# Brain Structural Abnormalities at the Onset of Schizophrenia and Bipolar Disorder: A Meta-analysis of Controlled Magnetic Resonance Imaging Studies

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**Abstract**: A number of structural brain imaging studies and meta-analytic reviews have shown that multiple subtle brain abnormalities are consistently found in schizophrenia and bipolar disorder. Several studies suggest that schizophrenia and affective psychoses share a largely common pattern of brain abnormalities. Aim of the present study was to compare, by means of a meta-analytic approach, brain structural abnormalities, as detected by Magnetic Resonance Imaging (MRI), found at the onset of schizophrenia and bipolar disorder in order to address the question of the specificity of brain abnormalities across diagnostic groups. Forty-five studies were identified as suitable for analysis. In both schizophrenic and bipolar patients significant overall effect sizes were demonstrated for intracranial, whole brain, total grey and white matter volume reduction as well as for an increase of lateral ventricular volume at disease onset. Thus, the available literature data strongly indicate that some brain abnormalities are already present in first-episode schizophrenia or bipolar disorder and that there is a significant overlap of brain abnormalities in affective and non-affective psychotic disorders at the onset of the disease. However, whole grey matter volume deficits and lateral ventricular enlargement appear to be more prominent in first-episode schizophrenia whereas white matter volume reduction seems more prominent in bipolar disorder. The common vs specific trajectories of brain pathomorphology in schizophrenia and bipolar disorder are discussed.

**Keywords:** Schizophrenia, bipolar disorder, psychosis, first-episode, brain morphology, magnetic resonance imaging, meta-analysis.

## INTRODUCTION

Neuroimaging studies have consistently shown that schizophrenia and affective psychoses are associated with subtle abnormalities of brain morphology. A large amount of computed tomography (CT) and magnetic resonance imaging (MRI) studies indicate that the most replicated findings in schizophrenia are ventricular enlargement, diffuse reduction of gray matter volume and of frontal and temporal lobe volumes [1,2]. On the other hand, affective psychoses and in particular bipolar disorder have been associated with enlargement of the ventricular system with changes in white matter structure and volume and with limbic system abnormalities [3,4]. Although these changes have been demonstrated also in patients at the onset of the diseases, their role in the pathophysiology of these illnesses is not yet completely understood and, even more relevant, it remains unclear if they are specific to schizophrenia, to bipolar disorder or are common to all "functional" psychoses. The literature on the issue has been quantitatively reviewed by some meta-analyses. In particular, those performed on MRI studies conducted with a Regions of Interest (ROI) methodology in first-episode schizophrenia showed a significant lateral and third ventricular volume increase as well as a reduction of whole brain and hippocampal volumes in both cerebral hemispheres [5,6]. Although consisting of a much more limited number of studies, the literature on MRI ROI investigations in first-episode BD demonstrates different cortical and subcortical brain changes at illness onset, i.e. the enlargement of the ventricular system [7], smaller area of the corpus callosum [8], reduction in neocortical grey matter [9], smaller amygdala volume [10] and larger striatum [11]. The presence of some brain abnormalities in first-episode BD patients has been documented also by a recent meta-analysis of MRI ROI studies in first episode BD patients [12], that found a significant reduction of total intracranial and white matter volumes, but not of gray matter and whole brain volumes.

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With this picture of partial overlap of brain abnormalities reported in first-episode schizophrenia and BD, the issue of specificity of such brain structural abnormalities for the two diseases has been directly addressed by a very limited number of studies that compared patients with schizophrenia and patients with a diagnosis of BD at onset to a healthy comparison group. The study by Takahashi *et al*. [13] analyzed superior temporal gyrus (STG) subregions and reported that first-episode schizophrenic patients had significantly less gray matter in the Heschl Gyrus (HG), Planum Temporale (PT), and caudal STG bilaterally compared to controls, whereas no such differences were detected between BD and controls for any of the STG subregions. The study of patients with schizophrenia and BD at their first hospitalization from Kasai and coll. [14] demonstrated a bilateral volume reduction in insular cortex gray matter only in first-episode schizophrenia; on the other hand, a reduction of the volume of the left temporal pole gray matter and an absence of normal left-greater-than-right brain asymmetry were detected in both first-episode groups.

Aim of the present study was to compare, by means of a meta-analytic approach, the MRI changes found at the onset of schizophrenia and BD in order to address the question of neuroanatomical specificity of brain abnormalities across diagnostic groups within the so called "functional psychoses".

## MATERIAL AND METHODS

### Selection Procedures

In order to avoid possible sources of error, we adopted a four-step search strategy for the selection of studies to be included in the analysis. First, we performed a computer search of the database MEDLINE and EMBASE using the Medical Subject Heading categories — magnetic resonance imaging (or MRI), schizophrenia and first-episode - for issues published between December 2004, - [(previous publication were checked and included in the meta-analysis on MRI studies in first-episode schizophrenia performed by our group (5)] - and 31 May 2011. Second, we performed a computer search of the same electronic databases using the Medical Subject Heading categories — magnetic resonance imaging (or MRI), bipolar disorder and first-episode, for issues published be-

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tween December 2008 - [(previous publication were checked and included in our previous published meta-analysis on MRI studies in first-episode BD (12)] - and 31 May 2011. Third, a systematic literature search using the Medical Subject Heading magnetic resonance imaging (or MRI), psychosis, and first-episode was also done to identify those papers directly comparing first-episode schizophrenic, bipolar, and control groups for issues published between December 2004 and May 2011[(previous publication were checked and included in our previous published meta-analysis on MRI studies in first-episode schizophrenia and BD [5,12]. Fourth, we reviewed all the reference lists of the papers identified for analysis in order to check for titles possibly missed.

Studies that analyzed a group of first-episode schizophrenic and/or bipolar patients and a group of controls were included in the analysis. When repeated studies by the same research group were available, and the patients included in one study were also included in a subsequent one, the first study was ignored. This criterion was followed for each of the cerebral regions examined. Studies performed using MRI were considered only if they reported absolute quantitative measurements of areas or volumes of cerebral structures in terms of means and standard deviations (SD) or as a variable that could be led back to such values (e.g. standard error values). Studies reporting qualitative or subjective assessments were not considered. Likewise excluded were the studies that reported separately mean and SD values for different subgroups (e.g. male and female subjects or good and poor outcome patients) due to the impossibility to obtain the pooled SDs for the whole sample of patients and/or controls. To ensure that the meta-analyses were sufficiently powered, we included in the analyses only those cerebral areas for which at least three studies were available.

### Meta-analytical Methods

Meta-analyses were carried out using Comprehensive Meta-Analysis Software version 2 (Biostat, Inc., Englewood, NJ, USA). The effect size was calculated for each study included in the meta-analyses.

As a measure of effect size, the Hedges' *g* was adopted, i.e., the difference between the means of the patient and control groups, divided by the SD and weighted for sample size in order to correct for bias from small sample sizes [15]. This metric is normally computed by using the square root of the mean square error from the analysis of variance testing for differences between the two groups, as indicated by the formula:

$$g = \frac{M_1 - M_2}{S_{\text{pooled}}}$$

where:

$$S = \sqrt{\sum \frac{(X - M)^2}{N - 1}}$$

and

$$S_{\text{pooled}} = \sqrt{\text{MS}_{\text{within}}}$$

where $X$ is the raw score, $M$ is the mean, and $N$ is the number of cases.

According to the classification adopted by Cohen [16], an effect size of 0.8 is considered large, an effect size of 0.5 is considered moderate, and an effect size of 0.2 is considered small. The 95% interval around the composite effect size was also calculated [15]. To determine whether the studies could reasonably be described as sharing a common effect size, a homogeneity (Cochran Q) test of the effect sizes was performed for each meta-analysis [15]. When a statistically significant heterogeneity between studies was observed, the source of such heterogeneity was investigated testing the influence of potential moderators of the effect size and, in particular, according to the aim of the present study, the role of the variable "diagnosis" (schizophrenia versus bipolar disorder) was analyzed by means of a subgroup meta-analysis. The composite effect size was calculated by means of fixed-effect model (when the Q test was not significant) or random-effect model in case of between studies heterogeneity. The Egger's test of publication bias was used to assess whether there was a tendency for selective publication of studies based on the nature and direction of their results [17].

## RESULTS

### Results of the Systematic Search

Forty-five studies were identified as suitable for analysis. Thirty-one investigated patients with schizophrenia, five patients with BD (Tab **1**) and nine compared patients with BD and schizophrenia to a sample of healthy controls. A total of 2895 subjects in the 45 studies were included, comparing n= 1198 schizophrenic patients and n= 315 bipolar patients with n= 1382 healthy controls. The following regions were included in the analysis (at least three studies available reporting the means and SDs of brain volumes of patients and controls according to our inclusion criteria): total intracranial volume, whole brain volume, total gray matter volume, total white matter volume, lateral ventricles volume, left and right lateral ventricle volumes. Among MRI studies of schizophrenic samples, all analyzed patients with schizophrenia, but some of them also included patients with related diagnoses. In particular, the studies of Nopoulos *et al*. [18], Gilbert *et al*. [19] and Takahashi *et al*. [13] included diagnoses of schizophrenia and schizo-affective disorder and the study of Lang *et al*., 2006 [20] diagnoses of schizophrenia, schizo-affective disorder and psychosis NOS (not otherwise specified); the studies of Fannon *et al*. [21] and Boonstra *et al*. [22] included diagnoses of schizophrenia, schizophreniform disorder and schizo-affective disorder; the study of Gur *et al*. [23] and Bottmer *et al*. [24] consisted of schizophrenic and schizophreniform patients; the study of Chua *et al*. [25] consisted of schizophrenic, schizophreniform and brief psychotic episode patients; the study of DeLisi *et al*. [26] included patients with schizophrenic like psychosis; the longitudinal study of Puri *et al*. [27] examined schizophreniform subjects diagnosed 1 year later as schizophrenics. As for MRI BD studies, some also included a few patients with first-episode major depression: Koo *et al*. [28] included three patients with first-episode depression out of the total group of 41 BD patients, and Kasai *et al*. [14] included two patients with major depressive disorder out of the total sample of 26 patients.

### Results of the Meta-analysis

#### *a. Pooled Analysis of Studies on First-episode Schizophrenia and BD Patients*

Table **2** presents the comparison of schizophrenic and bipolar patients and healthy controls. The Hedges' *g* indicated significant overall effect sizes for total lateral ventricular volume increase, and right and left ventricular volume increase in patients. Also, a volume reduction of intracranial, whole brain, total grey and total white matter volumes in first-episode patients were found. The Q statistics were not significant for any of the brain regions analyzed indicating that there was a substantial homogeneity between the results of the different studies, with the only exception of whole brain (Q=43.39; p=.02) and left lateral ventricle (Q=32.72; p=.003), for which a subgroup analysis was therefore conducted. However, this did not demonstrate a significant effect of diagnosis (schizophrenia vs BD) on the outcome measure for both the left lateral ventricles and the total brain volumes. The Egger statistics did not show significant publication bias of the study findings.

#### *b. Studies of First-episode Schizophrenic Patients*

Table **3** presents the meta-analysis of studies comparing schizophrenic patients and healthy controls. Patients showed a statistically significant volume increase of total lateral ventricles, right and left ventricular volumes, and a volume reduction of intracranial, whole

**Table 1. Summary of Studies Included in the Meta-analyses**

| | | | M/F ratio | | Mean age | | | |
|---|---|---|---|---|---|---|---|---|
| **Study** | **Year** | **Diagnosis** | **Patients** | **Controls** | **Patients** | **Controls** | **Scanner (Tesla)** | **Slice Thickness (mm)** |
| DeLisi *et al*. (26) | 1991 | 1 | 27/3 | 12/8 | 27.3 | 28.7 | 1.5 | 5.0 |
| Degreef *et al*. (54) | 1992 | 1 | 25/15 | 15/10 | 24.1 | 28.2 | 1 | 3.1 |
| Strakowski *et al*. (55) | 1993 | 2 | 7/10 | 7/6 | 28.4 | 30.9 | 1.5 | 6.0 |
| Nopoulos *et al*. (18) | 1995 | 1 | 12/12 | 12/12 | 23.3 | 24.2 | 1.5 | 1.5 |
| Gur *et al*. (23) | 1998 | 1 | 11/9 | 13/4 | 27.8 | 31.9 | 1.5 | 5.0 |
| Whitworth *et al*. (56) | 1998 | 1 | 41/0 | 32/0 | 24.5 | 30.5 | 1.5 | 0.9-1.4 |
| Zipursky *et al*. (57) | 998 | 1 | 25/21 | 34/27 | 26.2 | 26.6 | 1.5 | 3.0 |
| Del Bello *et al*. (58) | 1999 | 2 | 9/7 | 8/7 | 24 | 27 | 1.5 | 1.0 |
| James *et al*. (59) | 1999 | 1 | 20/9 | 12/8 | 16.7 | 16.1 | 1.5 | 5.0 |
| Fannon *et al*. (21) | 2000 | 1 | 26/11 | 17/8 | 24.2 | 24.2 | 1.5 | 1.5 |
| Hirayasu *et al*. (60) | 2000 | 3 | 18/6BD 16/4 SCZ | 20/2 | 23.6 27.3 | 24.5 | 1.5 | 1.5 |
| Gilbert *et al*. (19) | 2001 | 1 | 11/5 | 13/12 | 26.5 | 23.6 | 1.5 | 1.5 |
| Hirayasu *et al*. (61) | 2001 | 3 | 15/2 BD 15/2 SCZ | 15/2 | 22.6 22.8 | 22.2 | 1.5 | 1.5 |
| Lawrie *et al*. (62) | 2001 | 1 | 22/12 | 17/19 | 21.6 | 21.2 | 1 | 5 |
| Matsumoto *et al*. (63) | 2001 | 1 | 20/20 | 20/20 | 15.5 | 15.7 | 1.5 | 5.0 |
| Puri *et al*. (27) | 2001 | 1 | Nr | Nr | 28.4 | 27.9 | 1.5 | 1.5 |
| Cahn *et al*. (64) | 2002 | 1 | 29/5 | 30/6 | 26.2 | 24.5 | 1.5 | 1.2-1.6 |
| Salokangas *et al*. (65) | 2002 | 1 | 3/8 | 12/7 | 36.6 | 30.5 | 1.5 | 5.4 |
| Strakowski *et al*. (11) | 2002 | 2 | 11/7 | 16/16 | 22 | 25 | 1.5 | 1.5 |
| Chua *et al*. (66) | 2003 | 1 | 9/10 | Nr | 31.0 | 33.6 | 1.5 | 1.2-3.0 |
| Kasai *et al*. (14) | 2003 | 3 | 21/5 BD 23/4 SCZ | 24/5 | 23.2 25.2 | 24.6 | 1.5 | 1.5 |
| Molina *et al*. (67) | 2004 | 1 | 14/8 | 24/20 | 23.0 | 29.4 | 1.5 | 1.1-1.5 |
| Bottmer *et al*. (24) | 2005 | 1 | 20/17 | 9/9 | 25.6 | 25.5 | 1.5 | 1.8 |
| Farrow *et al*. (68) | 2005 | 3 | 4/4 BP 18/7 SCZ | 13/9 | m=18/f=17 m= 20/f=19 | m=20/f=21 | 1.5 | - |
| Nierenberg *et al*. (69) | 2005 | 1 | 12/12 | !2/12 | 18-55 | 18-55 | 1.5 | 1.5 |
| Preuss *et al*. (70) | 2005 | 1 | 25/0 | 50/0 | 27.9 | 30.1 | 1.5 | 1.5 |
| Lang *et al*. (20) | 2006 | 1 | 21/8 | 12/10 | 22.0 | 24.7 | 1.5 | 4 |
| Premkumar *et al*. (71) | 2006 | 1 | 24/10 | 12/6 | 23 | 25 | 1.5 | - |
| Velakoulis *et al*. (72) | 2006 | 3 | 11/11 BP 23/8 SCZ | 55/32 | 21.7 21.8 | 26.9 | 1.5 | 1.5 |
| Atmaca *et al*. (8) | 2007 | 2 | 6/6 | 6/6 | 28.2 | 26.8 | 1.5 | 2.4 |
| Chua *et al*. (25) | 2007 | 1 | 12/17 | 18/22 | 32 | 33 | 1,5 | 1,2 |
| Glenthoj *et al*. (73) | 2007 | 1 | 14/5 | 11/8 | 25.9 | 27.5 | 1,5 | - |
| Nakamura *et al*. (9) | 2007 | 3 | 26/8 BD 24/5 SCZ | 31/5 | 22.1 24.3 | 22.9 | 1.5 | 3 |
| Rosso *et al*. (10) | 2007 | 2 | 13/7 | 16/7 | 23 | 25 | 1.5 | 3 |

**(Table 1) Contd….**

| | | | M/F ratio | | Mean age | | | |
|---|---|---|---|---|---|---|---|---|
| **Study** | **Year** | **Diagnosis** | **Patients** | **Controls** | **Patients** | **Controls** | **Scanner (Tesla)** | **Slice Thickness (mm)** |
| Koo *et al*. (28) | 2008 | 3 | 32/9 BD 30/9 SCZ | 31/9 | 22.8 23.9 | 23 | 1.5 | 1.5 |
| Crespo-Facorro *et al*. (74) | 2009 | 1 | 50/32 | 52/31 | 30.7 | 27.5 | 1,5 | - |
| Takahashi *et al*. (13) | 2009a | 3 | 18/16 BD 34/12SCZ | 38/24 | 22 21.5 | 21.8 | 1.5 | 1.5 |
| Takahashi *et al*. (75) | 2009b | 1 | 16/7 | 12/10 | 21.6 | 22 | 1.5 | 1.5 |
| Thomann *et al*. (76) | 2009 | 1 | 15/15 | 9/12 | 27.7 | 27.4 | 1.5 | - |
| Ebdrup *et al*. (77) | 2010 | 1 | 26/12 | 30/13 | 26.2 | 26.9 | 3 | - |
| Takahashi *et al*. (78) | 2010 | 1 | 12/6 | 11/9 | 23.1 | 23.2 | 1.5 | 1 |
| Takayanagi *et al*. (79) | 2010 | 1 | 24/18 | 20/15 | 28.6 | 30.6 | 1.5 | 1 |
| Rosa *et al*. (29) | 2010 | 3 | 10/16 BP 45/17SCZ | 53/41 | 27.7 | 30.2 | 1.5 | - |
| Witthaus *et al*. (80) | 2010 | 1 | 16/7 | 17/12 | 26.4 | 25.7 | 1.5 | 1 |
| Boonstra *et al*. (22) | 2011 | 1 | 12/4 | 15/5 | 28.8 | 27.9 | 1.5 | 1.2-1.6 |

**Table 2. Summary of Pooled Meta-analysis of First-episode Schizophrenia and Bipolar Disorder Patients**

| Region (Volume) | No. of Studies | No. of Patients/controls | Effect size (95% Confidence Interval) | Effect size: p Value | Heterogeneity: Q p Value | Publication Bias: p Value |
|---|---|---|---|---|---|---|
| Intracranial | 24 | 734/872 | -0.18 (-0.28 to -0.08) | <.001 | 13.6 .93 | .47 |
| Whole brain | 28 | 817/1051 | -0.28 (-0.40 to -0.16) | <.001 | 43.39 .02 | .35 |
| Grey matter (total) | 16 | 478/506 | -0.33 (-0.47 to -0.20) | <.001 | 16.20 .36 | .46 |
| White matter ( total) | 12 | 328/376 | -0.20 (-0.34 to -0.05) | .008 | 9.74 .55 | .19 |
| Lateral ventricles (total) | 11 | 372/455 | 0.34 (0.20 to 0.48) | <.001 | 7.60 .66 | .42 |
| Right lateral ventricle | 15 | 461/581 | 0.32 (0.20 to 0.45) | <.001 | 19.20 .15 | .37 |
| Left lateral ventricle | 15 | 461/581 | 0.40 (0.20 to 0.60) | <.001 | 32.72 .003 | .47 |

**Table 3. Summary of Meta-analyses in First-episode Schizophrenia**

| Region (Volume) | No. of Studies | No. of Patients/Controls | Effect Size (95% Confidence Interval) | Effect Size: p Value | Heterogeneity: Q p Value | Publication Bias: p Value |
|---|---|---|---|---|---|---|
| Intracranial | 17 | 554/594 | -0.15 (-0.27 to -0.04) | .008 | 8.33 .93 | .24 |
| Whole brain | 21 | 686/772 | -0.26 (-0.40 to -0.12) | <.001 | 34.21 .02 | .20 |
| Grey matter (total) | 12 | 412/438 | -0.36 (-0.50 to -0.23) | <.001 | 13.23 .27 | .28 |
| White matter ( total) | 6 | 233/260 | -0.14 (-0.32 to 0.03) | .105 | 1.26 .93 | .25 |
| Lateral ventricles (total) | 8 | 308/319 | 0.38 (0.22 to 0.54) | <.001 | 3.62 .82 | .24 |
| Right lateral ventricle | 12 | 396/429 | 0.40 (0.26 to 0.54) | <.001 | 7.57 .75 | .08 |
| Left lateral ventricle | 12 | 396/429 | 0.49 (0.35 to 0.64) | <.001 | 11.09 .37 | .09 |

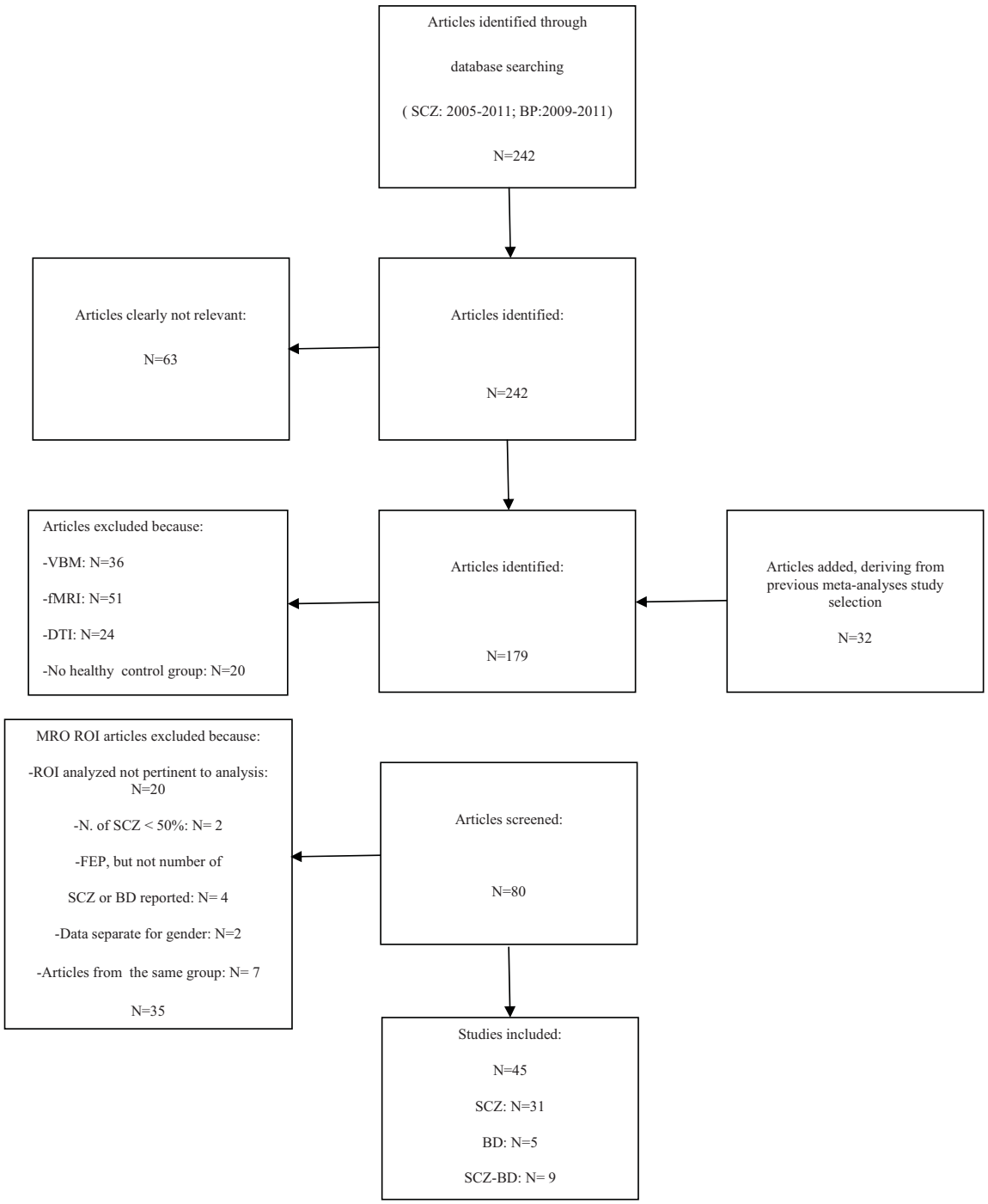


**Fig. (1).** Flow chart of study selection.

brain and total grey matter volumes. No difference emerged between schizophrenic and control groups as for white matter volume. The Q statistics were not significant for any of the brain regions analyzed indicating that there was a substantial homogeneity between the results of the different studies, with the only exception of whole brain (Q=34.21; p=.02). The Egger statistics did not show significant publication bias of the study findings.

### *c. Studies of First-episode Bipolar Patients*

Table **4** presents the meta-analysis of brain volumes comparing bipolar patients and healthy controls. Significant overall effect sizes were demonstrated for reduced intracranial, whole brain, total grey and total white matter volumes. On the other hand, no significant differences were detected between groups as for total, left and right lateral ventricles volumes. The Q statistics was statistically significant only in the case of the left lateral ventricle, indicating significant heterogeneity among studies that investigated this cerebral area in BD patients. The Egger statistics did not show significant publication bias of the study findings for any of the brain regions investigated.

## DISCUSSION

To our knowledge, this is the first meta-analysis that investigated conjunctly ROI MRI data of first-episode patients with schizophrenia and bipolar disorder compared to healthy controls.

**Table 4. Summary of Meta-analyses in First-episode Bipolar Disorder**

| Region (Volume) | No. of Studies | No. of Patients/Controls | Effect size (95% Confidence Interval) | Effect Size: p Value | Heterogeneity: Q p Value | Publication Bias: p Value |
|---|---|---|---|---|---|---|
| Intracranial | 7 | 180/278 | -0.25 (-0.44 to -0.06) | .009 | 4.53 .60 | .26 |
| Whole brain | 7 | 131/279 | -0.35 (-0.61 to -0.10) | .006 | 8.20 .22 | .06 |
| Grey matter (total) | 4 | 66/68 | -0.16 (-0.49 to 0.17) | .334 | 1.64 .65 | .42 |
| White matter ( total) | 5 | 95/116 | -0.33 (-0.60 to -0.05) | .017 | 7.20 .20 | .31 |
| Lateral ventricles (total) | 3 | 64/136 | 0.21 (-0.09 to 0.52) | .169 | 3.04 .21 | .06 |
| Right lateral ventricle | 3 | 65/152 | -0.21 (-0.31 to 0.27) | .888 | 5.11 .07 | .38 |
| Left lateral ventricle | 3 | 65/152 | -0.09 (-0.82 to 0.64) | .807 | 11.52 .003 | .30 |

When the studies relative to both schizophrenic and bipolar disorder patients were investigated as a whole and compared to healthy controls, several brain anomalies were found to be present at the onset of psychoses, and, in particular, a volume reduction of intracranial, whole brain, grey and white matter volumes. Moreover, in the same sample of studies, an increase of lateral ventricles volume was demonstrated.

These results are consistent with those of previous meta-analyses on brain volumes in first-episode schizophrenia [5,6] and bipolar disorder [12]. It is worth noting that the picture emerging from our analyses indicates a substantial overlap of brain changes across diagnostic groups in the early phases of psychosis. This result was confirmed by the absence of significant heterogeneity of volumetric changes between schizophrenic and BD patients for all the brain regions considered. Even in the regions that showed heterogeneity, i.e. whole brain and left lateral ventricles volumes, the subgroup analyses performed suggested that the observed heterogeneity of brain morphological findings in first episode psychoses was not attributable to the diagnostic category.

Thus, it appears that at their onset schizophrenia and BD share a largely common pattern of brain anomalies, i.e. schizophrenia and BDs do not appear to be clearly distinct entities at the level of the neuroanatomic phenotype at least in the first phases of the disease course.

At a closer inspection, our findings suggest however that some degree of specificity of brain morphological changes in each of the two disorders could be found. In particular, whole grey matter volume deficits appear to be more prominent in first-episode schizophrenia whereas white matter volume reduction seems to be more pronounced in first episode BD. Moreover, the increased volume of lateral ventricles is much more pronounced in first-episode patients with schizophrenia. Whether these apparent differences, not captured by the subgroup analyses (between groups comparisons) performed could be attributable solely to the different statistical power of the meta-analyses of schizophrenia or BD vs controls, with larger samples investigated in the case of first-episode schizophrenia, rather than to intrinsic neurobiological specificity, is still unknown. In any case, if it is well possible that nonsignificant results may be due to he low statistical power of the analyses (type 2 error), the differences found in spite of the low number of studies available should be not underestimated, in particular the significant difference in white matter volume between BD patients and controls.

The presence of definite brain abnormalities early in the course of schizophrenia and BD supports the hypothesis of their neurodevelopmental nature. According to the current formulations of the neurodevelopmental model, allelic variations of the candidate genes (particularly those involved in neurodevelopmental hits), and early insult of environmental origin are thought to act together, increasing the likelihood of the emergence of the disease [29,30]. The evidence that abnormal brain development contributes to schizophrenia comes from several areas of research, including: a) abnormalities of early motor and cognitive development and histories of obstetrical adversity [31,32]; b) the presence of subtle brain abnormalities both at the onset as well as in the prodromal phases of the disease [5,33]; c) the absence of neuronal degeneration, as seen in typical degenerative brain diseases, in post-mortem brains of patients suffering from schizophrenia [33]; and d) association of developmental pathological conditions with adult emergence of psychosis in animal models [35,36]. Conversely, even if neurodevelopmental factors have been implicated in the pathophysiology of BD, the evidence regarding their role in the disorder is still controversial and further research is needed to determine the precise extent of their contribution to the pathogenesis of this disease. Moreover, the timing and course of such developmentally mediated neurobiological alterations in BD also need to be determined [37].

On the other hand, it has been demonstrated that brain abnormalities progress over time in the psychoses. This is well demonstrated and has been included in recent reviews for schizophrenia [38,39], and has been also reported for bipolar disorder, although not systematically . However, the pathomorphological trajectory of schizophrenia and bipolar disorder could be somehow different. In the case of schizophrenia, early, diffuse brain abnormalities tend to progress over time, especially in the first years of the disease course [22, 40-43], involving in particular grey matter [44-47]. In BD, the most consistent changes in chronic cases may be ventricular enlargement and the appearance of white matter MRI hyperintensities on T2 weighted images. These different trajectories may be attributable to different pathophysiologic mechanismsand/or different causal processes. It could be speculated that genetic programs could underlie both early neurodevelopmental anomalies and subsequent proneness to progressive brain tissue loss in schizophrenia: however, the definitive demonstration of progressive volume change in schizophrenia awaits the results of new informative longitudinal studies, such as twin analyses [48]. Conversely, the brain of patients with bipolar disorder may be more sensitive to ageing and/or to pathological processes linked to it, involving the fine structure and function of cerebral white matter.

Even if different pathomorphological trajectories could be hypothesized in relation to the course of schizophrenia and BD, the abnormalities found at the onset of these disorders show more similarities than differences, suggesting that they may belong to a common biological phenotype. This is consistent with the existing evidence that schizophrenia and BD share some genetic [49-51], biochemical [52], and electrophysiologic [53] features, besides being characterized by overlapping symptomatological presentation and

response to antipsychotic treatment. To shed more light on these crucial issues, there is still a need for longitudinal studies conducted on first-episode cases, aimed at addressing the issues of the time of appearance and course of individual brain abnormalities in psychotic disorders, and taking into account the effects of several confounders.

The present study suffers from several limitations. First of all, common to all meta-analyses, no control was possible on the quality of the primary studies, that is, on the possibility that certain biases were present in the original studies. Moreover, our analysis was limited to the variables reported in the original studies. For instance, most of the studies considered in the meta-analysis included both drug-naive and previously treated first-episode schizophrenic or bipolar subjects without presenting separate results for these subgroups and only a large minority of the papers reported the amount of medication intake at study entry. Thus, the potential confounding effect of drug intake on brain morphology could not have been taken into account. A further limitation is the small number of published papers eligible for the analysis, especially in the case of BD: the rather restrictive criteria adopted (i.e. at least three studies reporting absolute area or volume measurements of a given cerebral structure) led to the exclusion of a number of studies, so that some brain regions potentially implicated in the pathophysiology of schizophrenia or BD could not be investigated. For example, several structures found to be changed in schizophrenic and BD patients also at the onset of the diseases, such as hippocampus, amygdala, and cingulate gyrus , could not be included in the present meta-analysis. Therefore, definitive conclusions about all the brain structural abnormalities detectable at illness onset cannot be drawn from the results of this meta-analysis, and its interpretation is therefore limited. This study only describes the state of the art on the issue and may promote further research in a given direction, but cannot generate completely new hypotheses.

Even with these limitations, the results of this study represent, in our opinion, a useful contribution to the present debate on the nature and meaning of brain structural abnormalities detected in schizophrenia and BD in relation to the natural history of these disorders.

Further studies are needed to better understand the biology of brain abnormalities in both schizophrenia and BD and their common or specific contribution to the pathogenesis of psychotic diseases.

## REFERENCES


[1] Elkis H, Friedman L, Wise A, Meltzer HY. Meta-analyses of studies of ventricular enlargement and cortical sulcal prominence in mood disorders. Comparisons with controls or patients with schizophrenia. Arch Gen Psychiatry 1995; 52(9): 735-46.

[2] Wrigh IC, Rabe-Hesketh S, Woodruff PWR, David AS, Murray RM, Bullmore ET. Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 2000; 157: 16- 25.

[3] Kempton MJ, Geddes JR, Ettinger U, Williams SC, Grasby PM. Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. Arch Gen Psychiatry 2008; 65: 1017-32.

[4] Pfeifer JC, Welge J, Strakowski SM, Adler CM, DelBello MP. Meta-analysis of amygdala volumes in children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2008; 47(11): 1289-98.

[5] Vita A, De Peri L, Silenzi C, Dieci M. Brain morphology in first-episode schizophrenia. A meta-analysis of quantitative magnetic resonance imaging studies. Schizophr Res 2006; 82: 75-88.

[6] Steen GR, Mull C, McClure L, Hamer RM, Lieberman JA. Brain volume in first-episode schizophrenia. Systematic review and meta-analysis of magnetic resonance imaging studies. Br J Psychiatry 2006; 188: 510-8.

[7] Strakowski SM, Wilson DR, Tohen M, Woods BT, Douglass AW, Stoll AL. Structural brain abnormalities in first-episode mania. Biol Psychiatry 1993; 33: 602-9.

[8] Atmaca M, Ozdemir H, Yildirim H. Corpus callosum areas in first-episode patients with bipolar disorder. Psychol Med 2007; 37: 699-704.

[9] Nakamura M, Salisbury DF, Hirayasu, Bouix S, Pohl KM, Yoshida T *et al*. Neocortical gray matter volume in first-episode schizophrenia and first-episode affective psychosis: a cross-sectional and longitudinal MRI study. Biol Psychiatry 2007; 62: 773-83.

[10] Rosso IM, Killgore WD, Cintron CM, Gruber SA, Tohen M, Yurgelun-Todd DS. Reduced amygdala volume in firstepisode bipolar disorder and correlation with cerebral white matter. Biol Psychiatry 2007; 61: 743-9.

[11] Strakowski SM, DelBello MP, Zimmerman ME, *et al*. Ventricular and periventricular structural volumes in first versus multiple-episode bipolar disorder. Am J Psychiatry 2002; 159: 1841-7.

[12] Vita A, De Peri L, Sacchetti E. Gray matter, white matter, brain, and intracranial volumes in first-episode bipolar disorder: a meta-analysis of magnetic resonance imaging studies. Bipolar Disord. 2009; 11(8): 807-14.

[13] Takahashi T, Wood SJ, Soulsby B, *et al*. An MRI study of the superior temporal subregions in first-episode patients with various psychotic disorders. Schizophr Res. 2009; 113(2-3): 158-66.

[14] Kasai K, Shenton ME, Salisbury DF, *et al*. Differences and similarities in insular and temporal pole MRI gray matter volume abnormalities in first-episode schizophrenia and affective psychosis. Arch Gen Psychiatry 2003; 60: 1069-77.

[15] Hedges LV, Holkin I. Statistical Methods for Meta-Analysis. New York: Academic Press, 1985.

[16] Cohen, J., 1988. Statistical Power Analysis for the Behavioural Sciences, 2nd ed. Lawrence Erlbaum Associates, Hillsdale, NY.

[17] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.

[18] Nopoulos P, Torres I, Flaum M, Andreasen NC, Ehrhardt JC, Yuh WT. Brain morphology in first-episode schizophrenia. Am. J. Psychiatry 1995; 152: 1721-3.

[19] Gilbert AR, Rosenberg DR, Harenski K, Spencer S, Sweeney JA, Keshavan MS. Thalamic volumes in patients with first-episode schizophrenia. Am. J. Psychiatry 2001; 158: 618- 24.

[20] Lang DJ, Khorram B, Goghari VM, *et al*. Reduced anterior internal capsule and thalamic volumes in first-episode psychosis. Schizophr Res. 2006; 87(1-3): 89-99.

[21] Fannon D, Chitnis X, Doku V, *et al*. Features of structural brain abnormality detected in first-episode psychosis. Am. J. Psychiatry 2000; 17 (11): 1829- 34.

[22] Boonstra G, van Haren NE, Schnack HG, *et al*. Brain volume changes after withdrawal of atypical antipsychotics in patients with first-episode schizophrenia. J Clin Psychopharmacol. 2011; 31(2): 146-53.

[23] Gur RE, Cowell P, Turetsky BI, *et al*. A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. Arch. Gen. Psychiatry 1998; 55: 145- 52.

[24] Bottmer C, Bachmann S, Pantel J, *et al*. Reduced cerebellar volume and neurological soft signs in first-episode schizophrenia. Psychiatry Res. 2005; 140(3): 239-50.

[25] Chua SE, Cheung C, Cheung V, *et al*. Cerebral grey, white matter and csf in never-medicated, first-episode schizophrenia. Schizophr Res. 2007; 89(1-3): 12-21.

[26] DeLisi LE, Hoff AL, Schwartz JE, *et al*. Brain morphology in first-episode schizophrenic-like psychotic patients: a quantitative magnetic resonance imaging study. Biol. Psychiatry 1991; 29: 159- 75.

[27] Puri BK, Hutton SB, Saeed N, *et al*. A serial longitudinal quantitative MRI study of cerebral changes in first-episode schizophrenia using image segmentation and subvoxel registration. Psychiatry Res. 2001; 106: 141- 50.

[28] Koo MS, Levitt JJ, Salisbury DF, Nakamura M, Shenton ME, McCarley RW. A cross-sectional and longitudinal magnetic resonance imaging study of cingulate gyrus gray matter volume abnormalities in first-episode schizophrenia and first-episode affective psychosis. Arch Gen Psychiatry 2008; 65(7): 746-60.

[29] Rosa PG, Schaufelberger MS, Uchida RR, *et al*. Lateral ventricle differences between first-episode schizophrenia and first-episode psychotic bipolar disorder: A population-based morphometric MRI study. World J Biol Psychiatry 2010; 11(7): 873-87.

[30] Di Forti M, Lappin JM, Murray RM. Risk factors for schizophrenia--all roads lead to dopamine. Eur Neuropsychopharmacol. 2007; 17 (Suppl 2): S101-7.

[31] Waddington JL, Torrey EF, Crow TJ & Hirsch SR. Schizophrenia, neurodevelopment, and disease. The Fifth Biannual Winter Workshop on Schizophrenia, Badgastein, Austria, January 28 to February 3, 1990. Arch Gen Psychiatry 1991; 48: 271−3.

[32] Geddes JR & Lawrie SM. Obstetric complications and schizophrenia: a meta-analysis. Br J Psychiatry 1995; 167: 786−93.

[33] Pantelis C, Velakoulis D, Wood SJ, *et al*. Neuroimaging and emerging psychotic disorders: the Melbourne ultra-high risk studies. Int Rev Psychiatry. 2007; 19(4): 371-81.

[34] Bernstein HG, Steiner J, Bogerts B. Glial cells in schizophrenia: pathophysiological significance and possible consequences for therapy. Expert Rev Neurother. 2009; 9(7): 1059-71.

[35] Ozawa K, Hashimoto K, Kishimoto T, Shimizu E, Ishikura H, Iyo M. Immune activation during pregnancy in mice leads to dopaminergic hyperfunction and cognitive impairment in the offspring: a neurodevelopmental animal model of schizophrenia. Biol Psychiatry 2006; 59: 546-54.

[36] Zuckerman L, Rehavi M, Nachman R, Weiner I. Immune activation during pregnancy in rats leads to a postpubertal emergence of disrupted latent inhibition, dopaminergic hyperfunction, and altered limbic morphology in the offspring: a novel neurodevelopmental model of schizophrenia. Neuropsychopharmacology 2003; 28: 1778-89.

[37] Sanches M, Keshavan MS, Brambilla P, Soares JC. Neurodevelopmental basis of bipolar disorder: a critical appraisal. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32(7): 1617-27.

[38] Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM. Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. Biol Psychiatry 2011; 70(1): 88-96.

[39] Kempton MJ, Stahl D, Williams SC, DeLisi LE. Progressive lateral ventricular enlargement in schizophrenia: a meta-analysis of longitudinal MRI studies. Schizophr Res. 2010; 120(1-3): 54-62.

[40] Lieberman J, Chakos M, Wu H, *et al*. Longitudinal study of brain morphology in first episode schizophrenia. Biol Psychiatry. 2001; 49(6): 487-99.

[41] Cahn W, Hulshoff Pol HE, Lems EB, *et al*. Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. Arch Gen Psychiatry. 2002; 59(11): 1002-10.

[42] Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M. Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. Arch Gen Psychiatry. 2003; 60(6): 585-94.

[43] Lieberman JA, Tollefson GD, Charles C, *et al*. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 2005; 62(4): 361-70.

[44] van Haren NE, Hulshoff Pol HE, Schnack HG, *et al*. Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. Biol Psychiatry 2008; 63(1): 106-13.

[45] Zipparo L, Whitford TJ, Redoblado Hodge MA, *et al*. Investigating the neuropsychological and neuroanatomical changes that occur over the first 2-3 years of illness in patients with first-episode schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32(2): 531-8.

[46] Whitford TJ, Grieve SM, Farrow TF, *et al*. Progressive grey matter atrophy over the first 2-3 years of illness in first-episode schizophrenia: a tensor-based morphometry study. Neuroimage 2006; 32(2): 511-9.

[47] Mané A, Falcon C, Mateos JJ, *et al*. Progressive gray matter changes in first episode schizophrenia: a 4-year longitudinal magnetic resonance study using VBM. Schizophr Res. 2009; 114(1-3): 136-43.

[48] van Haren NE, Bakker SC, Kahn RS. Genes and structural brain imaging in schizophrenia. Curr Opin Psychiatry 2008; 21(2): 161-7.

[49] Gill M, Donohoe G, Corvin A. What have the genomics ever done for the psychoses? Psychol Med. 2010; 40(4): 529-40.

[50] Maier W. Common risk genes for affective and schizophrenic psychoses. Eur Arch Psychiatry Clin Neurosci. 2008; 258 (Suppl 2): S37-40.

[51] Carroll LS, Owen MJ. Genetic overlap between autism, schizophrenia and bipolar disorder. Genome Med. 2009; 1(10): 102.

[52] Möller HJ. Bipolar disorder and schizophrenia: distinct illnesses or a continuum? J Clin Psychiatry 2003; 64 (Suppl 6): S23-7.

[53] Bestelmeyer PE, Phillips LH, Crombie C, Benson P, St Clair D. The P300 as a possible endophenotype for schizophrenia and bipolar disorder: Evidence from twin and patient studies. Psychiatry Res. 2009; 169(3): 212-9.

[54] Degreef G, Ashtari M, Bogerts B, *et al*. Volumes of ventricular system subdivisions measured from magnetic resonance images in first-episode schizophrenic patients. Arch. Gen. Psychiatry 1992; 49; 531-37.

[55] Strakowski SM, Wilson DR, Tohen M, Woods BT, Douglass AW, Stoll AL. Structural brain abnormalities in first-episode mania. Biol Psychiatry 1993; 33: 602-9.

[56] Whitworth AB, Honeder M, Kremser C, *et al*. Hippocampal volume reduction in male schizophrenic patients. Schizophr. Res. 1998; 31: 73- 81.

[57] Zipursky, R.B., Lambe, E.K., Kapur, S., Mikulis, D.J., Cerebral gray matter volume deficits in first episode psychosis. Arch. Gen. Psychiatry 1998; 55: 540- 6.

[58] DelBello MP, Strakowski SM, Zimmerman ME, Hawkins JM, Sax KW. MRI analysis of the cerebellum in bipolar disorder: a pilot study. Neuropsychopharmacology 1999; 21: 63-8.

[59] James, A.C., Crow, T.J., Renowden, S., Wardell, A.M., Smith, D.M., Anslow, P. Is the course of brain development in schizophrenia delayed? Evidence from onsets in adolescence. Schizophr. Res. 1999; 40: 1 -10.

[60] Hirayasu Y, McCarley RW, Salisbury DF, *et al*. Planum temporale and Heschl gyrus volume reduction in schizophrenia: a magnetic resonance imaging study of first-episode patients. Arch. Gen. Psychiatry 2000; 57: 692- 9.

[61] Hirayasu Y, Tanaka S, Shenton ME, Salisbury DF, DeSantis MA, Levitt JJ *et al*. Prefrontal gray matter volume reduction in first episode schizophrenia. Cereb. Cortex 2001;11: 374-81.

[62] Lawrie SM, Whalley HC, Abukmeil SS, *et al*. Brain structure, genetic liability, and psychotic symptoms in subjects at high risk of developing schizophrenia. Biol. Psychiatry 2001; 49: 811- 23.

[63] Matsumoto H, Simmons A, Williams S, Pipe R, Murray R, Frangou S. Structural magnetic imaging of the hippocampus in early onset schizophrenia. Biol. Psychiatry 2001; 49: 824-31.

[64] Cahn W, Hulshoff Pol HE, Bongers M, *et al*. Brain morphology in antipsychotic-naive schizophrenia: a study of multiple brain structures. Br. J. Psychiatry 2002; 43: 66- 72.

[65] Salokangas RK, Cannon T, Van Erp T, *et al*. Structural magnetic resonance imaging in patients with first-episode schizophrenia, psychotic and severe non-psychotic depression and healthy controls. Results of the schizophrenia and affective psychoses (SAP) project. Br. J. Psychiatry 2002; 43: 58- 65.

[66] Chua SE, Lam IW, Tai KS, *et al*. Brain morphological abnormality in schizophrenia is independent of country of origin. Acta Psychiatr. Scand. 2003; 108: 269-75.

[67] Molina, V., Sanz, J., Sarramea, F., Benito, C., Palomo, T. Lower prefrontal gray matter volume in schizophrenia in chronic but not in first episode schizophrenia patients. Psychiatry Res. 2004; 131, 45- 56.

[68] Farrow TF, Whitford TJ, Williams LM, Gomes L, Harris AW. Diagnosis-related regional gray matter loss over two years in first episode schizophrenia and bipolar disorder. Biol Psychiatry 2005; 58: 713-23.

[69] Nierenberg J, Salisbury DF, Levitt JJ, David EA, McCarley RW, Shenton ME. Reduced left angular gyrus volume in first-episode schizophrenia. Am J Psychiatry. 2005; 162(8): 1539-41.

[70] Preuss UW, Zetzsche T, Jäger M, *et al*. Thalamic volume in first-episode and chronic schizophrenic subjects: a volumetric MRI study. Schizophr Res. 2005; 73(1): 91-101.

[71] Premkumar P, Kumari V, Corr PJ, Sharma T. Frontal lobe volumes in schizophrenia: effects of stage and duration of illness. J Psychiatr Res. 2006; 40(7): 627-37.

[72] Velakoulis D, Wood SJ, Wong MT, *et al* . Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. Arch Gen Psychiatry 2006; 63: 139-49

[73] Glenthoj A, Glenthoj BY, Mackeprang T, *et al*. Basal ganglia volumes in drug-naive first-episode schizophrenia patients before and

after short-term treatment with either a typical or an atypical antipsychotic drug. Psychiatry Res. 2007; 154(3): 199-208.

[74] Crespo-Facorro B, Roiz-Santiáñez R, Pérez-Iglesias R, *et al*. Specific brain structural abnormalities in first-episode schizophrenia. A comparative study with patients with schizophreniform disorder, non-schizophrenic non-affective psychoses and healthy volunteers. Schizophr Res. 2009; 115(2-3): 191-201.

[75] Takahashi T, Wood SJ, Soulsby B, *et al*. Follow-up MRI study of the insular cortex in first-episode psychosis and chronic schizophrenia. Schizophr Res. 2009; 108(1-3): 49-56.

[76] Thomann PA, Roebel M, Dos Santos V, Bachmann S, Essig M, Schröder J. Cerebellar substructures and neurological soft signs in first-episode schizophrenia. Psychiatry Res. 2009; 173(2): 83-7.

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[77] Ebdrup BH, Glenthøj B, Rasmussen H, *et al*. Hippocampal and caudate volume reductions in antipsychotic-naive first-episode schizophrenia. J Psychiatry Neurosci. 2010; 35(2): 95-104.

[78] Takahashi T, Suzuki M, Zhou SY, *et al*. A follow-up MRI study of the superior temporal subregions in schizotypal disorder and first-episode schizophrenia. Schizophr Res. 2010; 119(1-3): 65-74.

[79] Takayanagi Y, Takahashi T, Orikabe L, *et al*. Volume reduction and altered sulco-gyral pattern of the orbitofrontal cortex in first-episode schizophrenia. Schizophr Res. 2010; 121(1-3): 55-65.

[80] Witthaus H, Mendes U, Brüne M, *et al*. Hippocampal subdivision and amygdalar volumes in patients in an at-risk mental state for schizophrenia. J Psychiatry Neurosci. 2010; 35(1): 33-40.