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# Anatomy of bipolar disorder and schizophrenia: A meta-analysis

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ABSTRACT

*Background:* Recent genetic results have indicated that the two major, classically distinct forms of psychosis – schizophrenia and bipolar disorder – may share causative factors in common. However it is not clear to what extent they may also have similar profiles of brain abnormality. We used meta-analytic techniques to generate and compare maps of brain structural abnormality in the large samples of patients with both disorders that have been studied using magnetic resonance imaging.

*Method:* A systematic search was conducted for voxel-based morphometry studies examining gray matter in patients with schizophrenia or bipolar disorder. The anatomical distribution of the co-ordinates of gray matter differences was meta-analysed using Anatomical Likelihood Estimation.

*Results:* Forty-two schizophrenia studies including 2058 patients with schizophrenia and 2131 comparison subjects were compared with fourteen bipolar studies including 366 patients with bipolar disorder and 497 comparison subjects. In schizophrenia, there were extensive gray matter deficits in frontal, temporal, cingulate and insular cortex and thalamus, and increased gray matter in the basal ganglia. In bipolar disorder, gray matter reductions were present in the anterior cingulate and bilateral insula. These substantially overlapped with areas of gray matter reduction in schizophrenia, except for a region of anterior cingulate where gray matter reduction was specific to bipolar disorder.

*Implications:* In bipolar disorder studies there were consistent regional gray matter reductions in paralimbic regions (anterior cingulate and insula) implicated in emotional processing. Gray matter reductions in schizophrenia studies were more extensive and involved limbic and neocortical structures as well as the paralimbic regions affected in bipolar disorder.



## 1. Introduction

Historically bipolar disorder and schizophrenia have been regarded as dichotomous illnesses. Therefore, there may not be any similarity in brain structural changes between the two disorders. However, there is accumulating evidence to suggest that bipolar disorder and schizophrenia share elements of pathology (Fischer and Carpenter, 2009). This includes evidence of co-aggregation of the two disorders in families (Van Snellenberg and de Candia, 2009; Lichtenstein et al., 2009) and sharing of susceptibility genes (Moskvina et al., 2009, International Schizophrenia Consortium et al., 2009).

Furthermore, theoretical models of the functional anatomy of bipolar disorder and schizophrenia have implicated overlapping neural systems. It has been proposed that the affective and psychotic symptoms of bipolar disorder result from dysfunction in a prefrontal–subcortical network interacting with a limbic network (Strakowski et al., 2005). In schizophrenia, models link psychotic and cognitive symptoms with dysfunction in limbic and frontal–temporal–subcortical networks (Shenton et al., 1992; Noga et al., 1995; Spence et al., 1997; Buchanan et al., 2004; Assaf et al.,

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2006; Goghari et al., 2009). Functional abnormalities in these networks may be associated with structural brain changes (Hugdahl et al., 2009; Bassett and Bullmore, 2009; Horn et al., 2009). However, there has been greater progress in mapping structural brain changes in schizophrenia compared with bipolar disorder (Gur et al., 2007; Harrison, 2002).

In schizophrenia, meta-analyses of 'region of interest' studies (measuring volumes of particular structures) have identified increased ventricular volumes and reduced volumes of regions such as the frontal lobe and hippocampus (Lawrie and Abukmeil, 1998; Wright et al., 2000; Shenton et al., 2001). A more detailed examination of regional structural changes within the brain has been achieved by voxel-based morphometry (VBM) studies. In this technique magnetic resonance images are analysed for structural change at the level of 'voxels' — the individual elements within a three-dimensional digital image (Wright et al., 1995; Ashburner and Friston, 2000). Voxel-based morphometry studies of schizophrenia have shown consistent gray matter reductions in the anterior cingulate, thalamus, bilateral insula/frontal lobe and bilateral hippocampal–amygdala region (Segall et al., 2009).

In bipolar disorder, meta-analyses have also identified reduced whole brain volume and increased lateral ventricular volume (McDonald et al., 2004a; Kempton et al., 2008) as well as reduced prefrontal lobe volume and increased globus pallidus volume (Arnone et al., 2009). However, the magnitudes of global brain changes are generally smaller than in schizophrenia. Voxel-based morphometry studies of bipolar disorder have produced inconsistent results, with some finding predominant gray matter decreases (Lyoo et al., 2004; Doris et al., 2004; Nugent et al., 2006; Yatham et al., 2007; Almeida et al., 2009; Ha et al., 2009; Stanfield et al., 2009), predominant increases (Adler et al., 2005, 2007) or no differences (McDonald et al., 2005; Bruno et al., 2004).

If the magnitude of brain changes in bipolar disorder is small, then inconsistent results between studies may occur because of small sample sizes with low power to detect changes. The integration of results from multiple studies may therefore identify brain regions showing consistent changes which are not otherwise apparent in the individual studies. Meta-analysis methods for voxel-based morphometry studies have recently been developed and applied to schizophrenia (Ellison-Wright et al., 2008a; Glahn et al., 2008; Fornito et al., 2009a; Chan et al., 2009), Attention Deficit Hyperactivity Disorder (Ellison-Wright et al., 2008b) and Obsessive–Compulsive Disorder (Radua and Mataix-Cols, 2009). However, meta-analyses of observational studies need to be interpreted with caution, because differences between cases and controls may arise from confounding factors or sample selection (Egger et al., 1998; Shrier et al., 2007).

In this study we conduct a meta-analysis of voxel-based morphometry studies of bipolar disorder and investigate whether there is a correspondence between the regional gray matter changes with those found in schizophrenia.

## 2. Methods

### 2.1. Data sources

A systematic search strategy was used to identify relevant studies. We carried out keyword searches of the MEDLINE, PsychINFO and EMBASE databases (from 1 January 1995–31 July 2009). We also used the reference lists of meta-analyses (Ellison-Wright et al., 2008a; Glahn et al., 2008; Fornito et al., 2009a; Chan et al., 2009) and searched the reference lists of the studies identified for inclusion. Table 1 lists the articles included in the meta-analysis.

### 2.2. Study selection

Studies were considered for inclusion if they were published as an article, if they compared a group of subjects with an appropriate patient group and a comparison group, if they utilised voxel-based analysis of gray matter to investigate differences in whole brain, and if they reported the three-dimensional co-ordinates of changes in stereotactic space.

Bipolar studies were considered if they consisted of subjects with bipolar disorder (or related diagnoses e.g., first episode bipolar disorder, first episode mania). Schizophrenia studies were considered if they included a group of subjects with schizophrenia (or schizophrenia and related diagnoses e.g., schizo-affective disorder, first episode schizophrenia).

Study data were excluded if insufficient data were reported to extract the number of subjects in each group, if there were fewer than six subjects in a sample, if the data contributed to another analysis or if an analysis included a common control group (in which case the analysis with the largest group size was selected). Analyses of bipolar data were preferred over analyses of schizophrenia data (to maximise sample data) and otherwise analyses were chosen to maximise the number of patients available for meta-analysis.

### 2.3. Data extraction

Co-ordinates that were reported in the stereotactic space of the Montreal Neurological Institute (MNI) were converted to Talairach co-ordinates (Talairach and Tournoux, 1988) using the Lancaster transform in GingerALE (Laird et al., 2005).

### 2.4. Meta-analysis

Meta-analyses were carried out using the rank-based Genome Scan Meta-Analysis (GSMA) (Wise et al., 1999; Lewis et al., 2003) modification of Activation Likelihood Estimation (ALE) (Ellison-Wright et al., 2008b; Ellison-Wright and Bullmore, 2009).

Meta-analyses for each disorder were carried out using a C++ program. For each study, the co-ordinates were modeled as the peaks of three-dimensional Gaussian probability density functions with full-width half-maximum of 7 mm, within a gray matter mask of 201 069 voxels of linear dimension 2 mm. The voxels in this probability image were then ranked from 201 069 (highest probability) to 1 (lowest probability), giving voxels of equal probability a mean rank. This created a rank image for each study which was smoothed with a 7 mm Gaussian filter. These study images were weighted by the square root of the number of patients in the study. The weighted images were summated to create a sum-rank image. A null distribution for sum-rank voxel values was derived by 20 000 permutations, using the sum of the rank of a randomly selected voxel from each study

(Eickhoff et al., 2009). The image-wise probability of a sum-rank under the null hypothesis was calculated as the proportion of permutations giving a value equal or greater than the actual value. The data set being tested was included in the ranking of all known outcomes (Levinson et al., 2003). The probability maps for the sum-rank images were ordered in magnitude and thresholded, controlling the image false discovery rate at $p<0.05$ (Verhoeven et al., 2005).

The Talairach location of significant clusters was assigned by identifying the location of the co-ordinate of the maximum sum-rank value in the automated Talairach atlas (http://www.talairach.org/) and this was manually checked in the Talairach atlas (Talairach and Tournoux, 1988).

### 2.5. Comparison between bipolar disorder and schizophrenia gray matter changes

We also investigated whether there was significant overlap between the bipolar disorder and schizophrenia gray matter changes. We used a Bernoulli distribution to test whether the bipolar disorder co-ordinates extracted from the primary studies were uniformly distributed within the entire gray matter brain mask or were over-represented within the regions of change identified in schizophrenia. The significance threshold was set at $p<0.01$.

### 2.6. Sensitivity analysis

There were more schizophrenia studies compared with bipolar disorder studies and a higher proportion of female subjects in the bipolar studies. Therefore we conducted a sensitivity analysis (Cooper and Hedges, 1994) by re-analysing a sub-sample of schizophrenia studies of equal number to the bipolar studies providing co-ordinates of gray matter reductions (thirteen). We selected the schizophrenia studies with the highest proportion of female patient subjects in order to achieve a comparable gender balance (Ananth et al., 2002; Chua et al., 2007; Hirao et al., 2008; Jayakumar et al., 2005; Lui et al., 2009; Marcelis et al., 2003; Meda et al., 2008; [JHU sample], Moorhead et al., 2004; Ohnishi et al., 2006; Salgado-Pineda et al., 2004; Suzuki et al., 2002; Yamada et al., 2007; Yoshihara et al., 2008).

## 3. Results

### 3.1. Studies ascertained

A total of fourteen bipolar disorder and forty-two schizophrenia studies were identified for inclusion in the meta-analysis (Table 1). The bipolar disorder studies included a total of 366 patients and 497 comparison subjects. The schizophrenia studies included a total of 2058 patients and 2131 comparison subjects.

Overall, the mean age of subjects in the bipolar disorder studies was 32.5 years for patients and 32.2 years for controls; in the schizophrenia studies the mean age was 33.4 years for patients and 32.6 years for controls. The patients in the bipolar disorder studies had a mean duration of illness of 12.3 years compared with 8.0 years in the schizophrenia studies. In the bipolar studies, 53% of patients were female compared with 53% of controls; in the schizophrenia studies 31% of patients were female compared with 40% of controls.

In the bipolar disorder studies overall (where the information was provided) 25% of patients were on no medication at the time of scanning, 37% were prescribed antipsychotics, 28% were prescribed anti-epileptic mood stabilisers and 29% were prescribed lithium (some were prescribed a combination). In the schizophrenia studies overall (where the information was provided) 14% of patients were on no medication at the time of scanning and 85% were prescribed antipsychotics (there were both first episode studies in which patients were mainly on no medication and studies of chronic schizophrenia in which most patients were prescribed antipsychotics).

### 3.2. Bipolar disorder

The fourteen bipolar studies included thirteen studies providing 76 co-ordinates of gray matter decreases and four studies providing 20 co-ordinates of gray matter increases.

Meta-analysis of this data identified four regions of gray matter decreases in bipolar subjects compared with controls on sum-rank analysis. The regions were in the right insula (A), perigenual anterior cingulate (B), left insula (C) and subgenual anterior cingulate (D). These regions are displayed on a brain template (Figs. 1 and 2) using the Mricron software program (Rorden et al., 2007).

No consistent regions of gray matter increase were identified by meta-analysis.

### 3.3. Schizophrenia

The forty-two schizophrenia studies included 587 co-ordinates of gray matter decreases and 61 co-ordinates of gray matter increases. Meta-analysis of this data identified two regions of gray matter decreases in schizophrenia subjects compared with controls on sum-rank analysis. The first was an extensive region (E) including the insula bilaterally (extending into dorsolateral prefrontal cortex and superior temporal cortex and bilateral hippocampal–amygdala region), thalamus, anterior cingulate and medial frontal gyrus. The second region (F) was in the posterior cingulate (Figs. 1 and 2).

Meta-analysis of gray matter increase co-ordinates in schizophrenia identified a region (G) extending from the right globus pallidus to the left caudate (Figs. 1 and 2).

### 3.4. Common changes in bipolar disorder and schizophrenia

For the gray matter decreases, there were 72 bipolar disorder co-ordinates within the gray matter brain mask (of size 201 069 voxels) of which 27 were inside the regions of gray matter reduction in schizophrenia (of size 36 016 voxels). This over-representation was significant ($p<0.01$).

### 3.5. Sensitivity analysis

In the schizophrenia sub-sample of thirteen studies used for the sensitivity analysis, there were 485 patients and 526 control subjects. The mean age for patients was and 35.5 years and for controls 35.7 years; the mean duration of

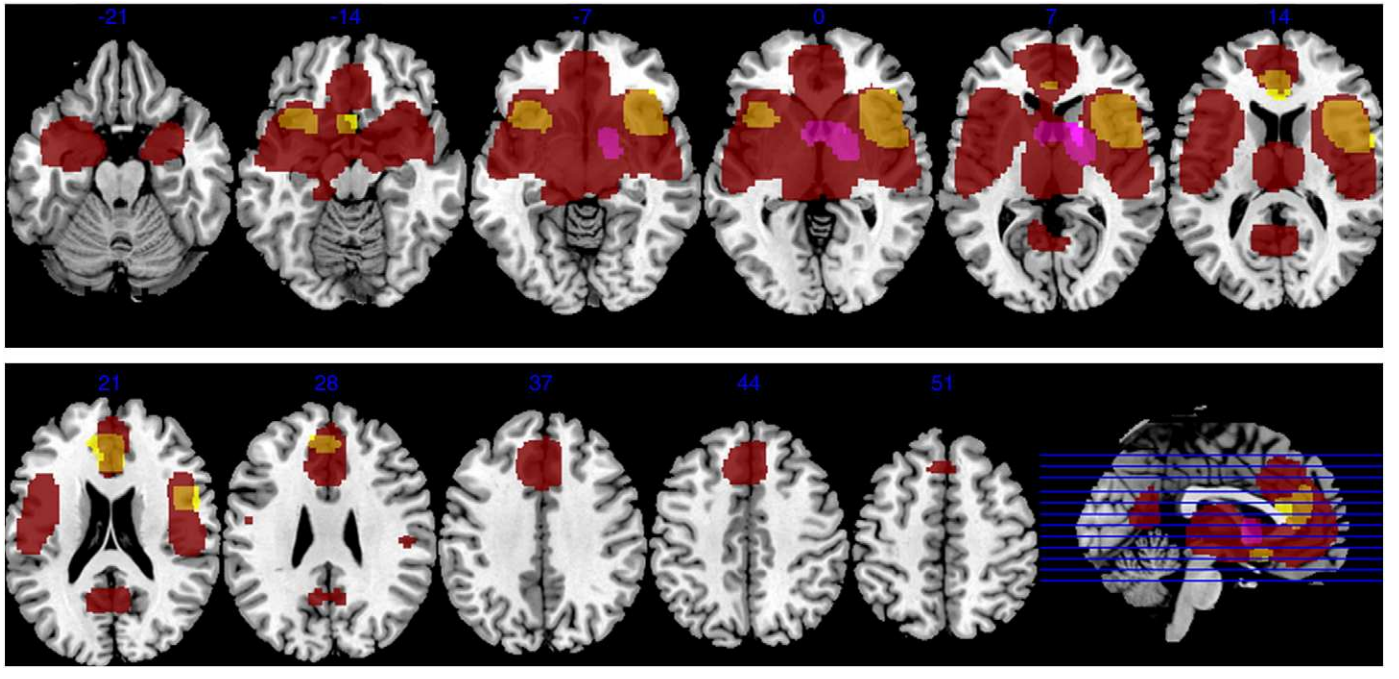


**Fig. 1.** Regions of gray matter change in bipolar subjects and schizophrenia subjects. Regions of gray matter decreases in bipolar subjects compared with controls (yellow) regions of gray matter decreases in schizophrenia subjects compared with controls (red), and regions of gray matter increases in schizophrenia subjects compared with controls (purple), displayed on a brain template. The left side of the image represents the left side of the brain. The Talairach level ($z$ co-ordinate) is given above each horizontal slice.

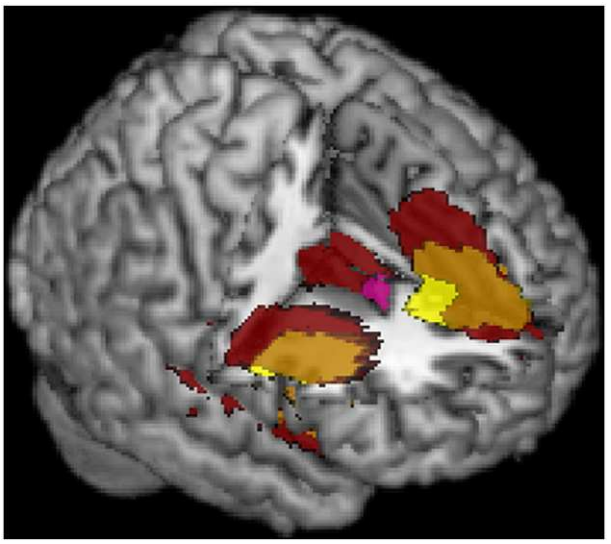

**Fig. 2.** Regions of gray matter change in bipolar subjects and schizophrenia subjects. Regions of gray matter decreases in bipolar subjects compared with controls (yellow) regions of gray matter decreases in schizophrenia subjects compared with controls (red), and regions of gray matter increases in schizophrenia subjects compared with controls (purple), displayed on a three-dimensional rendered brain with part of the right hemisphere removed.

illness was 6.9 years and 51% of patients were female compared with 52% of controls. Meta-analysis of this data identified similar (although smaller) regions of gray matter reduction compared with the whole schizophrenia sample. These reductions were in the bilateral insula, thalamus, anterior cingulate and bilateral hippocampal–amygdala region (although a reduction in the posterior cingulate was not identified). In this schizophrenia sub-sample, 12 668 voxels of gray matter reduction were identified compared with 5652 in the whole bipolar disorder sample (and 36 016 voxels in the whole schizophrenia sample).

## 4. Discussion

### *4.1. Gray matter changes in bipolar disorder and schizophrenia*

The meta-analysis identified consistent regions of gray matter reduction in bipolar disorder but no consistent areas of increase. The regions of gray matter reduction in bipolar disorder were less extensive than the gray matter reductions in schizophrenia but were substantially overlapping.

### *4.2. Methodological issues*

Meta-analysis of observational studies has a number of advantages over qualitative reviews (Cooper and Hedges, 1994). It utilises systematic and explicit rules for data collection and inclusion. It can improve statistical power. In the particular case of voxel-based morphometry studies it permits the integration of complex three-dimensional co-ordinate data which are otherwise difficult to visualise and synthesise. It avoids 'vote-counting' methods which can produce misleading results.

The meta-analysis in this study employed rank-based Anatomical Likelihood Estimation (ALE) which utilises methods from Genome Scan Meta-Analysis (GSMA) (Wise et al., 1999; Levinson et al., 2003) to overcome some of the conceptual drawbacks of classical ALE (as discussed by Eickhoff et al., 2009). Firstly it treats the spatial conjunction of co-ordinates from different studies as more significant than the conjunction of co-ordinates from the same study. Secondly it permits the weighting of studies by sample size. Thirdly it uses a gray matter mask to anatomically constrain the analysis and exclude regions of deep white matter.

However, there are potential methodological limitations of this approach (Cooper and Hedges, 1994). The differences in distributions of gray matter changes between the schizophrenia and bipolar studies may have a number of explanations other than differences in the pathology of the two disorders.

Firstly, the power to detect regional changes is limited by the number of studies included in the analysis. Therefore the brain changes in schizophrenia and bipolar disorder may be more extensive than the regions identified as significant. In particular there were only four bipolar studies finding regions of gray matter increase so the likelihood of detecting consistent regions of increase was small. Furthermore, the meta-analysis methods currently available for voxel-based morphometry studies utilise the co-ordinate results reported in primary studies. This represents a loss of information compared with the probability images obtained in the primary studies. Therefore it is possible that more widespread regions of change may become apparent in these disorders when larger numbers of subjects are investigated or when it becomes possible to meta-analyse probability images from primary studies (as more journals provide images in electronic data supplements).

Secondly, regional changes in case–control studies (and the meta-analyses based on these studies) may derive from confounding factors (e.g. due to differences in subject age or gender, stage of illness, medication effects, substance misuse or other confounding factors). For example, there is evidence

that brain structure is modulated by medication (Chakos et al., 1994; Nugent et al., 2006; Chen et al., 2007; Bearden et al., 2007; van der Schot et al., 2009) and smoking status (Tregellas et al., 2007). Therefore, confounding factors could potentially contribute to the differences in regional gray matter changes detected in the schizophrenia and bipolar disorder studies. Duration of illness, subject age and substance misuse are unlikely to be major confounding factors because the patients in the bipolar disorder studies had a mean duration of illness of 12.3 years compared with 8.0 years in the schizophrenia studies, the mean ages in the bipolar disorder studies were similar to those in the schizophrenia studies and the majority of studies specified substance misuse as an exclusion criterion. Although there were differences in the gender balance of the studies, gender is less likely to be a significant confounding factor contributing to these findings because our sensitivity analysis re-analysed a sub-sample of schizophrenia studies with a gender balance of subjects comparable to the bipolar studies and identified similar results to the analysis of the whole schizophrenia sample. Medication remains a potential confounding factor and it is theoretically possible that the greater use of antipsychotics in the schizophrenia samples may have led to more extensive gray matter deficits while the greater use of mood stabilisers in the bipolar subjects may have ameliorated gray matter deficits. However, the effects (if any) of these medications on gray matter changes remains uncertain.

Thirdly, an overlap in regional brain changes between bipolar disorder and schizophrenia studies could occur if there was a high level of misdiagnosis of cases within the bipolar studies included in the meta-analysis. However, this would need to consistently occur within the bipolar studies in order to produce a significant result after meta-analysis which seems unlikely.

Given the potential limitations of meta-analysis of observational studies, our interpretation of the results based on underlying disease pathology should be considered conjectural. However, in the absence of studies using large samples of subjects very closely matched for age, gender, medication status and other potentially confounding factors, meta-analyses provides an important source of hypotheses for further experimental testing.

### *4.3. Regions of gray matter reduction in bipolar disorder*

The regions of gray matter reduction in bipolar disorder were in the anterior cingulate and bilateral insula. These are considered paralimbic regions (Mesulam, 1985) involved in multiple functions including pain, reward, punishment and emotional processing (Beckmann et al., 2009). Our findings are consistent with results from previous meta-analyses of volumetric measurements in bipolar disorder. These identified reduced prefrontal lobe volume (Arnone et al., 2009) and reduced volumes (although non-significant) of left anterior cingulate (Arnone et al., 2009; Kempton et al., 2008) and left subgenual prefrontal cortex (McDonald et al., 2004b; Kempton et al., 2008). A meta-analysis of left and right amygdala volume found it was unchanged in bipolar disorder (Hajek et al., 2009).

In this meta-analysis, two subregions of the anterior cingulate cortex showed gray matter reductions: the perigenual anterior cingulate (pgACC) and subgenual anterior cingulate (sgACC). Changes in the anterior cingulate cortex are of particular interest because of previous studies finding abnormalities in this region in bipolar disorder and mood disorders (reviewed by Strakowski et al., 2005; Drevets et al., 2008; Monkul et al., 2005; Konarski et al., 2008).

The anterior cingulate comprises a number of cytoarchitectonically and functionally distinct regions which have been implicated both in affective regulation and cognition (Beckmann et al., 2009). The regions have been classified by a number of systems, more recently by connectivity-based parcellation (Beckmann et al., 2009). According to this system, the pgACC gray matter reduction identified in this meta-analysis included both pregenual cingulate cortex (anterior Brodmann area 24–Beckmann cluster 7) and perigenual paracingulate cortex (Brodmann area 32–Beckmann cluster 3). This region has interconnections with dorsal prefrontal cortex and dorsal striatum and is activated in functional studies of pain, conflict and reward. The sgACC gray matter reduction identified in this meta-analysis involved subcallosal cingulate cortex (Brodmann area 25–Beckmann cluster 1). This region has interconnections with hypothalamus, amygdala, hippocampus, ventral and dorsal striatum and medial orbitofrontal cortex. It is activated in functional studies of emotion and reward. Therefore the two regions of anterior cingulate gray matter reduction in bipolar disorder appear highly connected with frontal, striatal and limbic regions and are involved in affective function.

These findings of reductions in anterior cingulate gray matter are supported by other magnetic resonance imaging studies of the anterior cingulate in bipolar disorder subjects which have found reduced volume (Chiu et al., 2008; Kaur et al., 2005; Hirayasu et al., 1999; and in medication-free subjects by Atmaca et al., 2007; Sassi et al., 2004), as well as reduced cortical thickness (Lyoo et al., 2006) and reduced gray matter density (Wilke et al., 2004). Follow-up studies have also found progressive volume loss in the anterior cingulate cortex (Farrow et al., 2005; Koo et al., 2008; Kalmar et al., 2009). Gray matter changes in the anterior cingulate have been associated with associated with white matter reductions (Bruno et al., 2004) and fractional anisotropy reductions (Wang et al., 2008).

However, the MRI evidence is not entirely consistent. Some studies have found anterior cingulate volume to be unchanged in bipolar disorder (Zimmerman et al., 2006) or increased compared with control subjects (Fornito et al., 2009b; Javadapour et al., 2007), possibly linked to lithium treatment (Bearden et al., 2007).

Anterior cingulate dysfunction in bipolar disorder has also been suggested by functional imaging studies. These have identified functional attenuation in anterior cingulate in bipolar patients performing cognitive or emotional tasks (Lennox et al., 2004; Gruber et al., 2004), abnormal functional connectivity between the anterior cingulate and amygdala (Wang et al., 2009) and decreased anterior cingulate cortex connectivity with the thalamus, amygdala and striatum (Anand et al., 2009).

The meta-analysis also identified gray matter reductions in the bilateral insula in bipolar disorder subjects. The insula forms part of the paralimbic cortex (Mesulam, 1985) and is involved in the integration of affective information (Shirtcliff

et al., 2009), including fear conditioning (Sehlmeyer et al., 2009). In bipolar disorder patients with depression, decreased metabolism has been detected in a network including the insula, anterior cingulate, prefrontal cortex, and striatum (Brooks et al., 2009).

### 4.4. Regions of gray matter reduction in schizophrenia

The meta-analysis identified widespread regions of gray matter reduction in schizophrenia. The reductions were in the insula bilaterally (extending into dorsolateral prefrontal cortex and superior temporal cortex), thalamus, anterior cingulate, medial frontal gyrus and posterior cingulate. There were also increases in regional gray matter in a region extending from the right globus pallidus to the left caudate head. These findings are consistent with the results of previous volumetric meta-analyses of schizophrenia which found reduced frontal, hippocampal, amygdala (Lawrie and Abukmeil, 1998; Wright et al., 2000; Shenton et al., 2001) anterior cingulate (Baiano et al., 2007) and thalamus volumes (Konick and Friedman, 2001). They also confirm and extend the results of previous Anatomical Likelihood Estimation meta-analyses (which examined subsets of the studies in this meta-analysis) and which found gray matter deficits in similar regions (Ellison-Wright et al., 2008a; Glahn et al., 2008; Fornito et al., 2009a; Chan et al., 2009).

### 4.5. Location of bipolar disorder and schizophrenia changes

The regions of gray matter reduction in bipolar disorder substantially overlapped with the areas of gray matter reduction in schizophrenia. The left and right insula reductions in bipolar disorder were within the anterior sections of the insula reductions in schizophrenia. The subgenual anterior cingulate reduction was within a region of anterior cingulate/medial frontal gyrus reduction in schizophrenia. The perigenual anterior cingulate reduction partially overlapped with the anterior cingulate reduction in schizophrenia, although there was a distinct region of pregenual cingulate cortex (anterior Brodmann area 24) where gray matter reduction was detected in bipolar disorder studies but not schizophrenia studies.

These findings are consistent with a study which found that genetic risk for schizophrenia was associated with gray matter deficits in the bilateral fronto–striato–thalamic and left temporal regions, whereas genetic risk for bipolar disorder was associated with gray matter deficits in the right anterior cingulate gyrus and ventral striatum (McDonald et al., 2004b).

The sensitivity analysis which re-analysed a sub-sample of thirteen schizophrenia studies (equal in number to the thirteen bipolar studies providing co-ordinates of gray matter reductions) found similar regions of change compared with the whole schizophrenia sample. This indicated that the differences in gray matter reductions between bipolar disorder and schizophrenia were not simply explained by a difference in the number of studies available for analysis.

### 4.6. Future directions

The challenge for the future will be to identify whether the gray matter reductions in bipolar disorder and schizophrenia can be linked to specific genetic factors (Matsuo et al., 2009) and whether common susceptibility genes contribute to the overlap in regional brain changes. The identification of regions of structural change in bipolar disorder may localize targets for treatment interventions. Transcranial magnetic stimulation (TMS) of the prefrontal cortex has been investigated as a noninvasive treatment for depression (Paus and Barrett, 2004). It has been postulated that the anti-depressant action of TMS involves modulation of blood flow changes in the anterior cingulate (Paus and Barrett, 2004; Hayward et al., 2007). The subgenual anterior cingulate is targeted in deep brain stimulation (DBS) for treatment-resistant chronic depression (Johansen-Berg et al., 2008).

## 5. Conclusion

In summary, this meta-analysis provides evidence for anatomical brain changes in bipolar disorder with consistent regions of gray matter reduction in the anterior cingulate cortex and bilateral insula. These areas are inter-connected paralimbic structures which are key components of the functional systems involved in pain, reward, punishment and emotional processing. Regional changes in bipolar disorder may be found to be more extensive when larger subject groups are investigated and it is possible that medication may contribute to brain changes. However these results suggest that while brain changes in schizophrenia encompass limbic (amygdala, hippocampus, thalamus), paralimbic (anterior cingulate, insula) and neocortical structures (dorsolateral prefrontal and temporal cortex), the changes in bipolar disorder are more limited to paralimbic regions involved in emotional regulation.

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**Contributors**

Dr Ellison-Wright developed the meta-analysis method and drafted the manuscript. Professor Bullmore contributed to the design, co-ordination and writing of the manuscript. Both authors contributed to and have approved the final manuscript.

**Conflict of interest**

Professor Bullmore is employed half-time by the University of Cambridge and half-time by GlaxoSmithKline (GSK) and is a stockholder in GSK. Dr Ellison-Wright reports no conflict of interest.

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## Appendix A

**Table 1**
Studies included in the meta-analysis.

| Study | | Number of patients | Number of controls | Diagnosis of patients | Mean age of patients (years) | Mean age of controls (years) | Duration of illness (*) or treatment (#) (years) | % of patient sample female | % of control sample female |
|---|---|---|---|---|---|---|---|---|---|
| *Bipolar disorder studies* | | | | | | | | | |
| 1 | Adler et al., 2007 | 33 | 33 | BP-1 (FE) | 19.9 | 21.5 | NS | 55 | 42 |
| 2 | Adler et al., 2005 | 32 | 27 | BP-1 | 31.2 | 30.5 | 8.7* | 41 | 56 |
| 3 | Almeida et al., 2009 | 33 | 33 | BP-1 | 31.9 | 30.8 | 11.1* | 52 | 45 |
| 4 | Chen et al., 2007 | 24 | 25 | BP-1 | 38.2 | 38.4 | 14.2* | 75 | 72 |
| 5 | Dickstein et al., 2005 | 20 | 20 | BP | 13.4 | 13.3 | 3.3* | 35 | 35 |
| 6 | Doris et al., 2004 | 11 | 16 | BP-1 | 38.1 | 39.1 | 16.2* | 45 | 56 |
| 7 | Ha et al., 2009 (BP-1 sample) | 23 | 23 | BP-1 | 35.6 | 36 | 10.4* | 65 | 65 |
| 8 | Janssen et al., 2008 (BP sample) | 20 | 51 | BP-1 (FE) | 16.5 | 15.4 | 0.2* | 35 | 31 |
| 9 | Lochhead et al., 2004 | 11 | 31 | BP-1/BP-2 | 38.2 | 36 | 7.9* | 45 | 48 |
| 10 | Lyoo et al., 2004 | 39 | 43 | BP-1 | 38.3 | 35.7 | 19.7* | 59 | 56 |
| 11 | McIntosh et al., 2004 (MIX sample) | 19 | 49 | BP-1 | 39.7 | 35.3 | NS | 37 | 53 |
| 12 | Nugent et al., 2006 (medicated sample) | 20 | 65 | BP-1/BP-2 | 41.2 | 38 | 23* | 75 | 71 |
| 13 | Stanfield et al., 2009 | 66 | 66 | BP-1 | 36.4 | 39 | 15.4* | 55 | 53 |
| 14 | Yatham et al., 2007 | 15 | 15 | BP-1 | 36 | 36 | 3.9* | 60 | 60 |
| Total | | 366 | 497 | | | | | | |
| Mean | | | | | 32.5 | 32.2 | 12.3 | 53 | 53 |
| *Schizophrenia studies* | | | | | | | | | |
| 1 | Ananth et al., 2002 | 20 | 20 | SZ | 37.8 | 38.6 | 15.8* | 50 | 50 |
| 2 | Antonova et al., 2005 | 45 | 43 | SZ | 40.5 | 33.7 | 16.8* | 40 | 42 |
| 3 | Bassitt et al., 2007 | 50 | 30 | SZ | 31.7 | 31.2 | 11.4* | 24 | 30 |
| 4 | Chua et al., 2007 | 26 | 38 | SZ, SZF, BPSY (FE) | 32 | 33 | 0.33* | 65 | 58 |
| 5 | Cooke et al., 2008 | 52 | 30 | SZ, SZA | 38.4 | 32.1 | 13.9* | 23 | 20 |
| 6 | Douaud et al., 2007 | 25 | 25 | SZ (FE) | 16.5 | 16.2 | 1.4* | 28 | 32 |
| 7 | García-Martí et al., 2008 | 18 | 19 | SZ | 35.7 | 33.1 | 17* | 0 | 0 |
| 8 | Giuliani et al., 2005 | 41 | 34 | SZ, SZA | 39 | 34.7 | 17.4* | 29 | 50 |
| 9 | Ha et al., 2004 | 35 | 35 | SZ, SZF | 27.8 | 27.3 | 4.9* | 40 | 40 |
| 10 | Hirao et al., 2008 | 20 | 20 | SZ | 36.7 | 35 | 10.6* | 50 | 50 |
| 11 | Honea et al., 2008 | 169 | 212 | SZ, SZA, PNOS, SPD | 36.4 | 33.3 | NS | 22 | 51 |
| 12 | Hulshoff Pol et al., 2001 | 159 | 158 | SZ, SZF | 35.6 | 37.7 | 12.3* | 30 | 33 |
| 13 | Jayakumar et al., 2005 | 18 | 18 | SZ (FE) | 24.9 | 25.7 | 0# | 50 | 50 |
| 14 | Job et al., 2002 | 34 | 36 | SZ (FE) | 21.4 | 21.2 | NS | 32 | 53 |
| 15 | Kasparek et al., 2007 | 22 | 18 | SZ (FE) | 23.7 | 24.1 | 0.14# | 0 | 0 |
| 16 | Kawasaki et al., 2007 | 30 | 30 | SZ | 24.7 | 25.4 | 4.0* | 0 | 0 |
| 17 | Koutsouleris et al., 2008 | 175 | 177 | SZ | 31.7 | 31.5 | 1.6 | 26 | 31 |
| 18 | Kubicki et al., 2002 | 16 | 18 | SZ (FE) | 26 | 24 | 0.14# | 13 | 11 |
| 19 | Lui et al., 2009 | 68 | 68 | SZ (FE) | 24.2 | 24.7 | 0.71* | 56 | 54 |
| 20 | Marcelis et al., 2003 | 31 | 27 | SZ, SZA | 30.7 | 35.5 | 8.5* | 52 | 56 |
| 21 | Martí-Bonmatí et al., 2007 | 21 | 10 | SZ | 39 | 35 | 15* | 0 | 0 |
| 22 | McDonald et al., 2005 | 25 | 52 | SZ | 37.3 | 39.3 | 17.4* | 28 | 54 |
| 23 | Meda et al., 2008 (JHU sample) | 133 | 136 | SZ, SZA | 41.6 | 41.8 | NS | 47 | 51 |
| 24 | Meda et al., 2008 (WPIC sample) | 22 | 21 | SZ, SZA | 25.1 | 26.2 | NS | 36 | 38 |
| 25 | Moorhead et al., 2004 | 25 | 29 | SZ | 50.9 | 42.8 | NS | 44 | 55 |
| 26 | Neckelmann et al., 2006 | 12 | 12 | SZ | NS | NS | NS | NS | NS |
| 27 | Ohnishi et al., 2006 | 47 | 76 | SZ | 44.2 | 40.3 | 19.3* | 49 | 61 |
| 28 | Paillère-Martinot et al., 2001 | 20 | 20 | SZ | 29 | 26 | 10* | 0 | 0 |
| 29 | Salgado-Pineda et al., 2003 | 13 | 13 | SZ (FE) | 23.8 | 23.4 | 0 | 0 | 0 |
| 30 | Salgado-Pineda et al., 2004 | 14 | 14 | SZ | 25 | 25.1 | 1.8* | 50 | NS |
| 31 | Schaufelberger et al., 2007 (SZ sample) | 62 | 94 | SZ, SZF (FE) | 27.6 | 30.2 | 0.48* | 29 | 44 |
| 32 | Segall et al., 2009 | 237 | 266 | SZ | 35.3 | 33.7 | NS | 27 | 37 |
| 33 | Shapleske et al., 2002 | 72 | 32 | SZ | 34.1 | 33.3 | 11.5* | 0 | 0 |
| 34 | Sigmundsson et al., 2001 | 27 | 27 | SZ | 34.9 | 32.2 | 13.9* | 4 | 7 |
| 35 | Suzuki et al., 2002 | 45 | 42 | SZ | 26.4 | 26.1 | 5.2* | 49 | 48 |
| 36 | Tregellas et al., 2007 | 32 | 32 | SZ | 39.6 | 35.3 | NS | 34 | 56 |
| 37 | Whitford et al., 2005 | 41 | 47 | SZ (FE) | 19.8 | 19.3 | <0.25* | 39 | 30 |
| 38 | Wilke et al., 2001 | 48 | 48 | SZ | 33 | 33 | 8.5* | 44 | 44 |

**Table 1** (*continued*)

| Study | Number of patients | Number of controls | Diagnosis of patients | Mean age of patients (years) | Mean age of controls (years) | Duration of illness (*) or treatment (#) (years) | % of patient sample female | % of control sample female |
|---|---|---|---|---|---|---|---|---|
| *Schizophrenia studies* | | | | | | | | |
| 39 Wolf et al., 2008 | 28 | 14 | SZ | 33.1 | 30.9 | 5.8* | 29 | 36 |
| 40 Wright et al., 1999 | 42 | 52 | SZ | 34.6 | 32.1 | 12.2* | 26 | 35 |
| 41 Yamada et al., 2007 | 20 | 20 | SZ | 38.8 | 39.1 | 11.6* | 50 | 50 |
| 42 Yoshihara et al., 2008 | 18 | 18 | SZ (FE) | 15.8 | 15.8 | 1.2* | 50 | 50 |
| Total | 2058 | 2131 | | | | | | |
| Mean | | | | 33.4 | 32.6 | 8.0 | 31 | 40 |

All studies compared a patient group with a comparison group using voxel-based morphometry of gray matter (abbreviations: BP: bipolar disorder; BP-1: bipolar disorder, type 1; BP-2: bipolar disorder, type 2; BSY: brief psychotic disorder; FE: first episode; NS: not stated; PNOS: psychosis not otherwise specified; SPD: schizoid personality disorder; SZ: schizophrenia; SZA: schizo-affective disorder; SZF: schizophreniform disorder).

**Table 2**
Regions of gray matter changes in bipolar and schizophrenia subjects compared with controls.

| Cluster | Region | Talairach co-ordinates | | | Sum of ranks | *p* value (voxelwise) |
|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | |
| | *Bipolar meta-analysis* | | | | | |
| | Gray matter decreases | | | | | |
| A | Right insula | 44 | 18 | 8 | 43.5 | 0.00005 |
| B | Perigenual anterior cingulate (BA32) | 0 | 40 | 22 | 41.2 | 0.00010 |
| C | Left insula | −32 | 16 | −10 | 40.6 | 0.00010 |
| D | Subgenual anterior cingulate (BA25) | 0 | 14 | −12 | 37.4 | 0.00140 |
| | *Schizophrenia meta-analysis* | | | | | |
| | Gray matter decreases | | | | | |
| E | Left insula | −36 | 10 | 2 | 218.3 | 0.00005 |
| E | Right insula | 40 | 8 | 2 | 205.2 | 0.00005 |
| E | Left thalamus: medial dorsal nucleus | −4 | −14 | 4 | 181.3 | 0.00005 |
| E | Left frontal lobe: medial frontal gyrus (BA10) | −2 | 50 | 4 | 179.6 | 0.00005 |
| E | Left anterior cingulate (BA32) | −2 | 44 | −4 | 179.3 | 0.00005 |
| E | Left frontal lobe: medial frontal gyrus | −2 | 48 | 0 | 179.3 | 0.00005 |
| E | Left anterior cingulate (BA32) | −2 | 46 | −2 | 179.3 | 0.00005 |
| E | Left deep frontal lobe | −14 | 2 | −10 | 172.8 | 0.00005 |
| E | Left deep frontal lobe | −12 | 0 | −8 | 172.5 | 0.00005 |
| E | Left anterior cingulate (BA32) | −6 | 24 | 36 | 167.8 | 0.00010 |
| E | Right frontal lobe: medial frontal gyrus (BA9) | 2 | 42 | 26 | 157.1 | 0.00060 |
| E | Right frontal lobe: medial frontal gyrus (BA9) | 2 | 44 | 24 | 156.8 | 0.00070 |
| E | Right frontal lobe: medial frontal gyrus (BA9) | 2 | 48 | 22 | 156.5 | 0.00075 |
| F | Left posterior cingulate (BA23) | −8 | −60 | 12 | 158.0 | 0.00050 |
| | *Schizophrenia meta-analysis* | | | | | |
| | Gray matter increases | | | | | |
| G | Right globus pallidus | 16 | 0 | 4 | 71.6 | 0.00005 |
| G | Left caudate head | −6 | 8 | 4 | 67.8 | 0.00005 |

Regions identified by meta-analysis of co-ordinates from forty-two schizophrenia studies and fourteen bipolar studies (false discovery rate $p<0.05$). BA: Brodmann area.

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