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The relationship between brain volumes and intelligence in bipolar disorder

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Abstract

OBJECTIVES—Bipolar disorder type-I (BDI) patients show a lower Intelligence Quotient (IQ) and smaller brain volumes as compared with healthy controls. Considering that in healthy individuals lower IQ is related to smaller total brain volume, it is of interest to investigate whether IQ deficits in BD patients are related to smaller brain volumes and to what extent smaller brain volumes can explain differences between premorbid IQ estimates and IQ after a diagnosis of BD.

METHODS—Magnetic resonance imaging brain scans, IQ and premorbid IQ scores were obtained from 195 BDI patients and 160 controls. We studied the relationship of (global, cortical and subcortical) brain volumes with IQ and IQ change. Additionally, we investigated the relationship between childhood trauma, lithium- and antipsychotic use and IQ.

RESULTS—Total brain volume and IQ were positively correlated in the entire sample. This correlation did not differ between patients and controls. Although brain volumes mediated the relationship between BD and IQ in part, the direct relationship between the diagnosis and IQ remained significant. Childhood trauma and use of lithium and antipsychotic medication did not affect the relationship between brain volumes and IQ. However, current lithium use was related to lower IQ in patients.

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Contributors

RO was the principal investigator. RK was the leading on-site investigator. Recruitment and assessment of particpants was done by AV, LA, SV, AB. Data management and analyses were conducted by AV, LA, NvH and MB. AV and LA wrote the original manuscript. All authors reviewed and approved the final manuscript.

Conflict of interest

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

CONCLUSIONS—Our data suggest a similar relationship between brain volume and IQ in BD patients and controls. Smaller brain volumes only partially explain IQ deficits in patients. Therefore, our findings indicate that in addition to brain volumes and lithium use other disease factors play a role in IQ deficits in BD patients.

Keywords

bipolar disorder; IQ; brain volume; MRI

1. Introduction

Intelligence is impaired in euthymic bipolar disorder (BD) patients (Trotta *et al.* 2014; Vreeker *et al.* 2016). Despite high cognitive functioning *before* disease onset (Gale *et al.* 2013; MacCabe *et al.* 2010; Vreeker *et al.* 2016), clinical studies in BD patients demonstrate lower Intelligence Quotient (IQ) *after* disease onset as compared with healthy controls (McIntosh *et al.* 2005; Toulopoulou *et al.* 2006; Vreeker *et al.* 2016). The reason for this apparent IQ decline remains elusive; both environmental factors, such as a history of traumatic experiences or medication use (Aas *et al.* 2013; Wingo *et al.* 2009), and genetic factors (International Schizophrenia Consortium *et al.* 2009) may explain this decline to some extent. There is also evidence for smaller total brain volume, cortical volume, and subcortical volumes in BD patients relative to healthy individuals (Abramovic *et al*, 2016; Lan *et al*, 2014; Rimol *et al* 2010). These subtle brain abnormalities may be related to a lower IQ.

In healthy individuals, intelligence is positively associated with total brain volume, with correlations ranging from 0.33 to 0.38 (Deary *et al.* 2010; Posthuma *et al.* 2002; McDaniel, 2005; Rushton and Ankney, 2009). In addition, cortical thickness of the frontal, parietal, anterior cingulate and occipital regions have been positively related to intelligence (Brans *et al.* 2010; Schnack *et al.* 2014; Colom *et al.* 2006; Frangou *et al.* 2004; Haier *et al.* 2004; Wilke *et al.* 2003). Also, higher IQ has been related to more pronounced surface contraction with increasing age, particularly in the precentral, left medial frontal and right supramarginal and parietal cortices and cuneus (Schnack *et al.* 2014). Although the relationship of subcortical volumes with IQ is less clear, recent findings suggest a positive relationship between thalamus volume and IQ (Bohlken *et al.* 2014).

Previously, a study in BD patients showed that change in IQ measured before and after disease onset was significantly correlated with smaller volumes of the superior temporal gyri, the parahippocampal gyri and the uncus (Bruno *et al.* 2006). Based on the same sample, Gutierrez-Galve *et al.* (2012) reported a positive association between frontal cortical volume (measured after illness onset) and estimated premorbid IQ, but not with IQ after disease onset. However, the sample was relatively small (N=36), heterogeneous (bipolar I disorder (BD-I) and bipolar II disorder), and lacked a control group. The latter makes it difficult to interpret whether the reported associations in BD patients deviate from unaffected individuals.

Studies on the association of subcortical volumes and IQ in BD have not been conducted yet. Hartberg and colleagues did investigate the relationship between subcortical volumes

and several cognitive domains and reported a negative correlation between right putamen volume and executive functioning in bipolar disorder and schizophrenia patients, that significantly differed from the positive correlation in healthy controls (Hartberg *et al.* 2011).

Recently, we showed that BD-I patients have a lower intelligence than controls, but are more likely to have completed the highest level of education, suggesting that a subsequent fall in IQ may occur following illness onset (Vreeker *et al.* 2016). In addition, in a subset of this same sample, we convincingly showed that global brain volumes, such as total brain and ventricle volume, are smaller in patients with BD-I patients compared to controls (Abramovic *et al.* 2016). In the current study we investigate whether the lower IQ in BD-I patients can be explained by smaller brain volumes. First, we investigate whether lower IQ after disease onset in BD-I patients is related to smaller brain volumes and whether the relationship between brain volumes and IQ differs between BD-I patients and unaffected controls. Also, we study whether brain volumes mediate the relationship between bipolar disorder and IQ. In addition, we look at the relationship between premorbid-to-current IQ change and brain measures. Finally, the potential influence of childhood trauma, and lithium and antipsychotic use on the relationship between brain volumes and IQ is studied, as these factors have been suggested to play a role in lower IQ after disease onset.

2. Patients and methods

2.1 Participants

In this cross-sectional study we included 222 patients with BD-I and 162 healthy controls, across an age range of 19–80 years. All participants were part of the Dutch Bipolar cohort study, which was described previously (Vreeker *et al.* 2016). We included patients with a diagnosis of BD-I according to DSM-IV criteria from Dutch ancestry (defined as having at least three Dutch grandparents). To avoid including an unrepresentative healthy population, we only excluded controls when they or their first-degree relatives had a diagnosis of BD, schizophrenia or any other psychotic disorder.

In BD patients, diagnosis was confirmed using the Structured Clinical Interview for DSM-IV (SCID-I) (First *et al.* 1997). Age at onset (age of first medication use) and number of episodes were determined by the Questionnaire for Bipolar Illness (QBP-NL; Dutch translation by Akkerhuis, Groenesteyn, Nolen 1997; an adaption of the Enrolment Questionnaire as previously used in the Stanley Foundation Bipolar Network) (Leverich *et al.* 2001; Suppes *et al.* 2001). Patients were considered euthymic when they did not fulfill criteria for a mood episode according to the DSM-IV in the four weeks prior to the interview. In controls, the presence or absence of psychopathology was established by the M.I.N.I. (Mini International Neuropsychiatric Interview; Sheehan *et al.* 1998). Interviews were conducted by well-trained independent raters. In addition, an MRI scan was made. An independent radiologist evaluated the MRI scans and participants with major clinical outcomes were excluded. In addition, participants with a history of head trauma, a neurological illness or who had recent experience with the Wechsler Adult Intelligence Scale-III (WAIS-III) were excluded from the analyses. Written informed consent was obtained from all participants. The Humans Ethics Committee of the UMC Utrecht and the UCLA Human Subjects review board approved the study. The study was conducted

2.2 Intelligence

Four subtests of the Dutch version of the WAIS-III (Wechsler D., 1997) were used to estimate current IQ, being Digit Symbol Coding (processing speed), Block Design (visuospatial capacities), Arithmetic (working memory) and Information (general knowledge). These subtests measure general knowledge, visuospatial capacities, processing speed, and working memory, respectively. The combination of these four subtests has been shown to reliably estimate IQ in schizophrenia patients (R^2=0.90) and controls (R^2=0.86) (Blyler *et al.* 2000).

Premorbid IQ was estimated by the Dutch Adult Reading Test, the Dutch version of the National Adult Reading Test (NART) (Schmand *et al.* 1991), in which participants are asked to read out loud irregular words. The NART is considered to be the best predictor of premorbid IQ (Bright *et al.* 2002).

2.3 Confounders

We investigated whether childhood trauma, lithium use and antipsychotic use confounded the relationship between brain volumes and IQ. Childhood trauma was assessed using the Childhood Trauma Questionnaire – Short Version (CTQ; Bernstein *et al* 2003). Total trauma scores were used in the analyses as a continuous measure for childhood trauma. We assessed the effects of current lithium use in all patients (yes/no), and current antipsychotic use in a subgroup of patients (yes/no, N=182 (93.3%)), for whom we had detailed pharmacy-confirmed information available.

2.4 Brain imaging

Three-dimensional T1-weighted images were acquired on a 3 Tesla Philips Achieva scanner (Philips Healthcare, Best, the Netherlands), equipped with a commercial eight channel SENSE-headcoil. Fast field echo scans with 200 contiguous sagittal slices (TE=4.6 ms, TR=10 ms, flip angle=8°, FOV = 240mm, 0.75 × 0.75 × 0.80 mm^3 voxels) were made.

Post-processing was done on the neuroimaging computer network of the UMC Utrecht-Brain Center Rudolf Magnus, Utrecht, the Netherlands. We used the FreeSurfer 5.1.0 software package (http://surfer.nmr.mgh.harvard.edu) (Fischl *et al.* 2002) for automatic segmentation of (sub)cortical brain structures. In short, the T1-weighted images were registered to the Talairach atlas (Talairach, 1988) and intensity variations were corrected. The image was then skull-stripped (Segonne *et al.* 2004) and the remaining voxels were classified as white matter or non-white matter based on intensity and neighbor constraints. Cutting planes were computed in order to separate the hemispheres and remove the cerebellum and brain stem. Any interior holes in the components representing white matter were filled. The initial triangular tessellation was formed on the surface of this white matter mass to create a surface mesh representation, and then smoothed using a deformable surface algorithm to form the grey/white surface. The algorithm was further used to expand the surface to obtain the grey matter-cerebrospinal fluid surface (Dale *et al.* 1999; Fischl *et al.* 1999). Then, the images were registered to a spherical atlas and cortical thickness measures were obtained by calculating the distance between the grey/white matter boundary and the cortical surface at approximately 320,000 points across the cortex (Fischl and Dale, 2000).

Segmentation of grey and white matter was visually checked and control points were added if necessary. Subcortical volumes were extracted and quality checked according to the guidelines provided by the ENIGMA consortium (http://enigma.ini.usc.edu/) using Surfscan Visualiser (http://ibowman.com/surfscan/). Poorly segmented volumes were excluded. We extracted the volumes of the thalamus, hippocampus, amygdala, nucleus accumbens, caudate nucleus, putamen and pallidum (Buckner *et al.* 2004), in addition to thirty-four cortical parcellations (Desikan atlas). All images were coded to ensure investigator blindness to subject identification and group.

2.5 Statistical analyses

We compared demographic and clinical variables between BD-I patients and controls, using t-tests and $\chi 2$-tests as appropriate.

We adjusted the brain volumes for the influence of gender and age, by calculating standardized residuals for global and (sub)cortical volumes on the total sample. These standardized residuals were used for further analyses. As lithium use is associated with larger brain volumes (Hallahan *et al.* 2011; Abramovic *et al.* 2016) we corrected for the effects of lithium by applying a method previously described by van der Schot *et al.* (2009). In short, we calculated the difference in means for the separate adjusted volumes between patients who did and did not take lithium. This difference was then subtracted from the values of the lithium-using patients, resulting in an estimate of their adjusted volumes when lithium would not have been used.

Data on IQ and standardized residuals of brain volumes were examined for normality of the distribution and Cook's distances were calculated to investigate potential outliers. We used SPSS 21.0 statistical package for Windows (IBM Corp., Armonk, NY) and R (version 3.1.0) to perform statistical analyses.

2.5.1 The association between brain volumes and IQ—First, we investigated the correlation of total brain volume and IQ in the total sample and patients and controls separately, by calculating Pearson's r. We used the r^2 to establish how much variance in IQ was explained by total brain volume. Then, we performed separate linear regression analyses with adjusted brain volumes, diagnosis (BD-I patients or healthy controls) and an interaction of diagnosis-by-adjusted brain volumes as main determinants and IQ as outcome variable. Brain volumes were already corrected for age and gender by calculating standardized residuals for the analyses, but now we also adjusted for possible confounding by age and gender on intelligence by adding these variables as covariates.

To exclude that significant effects in local brain areas are driven by total brain volume, we repeated the analyses with (sub)cortical volumes adjusted for gender, age and total brain volume.

C4: We further examined whether adjusted brain volumes were differently related to the WAIS subtest scores between BD-I patients and controls. We performed multivariate analyses of covariance (MANCOVA) with the scaled scores of the WAIS subtests (Digit Symbol Coding, Block Design, Arithmetic and Information) as outcome variables, adjusted

brain volumes, diagnosis and diagnosis-by-adjusted brain volume interactions as main determinants and age and gender as covariates.

2.5.2 Mediation analyses—We investigated whether the relationship between a diagnosis of BD and IQ was mediated by brain volumes. For that, we used the mediation package in R (Tingley *et al.*, 2015). We investigated whether adjusted brain volumes mediate the relationship between IQ and diagnosis over and above the direct effect of diagnosis, age and gender on IQ. Point estimates for mediation and their 95% confidence intervals were estimated with 10,000 bootstrap resamples. An important assumption for causal mediation analysis is that of sequential ignorability (Imai *et al.*, 2010). We conducted sensitivity analyses to investigate the sequential ignorability assumption; Rho provides an indication of how well this assumption is met, ideally Rho should be 0.

2.5.3 The association between brain volumes and change in IQ—Subsequently, we investigated whether change in IQ (the difference between premorbid IQ and current IQ) was differently associated with brain volumes in BD patients compared with controls. Since premorbid IQ was measured by a reading task, we excluded participants who reported to have been diagnosed with dyslexia. We obtained change scores by subtracting z-scores of the current IQ from the z-scores of the premorbid IQ. Subsequently, this change score was used as outcome variable in linear regression models, with diagnosis, adjusted brain volumes and diagnosis-by-volume interactions as main determinants and age and gender as covariates.

2.5.4 Confounders—Last, we investigated whether our results were confounded by childhood trauma and current lithium and antipsychotic medication use. We calculated the correlation between childhood trauma and IQ within the entire sample. Within the patient sample, we studied the correlation between current lithium use (yes/no), current antipsychotic use (yes/no) and IQ. Previously we showed, in a largely overlapping sample, that lithium-free patients had more pronounced brain abnormalities as compared with those on lithium, and patients on antipsychotics showed subtle reductions is some local brain areas relative to those not using antipsychotics (Abramovic *et al*, 2016). In case of a significant correlation of childhood trauma with IQ, we added this variable separately to a linear model with adjusted total brain volume, diagnosis, gender and age as main determinants and IQ as outcome in the entire sample. In addition, in case of significant correlations for lithium and antipsychotic use with IQ, we added these variables to a linear model with total brain volume, gender and age as main determinants and IQ as outcome in the patient sample.

We report uncorrected and Bonferroni corrected p-values, in which case we considered $p<0.007$ (7 tests) in the subcortical analyses and $p<0.00147$ (34 tests) in the cortical analyses as statistically significant.

3. Results

3.1 Demographic and clinical measures

Measures of IQ and brain volumes were available for 222 BD-I patients and 162 healthy controls. Twenty-seven BD-I patients and 2 healthy controls were excluded: 22 BD-I

patients were not euthymic, 2 BD-I patients had recent experience with the WAIS-III and 3 BD-I patients and 2 controls had a physical condition that could have influenced IQ or brain volumes.

Excluding these participants resulted in a total sample of 195 BD-I patients and 160 healthy controls. BD-I patients did not differ significantly from healthy controls on gender and handedness. However, BD-I patients were significantly older than controls (t=−2.38, p=0.02). For demographic and clinical information, see Table 1.

3.2 The association of brain volume and IQ

As the current sample is a subset of a larger sample, on which we reported previously (Abramovic *et al.*, 2016; Vreeker *et al.*, 2016), we repeated the group comparisons on IQ and brain measures (see supplement). Findings were similar as in the previous publications.

Pearson's correlation between standardized residuals of total brain volume and IQ was 0.30 ($p<0.001$). Stratified by diagnosis, this correlation was r=0.24 (p=0.001) for BD-I patients and r=0.28 ($p<0.001$) for controls. Within the entire sample, total brain volume explained approximately 9% of the total variance in IQ. Stratified by diagnosis, total brain volume explained almost the same amount of variance in IQ within controls (R^2=7%) and BD-I patients (R^2=5%). Using linear regression analysis, we did not find a significant diagnosis-by-total brain volume interaction on IQ (beta=−0.03, p=0.55), indicating that the association of IQ and total brain volume was not significantly different between BD-I patients and controls (see Figure 1). Furthermore, for subcortical and cortical volumes, none of the diagnosis-by-brain volume interactions were significantly associated with IQ after Bonferroni correction. Table 2 provides an overview of the association between diagnosis-by-brain volume interactions and IQ.

Post-hoc analyses revealed that the association between the adjusted brain volumes and the subtests Digit Symbol Coding, Block Design, Information and Arithmetic did not differ between BD patients and controls after Bonferroni correction. Supplementary table 2 shows the results of the post-hoc analyses.

When we repeated the analyses and used local cortical and subcortical volumes that, in addition to gender and age, were also adjusted for total brain volume, we found similar results.

3.3 Mediation analyses

Adjusted total brain volume partly mediated the relationship between IQ and diagnosis of BD (proportion mediation: 20%; point estimate=−1.63; 95% CI [−2.85:−0.67], $p<0.001$). The direct effect of diagnosis, gender and age was still significantly related to IQ (point estimate=−6.56; 95% CI [−9.71:−3.40], $p<0.001$).

Additionally, mediation analyses of the separate cortical and subcortical brain volumes revealed that only superior temporal cortex volume mediated the relationship between diagnosis of BD and IQ significantly (proportion mediated: 13.7%; Beta=−1.16

[−2.23:−0.34], p=0.0008). Supplementary table 3 shows the results of the mediating effect of the other brain volumes on the association between a diagnosis of BD and IQ.

Sensitivity analyses revealed a Rho of 0.3 or smaller for all analyses, indicating that the mediating effect of brain volumes were moderately robust to unobserved confounding influences.

3.4 The association of brain volumes with premorbid-to-current change in IQ

Data on premorbid IQ were missing for 5 controls. In addition, 3 BD-I patients and 2 controls were excluded because of dyslexia.

Total brain volume was significantly associated with change in IQ in the entire sample (Beta=−0.11, p=0.04). When we added diagnosis, diagnosis-by-total brain volume interaction, age and gender to the model, we found that the relationship between total brain volume and IQ change did not differ significantly between BD-I patients and controls (Beta=0.05, p=0.31). In addition, the relationship between adjusted cortical and subcortical volumes and change in IQ did not differ significantly between groups either (see Supplementary table 4).

3.5 Childhood trauma, lithium and antipsychotic medication

Childhood trauma was significantly correlated with IQ (r=−0.19, p<0.001) in the entire sample. None of the correlations between the local cortical and subcortical volumes and childhood trauma were stronger than r=−0.15 (p<0.01; data not shown). Inclusion of childhood trauma in the model with total brain volume, age, gender and diagnosis as determinants did not change the relationship between total brain volume and IQ. In addition, childhood trauma was no longer significantly related to IQ in this model (Beta=−0.10, p=0.05). Supplementary table 5.a shows the multivariate linear model including childhood trauma exposure.

We found a significant negative correlation of IQ with current lithium use (r=−0.20, p=0.005), but not with current antipsychotic use (r=0.002, p=0.98) in patients. When lithium use was added to a linear model with total brain volume, age and gender as determinants, both total brain volume and lithium use were significantly related to IQ (total brain volume: Beta=0.24, p<0.001; Lithium use: Beta=−0.21, p=0.002). Furthermore, the variable lithium use improved the model fit from an adjusted R^2 of 5% to an adjusted R^2 of 15.6%. Supplementary table 5.b shows the multivariate linear model including lithium exposure.

4. Discussion

In the largest cross-sectional study to date on the association of total brain, local cortical and subcortical volumes and IQ in patients with bipolar disorder, we found that total brain volume and superior temporal volume mediated the relationship between diagnosis and IQ, but only explained a small part of the variance. The relationship between brain volumes and (change in) IQ did not differ significantly between patients and controls. Neither was there a different relationship between brain volumes and separate cognitive domains. Childhood trauma and use of antipsychotic medication did not significantly influence IQ, but current

lithium use was associated with lower IQ in BD-I patients. Since the relationship between brain volumes and IQ is similar in BD-I patients and healthy controls our results suggest that smaller brain volumes might only explain IQ deficits in BD-I patients to a limited extent.

The reported positive correlation between total brain volume and IQ in patients is similar to findings in healthy individuals (Deary *et al.* 2010; McDaniel, 2005; Posthuma *et al.* 2002; Rushton and Ankney, 2009) and concurs with earlier reports that cortical volumes are associated with IQ in BD patients (Gutierrez-Galve *et al.* 2012; Bruno *et al.* 2006). Our results suggest that lower total brain volume mediates the relationship between BD and IQ deficits in bipolar disorder patients. However, despite the partly mediating role of total brain volume, a diagnosis of BD-I remains independently associated with a lower IQ, which suggests that IQ deficits are not only the result of a smaller total brain volume, but that other disease-related influences are also at play. In addition, we found that volume of the superior temporal cortex partly mediated the relationship between a diagnosis of BD-I and IQ. Interestingly postmortem studies revealed significant decreased N-acetylaspartate in the superior temporal cortex of patient with BD as compared with controls, suggesting reduced neuronal or axonal dysfunction. As this disturbance was also present in schizophrenia patients, this deficit might generalize to psychotic illness (Nudmamud *et al.*, 2003).

Of the potential risk factors investigated here, we show that traumatic experiences during childhood may play a minor role in the lower IQ we found in BD-I patients. The use of antipsychotic medication did not correlate with IQ in our data. In contrast, lithium use was significantly related to lower IQ, which is in line with findings described in several reviews that lithium use is associated with a decrease in cognitive function in BD patients (Vreeker *et al.* 2015; Wingo *et al.* 2009). Nevertheless, total brain volume combined with lithium use only explained 15% of the variance in IQ in BD-I patients. Therefore, the question remains why BD-I patients demonstrate lower IQ after disease onset. One could argue that genetic background of BD patients has an impact on IQ, as previous studies reported that polygenic schizophrenia scores are associated with reduced IQ in healthy individuals (McIntosh *et al.* 2013). This may account for some of the IQ decline in BD patients considering that BD patients and schizophrenia patients share part of the genetic vulnerability (International Schizophrenia Consortium *et al.* 2009).

Our findings should be considered in light of several limitations. First, we used an estimation of current IQ. It is unlikely that this had a large influence because the combination of subtests that was used has shown to be highly correlated with full-scale IQ assessment in both patients with schizophrenia and healthy controls (Blyler *et al.* 2000). However, it may impede comparisons with other studies. Another limitation is that we calculated IQ change using different measures in a cross-sectional design. Although we attempted to control for assessment bias by calculating z-scores, we cannot be sure that our results would have been similar, had we conducted the same test in a fully longitudinal design. Furthermore, sub-analyses of the effects of medication use on the relationship between total brain volume and IQ only incorporated current use of lithium and/or antipsychotic medication, not duration and dosage. Duration of medication use has been found to be associated with worse cognitive function (Wingo *et al.* 2009) and we cannot rule out that duration of medication exposures explains part of the association between brain and

IQ. Also, we studied a clinical cohort and we cannot be sure that this sample is representative; lower IQ in clinical populations may be more closely related to factors leading to hospital admission or poor outcome as opposed to (lower) IQ in population-based samples.

Overall, our data suggest that IQ deficits in BD-I patients can only be partly attributed to a smaller total brain volume. In order to understand IQ deficits in BD-I patients, further studies are required that disentangle the dysfunction that underlies IQ decline in BD-I patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- No different correlation of brain volume and IQ between BD patients and controls
- Brain volumes partly mediate the relationship between BD and IQ
- Current lithium use is related to lower IQ in BD patients

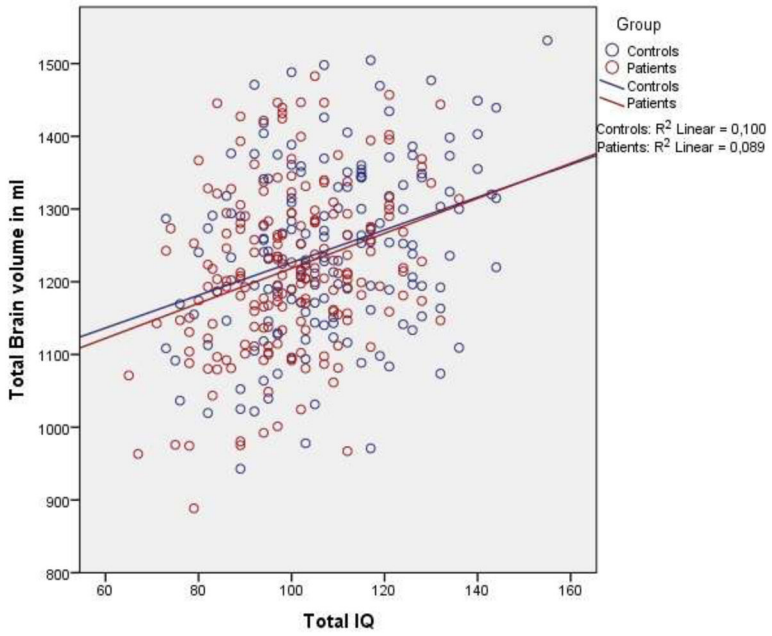

Figure 1.

Table 1

Demographical and clinical information of patients with bipolar disorder (N=195) and healthy controls (N=160)

Demographics	Bipolar patients (N = 195)	Control subjects (N = 160)	*t*-test/χ^2 (*p*-value)
Age in years, mean (s.d.) [range]	48.0 (12.1) [20–73]	44.6 (14.5) [19–78]	0.02
Sex, M/F (% male)	96/99 (49.2%)	78/82 (48.8%)	0.93
Handedness, R/L/B (% right)[a]	170/18/7 (87.2%)	135/19/5 (84.9%)	0.70
Premorbid IQ, mean (s.d.) [range]	107.4 (9.2) [82–130]	107.8 (9.4) [78–130]	0.62
Current IQ, mean (s.d.) [range]	99.6 (13.9) [65–136]	108.2 (16.8) [73–155]	**<0.001**
Number of episodes, median			
Mania	4		
Depression	4		
History of psychotic episodes, N (% yes)[b]	148 (78.7%)		
Medication, N (% on):			
Lithium[c]	134 (68.7%)		
Antipsychotic medication[d]	72 (39.6%)		
Childhood trauma, mean (s.d) [range]	41.2 (9.8) [25–75]	36.5 (7.3) [29–65]	**<0.001**

[a] missing of 1 control subject

[b] number of participants with a history of one or more psychotic episodes; missing of 7 subjects

[c] missing of 1 subjects

[d] missing of 13 subjects

Table 2

The association of diagnosis-by-volume interactions and IQ

Interaction	Beta	p-value
Diagnosis * caudal anterior cingulate	0.01	0.89
Diagnosis * lingual	0.06	0.22
Diagnosis * pars opercularis	0.02	0.75
Diagnosis * pars orbitalis	−0.01	0.88
Diagnosis * pars triangularis	0.04	0.48
Diagnosis * pericalcarine	−0.01	0.85
Diagnosis * posterior cingulate	−0.02	0.76
Diagnosis * frontal pole	0.02	0.65
Diagnosis * temporal pole	−0.10	0.04 *
Diagnosis * transverse temporal	−0.02	0.75
Diagnosis * bankssts	0.09	0.07
Diagnosis * caudal middle frontal	−0.01	0.87
Diagnosis * cuneus	0.02	0.77
Diagnosis * entorhinal	−0.03	0.52
Diagnosis * fusiform	−0.07	0.17
Diagnosis * inferior parietal	0.01	0.89
Diagnosis * inferior temporal	−0.01	0.86
Diagnosis * isthmus of the cingulate	−0.08	0.09
Diagnosis * lateral occipital gyrus	−0.02	0.75
Diagnosis * lateral orbitofrontal	−0.02	0.63
Diagnosis * medial orbitofrontal	0.02	0.70
Diagnosis * middle temporal	0.04	0.47
Diagnosis * parahippocampal	0.01	0.91
Diagnosis * paracentral	0.02	0.65
Diagnosis * postcentral	0.01	0.89
Diagnosis * precentral	−0.02	0.72
Diagnosis * precuneus	0.03	0.60
Diagnosis * rostralanteriorcingulate	0.01	0.90
Diagnosis * rostralmiddlefrontal	−0.05	0.36
Diagnosis * superiorfrontal	−0.04	0.42
Diagnosis * superior parietal	−0.10	0.06
Diagnosis * superior temporal	−0.002	0.97
Diagnosis * supramarginal	0.02	0.70

Interaction	Beta	p-value
Diagnosis * insula	−0.03	0.60
Subcortical volumes		
Diagnosis * thalamus	−0.001	0.98
Diagnosis * caudate nucleus	−0.04	0.41
Diagnosis * putamen	−0.01	0.88
Diagnosis * pallidum	−0.07	0.18
Diagnosis * hippocampus	0.11	0.83
Diagnosis * amygdala	0.001	0.99
Diagnosis * nucleus accumbens	−0.47	0.64

* $p < 0.05$

** $p<0.007$ for subcortical; $p<0.00147$ for cortical