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Research paper

The relationship between brain volumes and intelligence in bipolar disorder

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ABSTRACT

Objectives: Bipolar disorder type-I (BD-I) 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-I 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-I.

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-I 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.

Conclusions: Our data suggest a similar relationship between brain volume and IQ in BD-I 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-I patients.

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

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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 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., 1996). 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 in accordance with the declaration of Helsinki.

2.2. Intelligence

Four subtests of the Dutch version of the WAIS-III (Wechsler, 1997) were used to estimate current IQ, being Digit Symbol Coding (processing speed), Block Design (visuospatial capacities), Arithmetic (working memory) and Information (general knowledge). 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 T 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 = 240 mm, 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