The relationship between brain volumes and intelligence in bipolar disorder

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\textbf{A R T I C L E I N F O}

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\textbf{A B S T R A C T}

\textbf{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.

\textbf{Methods:} Magnetic resonance imaging brain scans, IQ and premorbid IQ scores were obtained from 195 BD-I 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.

\textbf{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.

\textbf{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.

\section{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 gyrri, 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 do-
 mains and reported a negative correlation between right putamen vo-
 

cus 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 rela-
tionship 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 li-
thium 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 partici-
 pants 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 un-
representative 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 episo-
de 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 (proces-
sing 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 schizo-
phrenia patients (R2 = 0.90) and controls (R2 = 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 anti-
psychotic 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 pa-
tients (yes/no, N = 182 (93.3%), for whom we had detailed phar-
macy-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 mm3
volumes) were made.

Post-processing was done on the neuroimagining 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/) using Surfscan Visualiser (http://ibowman.com/surfscan/).

Poorly segmented volumes were excluded. We extracted the volumes of

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