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# The role of general intelligence as an intermediate phenotype for neuropsychiatric disorders

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## Abstract

**Introduction—**Neurocognitive impairment is common to several neuropsychiatric disorders. The growing use of cognitive impairment as an intermediate phenotype, or "endophenotype", in psychiatry raises the issue of whether global measures of cognition, such as IQ, or assays of more specific cognitive domains, such as working memory, will best serve to enhance power in detecting susceptibility loci in molecular genetic studies.

**Methods—**This paper will review the research on general intelligence in schizophrenia and bipolar disorder and evaluate its strengths and weaknesses as a candidate intermediate phenotype.

**Results—**Although global measures of cognition may not be optimal as intermediate phenotypes in bipolar disorder, certain clinical traits that overlap between schizophrenia and bipolar disorder, such as psychosis, may be predictive of poor performance on global measures, regardless of DSM-IV categorisation.

**Conclusions—**Global measures of cognition represent good intermediate phenotypes in schizophrenia. Current research does not support the use of global measures of cognition as intermediate phenotypes for bipolar disorder. Assays of specific neurocognitive domains may have greater potential to detect genetic markers for bipolar disorder.

### Keywords

Bipolar disorder; Endophenotype; Genetic; Psychosis; Schizophrenia



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## INTRODUCTION

Neurocognitive dysfunction is a core feature of several psychiatric disorders, including schizophrenia (Keefe & Fenton, 2007) and bipolar illness (Balanzá-Martínez et al., 2008); however, the severity and pattern of cognitive impairment in these two disorders differs significantly (Daban et al., 2006), as does the timing of the onset of cognitive deficits. Specifically, deficits in global measures of cognition, such as intelligence quotient (IQ) or general cognitive ability composite scores (*g*), are very common in patients with schizophrenia (Keefe & Fenton, 2007) and are measurable prior to the onset of illness (Reichenberg et al., 2002), suggesting a genetic contribution to this trait in schizophrenia. In contrast, global cognitive impairment, less typical in patients with bipolar disorder (Torres, Boudreau, & Yatham, 2007), is noted only after the onset of the disease and may be restricted to acutely symptomatic periods (Balanzá-Martinez et al., 2008), suggesting that environmental, or disease-related features, may have more of a direct impact on IQ in bipolar disorder than risk factors related to genetics per se.

Despite differences in the nature or degree of global cognitive impairment in schizophrenia and bipolar disorder, several lines of evidence suggest that more specific aspects of cognition (i.e., working memory, executive function) may serve as useful “endophenotypes”, or intermediate phenotypes, in molecular genetic studies of both illnesses (Bora, Yucel, & Pantelis, 2009; Braff, Freedman, Schork, & Gottesman, 2007). Gottesman and Gould (2003) articulated the concept of utilising an “endophenotype” in psychiatry as a biological marker to obtain “simpler clues to genetic underpinnings than the disease syndrome itself ”. Neurocognition has received increasing attention as a potential intermediate phenotype, as it appears to be closely linked with genetic susceptibility for several major mental illnesses and fulfils the basic “endophenotype” criteria previously set forth. Specifically, the four criteria that make a disease-related trait a good candidate as an intermediate phenotype for a given illness include the following: (1) it is consistently present in probands with the disorder; (2) it is not state related, but is measurable very early in the course of the disease and/or during periods of remission; (3) it is heritable; and (4) it is found, albeit to a lesser extent, in healthy (unaffected) relatives of probands when compared with unrelated healthy individuals (Gottesman & Gould, 2003).

With regard to the heritability of intelligence, there is a robust body of evidence that suggests that intelligence is significantly influenced by genetic factors (e.g., Deary, Spinath, & Bates, 2006; Plomin, 1999). Indeed, the intelligence quotient (IQ) is the most extensively studied cognitive domain with regard to heritability (Plomin & Spinath, 2004). IQ is measured with a battery of standardised tests, typically 2–4 for a quick estimate and 11–13 for a more robust measure. Standard IQ batteries (e.g., WAIS; Wechsler, 1981) include measures of verbal and nonverbal abilities, speeded and nonspeeded processing, and working memory. The number and composition of tests in an IQ estimate have relevance to genetic research, as there is some variability in the genetic versus environmental (e.g., education) contributions to the abilities measured by different tests (Deary et al., 2006). Of the four factors identified by confirmatory factor analysis of the WAIS-III subtests (verbal comprehension, perceptual organisation, working memory, and processing speed; Wechsler, 1997), verbal comprehension may be most highly heritable (heritability estimate of .84 relative to .63 to .68 for the other indices; Posthuma et al., 2003).

Premorbid IQ is often estimated with a single test, typically a test of word reading. Vocabulary and word recognition are not only highly correlated with “full scale” measures of IQ, they reflect what has been termed “crystallised” intelligence, or knowledge gleaned from experience. Especially in the case of single word reading, these abilities are relatively immune to the effects of illness, insult, or ageing, as long as these events have not themselves diminished

years of education or other relevant experience. In contrast, tests such as the Raven's Progressive Matrices, also highly correlated with IQ and thus used to estimate IQ, have been considered measures of "fluid" intelligence, or the ability to reason and problem-solve abstractly and independent of prior learning or experience. Although more vulnerable to insult than word recognition, this more "fluid" intelligence is also highly heritable. In fact, in one study, roughly half of the variance in Raven's Progressive Matrices scores came from a genetic factor shared with all of the WAIS subtests (Rijsdijk, Vernon, & Boomsma, 2002).

This brings us to the psychometric construct of general cognitive ability (Spearman's *g*), first described in the early twentieth century (Spearman, 1904) and defined as the first factor of an unrotated principal component analysis (PCA). General cognitive ability *g* accounts for approximately 40% of the variance in performance on diverse neurocognitive measures (Jensen, 1998). The heritability of *g* has been established in multiple twin and family studies, with estimates generally ranging from 40% to 80% (Butcher, Davis, Craig, & Plomin, 2008). Although *g* differs somewhat from the notion of intelligence, as it is psychometrically defined and varies according to the specific battery by which it is determined, it is highly correlated with most measures of IQ and will be discussed here under the same rubric. However, to the degree that functioning within specific cognitive domains, such as memory or executive functioning, are genetically relevant to a specific disorder, composite scores or other *g* estimates from batteries in which these domains are included may have more endophenotypic promise than IQ.

In fact, recent attempts to parse out the genetics of more basic components of neurocognition have revealed that many specific neurocognitive domains have high degrees of heritability as well. Verbal ability, spatial ability, and memory also show substantial genetic influence, but less so than general intelligence (Plomin & DeFries 1998). More specifically, a strong genetic influence has been established in measures of attention (Fan, Wu, Fossella, & Posner, 2001), working memory (Dougherty et al., 2003), declarative memory (Finkel, Pedersen, McGue, & McClearn, 1995), and executive function (Swan & Carmelli, 2002), suggesting that these cognitive domains may also represent targets for use as intermediate phenotypes in molecular genetic studies. However, given the expectation that probands will demonstrate impairment, even during periods of remission, it is inherent that qualitative differences at the level of the cognitive phenotype in patient samples will be reflected by differences at the genetic level, such that genetic factors may play more or less of a role in different aspects of cognition in each disease. As such, certain cognitive domains may serve as ideal intermediate phenotypes in one psychiatric disorder, but not another, based on differing patterns of impairment in patients and their relatives. With this in mind, this manuscript will review the data supporting the use of cognition as an intermediate phenotype in schizophrenia and in bipolar disorder, with a specific focus on global measures of cognition (i.e., IQ, *g*).

## SCHIZOPHRENIA

Cognitive impairments have long been recognised as a core characteristic of schizophrenia (Bleuler, 1950; Elvevåg & Goldberg, 2000), with significant, diffuse impairment that includes intellectual deterioration, as well as more specific deficits in individual cognitive domains, such as working memory and executive functioning (Keefe & Fenton, 2007). Thus, measures of both general and discrete cognitive functions may be useful as intermediate phenotypes in schizophrenia. We will focus here on the use of broad, global measures such as IQ.

### Global cognitive deficits in schizophrenia probands

Deficits in intellectual functioning have been consistently reported in patients with schizophrenia. In a meta-analysis by Heinrichs and Zakzanis (1998) a large mean effect size for schizophrenia-healthy control differences was reported for measures of IQ (Cohen's *d* =

1.10). On average, the IQ scores of individuals with schizophrenia fell more than one standard deviation below those of healthy controls, with only 41.1% overlap in the two groups' distributions of scores.

Although the Heinrichs and Zakzanis (1998) meta-analysis was conducted on studies of chronic schizophrenia, recent data suggest a strikingly similar picture in schizophrenia patients experiencing their first-episode of psychosis, with large effect size differences noted in comparisons with healthy controls (Cohen's $d = 1.01$; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, in press). These data suggest that intellectual deficits are present early in the course of the illness and cannot be explained solely by chronic symptoms or medication effects. In fact, IQ deficits are present during the premorbid period, as early as IQ is reliably measured, and long before the onset of psychotic symptoms (Cohen's $d = 0.54$; Woodberry, Giuliano, & Seidman, 2008). IQ impairments are therefore not only reliably associated with schizophrenia, but present very early in the developmental process and independent of clinical state.

## Global cognitive deficits in relatives of schizophrenia probands

With the heightened interest in finding cognitive phenotypes that are more closely linked to the genetic susceptibility for schizophrenia, there have been numerous studies of neuropsychological functioning, including IQ, in the close relatives of patients with schizophrenia. The underlying premise of these family-based studies is that traits that are related to the expressed disorder will be present in the patient sample and absent in healthy relatives; in contrast, markers of genetic risk are expected to be present in both patients and close relatives when compared to unrelated healthy controls. In the majority of these studies relatives have demonstrated significant cognitive impairments in a number of specific domains, often strikingly parallel to those found in schizophrenia patient samples (e.g., Cannon et al., 1994; Kremen, Seidman, Pepple, Lyons, & Faraone, 1994). Given the heritability of both schizophrenia and IQ, it is perhaps not surprising that family studies have also found evidence of significantly greater IQ impairments in unaffected relatives of schizophrenia probands than in healthy controls (Cannon et al., 2000; Hughes et al., 2005; Kremen, Faraone, Seidman, Pepple, & Tsuang, 1998; McIntosh, Harrison, Forrester, Lawrie, & Johnstone, 2005).

It is important to note, however, that there have been a number of well-designed studies that have *not* found significant IQ impairment in schizophrenia relatives compared with controls (Goldberg et al., 1990, 1995; Toulopoulou, Quraishi, McDonald, &Murray, 2006). Methodological issues may help to explain discrepancies. For instance, Toulopoulou and colleagues (2006) tested a sample of relatives from families in which multiple members had schizophrenia and were thus at heightened genetic risk. Although they found no significant impairments in the relatives of schizophrenia patients compared with controls, the schizophrenia patients were selected to match a bipolar patient sample and appear to have been much less impaired than a typical schizophrenia sample. Indeed, a similar study of relatives at enhanced genetic risk, derived from multiplex families, did find significant intellectual impairment in this group (McIntosh et al., 2005).

Although results remain equivocal regarding the significance of IQ impairments in relatives of schizophrenia patients, the majority of studies reported IQ scores of relatives that were intermediate between healthy controls and schizophrenia probands. In addition, recent data derived from large-scale twin studies suggested that intellectual function was highly heritable within schizophrenia families (Greenwood et al., 2007; Toulopoulou et al., 2007). Further, using genetic model fitting to estimate the genetic relationship between cognition and schizophrenia, Toulopoulou et al. (2007) reported strong correlations between intelligence and schizophrenia, with shared genetic variance explaining more than 90% of the covariance between these traits. These data suggest that many of the same genes that contribute to variation

in intelligence are also likely to influence susceptibility to schizophrenia, and vice versa (Toulopoulou et al., 2007). Indeed, several studies have now reported an association between markers within alleged schizophrenia susceptibility genes (i.e., dysbindin, *DTNBP1*) and general cognitive ability (*g*) (Burdick et al., 2006) and intelligence (Zinkstok et al., 2007).

## BIPOLAR DISORDER

Historically, bipolar disorder has been differentiated from schizophrenia, at least in part, on the basis of a relatively complete interepisode recovery seen more often in the former than latter condition, particularly with regard to cognitive symptoms (Kraepelin, 1913). However, more recent data on neurocognition in bipolar disorder suggest that cognitive impairment is common and can be as severe as that noted in patients with schizophrenia, especially during acute episodes (Daban et al., 2006). Although the considerable effects of mood state on neurocognitive performance may confound data indicating neurocognitive impairment in acutely ill patients, patients with bipolar disorder also demonstrate neurocognitive impairment during periods of symptom remission. Specific deficits have been demonstrated in euthymic bipolar patients in the cognitive domains of attention, verbal learning, and executive function (for review, see Balanzá-Martinez et al., 2008; Torres et al., 2007).

### Global cognitive deficits in bipolar probands

Global and diffuse neurocognitive impairment, consistent with deficits in IQ measures, has been reported during acute episodes of mania and depression, with more pronounced deficits on measures of Performance IQ than on Full-Scale IQ or Verbal IQ (Bearden, Hoffman, & Cannon, 2001; Daban et al., 2006). However, the majority of studies to date which have focused on identifying trait-like or stable cognitive dysfunction, do not report deficits in general cognitive ability, or IQ, in bipolar patients during periods of euthymia (Frangou, Haldane, Roddy, & Kumari, 2005; Pirkola et al., 2006; Robinson et al., 2006; Torres et al., 2007).

There are a few studies that do report significant differences in IQ measures in bipolar probands as compared with healthy controls; however, bipolar patients' performance is still typically noted to be within normal range according to normative data (Frantom, Allen, & Cross, 2008;McIntosh et al., 2005; Toulopoulou et al., 2006). Other moderating factors may also impact IQ in bipolar patients resulting in discrepancies across studies, including genetic susceptibility to psychosis. In a recent family study, McIntosh et al. (2005) evaluated IQ in a sample that included bipolar probands with a family history of bipolar disorder but also included bipolar probands with a family history of schizophrenia. When compared with healthy subjects with no family history of affective or psychotic illnesses, differences on IQ measures were only significant in bipolar probands derived from families with at least one first or second degree relative with bipolar disorder *and* one first or second degree relative with schizophrenia; whereas bipolar subjects with a family history of bipolar disorder but not schizophrenia performed comparable to controls (McIntosh et al., 2005). Similarly, data from a family study by Toulopoulou and colleagues (2006) reported impaired IQ in bipolar patients who were drawn from a sample that included only families with a history of psychosis.

As discussed, there are a handful of studies that have reported impairment in current IQ performance in bipolar patients; however, when *premorbid* intellectual capacity has been evaluated, bipolar patients have consistently demonstrated performance comparable to control subjects (Gourovitch et al., 1999; Kremen et al., 1998; Malhi et al., 2007; McIntosh et al., 2005; Toulopoulou et al., 2006). Consistent with this, a recent meta-analysis including 1446 euthymic bipolar patients concluded that premorbid intellectual capacity in bipolar patients did not differ from healthy controls, and although current IQ tended to be lower in the patient sample, significant heterogeneity between studies was noted (Bora et al., 2009). These data suggest that IQ deficits in bipolar patients are likely to reflect a decline in functioning due to

the onset of the disease, and more specifically due to the onset of psychosis (Toulopoulou et al., 2006), suggesting a less substantial overlap between genetic susceptibility for bipolar disorder and IQ than that noted in patients with schizophrenia. Indeed, a genetic modelling study in families of bipolar probands found no significant relationship between genetic liability and measures of IQ (McIntosh et al., 2005).

### Global cognitive deficits in relatives of bipolar probands

Current data suggest that global intelligence in relatives of bipolar patients is comparable to controls (Balanzá-Martinez et al., 2008). Although there remains a paucity of data from family studies in bipolar disorder, there have been several small-scale investigations of the impact that genetic risk may have on several aspects of cognition, including IQ. In a small study of seven monozygotic twin pairs discordant for bipolar disorder, both affected and unaffected cotwins demonstrated normal premorbid and current IQ as compared to the healthy control twins; however, significant differences were noted for measures of verbal learning, with unaffected twins performing significantly worse than control twins in this domain (Gourovitch et al., 1999). In a small sample of 15 unaffected offspring of bipolar I probands, no deficits were found in Full-Scale IQ as compared to a control sample; however specific aspects of executive functioning were significantly impaired in the high-risk relative group (Frangou et al., 2005).

As with the mixed results noted in euthymic bipolar patients, there have been some studies that reported significant differences in current IQ in first-degree relatives of bipolar probands versus healthy control samples, although IQ scores were well within the normal range based on normative data (Frantom et al., 2008; McIntosh et al., 2005; Toulopoulou et al., 2006). As previously discussed, a genetic liability to psychosis in these studies was predictive of lower IQ in both the probands and their relatives, suggesting a specific effect of psychosis and family history of psychosis on intellectual function. Finally, at least one study has reported significantly *higher* IQ in a sample of first-degree relatives of bipolar probands with a negative history of psychosis as compared with healthy controls (Kremen et al., 1998), suggesting that higher IQ in individuals with a genetic liability for bipolar disorder may serve as a protective factor against the development of the illness.

Overall, data from IQ studies in first-degree relatives of bipolar patients are equivocal; although intact premorbid functioning is a consistent finding. Reported impairments in current IQ in bipolar relatives may be confounded by sampling issues, including the use of above average healthy control samples. Intellectual differences between bipolar relatives and healthy controls appear to be modest, with performance typically falling within the normal range. Furthermore, the pattern of IQ deficits reported also appears be impacted by factors including a family history of schizophrenia or psychosis in the proband.

Thus, general intelligence and comparable global measures of neurocognitive ability probably do not represent good intermediate phenotypes in bipolar disorder as a group. Although outside of the scope of this review, other more specific aspects of neurocognition, including attention, verbal memory, and executive functioning appear to meet all of the basic criteria for use as an intermediate phenotype in bipolar disorder (Bora et al., 2009). Consistent with this, variation within at least one putative susceptibility loci for bipolar disorder, catechol-o-methyl-transferase (COMT) has been shown to influence verbal memory performance in bipolar patients, with no impact on IQ (Burdick et al., 2007).

## CONCLUSION

Information derived from neurocognitive testing in neuropsychiatric dis-orders is undoubtedly useful for clinical planning, providing proxy measures of brain function by assessing both

general cognitive ability and more discrete aspects of cognition such as attention, memory, and executive functions. The inclusion of cognitive measures in molecular genetic studies has recently gained popularity, at least in part due to the ease with which these tasks can be administered to the large samples necessary for genetic analyses. However, not all cognitive measures or domains are equivalent with regard to their appropriateness as intermediate phenotypes, or endophenotypes in the context of DSM-IV categorisation (American Psychiatric Association, 1994). Consideration for their use in this way should be made in a disease-specific manner.

In this review we suggest that deficits in general intelligence, and other global measures of cognition such as *g*, represent good potential candidates for intermediate phenotypes in studies of schizophrenia, as they are consistently noted in probands and are apparent long before the onset of frank psychosis (Reichenberg et al., 2002). Further, cognitive deficits are stable over the course of the illness (Keefe & Fenton, 2007) and are present in healthy relatives of patients with schizophrenia when compared with individuals who do not have increased genetic liability for the disease (Cannon et al., 1994). In contrast, the cognitive profiles of patients with bipolar illness and their unaffected relatives do not support the use of IQ as an intermediate phenotype for bipolar disorder, an illness for which more specific measures of neurocognitive functioning (i.e., verbal memory) or composites more reflective of these specific domains of functioning may have greater potential as genetic markers of the disease. Thus, nuances in the measurement of cognitive ability (e.g., number and type of domains included in IQ estimates or composite scores) are not immaterial to molecular genetic research. The degree to which a given measure is more or less sensitive to genetic versus environmental (e.g., education) effects has direct implications for the measure's usefulness as an endophenotypic marker.

However, as one considers the utility of neurocognition as an intermediate phenotype in molecular genetic studies, it may indeed be useful to do away with categorising patients by diagnosis and to consider subjects along more of a continuum of symptoms that overlap among several neuropsychiatric disorders. For example, psychosis is not unique to schizophrenia and it appears to be a key predictor of the extent of neurocognitive impairment, such that the presence of psychosis results in poorer cognitive function and a more generalised pattern of impairment that crosses diagnostic boundaries. Patients with schizophrenia, by definition, have psychotic features as part of their illness, but this feature is present in only approximately 50% of bipolar I patients. Notably, as compared with bipolar patients who never experience psychosis, bipolar patients with a history of psychosis are more likely to have IQ deficits and present with a pattern of neurocognitive dysfunction similar to that typically seen in schizophrenia. As genes do not code for diagnostic categories per se, but rather influence risk for a disorder via their effects on specific illness-related behaviours or symptoms, it is likely that the shared symptom of global neurocognitive impairment in patients with schizophrenia and with psychotic bipolar disorder reflects an overlap at the level of genetic liability to psychosis. Thus, it would be predicted that genes that have an influence on susceptibility to psychosis would be good candidates as genes for IQ, or general cognitive impairment, regardless of diagnostic categorisation. Future studies focused on finding genes that influence key traits associated with susceptibility to major mental illnesses might be better served by relying less on DSM-IV labels and more on the behavioural presentation of the patient group.

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