current IQ:	Post-hoc, Games-Howell		ns
	Pre-SZ (N=24)	Pre-BP = NCC		-	

Study	Subjects	Main Findings ¹	Statistic Reported	Results	p-values
		Pre-BP = Pre-SZ Pre-SZ < NCC Premorbid IQ: Pre-BP = NCC = Pre-SZ	F-test	- - 1.19	ns < 0.05 ns
Meyer et al., 2004	Pre-BP (N=9)	Pre-BP < HC Pre-BP < Pre-UP Pre-BP < Pre-UP	t-test PIQ FSIQ	2.913 3.519 1.972	0.007 0.002 0.059
Family-based studies					
Gourovitch et al., 1999	BP Twin Pairs (N=7)	Current IQ: Affected Twin = Unaffected Twin Affected = Unaffected = Normal Premorbid IQ: Affected Twin = Unaffected Twin Affected = Unaffected = Normal	t-test F-test t-test F-test	0.70 0.67 0.12 0.74	0.51 0.58 0.98 0.52
Kieseppa et al., 2005	BP Twins (N=26) Non-BP Co-Twins (N=19)	Affected Twin = Control Twin Co-Twins = Control Twin	β	-1.2 2.6	ns ns
Pirkola et al., 2005 ²	BP Co-Twins (N=16) SZ Co-Twins (N=32)	BP Co-Twin $\approx$ Control Twins BP Co-Twin > SZ Co-Twin	nr nr	nr nr	nr nr
Keri et al., 2001	BP SIB (N=20) SZ SIB (N=25)	BP SIB = SZ SIB = HC	F-test	1.84	0.18
Klimes-Dougan et al., 2006	BPO (N=43)	BPO < HC	F-test	8.89	< 0.004
Maziade et al., 2009	BPO (N=23) SZO (N=22)	BPO < HC SZO < HC BPO = SZO	Post-hoc, LSD (Cohen's d reported)	-0.99 -1.56 -0.57	0.0002 < 0.0001 0.06
McDonough-Ryan et al., 2002	BPO (N=28)	Current IQ: BPO = HC	t-test FSIQ VIQ	-1.6 -0.43	0.10 0.70

Study	Subjects	Main Findings ¹	Statistic Reported	Results	p-values
		Premorbid IQ: BPO < HC	PIQ Reading Spelling Arithmetic	-1.8 -2.2 -3.5 -2.3	0.07 0.03 0.01 0.03
Frangou et al., 2005	BPO (N=15)	BPO = HC	F-test	nr	ns
First episode studies					
Hill et al., 2009	BP (N=22) SZ (N=30)	Premorbid IQ: BP = SZ = HC Current IQ: BP = SZ = HC	F-test	2.14 2.21	ns 0.12
Torres et al., 2010	BP (N=45)	Premorbid IQ: BP = HC	F-test	0.1	0.76
Zanelli et al., 2010	BP (N=37) SZ (N=65)	Current IQ: Premorbid IQ:	Post-hoc, Bonferroni	-	ns <0.007 <0.007 ns <0.007
Barrett et al., 2009	BP (N=32) SZ (N=46)	Current IQ: Premorbid IQ:	Post-hoc, Bonferroni	-	<0.05 <0.01 <0.01 <0.05 <0.01 ns

¹ Current IQ score is reported unless otherwise specified.

² Findings reported in this table are based on the comparison of reported means, however Pirkola and colleagues did not report statistical comparisons between these groups.

Abbreviations: AGCT: Army General Classification Test; ARIT: Arithmetic; BP: Bipolar; BPO: Bipolar Offspring; BPP: Børge Priens Prøve; BP SIB: Bipolar Sibling; FSIQ: Full Scale IQ; HC: Healthy Control; LSD: Least Significant Different; NCC: Non-Conversion Control; nr: not reported; ns: non-significant; PIQ: Performance IQ; SZ: Schizophrenia; SZF: Schizophreniform; SZO: Schizophrenia Offspring; SZ SIB: Schizophrenia Sibling; UP: Unipolar; VIQ: Verbal IQ; VR: Visuospatial Reasoning.

Table 2

Neurocognitive domain as a predictive measure of bipolar disorder.

Study	Subjects	Main Findings	Statistic Reported	Results	p-values
High-risk Studies					
Meyer et al., 2004	Pre-BP (N=9)	Executive Function Pre-BP < HC Pre-BP < Pre-UP	Mann-Whitney, z	-3.159 -2.715	0.002 0.007
Olvet et al., 2010	Pre-BP (N=8) Pre-SZ (N=24)	Pre-BP = NCC Global Composite Pre-BP = Pre-SZ Global Composite	Post hoc, Games-Howell	- -	ns ns
Family-based studies					
Christensen et al., 2006	BP Co-Twins (N=21)	BP Co-Twins < HC Twins CAMCOR Scores	β	-0.62	0.002
Frangou et al., 2005	BPO (N=15)	BPO < HC Response Inhibition HSCT Cat. A Errors HSCT Cat. B Errors BPO > HC Executive Function WCST Categories WCST Persever. Errors	Post hoc, Bonferroni	- - - -	0.01 0.01 0.05 0.04
Gourovitch et al., 1999	BP Co-Twins (N=7)	BP Co-Twin < HC Twins Memory CVLT Long Free Recall CVLT Long Cued Recall CVLT Discriminability WMS Memory Quotient	Post hoc	nr nr nr nr	nr nr nr nr

Study	Subjects	Main Findings	Statistic Reported	Results	p-values
		B-P Intrusions Attention WMS Mental Control		nr nr	nr nr
Keri et al., 2001	BP SIB (N=20) SZ SIB (N=25)	BP SIB < HC Long Delay Verbal Recall BP SIB > SZ SIB Working Memory Visual Backward Masking	Post hoc, Scheffe	- - -	< 0.005 < 0.005 < 0.05
Kieseppa et al., 2005	BP Co-Twins (N=19)	BP Co-Twins < HC Twins Total Recall Long Delay Verbal Recall	B /	-4.5 -1.3	0.04 0.05
Klimes-Dougan et al., 2006	BPO (N=43)	BPO < HC Verbal Memory Long Free Recall Perseverations Visual Memory Rey-O Organization Executive Function WCST (all variables) Attention CPT Dyscontrol	t-test t-test Mann-Whitney, z t-tests Mann-Whitney, z	-2.21 2.25 2.97 3.05-3.77 2.66	0.03 < 0.03 < 0.003 0.003 < 0.008
Maziade et al., 2009	BPO (N=23) SZO (N=22)	BPO < HC Executive Function WCST Total Errors Letter Fluency Test Problems Solved Attention CPT-hit error Verbal Memory	Post hoc, LSD (Cohen's d reported)	-0.98 -1.00 -0.88 -0.74**	0.0005 0.0003 0.001 0.007

Study	Subjects	Main Findings	Statistic Reported	Results	p-values
		CVLT Total Recall CVLT Delayed Recall Visual Memory Rey Immediate Recall Rey Delayed Recall BPO < SZO Executive Function WCST Total Errors		-0.94 -1.03 -0.73 -0.88 0.98	0.0005 0.0002 0.006 0.001 0.0045
Pirkola et al., 2005	BP Co-Twins (N=16) SZ Co-Twins (N=32)	BP Co-twins > HC Twins Auditory Attention BP Co-twins > SZ Co-Twins Visual Attention	Wald χ^2	4.76 10.01	0.03 < 0.01
First episode studies					
Barrett et al., 2009	BP (N=32) SZ (N=46)	BP < HC Visual Memory Verbal Memory Working Memory Language Response Inhibition Executive Function BP > SZ Response Inhibition Verbal Fluency Callosal Function	Post hoc, Bonferroni	- - - - - - - - - - -	< 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.01 < 0.05 < 0.01 < 0.05
Hill et al., 2009	BP (N=22) SZ (N=30)	BP < HC Working Memory Global Composite BP > SZ Verbal Memory	Post hoc, Hochberg	- - - -	nr nr nr

Study	Subjects	Main Findings	Statistic Reported	Results	p-values
		Executive Functioning Global Composite		- -	nr nr
Torres et al., 2010	BP (N=45)	BP < HC Memory Attention Spatial Reasoning Executive Functioning	F-test	9.8 4.5 8.9 12.7	0.003 0.04 ² 0.004 0.001
Zanelli et al., 2010	BP (N=37) SZ (N=65)	BP < HC Delayed Verbal Memory Category Fluency BP > SZ Vocabulary Comprehension Digit Symbol Letter-Number Span Block Design	Post hoc, Bonferroni	- - - - - - -	< 0.007 0.003 < 0.007 < 0.007 < 0.007 < 0.007 < 0.007

¹ Females only.

² Considered non-significant by authors after multiple comparison correction.

Abbreviations: BP: Bipolar; B-P: Brown-Petersen test; BPO: Bipolar Offspring; BP SIB: Bipolar Sibling; CVLT: California Verbal Learning Test (CVLT); HC: Healthy Control; HSCT: Hayling Sentence Completion Test; LSD: Least Significant Different; NCC: Non-Conversion Control; nr: not reported; ns: non-significant; SZ: Schizophrenia; SZF: Schizophreniform; SZO: Schizophrenia Offspring; SZ SIB: Schizophrenia Sibling; UP: Unipolar; WCST: Wisconsin Card Sorting Test; WMS: Wechsler Memory Scale.