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High educational performance is a distinctive feature of bipolar disorder; a study on cognition in 4,888 bipolar disorder or schizophrenia patients, relatives and controls

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Abstract

**Background:** Schizophrenia is associated with lower intelligence and poor educational performance relative to the general population. This is, to a lesser degree, also found in first-degree relatives of schizophrenia patients. It is unclear whether bipolar disorder I (BD-I) patients and their relatives have similar lower intellectual and educational performance as that observed in schizophrenia.

**Methods:** This cross-sectional study investigated intelligence and educational performance in two outpatient samples (494 BD-I patients, 955 schizophrenia patients), 2,235 relatives of BD-I and schizophrenia patients, 1,104 healthy controls and 100 control siblings. Mixed-effects- and regression models were used to compare groups on intelligence and educational performance.

**Results:** BD-I patients were more likely to have completed the highest level of education (OR=1.88 [1.66-2.70]) despite having a lower IQ compared with controls (β=-9.09, SE=1.27, p<0.001). In contrast, schizophrenia patients showed both a lower IQ (β=-15.33, SE=0.86, p<0.001) and lower educational levels compared with controls. Siblings of both patient groups had significantly lower IQ than control siblings, but did not differ on educational performance. IQ scores did not differ between BD-I parents and schizophrenia parents, but BD-I parents had completed higher educational levels.

**Conclusions:** Although BD-I patients had a lower IQ than controls, they were more likely to have completed the highest level of education. This contrasts with schizophrenia patients, who showed both intellectual and educational deficits compared to healthy controls. Since relatives of BD-I patients did not demonstrate superior educational performance, our data suggest that high educational performance may be a distinctive feature of bipolar disorder patients.

**Keywords:** Intelligence, IQ, educational performance, cognition, familial vulnerability, bipolar disorder, schizophrenia
1. Introduction

Cognitive deficits are a core feature of schizophrenia (Elvevag and Goldberg, 2000; MacCabe, 2008; Kahn and Keefe, 2013). Lower intelligence is already present before illness manifestation (Woodberry et al. 2008; Dickson et al. 2012) and poor scholastic achievement is associated with an increased risk for developing schizophrenia (van Oel et al. 2002; MacCabe et al. 2008). Several studies report that clinically unaffected first-degree relatives of schizophrenia patients also show lower Intelligence Quotient (IQ) and worse educational performance than healthy controls (Kremen et al. 1998; Cannon et al. 2000; Hughes et al. 2005; McIntosh et al. 2005), implying that an increased familial vulnerability to schizophrenia is associated with intellectual deficits.

Whether intellectual deficits also occur in euthymic bipolar disorder (BD) patients is unclear. Although deficits in specific cognitive domains, e.g. executive function, attention and verbal memory, are frequently reported (Martinez-Aran et al. 2004; Robinson et al. 2006; Torres et al. 2007), results on global intelligence in BD patients (both from individual studies and meta-analyses) are equivocal (McClellan et al. 2004; Pirkola et al. 2005; Frangou et al. 2005; McIntosh et al. 2005; Toulopoulou et al. 2006; Robinson et al. 2006; Frantom et al. 2008; Bora et al. 2009; Reichenberg et al. 2009; Eric et al. 2013). These inconsistent findings are possibly the result of methodological deficiencies: although there have been large register-based studies on the association between premorbid IQ and BD, studies that focused on IQ in BD patients have been small (n<90) (McIntosh et al. 2005; Toulopoulou et al. 2006), consisted of heterogeneous samples (Robinson et al. 2006) and in some cases lacked a control group (McClellan et al. 2004; Reichenberg et al. 2009).

What is known is that, in contrast to findings in schizophrenia, intellectual deficits do not appear to be present before onset of BD (Reichenberg et al. 2002; Zammit et al. 2004); and intelligence in first-degree relatives of BD patients appears to be preserved (Balanza-Martinez et al. 2008). In fact, recent studies suggest that high premorbid intelligence (Gale et al. 2013) and excellent scholastic performances
(MacCabe et al. 2010) are associated with an increased risk of developing BD. However, since intelligence after disease onset has not been examined in these studies, the question remains whether BD patients also had a higher IQ.

Given the strong genetic influence in schizophrenia (Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011) and BD (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011) and some degree of genetic overlap between them (International Schizophrenia Consortium et al. 2009), it is of interest to investigate the contribution of a familial vulnerability to differences in intelligence and educational performance. Additionally, delineating intelligence and educational performance is important, since other factors besides intelligence are predictive of educational performance (Chamorro-Premuzic and Furnham, 2003; Deary et al. 2007).

We investigate IQ after onset of disease and educational performance in schizophrenia and BD patients and healthy controls. We include parents and siblings of these patient groups and siblings of controls to investigate IQ and educational performance and the association of a familial vulnerability with the disorders.

2. Methods

2.1 Study design

Data were collected by three Dutch studies: Bipolar Genetics (BiG), Dutch Genetic Risk and Outcome in Psychosis (GROUP) and CannabisQuest. All studies were approved by the medical ethical committee and all participants gave written informed consent.

BiG is an ongoing case-control study that started in June 2011 and is part of a collaboration between the University of California Los Angeles and the Dutch health care institutes University Medical Center Utrecht (UMC Utrecht), GGZ Altrecht, GGz InGeest, University Medical Center Groningen, Delta Center for Mental Health Care, Dimence, Parnassia (PsyQ) and Reinier van Arkel Group. BiG investigates genetic and
phenotypic information of patients with bipolar disorder type I (BD-I), first-degree relatives and controls. Patients were recruited via clinicians, the Dutch patient association, pharmacies and advertisements. First-degree relatives were invited through the patients who participated. Controls were recruited via advertisements and among individuals who previously participated in scientific studies and agreed to be contacted for new research. Inclusion criteria for all participants were 1. Age 18 years or older 2. At least three Dutch-born grandparents 3. A good understanding of Dutch language. Patients with a somatic illness that could have influenced the diagnosis of BD were excluded. Participants were considered euthymic when they did not meet DSM-IV criteria for a mood episode in the last month according to the Structured Clinical Interview for DSM-IV (SCID-I).

The GROUP study is an ongoing longitudinal study that investigates gene-environment interaction and resilience in schizophrenia spectrum disorder (SCZ) patients, first-degree relatives, controls and siblings of controls (Korver et al. 2012). The GROUP study is conducted by four Dutch university departments of psychiatry (Amsterdam, Groningen, Maastricht and Utrecht). Patients were included when they were between 16 and 50 years of age, had a diagnosis of a non-affective psychotic disorder according to the DSM-IV and a good command of Dutch language. First-degree relatives were invited through the patients. The CannabisQuest study is a cross-sectional study that included adolescents and young adults from the general population (Schubart et al. 2011; Vinkers et al. 2013). Participants filled out an online questionnaire and were subsequently assessed by a psychiatric interview and neuropsychological tests at the UMC Utrecht.

2.1.1 Participants

For the current study, we included BD-I patients and first-degree relatives of BD-I patients (participants of BiG), SCZ patients and first-degree relatives of SCZ patients (participants of GROUP) and unrelated community controls. Controls were included from all three studies (BiG, GROUP, CannabisQuest), siblings
of controls were included by the GROUP study only. Participants were older than 15 years of age. The three studies used identical neuropsychological tests and educational assessment. All psychiatric and neuropsychological assessments occurred at the UMC Utrecht or one of their academic collaborative institutes. To avoid inclusion of an unrepresentative population, we did not exclude controls with a psychiatric diagnosis other than a psychotic disorder or BD. Controls and their siblings with a diagnosis of BD or a psychotic disorder or with a first-degree relative with BD or a psychotic disorder were excluded. After excluding participants who did not meet the inclusion criteria, data were available for 494 BD-I patients, 955 SCZ patients, 135 parents of BD-I patients (BD-I parents), 897 parents of SCZ patients (SCZ parents), 161 siblings of BD-I patients (BD-I siblings), 1,042 siblings of SCZ patients (SCZ siblings), 1,104 controls and 100 siblings of controls (control siblings). Table 1 shows the characteristics of the participants included in the analyses. For an overview of the excluded participants, see Supplementary Figure 1.

2.2 Diagnosis

BD-I patients were diagnosed using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al. 1997). Relatives of BD-I patients and controls included by the BiG study were diagnosed by the Mini-International Neuropsychiatric Interview (Sheehan et al. 1998). Participants included by the GROUP study were assessed through the Schedules for Clinical Assessment in Neuropsychiatry 2.1 (Wing et al. 1990) or the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al. 1992). Controls that participated in the CannabisQuest study were diagnosed by the SCID-I. Disease history was considered positive when lifetime criteria for any psychiatric disorder were met. We obtained family history of psychiatric diseases through the Family Interview Genetic Studies (Maxwell, 1992). For SCZ patients, age at onset was a composite score of age of first psychosis, age of first psychiatric treatment, age of first use of antipsychotic medication and age of first problems (whatever came first) as previously used (Apeldoorn et al. 2014). For BD-I patients, age at onset was defined as age of first medication as reported in the Dutch
version of the Questionnaire Bipolar Disorders (Leverich et al. 2001; Suppes et al. 2001), given the insidious onset of BD-I and the high probability of recall bias in the retrospective assessment of first reported symptoms. When age at first reported symptoms was used in the models instead of age at first medication, the reported results did not change.

2.3 Intelligence Quotient

To estimate IQ we used four subtests of the Dutch version of the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler D., 1997) consisting of the subtests ‘Information’, ‘Block Design’, ‘Digit Symbol Coding’ and ‘Arithmetic’. This combination of subtests has been shown to most fully account for full-scale IQ in both schizophrenia patients ($R^2=0.90$) and controls ($R^2=0.86$) (Blyler et al. 2000).

2.4 Educational performance

In the Netherlands, most schools are state schools which are ordinaly organized into primary, secondary and tertiary education tiers. From 4 until 12 years of age, all children receive primary education. After 12 years, children are streamed into four levels of secondary education (low, intermediate, high preparatory vocational and pre-university), each level requiring greater intellectual and scholastic abilities (Vonk et al. 2012). After passing the examinations in secondary education, there are three levels of tertiary education possible (intermediate professional education, higher professional education and university). After achieving a master’s degree at university, it is possible to enroll in a doctoral program. The Dutch school system, with different educational levels and similar quality of education across schools, allows a detailed insight into intellectual and scholastic ability.

We asked participants to record their highest completed level of education. To have approximately equally distributed groups, we delineated six categories: Level 1: Low (no education, primary education and low secondary education); Level 2: Intermediate secondary education; Level 3: Intermediate
professional education; Level 4: High preparatory vocational and pre-university; Level 5: Bachelor degree (Higher professional education) and Level 6: University (Master’s degree or PhD degree).

2.5 Statistical analyses

We studied the association of group status (five comparisons: 1. BD-I patients versus controls and SCZ patients versus controls 2. BD-I patients versus SCZ patients 3. BD-I siblings versus control siblings and SCZ siblings versus control siblings 4. BD-I siblings versus SCZ siblings 5. BD-I parents versus SCZ parents) with two outcome variables: IQ and educational performance. Since we did not include parents of controls, we compared BD-I parents with SCZ parents. The statistical analyses were carried out using the R package for statistical computing (R core team, 2014) and SPSS 20.0. Assumptions were checked before analysing data. Subjects with missing data were excluded listwise from the analyses. We used ANOVA and t-tests to compare the patient, control and parent groups for age and age at onset and χ²-tests to compare these groups for gender and disease history. We used mixed-effects models with ‘family’ (indicating the family a person belonged to, used to account for relatedness within the sibling samples) as random factor to compare the three sibling groups on age, gender and disease history. We checked whether selective drop-out had occurred for missing values by comparing the participants included in the IQ analyses with the participants included in the analyses on educational performance. We conducted χ²-tests for gender, disease history and frequency of subjects within the analyses and performed t-tests for age, age at onset and IQ.

First, we studied the association of the disorders with IQ. To investigate whether patients differed from controls, we used a linear mixed-effects model with two dummy variables (BD-I versus controls and SCZ versus controls) as main determinants and IQ as outcome. We included a random factor ‘study’ (indicating the study a participant belonged to) to control for bias that may occur when samples from different
studies are compared. To investigate whether siblings of patients differed from control siblings on IQ we used a linear mixed-effects model with two dummy variables (BD-I siblings versus control siblings and SCZ siblings versus control siblings) as main determinants, IQ as outcome and ‘study’ and ‘family’ as random factors.

Since the indicator ‘study’ was identical for the patient, parent and sibling groups, we were unable to use this indicator as random factor for comparisons between BD-I and SCZ patients and BD-I and SCZ relatives. Therefore, we conducted two separate linear models with IQ as outcome and patient (BD-I patients versus SCZ patients) and parent (BD-I parents versus SCZ parents) groups as main determinants. To compare BD-I siblings with SCZ siblings, we conducted a linear mixed-effects model with sibling group as main determinant and ‘family’ as random factor.

Subsequently, we studied the association of the disorders with educational performance. We applied five different thresholds for the six categories for level of education and compared participants that completed an educational level and above with the remaining group (threshold 1: completing ‘Intermediate secondary education’ or higher versus completing ‘Low’; threshold 2: completing ‘Intermediate professional education’ or higher versus below; threshold 3: completing ‘High preparatory vocational and pre-university’ or higher versus below; threshold 4: completing ‘Bachelor’ or higher versus below; threshold 5: completing ‘University’ versus below). We used logistic regression analyses with dummy coding for patients and controls to investigate the differences in educational performance between patients and controls. Furthermore, we conducted logistic regression analyses to investigate educational performance between patient groups and parent groups. In addition, to estimate differences between parents and controls in absence of a group of parents of controls, we ran 10,000 permutation tests in which we compared the parent groups with a random sample of 600 controls. We analysed educational performance of siblings with a generalized mixed model with ‘family’ as random factor. Since we used five
thresholds as outcome variables, we corrected for multiple testing by applying a Bonferroni correction and considered p-values <0.01 as statistically significant.

Additionally, to account for illness effects in siblings, we excluded 14 BD-I and 50 SCZ siblings with a psychotic disorder or BD and repeated the analyses of IQ and educational performance. We also repeated the IQ and educational performance analyses in BD-I patients, SCZ patients and controls older than 34 years of age to rule out that age differences between these groups influence the results.

Age and gender were covariates in all models and age at onset was a covariate in the comparison of BD-I patients and SCZ patients. We calculated Cook’s Distances to investigate potential outliers. For two thresholds in the sibling comparisons (‘Intermediate secondary education’ and ‘University’) we could not calculate Cook’s Distance due to non-convergence of the mixed-effects model, so we calculated Cook’s Distance without a random factor in a linear model.

3. Results

We included 4,888 participants. Data on educational performance were missing for 24 BD-I patients, 8 SCZ patients, 5 BD-I parents, 55 SCZ parents, 6 BD-I siblings, 17 SCZ siblings and 56 controls. Listwise exclusion of these participants resulted in a sample of 4,717 participants included in the analyses of educational performance. There was no evidence of selective drop-out for missing values; the frequency of subjects within each group did not change (Patients and controls: $\chi^2=0.55$, $p=0.76$; Patients: $\chi^2=0.27$, $p=0.60$; Parents: $\chi^2=0.04$, $p=0.85$; Siblings and controls: $\chi^2=0.05$, $p=0.98$; Siblings: $\chi^2=0.03$, $p=0.86$) and there were no differences in demographic characteristics between the participants included in the IQ analyses and the participants included in the analyses of educational performance (Gender: $\chi^2=0.01$, $p=0.94$; Age: $t=0.40$, $p=0.69$; IQ: $t=-0.60$, $p=0.55$; Age at onset: $t=0.25$, $p=0.80$; Disease history: $\chi^2=0.07$, $p=0.79$).
The groups differed on several demographic factors (see Table 1). Figures 1 and 2 show the distribution of IQ and educational performance by group.
### Table 1. Demographics: Participants included in IQ analyses

<table>
<thead>
<tr>
<th></th>
<th>Patients BD-I n=494</th>
<th>Parents BD-I n=135</th>
<th>Siblings BD-I n=161</th>
<th>Patients SCZ n=955</th>
<th>Parents SCZ n=897</th>
<th>Siblings SCZ n=1,042</th>
<th>Controls n=1,104</th>
<th>Control siblings n=100</th>
<th>BD-I patients vs. SCZ patients vs. controls</th>
<th>BD-I siblings vs. SCZ siblings vs. controls</th>
<th>BD-I vs. SCZ parents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender male (%)</strong></td>
<td>217 (43.9%)</td>
<td>57 (42.2%)</td>
<td>49 (30.4%)</td>
<td>743 (77.8%)</td>
<td>380 (42.4%)</td>
<td>481 (46.2%)</td>
<td>538 (48.7%)</td>
<td>41 (41.0%)</td>
<td>BD-I=controls&lt;SCZ</td>
<td>BD-I=control=SCZ</td>
<td>BD-I=SCZ</td>
</tr>
<tr>
<td><strong>Age mean (SD)</strong></td>
<td>49.3 (12.1)</td>
<td>65.0 (7.1)</td>
<td>54.4 (11.3)</td>
<td>27.2 (7.0)</td>
<td>54.8 (6.8)</td>
<td>28.0 (8.2)</td>
<td>28.9 (12.5)</td>
<td>30.3 (11.6)</td>
<td>BD-I&gt;controls&gt;SCZ</td>
<td>BD-I&gt;controls&gt;SCZ</td>
<td>BD-I&gt;SCZ</td>
</tr>
<tr>
<td><strong>Age at onset mean (SD)</strong></td>
<td>32.0 (10.5)</td>
<td></td>
<td>22.53 (6.53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BD-I &gt;SCZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease history n (%)</strong></td>
<td>31 (23.0%)</td>
<td>63 (39.1%)</td>
<td>195 (21.7%)</td>
<td>176 (16.9%)</td>
<td>274 (24.8%)</td>
<td>12 (12.0%)</td>
<td></td>
<td></td>
<td>BD-I&gt;control=SCZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IQ mean (SD)</strong></td>
<td>96.8 (14.1)</td>
<td>102.2 (15.1)</td>
<td>106.3 (16.1)</td>
<td>94.9 (15.8)</td>
<td>102.9 (17.0)</td>
<td>102.8 (15.7)</td>
<td>107.8 (15.2)</td>
<td>111.2 (15.1)</td>
<td>BD-I&lt;controls&gt;SCZ</td>
<td>BD-I&lt;controls&gt;SCZ</td>
<td>BD-I=SCZ</td>
</tr>
</tbody>
</table>

*Significant difference between groups at p<0.01

1. Lifetime psychiatric diagnosis. Controls with BD or a psychotic disorder or with first-degree relatives with BD or a psychotic disorder are not included.
Figure 1. Boxplots of IQ scores

1a. Controls, BD-I and SCZ patients

1b. Control siblings, BD-I siblings and SCZ siblings

1c. BD-I parents and SCZ parents
Figure 2. Educational performance by group

2a. Controls, BD-I and SCZ patients

2b. Control siblings, BD-I siblings and SCZ siblings

2c. BD-I parents and SCZ parents
3.2 BD-I and SCZ patients versus controls

Both BD-I and SCZ patients had a significantly lower IQ than controls (BD-I: $\beta=-9.09$, SE=1.27, $p<0.001$; SCZ: $\beta=-15.33$ SE=0.86, $p<0.001$). BD-I patients had a significantly higher IQ than SCZ patients ($\beta=4.55$, SE=1.35, $p=0.001$). SCZ patients had completed lower educational levels than BD-I patients and controls. In contrast, BD-I patients were more likely to have completed the highest educational level than controls. Table 2 shows the results of the analyses of educational performance in patients and controls.

To investigate whether the characteristics of BD-I patients with a low IQ and high educational performance differed from the other BD-I patients with high educational performance, we compared patients with an IQ below 95 (1/3 standard deviation below the average of 100) who had completed University ($n=15$) with normal IQ BD-I patients who had completed University ($n=92$). We found no differences between the groups for age ($t=1.74$, $p=0.09$), age at onset ($t=0.75$, $p=0.46$) and gender ($\chi^2=2.31$, $p=0.13$).

To account for the effect of age difference between the patients and controls, we repeated the IQ and educational performance analyses in patients and controls older than 34 years of age. We found very similar results as in the main analyses; BD-I patients and SCZ patients had a lower IQ than controls (BD-I: Beta=-8.08, SE=1.45, $p<0.001$; SCZ: Beta=-15.81, SE=1.66, $p<0.001$) and BD-I patients had a higher IQ than SCZ patients (Beta=5.77, SE=1.73, $p=0.001$). Furthermore, SCZ patients had lower educational performance than BD-I patients and controls, whereas BD-I patients were more likely to have completed University (See Supplementary table 1).
Table 2. The association of disorder with educational performance

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Highest completed education</th>
<th>BD-I versus SCZ OR and 95% CI</th>
<th>BD-I versus controls OR and 95% CI</th>
<th>SCZ versus controls OR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intermediate secondary education</td>
<td>3.34 [2.80-5.57]*</td>
<td>0.76 [0.64-1.24]</td>
<td>0.16 [0.14-0.22]*</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate professional education</td>
<td>2.63 [2.29-3.90]*</td>
<td>0.70 [0.62-0.99]</td>
<td>0.22 [0.20-0.27]*</td>
</tr>
<tr>
<td>3</td>
<td>High preparatory vocational and pre-university</td>
<td>2.55 [2.25-3.63]*</td>
<td>0.97 [0.88-1.28]</td>
<td>0.30 [0.28-0.36]*</td>
</tr>
<tr>
<td>4</td>
<td>Bachelor</td>
<td>3.41 [2.98-5.03]*</td>
<td>1.10 [1.00-1.44]</td>
<td>0.38 [0.35-0.48]*</td>
</tr>
<tr>
<td>5</td>
<td>University</td>
<td>5.78 [4.77-10.04]*</td>
<td>1.88 [1.66-2.70]*</td>
<td>0.43 [0.38-0.63]*</td>
</tr>
</tbody>
</table>

*Does not include unity

3.3 BD-I and SCZ siblings versus control siblings

BD-I and SCZ siblings had a similar IQ (β=3.49, SE=2.00, p=0.08), which was significantly lower than that of control siblings (BD-I: β=-5.77, SE=2.41, p=0.02; SCZ: β=-8.34, SE=1.68, p<0.01). Moreover, although Figure 2 suggests that BD-I siblings are higher educated than SCZ siblings and control siblings, the three sibling groups did not significantly differ in educational performance after adjusting for age and gender.

Analysis of (healthy) siblings without BD-I or a psychotic disorder revealed lower intelligence for SCZ siblings (β=-8.20, SE=1.67, p<0.001) but not for BD-I siblings (β=-4.73, SE=2.44, p=0.05) as compared with controls. Instead, BD-I siblings had a higher IQ than SCZ siblings (β=4.49, SE=2.06, p=0.03). The results for educational performance did not change: the three sibling groups did not significantly differ on educational performance (see Supplementary Table 2). Table 3 shows the results of the analyses of educational performance in relatives of patients and controls.
3.4 **BD-I parents versus SCZ parents**

BD-I parents had a similar IQ as SCZ parents (β=-1.22, SE=1.70, p=0.47), but were more often higher educated (see table 3). The results of 10,000 permutation tests revealed that BD-I parents had similar educational performance as random (unrelated) controls. SCZ parents had lower educational performance than unrelated controls (see Supplementary table 3).

**Table 3. The association of familial vulnerability with educational performance**

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Highest completed education</th>
<th>Siblings OR and 95% CI</th>
<th>Parents OR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intermediate secondary education</td>
<td>1.86 [0.79-22.21]</td>
<td>2.00 [1.64-3.56]</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate professional education</td>
<td>0.51 [0.40-1.07]</td>
<td>1.48 [1.27-2.33]</td>
</tr>
<tr>
<td>3</td>
<td>High preparatory vocational and pre-university</td>
<td>1.24 [1.02-2.17]</td>
<td>1.88 [1.63-2.87]*</td>
</tr>
<tr>
<td>4</td>
<td>Bachelor</td>
<td>0.63 [0.51-1.15]</td>
<td>1.83 [1.58-2.80]*</td>
</tr>
<tr>
<td>5</td>
<td>University</td>
<td>0.43 [0.17-5.68]</td>
<td>0.96 [0.77-1.84]</td>
</tr>
</tbody>
</table>

1. Age was left out due to problems converging the models
2. Does not include unity

3.5 **Analysis of outliers and ethnicity**

None of the participants fulfilled the criteria for outliers by Cook’s Distance. Since not all SCZ patients, SCZ relatives and controls were Dutch, we analysed the data from the Caucasian participants only (SCZ patients: n=756; SCZ parents: n=798; SCZ siblings: n=867; controls: n=1067; control siblings: n=92). The results of these analyses did not differ from the results we found for the entire group of participants (data not shown).
4. Discussion

In the largest cross-sectional study on IQ and educational performance in BD-I and SCZ patients and relatives to date, patients with established BD-I had a lower IQ, but superior educational performance relative to healthy controls. By contrast, SCZ patients had lower IQ as well as inferior educational performance compared to controls, suggesting that IQ in schizophrenia is affected in an earlier stage of the illness. The fact that educational performance of BD-I siblings and BD-I parents was comparable to that of controls while in patients it was higher, raises the question as to whether high educational performance is associated with bipolar disorder itself rather than with a familial vulnerability to develop the illness.

Cognitive deficits in BD-I patients have been reported previously (McIntosh et al. 2005; Toulopoulou et al. 2006) and our findings are in line with a recent meta-analysis in 1,026 euthymic BD patients (Mann-Wrobel et al. 2011). Lower IQ appears to be associated with the illness itself, as healthy BD-I siblings do not show a significantly reduced IQ compared with control siblings. In contrast, healthy SCZ siblings had a lower IQ than control siblings, indicating that lower IQ may be associated with a familial vulnerability for SCZ. The current study emphasizes that IQ may not fully account for educational performance, as we show different results for both domains in BD-I patients. Moreover, our results confirm findings by previous register-based studies that low educational performance is associated with schizophrenia and high educational performance is associated with BD (MacCabe et al. 2008; MacCabe et al. 2010).

One of the explanations for the contradictory finding regarding high educational performance and lower intelligence in BD-I patients is that intelligence may have been higher before onset of BD, but decreased after illness onset (Trotta et al. 2014) possibly as a result of number of hospitalizations (Robinson and Ferrier, 2006), traumatic experiences (Aas et al. 2011) or long-term medication use (Pachet and Wisniewski, 2003; Senturk et al. 2007; Wingo et al. 2009; Vreeker et al. in press).
Additionally, prodromal symptoms like elevated energy (Egeland et al. 2000) may have contributed to high educational performance.

Interestingly, BD-I siblings and BD-I parents did not have higher educational performance than controls, which suggests that high educational performance is associated with the illness itself, rather than with a familial vulnerability to BD. This is partly in line with earlier findings showing fewer completed years of education for non-bipolar co-twins, but not for bipolar co-twins, as compared with controls (Vonk et al. 2012). From an evolutionary perspective our results raise the question whether high (educational) achievement could be a result of an adaptive advantage of the disorder, associated with benefits in leadership (Akiskal and Akiskal, 2005).

**Limitations**

The current study has several limitations. First it should be noted that the cross-sectional design of our study does not allow us to conclude that there has been a decline in IQ in BD-I patients. Also, BD-I patients were significantly older than SCZ patients and controls which may have resulted in a greater opportunity for BD-I patients to attend higher education. However, analyses of patients and controls older than 34 years of age, yielded very similar results. Furthermore, younger people tend to be higher educated than older people in general (Barro and Lee, 2013) and the fact that BD-I patients were higher educated despite their higher age could also underscore their superior educational performance.

Despite careful analysis that incorporate multilevel analysis, sensitivity analysis and exploration of a range of possible confounders, residual confounding may remain as we are unable to adjust for all possible factors (e.g. medication use, comorbid disorders) that could have influenced IQ scores. Particularly, information on parental socioeconomic status is absent and we cannot rule out the possibility that differences in parental socioeconomic status may have influenced our results. However, since tuition fees are low and income differences are substantially reduced by social security and taxes in the Netherlands we do not expect that differences in socioeconomic status may have accounted for our results on educational performance.
A final limitation is that, despite our large sample, we cannot be sure that our populations are representative; inherent to clinical cohorts is Berkson's bias (bias toward those willing to participate and those under treatment) (Regeer et al. 2009).

Conclusions
We show that despite BD-I patients having a lower IQ relative to controls, they are more likely to have completed the highest level of education. This contrasts with our findings in SCZ patients, who demonstrate both lower IQ and lower educational performance. The fact that BD-I patients, but not BD-I parents or BD-I siblings, had more often completed the highest level of education compared with controls suggests that high educational performance may be a distinctive feature of the illness itself.
Appendix

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Kahn, R. S. & Keefe, R. S. (2013). Schizophrenia is a cognitive illness: time for a change in focus. *JAMA Psychiatry* **70**, 1107-1112.


## Supplementary tables and figures

### Table S1. Educational performance of BD-I patients, SCZ patients and controls older than 34 years

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Highest completed Education</th>
<th>BD-I patients versus controls</th>
<th>SCZ patients versus controls</th>
<th>BD-I patients versus SCZ patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intermediate secondary education</td>
<td>1.36 [1.12-2.38]</td>
<td>0.17 [0.13-0.32]*</td>
<td>7.33 [5.62-15.91]*</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate professional education</td>
<td>1.08 [0.94-1.65]</td>
<td>0.25 [0.21-0.42]*</td>
<td>4.50 [3.68-8.12]*</td>
</tr>
<tr>
<td>3</td>
<td>High preparatory vocational and pre-university</td>
<td>1.32 [1.18-1.84]</td>
<td>0.44 [0.38-0.67]*</td>
<td>3.00 [2.54-4.85]*</td>
</tr>
<tr>
<td>4</td>
<td>Bachelor</td>
<td>1.38 [1.24-1.90]</td>
<td>0.48 [0.41-0.74]*</td>
<td>2.83 [2.40-4.56]*</td>
</tr>
<tr>
<td>5</td>
<td>University</td>
<td>2.53 [2.17-3.96]*</td>
<td>0.78 [0.62-1.48]</td>
<td>3.77 [3.01-7.20]*</td>
</tr>
</tbody>
</table>

*Does not include unity

### Table S2. The association of familial vulnerability with educational performance in siblings without BD or a psychotic illness

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Highest completed education</th>
<th>BD-I siblings versus SCZ siblings OR and 95% CI</th>
<th>BD-I siblings versus control siblings OR and 95% CI</th>
<th>SCZ siblings versus control siblings OR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intermediate secondary education</td>
<td>1.80 [0.89-14.07]</td>
<td>1.33 [0.54-17.80]</td>
<td>0.60 [0.47-1.23]</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate professional education</td>
<td>0.43 [0.32-0.94]</td>
<td>0.37 [0.27-0.95]</td>
<td>0.92 [0.75-1.70]</td>
</tr>
<tr>
<td>3</td>
<td>High preparatory vocational and pre-university</td>
<td>1.14 [0.93-2.04]</td>
<td>0.72 [0.57-1.45]</td>
<td>0.64 [0.54-1.03]</td>
</tr>
<tr>
<td>4</td>
<td>Bachelor</td>
<td>0.60 [0.48-1.10]</td>
<td>0.87 [0.67-1.82]</td>
<td>1.47 [1.21-2.55]</td>
</tr>
<tr>
<td>5</td>
<td>University</td>
<td>0.47 [0.19-6.35]</td>
<td>1.01 [0.29-38.24]</td>
<td>2.11 [0.75-43.33]</td>
</tr>
</tbody>
</table>

1Age was left out due to problems converging the models

*Does not include unity
<table>
<thead>
<tr>
<th>Threshold</th>
<th>Highest completed education</th>
<th>BD-I parents versus random controls</th>
<th>SCZ parents versus random controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intermediate secondary education</td>
<td>0.76 [0.57-1.78]</td>
<td>0.34 [0.28-0.59]*</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate professional education</td>
<td>0.54 [0.43-1.03]</td>
<td>0.39 [0.34-0.60]*</td>
</tr>
<tr>
<td>3</td>
<td>High preparatory vocational and pre-university</td>
<td>0.92 [0.76-1.61]</td>
<td>0.48 [0.42-0.69]*</td>
</tr>
<tr>
<td>4</td>
<td>Bachelor</td>
<td>0.82 [0.68-1.43]</td>
<td>0.62 [0.55-0.90]</td>
</tr>
<tr>
<td>5</td>
<td>University</td>
<td>0.62 [0.47-1.38]</td>
<td>0.66 [0.55-1.12]</td>
</tr>
</tbody>
</table>

*Does not include unity
Figure S1. Flowchart of participants

Bipolar Genetics:
- 540 BD-I patients
- 135 Parents of BD-I patients
- 162 Siblings of BD-I patients
- 193 Controls

GROUP:
- 970 SCZ patients
- 897 Parents of SCZ patients
- 1,042 Siblings of SCZ patients
- 476 Controls
- 101 siblings of controls

CannabisQuest:
- 483 Controls

Excluded patients:
- 2 patients had prior experience with the WAIS
- 8 patients with a somatic illness that could have influenced the results
- 36 BD-I patients that were not euthymic during the interview
- 15 patients did not fulfill criteria for a schizophrenia spectrum disorder

Excluded family members:
- 1 BD sibling was not euthymic during the interview

Excluded controls:
- 8 controls with a diagnosis of BD or any psychotic disorder
- 37 controls with first-degree relatives with a diagnosis of BD or any psychotic disorder
- 1 control experienced a depressive episode during the interview
- 2 controls with a somatic illness that could have influenced the results
- 1 control sibling with a diagnosis of a psychotic disorder

Participants included in analyses IQ:
- 494 BD-I patients
- 955 SCZ patients
- 1,104 controls

Missing data on level of education:
- 24 BD-I patients
- 8 SCZ patients
- 56 Controls
- 17 Siblings of SCZ patients

Participants included in analyses level of education:
- 470 BD-I patients
- 947 SCZ patients
- 130 parents of BD-I patients
- 842 parents of SCZ patients
- 155 siblings of BD-I patients
- 1,025 siblings of SCZ patients
- 1,048 controls
- 100 siblings of controls