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Neuropsychological study of IQ scores in Offspring of parents with Bipolar I Disorder

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Keywords

bipolar disorder, offspring, IQ, socio-economic status

Abstract

Introduction

Studies comparing IQ in Offspring of Bipolar Parents (OBP) with Offspring of Healthy Controls (OHC) have reported conflicting findings. They have included OBP with mental health/neurodevelopmental disorders and/or pharmacological treatment which could affect results. This UK study aimed to assess IQ in OBP with no mental health/neurodevelopmental disorder and assess the relationship of sociodemographic variables with IQ.

Methods

IQ data using the Wechsler Abbreviated Scale of Intelligence (WASI) from 24 OBP and 34 OHC from the North East of England was analysed using mixed-effects modelling.

Results

All participants had IQ in the average range. OBP differed statistically significantly from OHC on Full Scale IQ ($p=0.001$), Performance IQ (PIQ) ($p=0.003$) and Verbal IQ (VIQ) ($p=0.001$) but not on the PIQ-VIQ split. OBP and OHC groups did not differ on socioeconomic-economic status (SES) and gender. SES made a statistically significant contribution to the variance of IQ scores ($p=0.001$).

Conclusions

Using a robust statistical model of analysis, the OBP with no current/past history of mental health/neurodevelopmental disorders had lower IQ scores compared to OHC. This finding should be borne in mind when assessing and recommending interventions for OBP.

Introduction

Bipolar Disorder (BD) characterised by recurrent periods of extreme mood including depression, mania and mixed affective states (Goodwin & Jamison, 2007) has a prevalence of 0.6–2.4% in adults in the general population (Merikangas et al., 2011). Over the last decade there has been considerable interest and awareness regarding the diagnosis of BD in children and adolescents (Blader & Carlson, 2007). A recent meta analysis reported rates of early onset BD (diagnosed onset before the age of 21) as 1.8% (Van Meter, Moreira, & Youngstrom, 2011) .

BD was ranked 18th in all health conditions in years lived with disability (Vos et al., 2012). Large scale studies of adults with BD have reported that retrospectively 1 in 5 had evidence of illness before age 19 years, with extensive delay in individuals receiving an accurate diagnosis and commencing treatment (Post et al., 2008). Delay in diagnosis and access to appropriate treatment may adversely impact on the lives of affected young people and their families and contribute to the economic and public health burden of the disorder (Hong, Reed, Novick, Haro, & Aguado, 2011). The progressive nature of the illness further supports this hypothesis that early diagnosis and treatment may alter the temporal trajectory of the illness. Furthermore, it has been proposed that early treatment of BD may be neuroprotective which in turn may reduce or prevent the identified neurocognitive changes which take place with chronicity (Berk et al., 2010).

Offspring of Bipolar Parents (OBP) are at an increased risk of developing a range of mental health/neurodevelopmental disorders (Lapalme, Hodgins, & LaRoche, 1997). Genetic factors are key in the development of BD (Roybal et al., 2012). A meta-analysis of 17 studies found that OBP were 2.5 times more likely to develop a psychiatric disorder and 4.0 times more likely to develop an affective disorder in their lifetime in comparison with offspring of healthy controls (OHC) (Lapalme et al., 1997). In addition, OBP are living in families where their biological parent has a chronic episodic mood disorder which can contribute to changes in family environment when compared with families with no history of BD. These changes in family environment include higher rates of conflict

and lower levels of cohesion (Barron et al., 2014; Chang, Blasey, Ketter, & Steiner, 2001). These changes in the family environment could impact on the developmental trajectory of the offspring (Barron et al., 2014).

One way of considering the impact on developmental trajectory includes assessment of cognitive function. Several studies (de la Serna et al., 2016; Decina et al., 1983; Diwadkar et al., 2011; Kestenbaum, 1979; Klimes-Dougan, Ronsaville, Wiggs, & Martinez, 2006; Kron et al., 1982; Maziade et al., 2009; McDonough-Ryan et al., 2002; Waters, Marchenko-Bouer, & Smiley, 1981; Winters, Stone, Weintraub, & Neale, 1981) have assessed IQ (a summative measure of cognitive function) but the results have been conflicting (see Table 1). Some studies (Kestenbaum, 1979) have reported higher IQ in OBP, others (de la Serna et al., 2016; Diwadkar et al., 2011; McDonough-Ryan et al., 2002; Waters et al., 1981) have reported no difference in IQ while some (Klimes-Dougan et al., 2006; Maziade et al., 2009) have reported lower IQ in OBP.

Insert Table 1 about here

The studies summarised in table 1 have a variety of methodological limitations such as small sample size (Kestenbaum, 1979) and heterogeneity in the type of BD in parents [Offspring of parents with Bipolar I (BDI) and Bipolar II (BDII) disorder]. BDI and BDII are clinically different disorders with some authors reporting differing neurocognitive profiles (Winters et al., 1981). Other limitations include selection of inappropriate statistical analysis such as using ANOVA for multiplex families (which violates the assumption of ANOVA) and the inclusion of OBP with existing mental health/neurodevelopmental disorder some of whom required psychotropic medication (both these latter factors are known to impact on IQ assessments).

This led the authors of the current study to hypothesise that IQ in OBP will show no difference when compared to a group of OHC matched on age. The primary aim of this UK study was to compare Full Scale IQ (FSIQ), Verbal IQ (VIQ) and Performance IQ (PIQ) in unmedicated OBP (offspring of

adults with Bipolar I Disorder) with OHC with no previous or current history of mental health and/or neurodevelopmental disorders and not receiving psychotropic medication.

Method

This study took place in the North East of England and received funding from the Research Innovation and Clinical Effectiveness Department of Northumberland Tyne and Wear NHS Foundation Trust. A positive ethical opinion was obtained from Northumberland Research Ethics Committee (ref 08/40902/12).

Participants

The main inclusion criterion for subjects in the OBP group was having one biological parent with a diagnosis of BDI. For subjects in the OHC group the main inclusion criteria included having biological parents and first degree relatives with no current and/or past history of mental health disorders. In addition, subjects in both OBP and OHC groups were all: in the age range of 6 to 14 years at the time of the assessment; FSIQ $\geq$70 and sufficiently familiar with the use of the English language to complete the assessments. Exclusion criteria for subjects in the OBP and OHC groups included the presence of a currently recognised medical condition and/or substance use/dependence that would impact on the assessment.

Recruitment Procedure: OBP

Consultant Psychiatrists in Community Adult Mental Health Teams approached adult patients with BDI who had their biological offspring (age 6-14 years) living with them. Written information sheets (adult version for parent with BDI and child version for their offspring) and an Expression of Interest (EOI) form were given to these patients.

Recruitment Procedure: OHC

Subjects in the OHC group were recruited through primary and secondary schools attended by OBP in the North East of England with the aim of recruiting a sample matched on age, gender and SES.

Appropriate versions of the written information sheets (adult version and child version) and an EOI Form were provided. Families in both groups contacted the research team, using contact details provided on the EOI form if they were interested in taking part in the research. Written informed consent from the parent and assent from any child 10 years or older participating in the study was obtained.

Assessment

Parental diagnosis of BDI in the OBP group and absence of family history of mental health disorders in OHC group was confirmed using the Structured Clinical Interview for DSM-IV Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 2002). The offspring underwent an assessment of psychopathology using the WASH-U-KSADS (Geller, Williams, & Zimerman, 1998). Parental Socio-Economic Status (SES) was ascertained using the Hollingshead 2 Factor index (Hollinghead, 1971). IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). The WASI consists of 4 subtests: Vocabulary, Block Design, Similarities and Matrix Reasoning. The format of the subtests is similar to their counterparts in the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler, 1991) and the Wechsler Intelligence Scale for Children – Third Edition (WISC-III) (Wechsler, 1991). The Internal Consistency for the WASI is reported to be between 0.95 to 0.97 for the abbreviated FSIQ-4 and 0.93 to 0.96 for VIQ and PIQ for the average age reliability coefficients (Wechsler, 1999). The WASI allows for verbal-performance discrepancy analyses in two different aspects; both statistical significance and clinical significance can be estimated. Wechsler reported that a 20 point or more difference between VIQ and PIQ (either way) on the WASI can be regarded as clinically meaningful (Wechsler, 1999).

Data analysis

An a priori decision was made to use mixed-effects models to assess differences in the FSIQ, VIQ and PIQ of children as the sample included some participants from multiplex (more than one child recruited per family) families. Families were grouped according to their status (OBP or OHC) and

the bipolar status of the parent was designated as a random effect. Socio-demographic variables (namely age, socio-economic status and gender) were included as fixed-effects. All analyses were undertaken in the R package for Statistical computing, release R 2.11.1 (R Development Core Team, 2010).

Results

Recruitment, Clinical and Socio-demographic variables

Thirty-four OBP from 25 families where 1 parent had BDI were identified. Two of these families did not complete the EOI form, 1 family did not consent and 2 families withdrew consent during the study. Data from 5 OBP from 3 families who displayed psychopathology were excluded from the analysis. The final dataset consisted of 24 OBP and 34 OHC. The socio-demographic characteristics are presented in table 2. Subjects in OBP and OHC were matched on age and there were no significant differences between the groups on gender and SES.

Insert table 2 about here

IQ in OBP versus OHC.

FSIQ in OBP (92.8$\pm$11.7) was statistically lower (p=0.001) than in OHC (106.9$\pm$16.6). A similar pattern was also found when VIQ and PIQ scores were compared between OBP and OHC. The effect sizes for differences in FSIQ, VIQ and PIQ between OBP and OHC were 0.3, 0.4 and 0.2 respectively.

Insert table 3 about here

PIQ-VIQ split

PIQ-VIQ split was investigated using Mixed Models analysis and no statistical difference (p=0.134) between the OBP and OHC groups was found. The Kaufman (Kaufman, 1979) method was employed to further study the discrepancy in VIQ and PIQ scores and 37.5% of OBP (n=9) had a discrepancy equal to or greater than 15 points which is normally seen in less than 13% of the population and

therefore suggestive of a significant discrepancy. Further, 25% of OBP had a variation of more than 20 points which is defined as clinically significant according to the WASI Manual (Wechsler, 1999) compared to 14.7% of OHC.

Contributions made by the socio-demographic variables

Results from mixed models showed there was a statistically significant contribution of socioeconomic status (SES) to the variance in FSIQ ($P< 0.001$) (the higher the SES of children under study the higher the FSIQ), VIQ ($p<0.001$) and PIQ ($p=0.02$) scores for both groups. This finding was independent of the bipolar status of the parents. Age and gender did not contribute significantly to the variance in IQ scores .

Insert Table 4 about here

Discussion

Key findings

As far as the authors are aware, this is the first study to assess FSIQ, VIQ and PIQ in OBP who had no current and/or past history of diagnosed mental health/neurodevelopmental disorders (and were not receiving medication at the time of the study) and compare the findings with an age-matched sample of OHC. The OHC group did not differ from OBP on SES and gender. The principal finding from this study was the consistently lower IQ (FSIQ, VIQ and PIQ) albeit still in the average range of intellectual ability in OBP compared to OHC. The proportion of OBP compared with OHC that had significantly higher PIQ compared to VIQ using both the Kaufman method (Kaufman, 1979) and as outlined in the WASI manual (Wechsler, 1999) was higher. However, using mixed models analysis, this difference did not reach statistical significance. One of the reasons for this could be, that mixed models analysis (as with statistical analyses in general) does not take into account the direction of difference in IQ. On the other hand, in a normal population there is no significant difference between VIQ and PIQ (Weschler, 2004). The higher PIQ than VIQ in our study could be

explained by the observation that PIQ is likely to be more a test of an innate ability, whilst VIQ is more likely to be influenced by factors such as education and SES. These findings could be the result of the child's ability to process and learn new material in educational settings and/or supportive of the theoretical evidence that PIQ and VIQ reflect right (performance ability) and left (verbal ability) hemispheric function respectively. A low VIQ relative to PIQ may be an indicator of left hemispheric dysfunction (Kaufman, 1990), which may be a result of emotional trauma and/or low auditory processing and conceptualising skills (Crawford, Parker, Steward, Besson, & De Lacey, 1998). This finding of lower VIQ relative to PIQ could also be accounted for by factors that were not part of the research study design and hypotheses such as impact of severity of parental BD, timing of diagnosis of parental BD and other environmental factors.

The study has replicated findings from previous studies (Klimes-Dougan et al., 2006; Maziade et al., 2009) that have attempted to study and compare FSIQ between OBP and OHC. Other studies (de la Serna et al., 2016; Diwadkar et al., 2011; McDonough-Ryan et al., 2002; Waters et al., 1981; Winters et al., 1981) have reported no difference on FSIQ between OBP and OHC. However, it is noteworthy that Waters et al (1981) relied on retrospective collection of FSIQ scores conducted by school boards using various IQ assessment techniques. In another study (Decina et al., 1983) it is likely that the sample of OBP included subjects from multiplex families and therefore nested within families, violating the assumptions of ANOVA used for data analysis. An earlier study (Kestenbaum, 1979) reported a higher VIQ when compared to PIQ in a significant proportion of the OBP cohort studied compared to OHC (by populations norms) (Kaufman, 1979). The more recent study by Klimes-Dougan et al., (2006) have not reported VIQ and PIQ data so comparisons are not possible. In the recent study by de la Serna (2016), no differences were reported between FSIQ, VIQ and PIQ when comparing OBP and OHC. However, their study included offspring with existing mental health/neurodevelopmental disorders which could have contributed to the finding.

Covariates of significance

This study also investigated the potential contribution made by pre-specified socio-demographic variables to the variance of scores of FSIQ, PIQ and VIQ. It is perhaps not surprising that higher SES contributed significantly to higher FSIQ, PIQ and VIQ scores (Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003). In fact, in a study of adopted children slightly less than half of the SES-related IQ variability in the adopted children was attributable to the SES of the adoptive family rather than the biological (Capron & Duyme, 1989). SES is proposed to modify the heritability of IQ, such that in families with higher SES, genes account for most of the variance in IQ because environmental influences are in effect 'at ceiling' in this group, whereas in the lowest SES families, variance in IQ is overwhelmingly dominated by environmental influences and so are in effect the limiting factor for this group (Turkheimer et al., 2003). Differences in the quality of schooling has also been proposed to explain differences in IQ (Hackman & Farah, 2009); however in our study the participants in both groups were recruited from schools in North East England with similar if not the same characteristics.

Age did not contribute to the variance of IQ scores. This was perhaps not surprising given that IQ scores had been converted into standardised scores (which take age into account). However, in light of longitudinal studies reporting an early IQ impairment that is stable from childhood until late adolescence in children who later develop major psychoses including BD (Maziade et al., 2011), it was important to consider this in the analysis. Gender too did not contribute significantly to the variance of IQ. It was important to study this as previous studies have reported lower IQ scores in male compared to female children (Sylva et al., 2011).

The association between premorbid IQ and development of BD to date remains inconclusive (Zammit et al., 2004). Some studies report an association between high academic performance and a subsequent increased risk of developing BD (MacCabe et al., 2010; Quakenbush, Kutcher, Robertson, Boulos, & Chaban, 1996). In their longitudinal study Quakenbush et al (1996) reported that adolescents who developed BD, had good to excellent premorbid school functioning which was followed by a marked deterioration in work effort, academic achievement, peer relationships and

extracurricular achievement following the onset of BD. In a national cohort study, MacCabe et al (2010) reported that male individuals with excellent school performance had a nearly fourfold increased risk of later BD compared with those with average grades but students with the poorest grades were also at moderately increased risk of BD. In a sample of typically developing adolescents, Deary and colleagues found that 50–60% of the variance in examination results at age 16 could be explained by IQ at age 11 (Deary, Strand, Smith, & Fernandes, 2007). This suggests that IQ is only one of several factors such as school attendance and engagement, long-term memory, attention, motivation, diligence, organisational abilities, creativity and social skills influencing school performance. Thus the associations with risk for BD in the study by MacCabe et al (2010) may have been driven as much by these other factors as by IQ, and the associations with excellent and poor performance may each be mediated by different factors. Further a recent study assessed IQ at age 7 in a cohort of children who later developed BD, and reported that IQ was statistically indistinguishable from controls (Seidman et al., 2013).

The finding of statistically significantly lower IQ in OBP compared to OHC may impact on their (OBP) ability to meet expected academic targets. This finding should be borne in mind when assessing and recommending interventions for OBP. Further, whether these lowered IQ scores when considered alongside findings of family environment (Barron et al., 2014), might contribute to the well replicated finding of increased risk for OBP of developing other difficulties including BD in the longer term. A longitudinal study of a cohort of well characterised OBP would allow further investigation of these proposed interactions *viz.* cognitive vulnerability and family environment.

Strengths of the Study

There are several strengths to the methodology employed in this study including the recruitment of offspring of BDI (which provides increased homogeneity of diagnosis of the parent proband); the recruitment of OBP who did not have any diagnosed mental health/neurodevelopmental disorder and were not receiving any psychotropic medication (all factors known to influence measures of

cognition); and the use of a robust statistical analysis (mixed models of analysis which allowed the investigation of particular pre-specified co-variants on IQ).

Limitations of this study

The findings should be interpreted with caution in light of the relatively small sample size. However it is of relevance that the sample size is comparable to other studies. Further, the sample size reduced the ability to use structured equation modelling techniques, to assess the impact of severity of parental BD and hospitalisation on the IQ of OBP. The use of the WASI (Weschler, 2004) although a well validated, reliable brief measure of intellectual ability, did not provide an opportunity to assess a broader range of cognitive abilities. As the project started prior to the availability of WASI-2 in 2011, the authors could not utilise more current age-corrected scores and reference groups. The study excluded participants with an IQ <70 by design as our ethical approval was contingent on recruitment of subjects who could undertake the assessments and for those over the age of 10 years, give informed assent to take part in the research. This could potentially impact on the generalisability of the findings. However, no offspring were excluded from recruitment in our study based on this criterion. In addition, the wide age range of participants in the study needs to be acknowledged. However, the WASI is normed and validated for use in the age range of 6-90 years. Another limitation to consider is the lack of parental IQ data. It may be that the parents who consented for their children to participate in the OHC group, may for example, have had specific characteristics such as higher IQ compared to the local general population. This potential recruitment bias could have contributed to the statistically significant difference between participants in the OBP and OHC groups. However, data were collected on parental educational attainment as part of the SES assessment and were found to be comparable across both groups. Therefore it is unlikely that this was a major contributing factor.

Conclusions

The findings from this study have identified lower IQ in OBP. However the longer term impact of this finding requires further investigation. Parents with BD need to balance the management of their

own BD alongside their parental responsibility to consider any indications for proactive support for their OBP in a range of social settings including education. This finding should be borne in mind when assessing and recommending interventions for OBP.

Conflicts of interest

Prof Heinz Grunze has been in receipt of honoraria or consultation fees from: Gedeon-Richter, Lundbeck, Hofmann-LaRoche and has participated in company sponsored speaker's bureau for: BMS, Ferrer, Janssen-Cilag, Otsuka, Lundbeck, Pfizer. None of the other authors have any conflicts of interest.

Bibliography

Barron, E., Sharma, A., Le Couteur, J., Rushton, S., Close, A., Kelly, T., . . . Le Couteur, A. (2014). Family environment of bipolar families: a UK study. *J Affect Disord, 152-154*, 522-525. doi: 10.1016/j.jad.2013.08.016

Berk, M., Hallam, K., Malhi, G. S., Henry, L., Hasty, M., Macneil, C., . . . McGorry, P. D. (2010). Evidence and implications for early intervention in bipolar disorder. *J Ment Health, 19*(2), 113-126. doi: 10.3109/09638230903469111

Blader, J. C., & Carlson, G. A. (2007). Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996-2004. *Biol Psychiatry, 62*(2), 107-114. doi: 10.1016/j.biopsych.2006.11.006

Capron, C., & Duyme, M. (1989). Assessment of effects of socio-economic status on IQ in a full cross-fostering study. *Nature, 340*(6234), 552-554

Chang, K. D., Blasey, C., Ketter, T. A., & Steiner, H. (2001). Family environment of children and adolescents with bipolar parents. *Bipolar disorders, 3*(2), 73-78

Crawford, J. R., Parker, D. M., Steward, L. E., Besson, J. A. O., & De Lacey, J. (1998). Predication of WAIS with National Adult Reading Test: Cross validation and Extension. *British Journal of Clinical Psychology, 28*(28), 267-273

de la Serna, E., Vila, M., Sanchez-Gistau, V., Moreno, D., Romero, S., Sugranyes, G., . . . Castro-Fornieles, J. (2016). Neuropsychological characteristics of child and adolescent offspring of patients with bipolar disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 65*, 54-59. doi: http://dx.doi.org/10.1016/j.pnpbp.2015.08.014

Deary, I. J., Strand, S., Smith, P., & Fernandes, C. (2007). Intelligence and educational achievement. *Intelligence, 35*(1), 13-21. doi: http://dx.doi.org/10.1016/j.intell.2006.02.001

Decina, P., Kestenbaum, C. J., Farber, S., Kron, L., Gargan, M., Sackeim, H. A., & Fieve, R. R. (1983). Clinical and psychological assessment of children of bipolar probands. *Am J Psychiatry, 140*(5), 548-553. doi: 10.1176/ajp.140.5.548

Diwadkar, V. A., Goradia, D., Hosanagar, A., Mermon, D., Montrose, D. M., Birmaher, B., . . . Keshavan, M. S. (2011). Working memory and attention deficits in adolescent offspring of schizophrenia or bipolar patients: comparing vulnerability markers. *Progress in neuro-psychopharmacology & biological psychiatry, 35*(5), 1349-1354. doi: 10.1016/j.pnpbp.2011.04.009

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). Structured Clinical Interview for DSM-IV TR Axis I Disorders-Patient Edition (SCID-I/P). New York: New York Psychiatric Institute, Biometric Research.

Geller, B., Williams, M., & Zimerman, B. (1998). Prepubertal and young adolescent biopolarity versus ADHD; assessment and vlidaity using the WASH-U-KSADS, CBCL and TRF. J. *J Affect Disorders, 51*, 93-100

Goodwin, F. K., & Jamison, K. R. (2007). *Bipolar Disorder and Recurrent Depression* (2nd ed.). New York: Oxford University Press.

Hackman, D. A., & Farah, M. J. (2009). Socioeconomic status and the developing brain. *Trends Cogn Sci, 13*(2), 65-73. doi: 10.1016/j.tics.2008.11.003

Hollinghead, A. (1971). Commentary on "The indiscriminate state of social class measurement". *Social Forces*

Hong, J. H., Reed, C., Novick, D., Haro, J. M., & Aguado, J. (2011). Clinical and economic consequences of medication non-adherence in the treatment of patients with a manic/mixed episode of bipolar disorder: Results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) Study. *Psychiatry Research, 190*(1), 110-114. doi: 10.1016/j.psychres.2011.04.016

Kaufman, A. (1979). Intelligent Testing with the WISC-R. New York: John Wiley & Sons.

Kaufman, A. (1990). Assessing Adolescent and Intelligence

Kestenbaum, C. J. (1979). Children at risk for manic-depressive illness: possible predictors. *The American journal of psychiatry, 136*(9), 1206-1208

Klimes-Dougan, B., Ronsaville, D., Wiggs, E. A., & Martinez, P. E. (2006a). Neuropsychological functioning in adolescent children of mothers with a history of bipolar or major depressive disorders. *Biol Psychiatry, 60*(9), 957-965. doi: 10.1016/j.biopsych.2006.03.031

Kron, L., Decina, P., Kestenbaum, C. J., Farber, S., Gargan, M., & Fieve, R. (1982). The offspring of bipolar manic-depressives: clinical features. *Adolescent psychiatry, 10*, 273-291

Lapalme, M., Hodgins, S., & LaRoche, C. (1997). Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. *Can J Psychiatry, 42*(6), 623-631

MacCabe, J. H., Lambe, M. P., Cnattingius, S., Sham, P. C., David, A. S., Reichenberg, A., . . . Hultman, C. M. (2010). Excellent school performance at age 16 and risk of adult bipolar disorder: national cohort study. *Br J Psychiatry, 196*(2), 109-115. doi: 10.1192/bjp.bp.108.060368

Maziade, M., Rouleau, N., Cellard, C., Battaglia, M., Paccalet, T., Moreau, I., . . . Mérette, C. (2011). Young Offspring at Genetic Risk of Adult Psychoses: The Form of the Trajectory of IQ or Memory May Orient to the Right Dysfunction at the Right Time. *PLoS ONE, 6*(4), e19153. doi: 10.1371/journal.pone.0019153

Maziade, M., Rouleau, N., Gingras, N., Boutin, P., Paradis, M. E., Jomphe, V., . . . Roy, M. A. (2009). Shared neurocognitive dysfunctions in young offspring at extreme risk for schizophrenia or bipolar disorder in eastern quebec multigenerational families. *Schizophrenia bulletin, 35*(5), 919-930. doi: 10.1093/schbul/sbn058

McDonough-Ryan, P., DelBello, M., Shear, P. K., Douglas Ris, M., Soutullo, C., & Stakowski, S. M. (2002). Academic and Cognitive Abilities in Children of parents with Bipolar Disorder: A Test of the Nonverbal Learning Disability Model. *Journal of Clinical and Experimental Neuropsychology, 24*(3), 280-285

Merikangas, K. R., Jin, R., He, J. P., Kessler, R. C., Lee, S., Sampson, N. A., . . . Zarkov, Z. (2011). Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Archives of general psychiatry, 68*(3), 241-251. doi: 10.1001/archgenpsychiatry.2011.12

Post, R. M., Luckenbaugh, D. A., Leverich, G. S., Altshuler, L. L., Frye, M. A., Suppes, T., . . . Walden, J. (2008). Incidence of childhood-onset bipolar illness in the USA and Europe. *British Journal of Psychiatry, 192*(2), 150-151. doi: 10.1192/bjp.bp.107.037820

Quakenbush, D., Kutcher, S., Robertson, H. A., Boulos, C., & Chaban, P. (1996). Premorbid and postmorbid school functioning in bipolar adolescents: description and suggested academic interventions. *Canadian Journal of Psychiatry, 41*, 16-22

R Development Core Team. (2010). R: A Language and Environment for Statistical Computing. Vienna: R Foundation for Statistical Computing.

Roybal, D. J., Singh, M. K., Cosgrove, V. E., Howe, M., Kelley, R., Barnea-Goraly, N., & Chang, K. D. (2012). Biological Evidence for a Neurodevelopmental Model of Pediatric Bipolar Disorder. *The Israel journal of psychiatry and related sciences, 49*(1), 28-43

Seidman, L. J., Cherkerzian, S., Goldstein, J. M., Agnew-Blais, J., Tsuang, M. T., & Buka, S. L. (2013). Neuropsychological performance and family history in children at age 7 who develop adult schizophrenia or bipolar psychosis in the New England Family Studies. *Psychol Med, 43*(1), 119-131. doi: 10.1017/S0033291712000773

Sylva, K., Stein, A., Leach, P., Barnes, J., Malmberg, L., & the, F.-t. (2011). Effects of early child-care on cognition, language, and task-related behaviours at 18 months: An English study. *British Journal of Developmental Psychology, 29*(1), 18-45. doi: 10.1348/026151010X533229

Turkheimer, E., Haley, A., Waldron, M., D'Onofrio, B., & Gottesman, II. (2003). Socioeconomic status modifies heritability of IQ in young children. *Psychol Sci, 14*(6), 623-628

Van Meter, A. R., Moreira, A. L., & Youngstrom, E. A. (2011). Meta-analysis of epidemiologic studies of pediatric bipolar disorder. *J Clin Psychiatry, 72*(9), 1250-1256. doi: 10.4088/JCP.10m06290

Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., . . . Memish, Z. A. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet, 380*(9859), 2163-2196. doi: 10.1016/S0140-6736(12)61729-2

Waters, B. G., Marchenko-Bouer, I., & Smiley, D. (1981). Educational achievement, IQ and affective disorder in the adult offspring of bipolar manic-depressives. *The British journal of psychiatry : the journal of mental science, 139*, 457-462

Wechsler, D. (1991). Manual for the Weschler Intellegence Scale for Children - Third Edition. San Antonio, Tx: The psychological corporation.

Wechsler, D. (1999). Wechsler Abbreviated Scale of Intelligence: The Psychological Corporation.

Weschler, D. (2004). Weschler Intelligence Scale for Children- Fourth UK Edition (WISC-IV).

Winters, K., Stone, A., Weintraub, S., & Neale, J. (1981). Cognitive and attentional deficits in children vunreable to psychopathology. *Journal of Abnormal Psychology*, *9*(4), 435-453

Winters, K. C., Stone, A. A., Weintraub, S., & Neale, J. M. (1981). Cognitive and attentional deficits in children vulnerable to psychopathology. *Journal of Abnormal Child Psychology*, *9*, 435-453

Zammit, S., Allbeck, P., David, A., Daman, C., Heemmingsson, T., Lundberg, I., & G, L. (2004). A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression and other nonaffective psychoses. *Archives General Psychiatry, 61*, 354-360

Table 1: Studies of IQ in OBP

Author	Sample Size	IQ Assessment	Results
Kestenbaum (1979)[13]	OBP (n=13)	WISC (version not known)	6 of 13 OBP had significantly higher VIQ than PIQ using Kaufman technique
Waters et al (1981) [14]	BD (n=17) and OBP (n=38)		No difference in IQ between OBP and young persons with BD.
Winters et al (1981) [15]	OBP (n=40) and OHC(n=61)	WISC (version not known)	No differences in VIQ and PIQ in OBP compared to OHC
Kron et al (1982) [16]	OBP (n=39) and OHC (n=18)	WISC- R	12 out of 31 OBP (39%) compared to 2 out of 18 OHC (11%) had a VIQ to PIQ discrepancy of more than 15 points
Decina et al (1983) [17]	OBP (n=31) and OHC (n=18)	WISC- R	12 (39%) OBP vs. 2 (11%) OHC had discrepancies of 15 points or more on VIQ than PIQ ($p<0.05$). PIQ was significantly lower in OBP compared to OHC ($p<0.05$). No discrepancy between VIQ and PIQ ($p=0.16$)
McDonough-Ryan et al (2002) [18]	OBP (n=28) and OHC (n=24)	WISC III	Statistically significant VIQ>PIQ split between OBP and OHC. No difference in FSIQ and VIQ in both groups
Klimes-Dougan et al (2006) [19]	OBP (n=43) from 26 families and OHC (n=50) from 30 families	WISC- R	FSIQ scores (mean 112.5) in OBP to be lower than OHC (FSIQ mean 121.4) $p<0.004$.

Maziade et al (2009) [20]	OBP (n=35) and OHC (n=76)	WISC-III for OBP and WAIS-III for OHC	Statistical significance between FSIQ of OBP (99.6) and OHC (108.3) p=0.0002), Effect size 0.99.
Diwadkar et al (2011) [21]	OBP (n=23) and OHC (n=41)	The authors do not specify the instrument used to measure FSIQ	The groups did not differ on IQ, FSIQ (101.5 $\pm$ 12.9) and OHC (101.8 $\pm$18.2)
de la Serna et al [22]	OBP (n=90) and OHC (107)	WISC-IV	The groups did not differ on IQ, verbal and performance IQ

Table 2: Participant Demographics

	OBP	OHC
Parents		
	(n=17)	(n=23)
M:F ratio	1:16	-
Socioeconomic status (Hollingshead and Redlich Scale)		
1	1 (5.9%)	1 (4.3%)
2	5 (29.4%)	8 (34.8%)
3	9 (52.9%)	11 (47.8%)
4	2 (11.8%)	3 (13.1%)
Offspring Characteristics		
	(n=24)	(n=34)
M:F	14:10	21:13
Age Range (months)	76-178	76-179
Mean age+SD (months)	141.1+31.9	124.2+28.9

Table 3: IQ of OBP and OHC (* indicates statistical significance)

OBP				OHC				
IQ	Mean	Range	SD	Mean	Range	SD	P value	Effect size (r)
FSIQ	92.8	74 - 109	11.7	106.9	81 – 146	16.6	0.001	-0.3
VIQ	89.1	72 – 112	12.1	106.4	64 – 136	18.4	0.001	-0.4
PIQ	97.9	80 - 126	12.5	106.1	81 – 146	14.8	0.03	-0.2

Table 4: Mixed Models analysis showing the contributions made to the model by pre-specified study covariates.
(* indicates statistical significance)

	FSIQ (p value)	VIQ (p value)	PIQ (p value)	VIQ-PIQ (p value)
Bipolar status of parent	0.001*	0.001*	0.003*	0.1
SES	0.004*	0.001*	0.02*	0.1
Age	0.3	0.2	1.0	0.3
Gender	0.7	1.0	0.8	1.0