The influence of manic episodes on grey matter volumes and general intellectual functioning in bipolar I patients

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The influence of manic episodes on grey matter volumes and general intellectual functioning in bipolar I patients

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Foreword

For this thesis I completed a research internship at Bipolar Genetics at the University Medical Centre in Utrecht (UMCU), a large study on the genetic, neuroanatomical, and psychosocial foundations of bipolar disorder. With great pleasure I managed not only be involved in the main study, but also to participate in the additional MRI follow-up study. This was very exciting for me, since I had been curious about neuroimaging research for a long time. For a short period of time my imagination randomly started producing all sorts of spectacular three dimensional and colourful images of the human brain. On my first encounter with the MRI scanner, I discovered that, although intriguing, doing neuroimaging research was mostly hard work. It demanded a significant amount of determination, enthusiasm, a meticulous way of working, and technical insight. Next to the experience with neuroimaging research, this internship helped me develop a number of important skills, such as conducting a semi-structured interview and neuropsychological tests, and drawing blood, which I found specifically spectacular. But the thing I will remember most are the impressive, sometimes sad, sometimes hilarious, stories of patients I have spoken with. They really brought life into doing research.

As with every learning experience, I have many people to thank for making this thesis possible. First of all I would like to thank my supervisor in the UMCU, Lucija Abramovic, who guided me trough every step of this study. Her enthusiasm and teaching skills motivated me and helped me persevere through tough segmenting times. I had a great time working together and wish you all the best in the completion of your study and PhD trajectory. Furthermore, I would like to thank the whole Bipolar Genetics research team for sharing all their knowledge and frustrations, which made participating in this study a memorable experience. In addition, I would like to thank my supervisor of the University of Utrecht, Linda Schoo, for her quick replies and constructive criticism. And finally, I would like to thank my partner, Jeroen, for supporting me through the process of writing my second thesis. Again, he listened to my never-ending stories, frustrations, and revelations, and supported me with reassuring words and huge quantities of tea.

I would like to dedicate this thesis to my parents, because studying is quickly taken for granted, and without their support it would have been a whole lot harder.

Karlijn Schols

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Summary

Objective: This study focused on the effects of manic episodes on total brain and grey matter volumes and general intelligence (IQ) in patients with a bipolar type I disorder (BPI). Volumetric reductions of the total brain and grey matter have been observed in patients with BPI. In addition, cognitive impairments are found to persevere in a euthymic state, which implicates enduring poorer cognitive functioning after mood episodes. The severity of the illness, including the number of mood episodes, has been related to these structural and cognitive impairments. The precise relation of manic episodes on neuroanatomical changes and change in cognitive functioning remains inconclusive, and will therefore be examined in this study. *Methods*: A total of 64 euthymic patients diagnosed with BPI and 45 healthy control subjects participated in this study. The BPI diagnosis and the euthymic state were verified using the Structured Clinical Interview for DSM-IV disorders (SCID-I). Participants completed a number of questionnaires, a structured interview, and five neuropsychological tasks. Of the participants, 62 patients and 16 control subjects participated in the magnetic resonance imaging (MRI) follow-up appointment, which included a number of structural scans. *Results*: Patients had smaller total brain volumes than control participants, but similar grey matter volumes. No relation between grey matter volumes and general IQ was found. However, patients had a lower general IQ compared to controls participants, whilst the groups did not differ in premorbid IQ. Furthermore, patients who experienced multiple manic episodes showed a larger decrease in general IQ compared to patients who experienced a single manic episode. *Conclusions*: This study indicates that manic episodes have a specific negative effect on total brain volumes and general IQ. Since the level of general IQ has been related to the functional outcome of the disorder, a higher number of manic episodes can have a negative effect on the psychosocial level of functioning and the quality of life of patients. Future research should therefore continue to investigate the effects of manic episodes on a structural as well as a functional level.

Contents

Introduction

Bipolar disorder is a mood disorder also known as manic-depressive disorder (Kupka & Nolen, 2008). There are several types of bipolar disorder of which the bipolar type I (BPI) is the most well known. Patients suffering from BPI experience manic episodes that are often alternated by depressive episodes (Ten Have, Vollebergh, Bijl & Nolen, 2002). Recent cross-national epidemiological studies have found a 2.4% prevalence of bipolar spectrum disorders, and a 0.6% prevalence of BPI (Merikangas et al., 2011). In an elaborate study in the Netherlands a lifetime prevalence of 5% for all bipolar spectrum disorders was found and 2% for the BPI disorder (Regeer, et al., 2004). Bipolar disorder is a very severe psychopathology and has a distinct impact on patient's daily lives (Bentum & Ree, 2008). Next to difficulties in accepting a chronic diagnosis, 30 – 60% of bipolar spectrum patients experience significant problems in multiple area's of functioning including social, work and family life (Bentum & Ree, 2008; Sanchez-Moreno et al., 2009). Furthermore, patients with BPI report a lower quality of life with more pain, poorer mental health, more emotional role limitations and lower social functioning, than patients with other bipolar spectrum disorders, other psychiatric diagnoses or healthy controls (Ten Have et al., 2002). In addition, one in every four patients with BPI reported a history of suicide attempts (Merikangas et al., 2011).

For diagnosing BPI, following the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR), patients must have experienced at least one manic episode. A manic episode is characterized by a continuous heightened, euphoric, or agitated mood that lasts for at least one week or is followed by hospitalization (American Psychiatric Association [APA], 2000). Next to a heightened mood patients often portray an enhanced self-esteem, excessive optimism or even feelings of grandeur, increased speech, thought flight, increased associativity and distractibility, a decreased need for sleep, increased libido, agitation and dynamism (Kupka & Nolen, 2008).

Previous research has demonstrated that patients with BPI disorder often show structural neuroanatomical changes. Most frequently reported changes are: enlargement of the lateral ventricles and the third ventricle (Arnone et al., 2009; Kempton, Geddes, Ettinger, Williams & Grasby, 2008; McDonald et al., 2004; Monkul, Gin & Soares, 2005), a decrease in total brain volume (Arnone et al., 2009), and reduction of grey matter volumes (Drevets et al., 1997; Ellison-Wright & Bullmore, 2010; Emsell & McDonald, 2009; López-Larson, Delbello, Zimmerman, Schwiers & Strakowski, 2002; Stanfield, et al., 2009). However, these findings remain inconclusive, since non-significant results between healthy controls and BPI patient's total brain and grey matter volumes have been reported as well (Emsell & McDonald, 2009; Scherk, et al., 2008). Important possible confounders in imaging studies are medication use.

Especially lithium, one of the most widely employed mood stabilizers for bipolar disorder (Wingo, Wingo, Harvey & Baldessarini, 2009), is found to have protective and regenerative effects on grey matter volumes (Emsell & McDonald, 2009; Kempton et al., 2008; Lyoo et al., 2010).

These structural changes have been related to several aspects of the disorder, such as the duration and severity of the illness (Arnone, et al., 2009, Hauser et al., 2000, López-Larson et al., 2002), and the number of mood episodes (Strakowski, et al., 2002). The effect of depressive episodes on the brain of patients suffering from major depression disorder or bipolar disorder, has been frequently studied and is been associated with, amongst others, volumetric changes in the prefrontal cortex (PFC) (Bremner et al., 2002; Konarski et al., 2008; Sheline, 2003) and temporal cortex, and enlargement of the lateral en third ventricles (Strakowski, Adler & Delbello, 2002). In contrast to the effect of depressive episodes on brain anatomy, the effect of manic episodes has been scarcely studied, and many results are contradictory. Moorhead et al. (2007) found that greater grey matter loss in the cerebellar and temporal lobe was associated with a higher number of (hypo)manic episodes. In addition, findings from Strakowski, et al. (2002) indicated that multi-manic episode patients had a smaller total brain volume and larger lateral ventricles compared to single-episode patients. Thus, depressive and manic episodes are both related to grey matter loss in the temporal lobe and enlargement of the lateral ventricles. However, there are also distinct effects of manic episodes on the brain compared to depressive episodes, such as a decrease in total brain volume. These effects will be examined in this study in order to comprehend the specific role of manic episodes on structural changes in the brain.

In addition to neuroanatomical changes, cognitive functioning has been compromised in patients with BPI disorder. Numerous studies have shown that BPI is associated with neurocognitive deficits. In contrast to previous beliefs, these deficits persist in a euthymic state, reflecting enduring cognitive impairments (Bearden, Hoffman & Cannon, 2001; Savitz, Solms & Ramesar, 2005). Frequently reported affected cognitive domains are: executive functioning (Martínez-Arán et al., 2004; Robinson et al., 2006), attention and working memory (Bora, Yucel & Pantelis, 2009), processing speed, and learning and memory (Hellvin et al., 2012; Martínez-Arán et al., 2007; Torres, Boudreau & Yatman, 2007). In addition to problems in these neurocognitive domains, significant differences in general intelligence in patients with BPI and healthy controls, when controlled for premorbid intelligence, are reported (Frantom, Allen & Cross, 2008; McIntosh, Harrison, Forrester, Lawrie & Johnstone, 2005; Toulopoulou, Quraishi, McDonald & Murray, 2006). Furthermore, poorer neuropsychological functioning and a lower intelligence have been related to the severity of the illness (Bearden et al., 2001; Denicoff et al., 1999) including the number of mood episodes (Cavanagh, Beck, Muir & Blackwood, 2002; Zubieta,

Huguelet, O'Neill & Giordani, 2001). However, to our knowledge, the precise effect of manic episodes on general intelligence in patients with BPI has yet to be examined. Therefore, this study will focus on the interaction between manic episodes and general intelligence.

The neuroanatomical changes found in bipolar patients, as described above, have been related to the problems in neuropsychological functioning (Smith, Gorp, Sobczak & Honig, 2008). Grey matter reductions found in BPI patients are associated with poorer neurocognitive functioning and lower general intelligence scores. Bruno, Papadopoulou, Cercignani, Cipolotti and Ron (2006) found that the difference between estimated pre-morbid intelligence and current intelligence was significantly correlated with reduced grey matter in the left temporal lobe. Likewise, Moorhead et al. (2007) associated reductions in general intelligence and performance intelligence with grey matter loss in the temporal lobes. As mentioned above, the grey matter loss in the temporal lobes was also associated with the number of manic episodes.

A noteworthy methodological problem with studies on bipolar patients is the inconsistent use of diagnostic criteria for defining the bipolar patient group (Smith et al., 2008). Diagnoses of BPI, bipolar disorder type II, or bipolar disorder not otherwise specified are commonly used to represent one group of bipolar patients. Next to that, patients are included regardless if they are experiencing a current mood episode or are in a euthymic state. This could contribute to the inconsistent findings in neuroimaging and neuropsychological studies and calls for more precise definitions of the bipolar patient group.

In conclusion, structural neuroanatomical changes and poorer neuropsychological functioning have been frequently reported in patients with BPI. These structural changes and poorer neuropsychological functioning have been related to each other. Furthermore, research has indicates that structural changes and problems with neuropsychological functioning are related to the severity of the illness, including the number of mood episodes. However, little research has been done on the exact effects of manic episodes on structural changes, and none, to our knowledge, on general intelligence. Next to that, the definition of bipolar disorder differs among studies and forms a serious methodological problem.

With these considerations in mind, the aim of this study was to examine the effects of manic episodes on total brain and grey matter volumes in patients with BPI disorder. In addition, we will examine the relation between these neuroanatomical changes and general cognitive functioning by analyzing the effect of manic episodes on general intelligence. We hypothesize that: patients will show (1) smaller grey matter volumes and (2) lower general intelligence scores compared to controls, and that (3) grey matter volumes are related to general

intelligence. For patients we expect (4) a higher number of manic episodes to be related to smaller grey matter volumes, and (5) a larger decrease in general intelligence.

Methods

Participants

A total of 64 patients diagnosed with BPI disorder and 45 control participants participated in this study. The BPI diagnosis was verified using the Structured Clinical Interview for DSM-IV Disorders (SCID-I). An euthymic state was determined by the absence of a current mood episode using the SCID-I. Control participants were screened for any mental disorders using the Mini-International Neuropsychiatric Interview (MINI).

Control participants were excluded if they met criteria for a diagnosis in the bipolar- or psychotic spectrum. However, subjects with other DSM-IV diagnoses were accepted to prevent an unrealistic healthy control group. Further exclusion criteria for both groups were: an age younger than 18 years, a premorbid IQ score below 80, persons unable to read, speak or understand Dutch, or if less than three grandparents were of Dutch origin. These criteria were presented to establish a high degree of homogeneity in the sample population. Furthermore, subjects were excluded for the MRI scan when scanning was impossible due to ferrous objects in or around the body, claustrophobia, or when persons had a history of closed-head injury with loss of consciousness, a neurological illness, or endocrinological dysfunction.

Of the 109 participants a total of 100 were selected for analyses. Our patient group consisted of 62 patients, 29 women and 33 men (mean age: 46, SD = 12.5). The control group consisted of 38 subjects, 24 women and 14 men (mean age: 38, SD = 17,5). Two patients were excluded, one due to a current mood episode and a faulty scan, and one due to a premorbid intelligence score below 80. In addition, seven control participants were excluded, three due to a premorbid intelligence score below 80, one due to violating the criterion of having three Dutch grandparents, two because they had experienced psychotic symptoms, and one due to a current mood episode. Of the selected 100 participants, all 62 patients, but only 16 control participants participated in the MRI follow up appointment (see protocol). Details of the groups are presented in table 1.

Table 1. Demographic and clinical characteristics of the patient and control group.

Characteristic	Patient group (*n*=62)		Control group (*n*=38)		Difference
	M	SD	*M*	SD	
Age (years)	47	12.5	38	17.5	788.50**[b]
Premorbid IQ, *n*=89	109.0	8.1	108.9	9.3	-.04[a]
	n	%	*n*	%	
Educational level					1054.00[b]
Elementary school	0	0	2	5.3	
Lower secundary education	6	9.8	0	0.0	
Higher secondary education	21	34.4	13	34.2	
Bachelor degree	21	34.4	12	31.6	
Master degree	13	21.3	11	28.9	
Sex					2.54[c]
Male	33	53.2	14	36.8	
Female	29	46.8	24	63.2	
Current medication, *n*=98					
Lithium	43	71.7	-	-	
Anti-depressants	23	38.3	-	-	
Anti-psychotics	33	55.0	-	-	
	M	SD	*M*	SD	
Age of onset	25	10.0	-	-	
Age of first hospitalization	33	11.3	-	-	
Number of hospitalizations	2	2.4	-	-	
Number of manic episodes	4	4.5	-	-	
Number of depressive episodes	6	8.8	0	0.8[l]	

Note. **$p < .01$, [a] = independent samples *t*-test, [b] = Mann-Whitney U test, [c] = Chi square test. [l]: Of the control participants 4 experienced a depressive episode.

Protocol

Subjects were recruited in various ways, including clinical recruitment of patients under treatment in one of the participating mental health care centres, through pharmacies, via the Dutch knowledge centre bipolar disorders (Kenniscentrum Bipolaire Stoornissen), through the Psychiatric Case Registry Midden Nederland and population based recruitment through the media. When subjects expressed their interest in participation, an appointment was made at the University Medical Centre Utrecht (UMCU). The inclusion criteria, in specific, the bipolar type I diagnosis (patients only) and the Dutch origin of three grandparents, were verified and additional information about the study was given orally and by letter. The first appointment lasted two hours for controls and three hours for patients, and consisted of signing an informed consent, the completion of three self-report questionnaires (patients only), a psychiatric interview and a series of neuropsychological tests. All assessment tools are described in detail

below. Patients were given an incentive of €30,- and controls of €20,- next to traveling expenses. Afterwards, subjects were asked if they were interested in a follow up appointment for the MRI scan. Before making the appointment a safety checklist was conducted to ensure that none of the exclusion criteria for the MRI scanner were present. This second appointment lasted one and a half hours and consisted of signing the informed consent form, a short briefing on the scanning protocol, a second conduction of the safety checklist to reaffirm the absence of any potential dangers, followed by a series of MRI scans (Achieva 3T, Philips). The total time in the scanner was 43 minutes. For participating in the MRI study all subjects were given an additional incentive of €20,- and were compensated for travelling expenses. Furthermore, during both appointments, all subjects were provided with a lunch voucher that was exchangeable in hospital restaurants.

Assessment

Dutch version of the Questionnaire for Bipolar Illness (QBP-NL). The Dutch version of the Questionnaire for Bipolar Illness (QBP-NL) is a questionnaire used to assess basic demographic and clinical data of patients with bipolar disorder (Leverich, et al., 2001).

Structured Clinical Interview for DSM-IV Disorders (SCID-I). The Structured Clinical Interview for DSM-IV disorders (SCID-I) is a semi-structured interview for diagnosing the major DSM-IV Axis I disorders (First, Spitzer, Gibbon & Williams, 1997). In this study the research version of the SCID was used to assess the BPI diagnosis, and the presence of a current depressive or manic episode.

Mini-International Neuropsychiatric Interview (MINI). The Mini-International Neuropsychiatric Interview (MINI) is a short structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders (Sheehan et al., 1998). The validity and reliability of the diagnoses made with the MINI are considered good compared to more extensive interviews such as the SCID (Sheehan et al., 1998).

Wechseler Adult Intelligence Scale (WAIS-III). The Wechseler Adult Intelligence Scale (WAIS-III) is the most widely used standard test of intelligence (Blyler, Gold, Iannone & Buchanan, 2000). A short form version for clinical and research purposes was developed and includes four subtasks of the WAIS-III: Information, Arithmetic, Block Design, and Digit Symbol. Previous research indicates that these four subtasks provide an adequate estimate for the general level of cognitive competence (Blyler et al., 2000). Therefore, this short form version of the WAIS-III was used in this study to assess general intelligence.

The Dutch Adult Reading Test (NLV). The Dutch Adult Reading Test (NLV) is a task that consists of a series of 50 words that have irregular pronunciations and need to be read out loud by the patient (Schmand, Lindeboom & Harskamp, 1992). The NLV is used to estimate premorbid intelligence for patients with cerebral damage, because it relies on verbal intelligence which is relatively unaffected by cerebral damage.

Imaging and volumetric processing

Structural MRI scans of the whole brain were acquired on a Philips Achieva 3T medical scanner. A three dimensional (3D) anatomical T_1-weighed image of the whole head was acquired (Three Dimensional - Fast Field Echo (3D-FFE); Coronal; 256 x 256 matrix, 160-180 0.8-mm contiguous slices of 1,2 mm., echo time [TE] = 4.6 ms., repetition time [TR] = 30 ms., flip angle = 30º, Field of View (FOV) = 256 mm./70%). Volumetric processing was performed, using in-house developed software to measure total brain, grey and white matter, cerebellar, lateral and third ventricle volumes. All brain images were coded to assure investigator blindness and prevent bias during segmentation.

The T_1-weighed images were automatically placed in Talairach orientation (Talairach and Tournoux, 1988) without scaling, by registering them to a model brain, and were corrected for magnetic field inhomogeneities. After correction the T_1-weighed brain images were used to create intercranial masks. These intercranial masks were, where necessary, manually edited and used as a model for all further segmentation steps. Grey and white matter intensities were directly estimated from the image using automatic segmentation software. This software included histogram analysis algorithms, anatomical knowledge based decision rules and series of mathematical morphological operators to connect all voxels of interest (Schnack et al., 2001a; Schnack, Hulshoff Pol, Baaré, Viergever & Kahn, 2001b). Furthermore, for separating grey and white matter, the amounts of pure and partial volume voxels were modelled in a non-uniform partial volume density, which was fitted into an intensity histogram (Schnack et al, 2001a). Total brain volume was calculated by adding the grey and white matter volumes. Masks for the lateral ventricles were created using automated computer-incorporated anatomical knowledge of the location of the lateral ventricles in the brain, for example the knowledge that the lateral ventricles are encapsulated by white matter (Schnack et al, 2001b). The limits of the third ventricle masks were based on the anterior and posterior commissures, and the upper boundary was set via a plane through the plexus choroideus ventriculi tertii perpendicular to the midsaggital slice. A plane through the fourth ventricle and the aqueduct set the cerebellum mask. Similar to the intercranial masks, the ventricular and cerebellar masks were manually checked and where necessary edited to improve accuracy of segmentation.

Statistical analyses

The data was analyzed using the Statistical Package for the Social Sciences (IBM, version 20.0; SPSS Inc., Chicago, IL, USA). Data was examined for outliers and extreme values and normality of the distribution. An independent samples t-test, Mann-Whitney U tests, and a Chi-square analysis were performed to compare group differences on estimated premorbid intelligence (IQ) scores, age, level of education, and sex ratio. To examine possible confounding effects of age, intercranial volume, sex, and lithium on total brain and grey matter volumes, correlation analyses were run. For the relation between age, intercranial volume and total brain and grey matter volumes Pearson correlation analyses were conducted. However, for cerebrum grey matter volume (BBGM) and cerebrum grey matter volume right (BBGMR) Spearman's Rho correlation analyses were run due to the violation of the assumption of normality. In addition, the relation between sex, lithium and total brain and grey matter volumes was examined with logistic regression analyses. All assumptions for logistic regression were met except for the multicollinearity assumption for sex and intercranial volume. To assess group differences on total brain and grey matter volumes analyses of covariance (ANCOVA) were conducted with age, intercranial volume, sex, and lithium as covariates. Of these ANCOVA's assumptions were checked for randomness and independent sampling, normal distribution, heterogeneity of variance, and heterogeneity of regression slopes. The assumption of normality was violated for the following volumes of the patient group: total brain volume (TB), TBR, total brain volume left (TBL), cerebrum grey matter (BBGM), and cerebrum grey matter volumes right (BBGMR). However, the analyses were run, since ANCOVA is considered to be a robust statistic (Harwell, 2003). It is therefore important to critically interpret these results. For testing the relation between grey matter volumes and estimated IQ Pearson correlation analyses were conducted. For TBR, BBGM, and BBGMR a Spearman's Rho correlation analysis was performed, again due to the violation of the assumption of normality. For similar reasons, the relation between the number of manic episodes and grey matter volumes and estimated current IQ was assessed via Spearman's Rho correlation analyses. Change in IQ was calculated by subtracting the current estimated IQ score from the estimated premorbid IQ score. Finally, group differences on grey matter volumes and change in IQ ware assessed via independent samples *t*-tests, with the exception of group differences on BBGM and BBGMR, which were compared using a Mann-Whitney *U* test for above mentioned reasons.

Results

Demographic and clinical characteristics

As stated above a total of 62 patients and 38 control participants were included for analyses. The patient and control group did not differ on premorbid intelligence scores, educational level or male/female ratio. However, patients were significantly older (mean age: 46, SD = 12.5) than control participants (mean age: 38, SD = 17,5) (U = 788.50, p = .006). In the patient group the mean age of onset for BPI disorder was 25 years (range 9 – 51), and the mean age for the first hospitalization was 33 years (range 14 – 61). A total of 51 patients (82.26%) was at least hospitalized once, with an average of two hospitalizations. Furthermore, patients reported a mean of four manic and six depressive episodes. Of the control group four people reported having experienced one or more depressive episodes.

Group differences on grey matter volumes and general intelligence

Before analysing whether patients had smaller grey matter volumes than control subjects, covariates that were considered possible confounders, thus are expected to influence grey matter volumes, were assessed and are presented in table 2.

Table 2. Relations between age, intercranial volume, sex and total brain and grey matter volumes of patients and control participants, and the relation between lithium and total brain and grey matter volumes for patients.

	Age	**IC**	**Sex**	**Lithium**
Age	-	-	-	-
IC	-.038[d]	-	-	-
Sex	2.962[f]	16.564***[f]	-	-
Lithium	.508[f]	1.014[f]	.395[c]	-
TB	-.397***[d]	.850***[d]	11.227**[f]	.350[f]
TBL	-.402**[d]	.840***[d]	11.267**[f]	.379[f]
TBR	-.387***[d]	.855***[d]	11.122**[f]	.320[f]
BBGM	-.430***[e]	.747***[e]	7.937**[f]	.146[f]
BBGML	-.512***[d]	.762***[d]	8.169**[f]	.136[f]
BBGMR	-.421***[e]	.759***[e]	7.647**[f]	.155[f]
CBGM	-.251*[d]	.600***[d]	11.288**[f]	.824[f]
CBGML	-.252*[d]	.560***[d]	10.199**[f]	1.445[f]
CBGMR	-.230*[d]	.592***[d]	10.725**[f]	.344[f]

Note. IC: intercranial volume, TB: total brain volume, TBL: total brain volume left, TBR: total brain volume right, BBGM: cerebrum grey matter volume, BBGML: cerebrum grey matter volume left, BBGMR: cerebrum grey matter volume right, CBGM: cerebellum grey matter volume, CBGML: cerebellum grey matter volume left, CBGMR: cerebellum grey matter volume right. *p < .05, **p < .01, ***p < .001. [c] = Chi square test, [d] = Pearson correlation, [e] = Spearman's Rho correlation, [f] = Logistic regression analysis (Wald statistic).

All above-mentioned confounders were used as covariates in the following analyses on differences in total brain and grey matter volumes between the groups. Although lithium did not seem to have a significant relation with total brain and grey matter volumes in the patient group, it was still was still taken as a covariate on theoretic grounds (Kempton et al., 2008; Lyoo et al., 2010). When controlled for age, intercranial volume, sex, and lithium use, patients and control subjects showed significant differences in total brain ($F(1, 68) = 8.120$, $p = .006$), total brain left ($F(1, 68) = 7.802$, $p = .007$), and total brain right ($F(1, 68) = 7.948$, $p = .006$) volumes. No differences in grey matter volumes for the cerebrum of cerebellum were found. Details are presented in table 3.

Table 3. Volumetric specifics of total brain and grey matter volumes (in cm^3) of the patient and control group and differences between the groups controlled for age, intercranial volume, sex, and lithium use.

Structure	**Patient group** (*n*=60)		**Control group** (*n*=16)		**Difference**[g]	**Significance**
	M	SD	*M*	SD		
TB	1193.73	98.66	1200.31	149.59	8.120	.006
TBL	595.26	48.94	599.68	75.33	7.802	.007
TBR	598.47	50.09	600.63	74.42	7.948	.006
BBGM	567.64	46.90	566.13	78.38	.427	.516
BBGML	283.50	23.41	283.39	38.81	.507	.479
BBGMR	284.14	23.67	282.74	39.68	.330	.568
CBGM	93.88	9.39	94.03	10.88	1.345	.250
CBGML	47.20	4.81	47.28	5.72	1.439	.234
CBGMR	46.67	5.05	46.76	5.32	1.019	.316

Note. IC: intercranial volume, TB: total brain volume, TBL: total brain volume left, TBR: total brain volume right, BBGM: cerebrum grey matter volume, BBGML: cerebrum grey matter volume left, BBGMR: cerebrum grey matter volume right, CBGM: cerebellum grey matter volume, CBGML: cerebellum grey matter volume left, CBGMR: cerebellum grey matter volume right. [g] = ANCOVA.

Next to grey matter volumes the estimated general intelligence (IQ) scores of patients and control participants were analysed. Because the IQ scores were normed by age they automatically controlled for the age difference between the groups. Results indicated that the mean estimated general IQ score for control subjects ($M = 107.87$, SD = 19.72) was significantly higher than that of patients ($M = 100.05$, SD = 12.96) ($t(58.2) = 2.15$, $p = .036$). So a difference in estimated general IQ was found although the groups did not differ in estimated premorbid IQ scores. See figure 1 below.

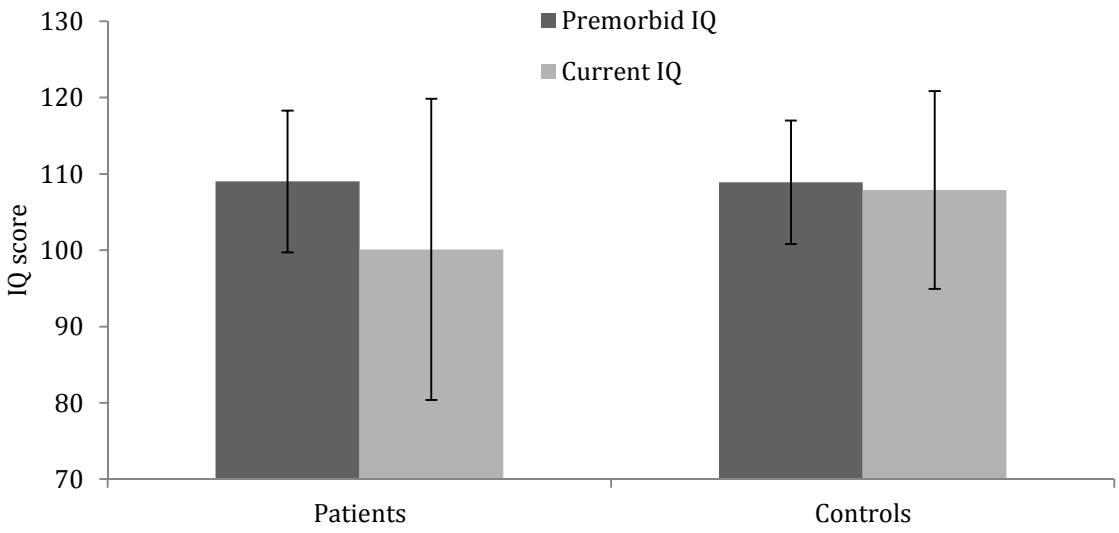

Figure 1. Mean estimated premorbid IQ scores and estimated general IQ scores of patients and control participants. Standard deviation is shown in error bars.

Correlation analyses

A possible relation between grey matter volumes and estimated general IQ scores was assessed via correlation analyses. Correlations with IQ and cerebellar, cerebrum total, and cerebrum left grey matter volumes were clearly non-significant ($p > .5$). Cerebrum grey matter left showed a somewhat stronger, although still clearly non-significant, correlation with general IQ ($r = .170$, $p = .148$). When the relation between general IQ and grey matter volumes was examined for patients and controls separately, the same results were found in the patient group. So, cerebellar, cerebrum total, and cerebrum left grey matter volumes were, again, clearly non-significant ($p > .5$), and cerebrum grey matter left showed a stronger, but non-significant, correlation with general IQ ($r = .209$, $p = .125$).

This deviating correlation for cerebrum grey matter left was not found for control participants. For the control group there were no significant relations between IQ and grey matter volumes ($p > .5$).

Following group analyses, further analyses were performed on the patient group solely to evaluate the relation between the number of manic episodes, and grey matter volumes and change in IQ. These analyses showed that there is no significant correlation between the number of manic episodes and grey matter volumes (all $p > .4$). In addition, when patients were divided into a single-manic and a multiple-manic group no significant difference in mean grey matter volumes scores were found between the groups (all $p > .4$, except cerebellum grey matter left: $t = 1.366$, $p = .177$).

Finally the relation between the number of manic episodes and change in IQ was assessed. Results showed that there is no significant relation between the number of manic episodes and a change in IQ (r_s = .24, p = .088). However, when patients were divided into a single-manic and a multiple-manic group the average negative change in IQ was significantly larger for the multiple-manic group (M = 11.47, SD = 12.17) than for the single-manic group (M = 4.00, SD = 12.84) (t(53) = -2.07, p = .043). The change in IQ did not significantly correlate to the age of onset of the disorder, the number of hospitalizations, the age at first hospitalization or the number of depressive episodes. Furthermore, no significant difference in change in IQ was found for the use of lithium, antidepressants, or antipsychotics.

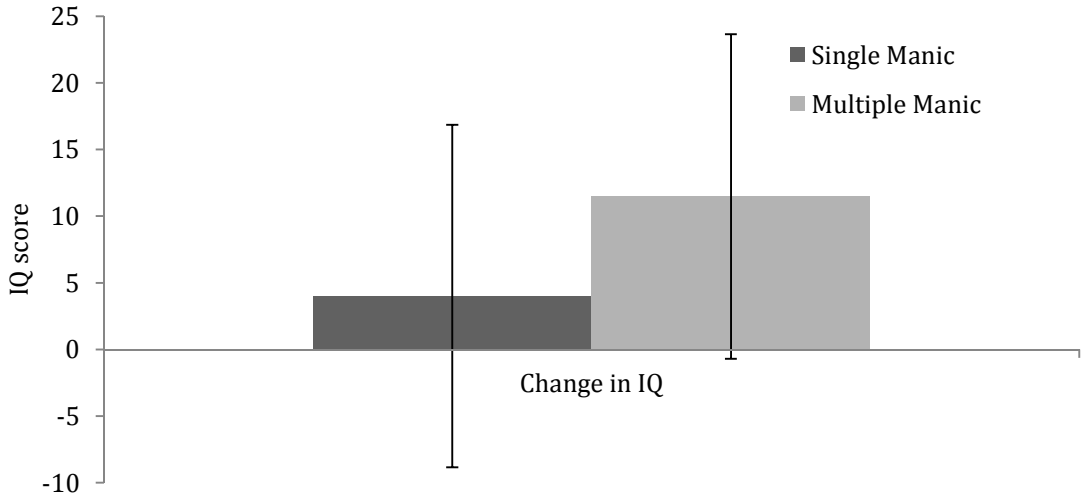

Figure 2. Mean change in IQ for single manic and multiple manic patients. Standard deviation is shown in error bars. A higher score reflects a decline in IQ.

Discussion

The aim of this study was to examine the effect of manic episodes on total brain and grey matter volumes and general intellectual functioning in patients with a bipolar type I disorder (BPI). Our volumetric data showed that patients had smaller total brain volumes than control participants. No difference in grey matter volumes between the groups were found. In addition, no relation between grey matter volumes and general intelligence (IQ) was found. However, patients showed lower general IQ scores than control participants, while no difference in premorbid IQ was found. In addition, patients who experienced multiple manic episodes showed a larger decrease in general IQ compared to patients who experienced only a single manic episode. There was no relation between the number of manic episodes and grey matter volumes, nor was there a difference in grey matter volumes between single-manic and multiple-manic patients.

Our findings on structural changes in total brain and grey matter volumes indicated that patients had smaller total brain volumes, but similar grey matter volumes compared to control subjects. Reduction in total brain volume is consistent with previous findings (Arnone et al., 2009; Strakowski, et al., 2002). However, there is some controversy on total brain volumes in patients with BPI, since preservation of total brain is more often reported (Emsell & McDonald, 2009; McDonald et al., 2004; Strakowski, Adler, et al., 2002). Arnone et al. (2009) suggest that a smaller total brain volume in bipolar patients is a small effect that can only be observed in large sample sizes. The strong homogeneity of the patient group in this study forms a possible explanation for finding this effect in a smaller sample size. Furthermore, more specific volumetric structures, that were not defined and therefore not examined in this study, could explain the difference in total brain volumes between the groups. No differences in grey matter volumes between patients and control participants were found. This corresponds to previous studies that reported no change in grey matter volumes (McDonald et al., 2004; Scherk, et al., 2008). However, a fair amount of studies and recent meta-analyses did report changes in grey matter volumes (Arnone et al., 2009; Drevets et al., 1997; Emsell & McDonald, 2009; Monkul et al., 2005; Strakowski, Adler, et al., 2002). In these studies most reported grey matter reductions are in the frontal and temporal cortical areas. Since our study did not specify cerebral regions, possible reductions in smaller prefrontal or temporal volumes could have been missed. Furthermore, in this study we only included patients with a BPI diagnosis. Since heterogeneity in the patient group is frequently reported as a methodological problem (Smith et al., 2008), our homogeneity can account for the inconsistency in results with previous research.

Next to structural differences, the estimated general IQ was assessed to evaluate the general intellectual functioning. We observed a significant difference in general IQ between patients

with BPI and control subjects, when groups were matched on estimated premorbid IQ. This concurs with previous findings of a lower IQ in patients with BPI compared to control subjects (Frantom et al., 2008; McIntosh et al., 2005; Toulopoulou et al., 2006). Since general IQ is a useful single descriptive measure for overall intellectual ability (Blyler et al., 2000), these results indicate that the disorder negatively influences the level of intellectual functioning. This has important implications for the functional status of patients since a lower level of intellectual functioning has been related to poorer psychosocial functioning (Wingo, Harvey & Baldessarini, 2009) and a lower quality of life (Brissos, Dias, Carita & Martínez-Arán, 2008). Additionally, more severe cognitive impairments have been observed in low-functioning patients, compared to high-functioning patients (Martínez-Arán et al., 2007).

In addition to the observed difference in IQ for patients and control subjects, the change in general IQ was larger for patients who experienced multiple manic episodes, compared to patients who experienced only one manic episode. This corresponds to previous findings of a relation between intellectual functioning and the duration (Donaldson, Goldstein, Landau, Raymont & Frangou, 2003) and severity of the illness (Bearden et al., 2001; Denicoff et al., 1999). Our findings differ from studies that related the number of depressive episodes, and not manic episodes, to a poorer functional outcome (Forcada et al., 2011) and a higher risk of cognitive abnormalities (Bruno et al., 2006). However, in our study, the change in IQ could not be explained by other clinical factors, such as the age of onset, age at first hospitalization, number of hospitalizations, or the number of depressive episodes. This suggests that manic episodes have a specific effect on the level of general intellectual functioning. In combination with the functional outcomes of poorer intellectual functioning found in bipolar patients, this implicates that a larger number of manic episodes can negatively influence the level of psychosocial functioning and quality of life. These results stress the importance of prevention of manic episodes and strengthening cognitive abilities to achieve a better functional outcome.

Finally, our study did not find an effect of manic episodes on total brain or grey matter volumes. Nor was there a relation between total brain and grey matter volumes and general IQ. However, an effect of manic episodes on cerebellar and temporal lobe grey matter volumes has been observed in previous research (Moorhead et al., 2007). The absence of more specific cerebral volumes in this study could help explain the absence of significant effects of manic episodes on brain volumes.

This study has some limitations. First, several methodological shortcomings can be identified in the sample groups. There was a significant age difference between the patient and control group. Next to that, the number of control participants for the volumetric data was small, and

noticeably smaller than the patient group. In the overall analyses the number of patients was also larger than the number of control participants, which could have influenced analyses. Also, the sample size for the patient group was quite small when they were divided into a single-manic and multiple-manic group. Secondly, the volumetric data consisted of large brain areas, which could have caused more subtle differences between the groups to go unnoticed. Furthermore, our intelligence data was based on four subtasks of the WAIS-III. This offered an estimate of the general IQ, and although this has been found reliable in a schizophrenic population (Blyler et al., 2000), it has not been tested within a bipolar population. Next to these limitations our study had several strengths. First of all, a very homogenous patients sample was selected, since the diagnosis and absence of a current mood episode was evaluated. If there was any doubt on a current episode, patients were excluded from analyses. Next to that, volumetric data and general IQ were assessed in one study, which allowed for elaborate comparisons of total brain and grey matter volumes and the relation to general IQ. Finally, to our knowledge, this is the first study that has scrutinized the precise effects of manic episodes on general IQ.

Concluding, this study aimed to investigate the effects of manic episodes on total brain and grey matter volumes and general IQ in patients with BPI. Patients showed smaller total brain volumes than control participants, but similar grey matter volumes. There was no relation between total brain and grey matter volumes and general IQ. However, patients did show lower IQ scores than control subjects, and patients who experienced multiple manic episodes had a larger decrease in IQ than patients who only experienced a single manic episode. This indicates that manic episodes have a specific negative effect on general IQ. Since the level of general IQ has been related to the functional outcome of the disorder, a higher number of manic episodes could negatively influence the psychosocial level of functioning and the quality of life of patients.

Future researched should continue to investigate the effects of manic episodes compared to other clinical factors, especially depressive episodes. The effects of manic episodes on the brain should be assessed using specific regions of interest, such as the prefrontal and temporal areas. For interpreting the effect of manic episodes on general IQ more reliable results can be established by conducting a full-scale IQ test. Also, a full-scale IQ allows for the interpreting of a more detailed cognitive profile and the comparing of verbal and performance IQ. Finally, longitudinal research would be ideal to evaluate the precise effect of manic episodes on total brain and grey matter volumes, as well as on general IQ.

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