

Review article

Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis

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Background

Several magnetic resonance imaging (MRI) studies have identified structural abnormalities in association with bipolar disorder. The literature is, however, heterogeneous and there is remaining uncertainty about which brain areas are pivotal to the pathogenesis of the condition.

Aims

To identify, appraise and summarise volumetric MRI studies of brain regions comparing bipolar disorder with an unrelated control group and individuals with schizophrenia.

Method

A systematic review and random-effects meta-analysis was carried out to identify key areas of structural abnormality in bipolar disorder and whether the pattern of affected areas separated bipolar disorder from schizophrenia. Significant heterogeneity was explored using meta-regression.

Results

Participants with bipolar disorder are characterised by whole

brain and prefrontal lobe volume reductions, and also by increases in the volume of the globus pallidus and lateral ventricles. In comparison with schizophrenia, bipolar disorder is associated with smaller lateral ventricular volume and enlarged amygdala volume. Heterogeneity was widespread and could be partly explained by clinical variables and year of publication, but generally not by differences in image acquisition.

Conclusions

There appear to be robust changes in brain volume in bipolar disorder compared with healthy volunteers, although most changes do not seem to be diagnostically specific. Age and duration of illness appear to be key issues in determining the magnitude of observed effect sizes.

Declaration of interest

None.

Great interest has been focused on studying brain structure in individuals with bipolar disorder and schizophrenia. Several neuroimaging studies have been published, but there is still uncertainty about the key areas involved in the pathogenesis of these conditions. Meta-analysis as a technique is a tool to combine quantitative data from individual studies, increasing power to detect anatomical differences and investigate causes of heterogeneity.^{1,2}

In schizophrenia and bipolar disorder meta-analyses of volumetric magnetic resonance imaging (MRI) studies have indicated that differences exist between affected individuals and healthy controls. In schizophrenia, meta-analyses have found evidence of reductions in the volumes of thalamus, hippocampus, anterior cingulate cortex^{3–5} and in the area of the corpus callosum.^{6,7} Wright *et al* broadly replicated the above findings but also showed reductions in cerebral volume with an enlarged ventricular system, particularly lateral ventricles.² A more recent voxel-based meta-analysis also showed similar volumetric reductions in schizophrenia.⁸ In bipolar disorder, mild ventricular enlargement and the presence of white matter hyper-intensities^{9,10} are among the most consistently reported abnormalities. Kempton *et al* also reported larger lateral and third ventricles and smaller hippocampi in individuals with schizophrenia compared with those with bipolar disorder. Kempton *et al* considered a limited number of confounders and lithium prescribing was also associated with volumetric grey matter increases in bipolar disorder.¹⁰

In this meta-analysis we sought to update the work carried out by McDonald *et al* (2004)⁹ by focusing only on MRI studies. We extended our search strategy to: systematically include studies comparing people with bipolar disorder with those with schizophrenia apart from controls in an attempt to identify diagnosis-specific differences; and sought to quantify and explain between-study heterogeneity using meta-regression

to examine the influence of key clinical and methodological variables.

Method

Search strategy

A systematic search was conducted from a range of electronic databases, including The Cochrane Library, EMBASE, PsycINFO, OVID and PubMed and complemented by a manual search with bibliographic cross-referencing. Key words used to identify the studies were: magnetic resonance imaging, MRI, bipolar disorder, mania, mood disorders and schizophrenia. Studies were included if they presented original data and were published by March 2008, compared individuals with schizophrenia, bipolar disorder and/or healthy controls, reported volumetric measures of brain areas according to the international system of units (SI units) as means and standard deviations. If standard deviations were missing from the published articles, these were conservatively estimated from the largest standard deviation of other studies that measured the same structure in the same volumetric units. Studies that included participants with unipolar depression were included provided participants with bipolar disorder made up more than 79% of the sample. Researchers were contacted if this information was not readily available. Studies were excluded if data were subsumed in more recent larger studies. Information systematically extracted from the studies included diagnosis according to diagnostic criteria, volumetric measurements and number of participants essential to calculate effect sizes, but also a number of potentially critical confounding variables. These included demographics (age, gender), illness variables (age at onset, duration of illness, presence of euthymia, medication, chronicity of the condition), year of publication, magnetic field strength of the scanner and slice

thickness. Conference abstracts and letters were included only if there were no other publications from the same study that had been published in full as peer reviewed articles. Where a single study was published in several journal articles, the article reporting the largest group size for that volume of interest was used. When multiple publications were identified, disagreement was resolved by consensus between the authors. Studies were excluded when there was a comorbid diagnosis of intellectual disability, chromosomal or genetic disorder. Studies were included irrespective of slice thickness, although these factors were recorded as potential sources of heterogeneity. Studies were not included when the control group were genetically related to affected probands.

Statistical analysis

Statistical analysis was conducted using STATA 8.0 for Windows (Stata Corp, College Station, Texas) supplemented by Metan software (www.stata.com/stb/stb44/sbe24/metan.hlp; downloadable from the Centre for Statistics in Medicine, Oxford, UK). Standardised mean differences were calculated using Cohen's *d* statistic.

Random effects analyses¹¹ were used throughout to weight each study. The presence of heterogeneity was tested using the Q-test and its magnitude estimated using I^2 and can be interpreted as the proportion of variance in effect size due to heterogeneity.¹² When the Q-test was significant, we used a Galbraith plot to identify those studies contributing the greatest amount to that heterogeneity, in order to investigate potential causes. Publication bias, which describes the tendency of small studies to report large effect sizes, was examined using the Egger's test.¹³ The significance level was set at $P < 0.05$.

To further investigate causes for heterogeneity, meta-regression analyses were performed for the following variables: age at onset, duration of illness, presence of euthymia, chronicity, mean age, scanner strength, slice thickness, year of publication, and current medication, including mood stabilisers, antipsychotics and antidepressants. The STATA program 'metareg.ado' was used throughout and the REML (restricted maximum likelihood) method used to estimate the model parameters.

Results

Systematic search

Seventy-two reports^{14–85} from 180 studies identified met criteria for inclusion in the meta-analysis and are described in detail in online Table DS1. Sixty-five compared people with bipolar disorder with controls. Of these 65, 18 articles included a further comparison group of individuals diagnosed with schizophrenia,^{15,16,36,46,49,52–54,56,58,59,65,68,75,80–82,85} one article added a third comparison group, of schizoaffective disorder⁸³ and one compared with schizoaffective disorder but not with schizophrenia.⁴⁵ Only two reports compared bipolar disorder with schizophrenia without the comparator of healthy controls.^{44,66}

Thirty-six reports did not meet inclusion criteria mainly because authors used alternative or qualitative measurements of brain areas, reports were superseded by subsequent inclusive publications, volumes were not retrievable or there were fewer than three studies available for a given brain region. Years of publication ranged from 1990 to 2008. Studies were exclusively published in English. Studies used comparable diagnostic criteria and tested a total of 1823 participants with bipolar disorder, 670 with schizophrenia, 29 with schizoaffective disorder, 106 with unipolar depression (not included in the analysis) and 1940

healthy controls. This number includes duplicate publications investigating different brain regions. Same samples were considered only once in each individual analysis.

Studies generally considered individuals with recurrent episodes of illness who were treated with one or more mood stabilisers. Basic demographic characteristics were generally well reported but clinical details such as medication status, number of episodes, duration of illness, age at first presentation and illness subtype were not. Most studies included male and female participants but only a few offered separated analyses according to gender. There were 926 male participants with bipolar disorder, equivalent to 51% of the total sample. Age ranged from 10.6 to 58.8 years with a mean of 29.4 (s.d. = 11.8).

Bipolar disorder in comparison with healthy controls

Comparisons of regional brain volumes between people with bipolar disorder and healthy controls are described in detail in online Table DS2. There was a small but significant reduction in whole brain volume in bipolar disorder ($n = 661$) compared with healthy controls ($n = 723$) with an estimated standardised effect size of -0.15 (95% CI -0.27 to -0.02) and without significant heterogeneity ($I^2 = 0.23$, $P = 0.15$) or publication bias (Egger's $P = 0.9$). Left and right lateral ventricles were significantly enlarged in bipolar disorder ($n = 157$, healthy controls $n = 179$) with an effect size estimate of 0.27 (95% CI 0.05 – 0.49) with no heterogeneity ($I^2 = 0$, $P = 0.7$) or publication bias (Egger's $P = 0.07$). A larger number of studies ($n = 11$) measured lateral ventricles separately, suggesting a significant contribution of the left but not the right lateral ventricle, with no significant heterogeneity or publication bias. An analysis of five studies that measured the volume of the globus pallidus bilaterally ($n = 135$, healthy controls $n = 106$) showed a significantly increased volume in participants with bipolar disorder (estimate 0.57 , 95% CI 0.03 – 1.11) with a significant level of heterogeneity ($I^2 = 0.74$, $P = 0.004$) and publication bias (Egger's $P = 0.02$). This effect was not evident in the analysis of the three studies which measured the volume of the left and right globi pallidi separately (Table DS2).

Bipolar disorder in comparison with schizophrenia

Table DS2 shows that in comparison with schizophrenia, people with bipolar disorder showed an increased right amygdala volume ($n = 115$ v. $n = 200$), effect size estimate 0.47 , 95% CI 0.21 – 0.73 , $I^2 = 0$, Egger's $P = 0.59$. Lateral ventricles in bipolar disorder appeared bilaterally smaller than in schizophrenia ($n = 126$ v. $n = 158$). The effect size estimate for the left lateral ventricle was: -0.35 , 95% CI -0.59 to -0.11 , $I^2 = 0.007$, Egger's $P = 0.11$; for right lateral ventricle it was: -0.26 , 95% CI -0.49 to -0.02 , $I^2 = 0$; Egger's $P = 0.06$. This effect was not present in the analysis of the three studies that measured the cumulative volume of left and right lateral ventricles (Table DS2).

Heterogeneity and publication bias

Heterogeneity and publication bias were not detected in structures that showed significant volumetric differences, except for whole brain grey matter and globus pallidus in the comparison of bipolar participants with healthy controls. Heterogeneity was, however, detected in a larger number of structures (as shown in Table DS2) and it is likely that methodological differences and clinical sample variation (including the effect of medication) are accountable for such an effect. With the limitation of selective reporting of relevant

Table 1 Meta-regression analyses of the effect of illness characteristics and demographic variables on volumetric differences of brain structures that showed statistically significant levels of heterogeneity. ^a Results are expressed as regression coefficient (C), Z-statistic and P

| Structure | Mean age, years | | | Duration of illness, years | | | Euthymia | | | Age at onset, years | | | Chronicity | | | Male participants | | |
|--|-----------------|-------------|----------------|----------------------------|-------------|--------------|-------------|-------------|--------------|---------------------|-------------|--------------|------------|------|-------------|-------------------|--------------|---|
| | C | Z | P | C | Z | P | C | Z | P | C | Z | P | C | Z | P | C | Z | P |
| Bipolar disorder in comparison with healthy controls | | | | | | | | | | | | | | | | | | |
| Whole brain (grey matter) | 0.0045 | 0.21 | 0.83 | 0.09 | 2.38 | 0.02 | 0.66 | 1.08 | 0.28 | -0.23 | -1.29 | 0.2 | NA | NA | -1.19 | -1.49 | 0.14 | |
| Amygdalae | 0.033 | 1.42 | 0.16 | 0.05 | 1.04 | 0.30 | 0.17 | 0.20 | 0.84 | 0.006 | 1.13 | 0.26 | NA | NA | 2.16 | 1.64 | 0.1 | |
| Left amygdala | 0.032 | 1.91 | 0.056 | 0.08 | 2.21 | 0.03 | -0.01 | -0.02 | 0.98 | 0.022 | 0.74 | 0.46 | 0.04 | 0.07 | 0.08 | 0.03 | 1 | |
| Right amygdala | 0.025 | 1.49 | 0.14 | 0.06 | 1.07 | 0.30 | -0.16 | -0.30 | 0.76 | 0.02 | 0.38 | 0.7 | 0.11 | 0.21 | -1.32 | -0.53 | 0.6 | |
| Hippocampi | -0.017 | -1.53 | 0.13 | 0.024 | 0.75 | 0.45 | 0.66 | 1.53 | 0.13 | 0.063 | 2.96 | 0.003 | 0.12 | 0.32 | 0.63 | 0.65 | 0.51 | |
| Globi pallidi | 0.022 | 0.64 | 0.52 | 0.15 | 0.91 | 0.36 | -0.76 | -0.80 | 0.42 | 0.02 | 0.67 | 0.5 | NA | NA | 6.23 | 1.55 | 0.12 | |
| Right globus pallidus | -0.05 | -1.16 | 0.25 | -0.08 | -2.39 | 0.02 | -2.07 | -2.76 | 0.006 | NA | NA | NA | NA | NA | 6.85 | 1.08 | 0.28 | |
| Left anterior cingulate cortex | 0.13 | 1.58 | 0.12 | 0.028 | 0.83 | 0.41 | -8.82 | -1.66 | 0.1 | NA | NA | NA | NA | NA | -0.04 | -1.23 | 0.22 | |
| Thalami | 0.004 | 0.34 | 0.73 | 0.28 | 1.98 | 0.047 | -0.13 | -0.26 | 0.8 | NA | NA | NA | NA | NA | 2.0 | 1.21 | 0.228 | |
| Temporal lobes | 0.03 | 2.92 | 0.004 | 0.054 | 2.87 | 0.004 | 0.89 | 0.75 | 0.45 | NA | NA | 0.92 | NA | NA | 0.54 | 0.48 | 0.63 | |
| Left temporal lobe | 0.012 | 0.70 | 0.48 | 0.07 | 1.09 | 0.3 | -1.34 | -1.46 | 0.14 | -0.0071 | -0.09 | 0.92 | NA | NA | 0.74 | 0.97 | 0.33 | |
| Right temporal lobe | -0.012 | -0.66 | 0.51 | 0.076 | 2.22 | 0.03 | 0.83 | 0.50 | 0.62 | 0.091 | 1.04 | 0.3 | NA | NA | 0.90 | 1.12 | 0.3 | |
| Pituitary gland | -0.014 | -1.58 | 0.11 | NA | NA | NA | -1.09 | -1.65 | 0.1 | NA | NA | NA | NA | NA | -5.80 | -2.37 | 0.02 | |
| Bipolar disorder in comparison with schizophrenia | | | | | | | | | | | | | | | | | | |
| Intracranial volume | 0.072 | 0.97 | 0.33 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 2.66 | 1.32 | 0.19 | |
| Whole brain (white matter) | 0.15 | 1.64 | 0.1 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 1.94 | 2.55 | 0.011 | |
| Left amygdala | 0.016 | 0.58 | 0.6 | NA | NA | NA | 0.98 | 2.10 | 0.035 | NA | NA | NA | NA | NA | 2.30 | 1.41 | 0.16 | |
| Left hippocampus | 0.043 | 4.29 | < 0.001 | NA | NA | NA | 1.62 | 3.43 | 0.001 | 0.043 | 1.28 | 0.2 | NA | NA | 1.3 | 0.97 | 0.33 | |
| Right hippocampus | 0.039 | 4.04 | < 0.001 | NA | NA | NA | 1.73 | 3.45 | 0.001 | 0.04 | 1.19 | 0.23 | NA | NA | 1.58 | 1.25 | 0.21 | |

NA, information not sufficiently available or varied to allow meta-regression analyses.
a. Results in bold are significant.

Table 2 Meta-regression analyses of the effect of medication, scanner strength and year of publication on volumetric differences of brain structures that showed statistically significant levels of heterogeneity. ^a Results are expressed as regression coefficient (C), Z-statistic and P

| Structure | Mood stabilisers | | | Antipsychotics | | | Antidepressants | | | Scanner strength, T | | | Slice thickness, mm | | | Year of publication, years | | |
|--|------------------|-------------|--------------|----------------|-------|--------------|-----------------|-------|--------------|---------------------|-------|------|---------------------|-------|-------------|----------------------------|-------|--------------|
| | C | Z | P | C | Z | P | C | Z | P | C | Z | P | C | Z | P | C | Z | P |
| Bipolar disorder in comparison with healthy controls | | | | | | | | | | | | | | | | | | |
| Whole brain (grey matter) | -0.40 | -0.41 | 0.68 | -1.13 | -2.46 | 0.014 | -0.93 | -1.28 | 0.2 | 0.22 | 0.98 | 0.32 | 0.006 | 0.05 | 1 | 0.005 | 0.13 | 0.9 |
| Amygdalae | 2.28 | 2.33 | 0.02 | -0.8 | -0.48 | 0.63 | -2.02 | -1.64 | 0.1 | -0.51 | -0.83 | 0.41 | -0.16 | -0.31 | 0.75 | -0.29 | -3.31 | 0.001 |
| Left amygdala | 0.19 | 0.14 | 0.89 | -0.63 | -1.26 | 0.21 | -1.2 | -1.83 | 0.067 | -0.4 | -0.98 | 0.33 | -0.04 | -0.43 | 0.70 | -0.03 | -0.71 | 0.50 |
| Right amygdala | -0.19 | -0.23 | 0.82 | -1.28 | -2.38 | 0.017 | -1.67 | -2.08 | 0.038 | -0.50 | -1.49 | 0.13 | 0.01 | 0.13 | 0.90 | -0.05 | -1.31 | 0.20 |
| Hippocampi | 0.98 | 1.31 | 0.19 | -1.05 | -1.85 | 0.065 | 0.18 | 0.20 | 0.84 | 0.21 | 0.53 | 0.60 | 0.03 | 0.11 | 0.91 | -0.06 | -0.72 | 0.50 |
| Globi pallidi | 2.32 | 2.70 | 0.007 | 0.67 | 0.58 | 0.56 | -0.46 | -0.44 | 0.66 | NA | NA | NA | -0.16 | -0.72 | 0.47 | 0.022 | 0.64 | 0.52 |
| Right globus pallidus | 3.22 | 2.72 | 0.007 | 1.48 | 1.30 | 0.19 | 2.3 | 0.40 | 0.69 | NA | NA | NA | -1.29 | -0.78 | 0.43 | -0.006 | -0.03 | 1.0 |
| Left anterior cingulate cortex | -7.91 | -9.93 | 0.35 | 0.25 | 0.04 | 0.97 | -2.59 | -0.69 | 0.49 | -3.28 | -0.47 | 0.64 | NA | NA | 0.33 | 0.42 | 0.70 | |
| Thalami | 1.27 | 1.08 | 0.28 | -0.86 | -1.82 | 0.069 | -0.77 | -1.23 | 0.22 | -0.07 | -0.21 | 0.83 | -0.46 | -2.38 | 0.02 | -0.15 | -2.92 | 0.003 |
| Temporal lobes | 2.23 | 2.69 | 0.007 | -1.62 | -1.06 | 0.3 | -1.48 | -0.73 | 0.46 | -0.29 | -0.61 | 0.54 | -0.07 | -0.29 | 0.8 | -0.11 | -1.59 | 0.11 |
| Left temporal lobe | -1.76 | -0.37 | 0.71 | NA | NA | NA | -0.32 | -0.37 | 0.71 | 0.09 | 0.29 | 0.77 | 0.012 | 0.25 | 0.81 | -0.044 | -1.71 | 0.09 |
| Right temporal lobe | -2.15 | -0.15 | 0.88 | NA | NA | NA | -0.39 | -0.15 | 0.88 | 0.24 | 0.74 | 0.5 | -0.053 | -1.03 | 0.3 | -0.044 | -1.55 | 0.12 |
| Pituitary gland | -1.58 | -0.98 | 0.32 | NA | NA | NA | NA | NA | NA | NA | NA | NA | -3.65 | -0.97 | 0.33 | 0.18 | 1.39 | 0.17 |
| Bipolar disorder in comparison with schizophrenia | | | | | | | | | | | | | | | | | | |
| Intracranial volume | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.16 | 0.54 | 0.6 |
| Whole brain (white matter) | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.016 | 0.58 | 0.56 | |
| Left amygdala | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.0076 | 0.009 | 0.93 | |
| Left hippocampus | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.44 | 0.69 | 0.49 | -0.34 | -1.63 | 0.1 | -0.024 | -0.58 | 0.56 |
| Right hippocampus | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.44 | 0.73 | 0.5 | -0.062 | -1 | 0.31 | -0.02 | -0.45 | 0.65 |

NA, information not sufficiently available or varied to allow meta-regression analyses.
a. Results in bold are significant.

variables across the included studies we systematically investigated causes of heterogeneity in multiple meta-regression analyses. The results are displayed in Tables 1 and 2 and the main findings described below.

Bipolar disorder in comparison with healthy controls

In the comparison between people with bipolar disorder and healthy controls significant heterogeneity was found for several regions. The effect size for whole grey matter volume correlated with duration of illness ($C=0.09$, $Z=2.38$, $P=0.02$) and use of antipsychotic medication ($C=-1.13$, $Z=-2.46$, $P=0.014$), suggesting larger bipolar *v.* control differences in people with longer durations of illness and larger reductions with use of antipsychotics, perhaps a proxy for a more severe illness. The differences in the right globus pallidus correlated with length of illness ($C=-0.08$, $Z=-2.39$, $P=0.02$), percentage of participants with euthymia ($C=-2.07$, $Z=-2.76$, $P=0.006$) and mood stabilisers ($C=3.22$, $Z=2.72$, $P=0.007$), suggesting smaller differences with increasing illness duration and euthymia and increased differences with the use of mood stabilisers. In the amygdalae, volumetric differences tended to increase with the use of mood stabilisers ($C=2.28$, $Z=2.33$, $P=0.02$) and to decrease with increasing year of publication ($C=-0.29$, $Z=-3.31$, $P=0.001$). In the left amygdala, volumes increased with duration of illness ($C=0.08$, $Z=2.21$, $P=0.03$). In the right amygdala, volumes decreased in relation to use of antipsychotic and antidepressant medication ($C=-1.28$, $Z=-2.38$, $P=0.017$ and $C=-1.67$, $Z=-2.08$, $P=0.038$ respectively). The hippocampi differences between participants with bipolar disorder and controls correlated positively with age at onset ($C=0.063$, $Z=2.96$, $P=0.003$), suggesting larger bipolar *v.* control hippocampal differences in individuals with a later age at onset. The effect size with respect to the thalami correlated negatively with year of publication ($C=-0.15$, $Z=-2.92$, $P=0.003$) and slice thickness ($C=-0.46$, $Z=-2.38$, $P=0.02$), and positively with duration of illness ($C=0.28$, $Z=1.98$, $P=0.047$). These findings suggest that the thalami may have been smaller in individuals with bipolar disorder in more recently published studies and in studies where larger voxel sizes were used. However, the observed non-significant reductions in participants with bipolar disorder may be less evident in those with longer durations of illness. Pituitary volumes were negatively associated with percentage of male participants ($C=-5.80$, $Z=-2.37$, $P=0.02$). Volumetric differences in the temporal lobes correlated positively with mean age ($C=0.03$, $Z=2.92$, $P=0.004$), duration of illness ($C=0.054$, $Z=2.87$, $P=0.004$) and use of mood stabilisers ($C=2.23$, $Z=2.69$, $P=0.007$). These results suggest smaller volumetric differences in this region in bipolar disorder with increasing age, duration of illness and the use of mood stabilisers. Duration of illness was positively associated with bipolar-control differences in right temporal lobe volume ($C=0.076$, $Z=2.22$, $P=0.03$).

Bipolar disorder in comparison with schizophrenia

In the bipolar disorder *v.* schizophrenia comparison, whole brain volume was positively associated with percentage of male participants ($C=1.94$, $Z=2.55$, $P=0.011$). Left amygdala volume was positively associated with number of participants with euthymia ($C=0.98$, $Z=2.10$, $P=0.035$). Volume differences in the left and right hippocampus were positively associated with age ($C=0.043$, $Z=4.29$, $P<0.001$ and $C=0.039$, $Z=4.04$, $P<0.001$ respectively) and number of participants with euthymia

($C=1.62$, $Z=3.43$, $P=0.001$ and $C=1.73$, $Z=3.45$, $P=0.001$ respectively).

Discussion

Findings from this report suggest that individuals with bipolar disorder in comparison with healthy controls are characterised by significant whole brain and prefrontal lobe reductions and by enlargement of the lateral ventricles and globus pallidus. These findings did not separate bipolar disorder from schizophrenia however, although schizophrenia was characterised by a greater degree of ventricular enlargement and by amygdala volume reduction.

The finding of a global brain volume reduction reported in this meta-analysis is a relatively novel one and is in keeping with a mild but significant increase in the volume of the lateral ventricles and sulcal prominence in mood disorders as demonstrated by Elkis *et al.*⁸⁶ The fact that two previous meta-analyses, by Hoge *et al.*⁸⁷ and McDonald *et al.*,⁹ which included 7 and 11 studies respectively did not find such a reduction suggests the presence of a small effect which might require a larger pool of studies ($n=25$, 661 patients and 723 controls) to allow detection. Our finding is supported by an absence of publication bias and lack of significant heterogeneity. Interestingly, we found that people with schizophrenia are characterised by a greater ventricular enlargement compared with those with bipolar disorder. Wright *et al.* reported decreased mean cerebral volume in participants with schizophrenia in comparison with controls and a concordant ventricular system enlargement particularly evident in the left lateral ventricle.² The significance of an enlarged lateral ventricular system in the pathophysiology of these two conditions and the more pronounced effect in schizophrenia could be attributable to a similar disease process with a different intensity or two separate processes with a similar outcome. Elkis *et al.* found a similar effect in their meta-analysis of 11 studies but extended inclusion criteria to more generic mood disorder rather than bipolar disorder and to the whole ventricular system.⁸⁶

No volumetric changes were detected in the amygdala in bipolar disorder compared with controls and this structure was significantly larger than in individuals with schizophrenia. Although current evidence indicates that the amygdala may be implicated in the aetiology and pathogenesis of unipolar depression, this role is not entirely established in bipolar disorder. In unipolar depression evidence from both structural and functional MRI studies suggests a possible volumetric reduction in the amygdala⁸⁸ mirrored functionally by a biased emotional response in the recognition of different emotional states, particularly fear.⁸⁹ With reference to bipolar disorder, the literature reports both increased^{16,37,78} and decreased volumetric changes in the amygdala, almost exclusively in adolescents with bipolar disorder.^{21,30} Although this discrepancy can be explained as an abnormal development trajectory in bipolar disorder,⁹⁰ it is also possible that other variables/and or confounders might play a role. Abnormal activation of the amygdala has been reported in several functional MRI (fMRI) studies of schizophrenia using fearful faces.^{91–93} Our findings extend previous reports that suggest a mechanistic role for the amygdala in schizophrenia, by suggesting that volumetric deficits may be disease specific.⁹⁴

Consistent with our finding of globus pallidus enlargement, several strands of evidence suggest that the basal ganglia are implicated in the aetiology of mood dysregulation in bipolar disorder.⁹⁵ Caligiuri *et al.*, by using a motor reaction time task, showed that individuals with euthymia or hypomania exhibited

increased caudate activity bilaterally and in the left globus pallidus whereas an increase in severity of depression was associated with a decrease in activity in the external segment of the right globus pallidus.⁹⁶ In an earlier study with a similar design, the same group found that either people with mania or depression exhibited abnormally elevated blood oxygen level-dependent (BOLD) responses in cortical and subcortical areas. Individuals with mania and bipolar disorder had significantly higher BOLD responses in the left globus pallidus and significantly lower BOLD responses in the right globus pallidus compared with people with depression and bipolar disorder.⁹⁷ Malhi *et al* (2004) in an fMRI experiment also found that people with bipolar disorder in the depressed phase shown pictures designed to evoke affective change recruited prefrontal and anterior cingulate cortices and additional subcortical limbic systems when compared with healthy individuals, in particular in the amygdala, thalamus, hypothalamus and medial globus pallidus. Patients and comparison participants displayed differential sensitivity to affective change with negative and positive affect induction producing converse patterns of activation.⁹⁸

The finding of increased volumes in the globus pallidus is in keeping with several reports suggesting that antipsychotic drugs affect this structure, although this result was not confirmed in the left and right analysis of the structure, and the presence of publication bias and statistically significant unexplained heterogeneity limits the validity of results. Whether these changes are related to alterations in gamma-aminobutyric acid (GABA)/dopamine neurotransmission or possibly the result of artefacts in the presence of ventricular enlargement will require further investigation.

In agreement with Kempton *et al*'s meta-analysis,¹⁰ in the bipolar disorder *v.* healthy controls comparison we found evidence of lateral ventricular enlargement in the absence of heterogeneity or publication bias. We also found evidence of whole brain and prefrontal lobe volume reductions, and globus pallidus volumetric increase. Similarly, in comparison with schizophrenia, bipolar disorder was associated with smaller lateral ventricular volume and enlarged amygdala volume. Our analysis did not confirm volumetric differences affecting the third ventricle or the hippocampi. Extensive meta-regression analyses confirmed the effect of mood stabilisers and other pharmacological compounds such as antipsychotics and antidepressants on morphometric differences. Finally several clinical and demographic variables exercise an effect on brain volumes. It is likely that the ability of meta-regression analyses to detect small differences is relatively limited. This observation, together with a different methodology can explain discrepancies in findings, although this meta-analysis largely confirms Kempton *et al*'s findings.¹⁰

Some of the analyses reveal modest effect sizes. Whether these are clinically significant or scientifically important is, however, difficult to judge, as a very small change in the volume of a particular structure may have significant effects on behaviour. There is evidence of significant heterogeneity in several analyses. We predicted this would be the case and used random effects analyses that take heterogeneity into account when calculating all summary effect sizes. The effect of heterogeneity is to reduce the precision of the summary effect sizes and in general this reduces the significance of any findings. We have gone to considerable lengths to investigate this heterogeneity using meta-regression that we think has provided some much needed clarification for the considerable inconsistency in the published literature. Although this meta-analysis is limited by an inconsistency in the published literature, heterogeneity can provide important aetiological and methodological insights that

can guide future research. We found several effect size associations with a number of both methodological and clinical variables (e.g. course/phase of bipolar disorder, medication status and treatment modalities) that should be borne in mind when designing future studies.

Another further potential limitation is the lack of studies that included a longitudinal perspective, such that it is difficult to exclude the possibility that the observed brain changes occur as a consequence of illness or its treatment. More neuroimaging studies with a longitudinal perspective could help clarify the natural evolution of brain abnormalities. Moorhead *et al* for instance found that people with bipolar disorder tend to lose hippocampal, fusiform and cerebellar grey matter at an accelerated rate compared with healthy controls and that tissue loss is associated with deterioration in cognitive function and illness course.⁹⁹ Further understanding could also emerge from clear reporting of clinical variables such as duration of illness, age at onset and number of previous episodes. Finally, the selective reporting and publication of positive results is a further potential limitation to all meta-analyses. Although this limitation cannot be definitively excluded, we found evidence of publication bias only in a very limited number of structures.

In summary, we found that bipolar disorder is associated with global and prefrontal volumetric brain reductions, enlarged lateral ventricles and an enlarged globus pallidus. Compared with individuals with schizophrenia, people with bipolar disorder presented with a reduced right amygdala volume and smaller lateral ventricles.

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Why I chose psychiatry

Ian Rowbotham

Part one – In the Beginning

'Most of you will become GPs', said the smooth lecturer, himself a consultant, a word which once meant Great Beast of the Swamplands. But gene dilution diminished its potency; thus it begat consultant nurse, consultant physiotherapist, consultant (car sales) and consultant hospital cardiac specialist (drug rep.), consultant accountant (turf) and subspecies too numerous and complicated to spell.

With DNA weakened, having neither Awayday awareness certificate nor distance learning MSc to protect against the approaching cataclysm, they were hit hardest. General practitioner (*prosapiamedicus*), no longer 'slacker' and 'also ran', walked over the Earth, terrorising governments. These intelligent, well-adjusted creatures mated early, saw their progeny grow up and drank in the bounteous new dawn.

The old, lumbering predators grew scarce, further handicapped by the twin eruptions of 'Emmehsi' and 'Emtasse' in 2007. Their descendants ran amok panicking, stricken by shortages, blinded by fallout, even charging round on 7-hour ward rounds at night and weekends, as their dominion shrivelled and the more nimble-footed opt-out doctors (*Cotidieopus*) joined the ascendancy.

Part two – Apres le Déluge (moi)

A mature student of mature years, I had watched in wonderment from the first rumblings of Tomorrow's Doctors. I had seen two great eras: Surgery and Medicine. Next came the Paediatrics and the Age of Endocrinement, then, as a meteor paints the sky with its single daub of brilliance, Psychiatry. Seven weeks of revelation followed. I could understand its language, follow the puzzling, yet attractive logic and uncertainty; there were also many people. The full tide of human existence was not, as Samuel Johnson put it, at Charing Cross but right here in the vortex of my medical school career. These were not bags of symptoms to be diagnosed, treated and pressure-hosed through the rotating door of MAU, but human lives; part of the joyful, tragic, brutal, desperate web of experience.

Our course organiser, and head of year, made sure Psychiatry formed a good chunk of exams (wake up!). We visited a secure hospital, attended interactive lectures and clinics, saw child, liaison, eating disorders and drug and alcohol psychiatry culminating with a forensic flourish in a mock murder trial.

Part three – flying solo

FY1 colleagues asked, 'What did you do before medicine?' (I made musical noises on a piece of wood) and, 'Are you going to do General Practice? (I'll do anything, make the tea). But was I a GP? It was an obvious choice, but Psychiatry's small flame persisted, illuminating the hallways and passages of my mind.

Psychiatry at FY2 (getting serious) was another positive experience. Then came Orthopaedics (deeply enjoyed but never intended as a career). I set 4 months to decide, but the Damascene moment came during the second week, when I was asked to review a frail elderly man, debilitated with Parkinson's disease, who had been given a new hip. He had become agitated 3 days post op and had 'punched' the physiotherapist (how?) and 'throttled' a nurse (serious cricoid trauma was, fortunately, avoided). What I subsequently found may have decided my choice of career. Clearly frightened, he believed patients were being systematically murdered (they were being discharged), addressed me as Dr Death (justifiable given my spirited drilling technique) and claimed police were outside to interview me about the killings. He was plainly terrified and, after further investigation, plainly psychotic. Owing to his severe Parkinson's, I prescribed Quetiapine 25 mg, had a further rootle through his notes and found he was already on it, a fact recorded in the A&E admitting notes but never entered on his chart. A simple mistake was corrected and this man was allowed freedom from his demons. Psychiatry's die was, if not fully set, cast.

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