An MRI study of amygdala in schizophrenia and psychotic bipolar disorder

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ABSTRACT

Meta-analyses report larger amygdala in subjects with bipolar disorder compared to schizophrenia. However, few studies have compared the size of amygdala in psychotic bipolar disorder with schizophrenia. Here we examine size of amygdala in a sample of 36 patients with psychotic bipolar disorder, 31 patients with schizophrenia and 27 healthy comparison subjects. Patients with schizophrenia had smaller amygdala compared with patients with psychotic bipolar disorder (p=0.014). These results suggest that change in volume of amygdala may represent a morphologic feature distinguishing psychotic bipolar disorder from schizophrenia.

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1. Introduction

Epidemiologic and genetic studies suggest a shared susceptibility to bipolar disorder and schizophrenia (Craddock and Owen, 2010). Of interest is whether there are also common neuroanatomical changes associated with these disorders. The amygdala has been of particular interest as it plays a role in emotion. Stimulation of amygdala in humans evokes emotions as well as complex hallucinations (Gloor et al., 1981, 1982). Several structural magnetic resonance imaging (MRI) studies have compared morphometry of amygdala in schizophrenia and bipolar disorder, yielding conflicting results (Swayze et al., 1992; Pearlson et al., 1997; Altshuler et al., 1998; Altshuler et al., 2000; Brown et al., 2011). Recently, several meta-analyses have reported enlarged amygdala in bipolar disorder as compared to schizophrenia (Arnone et al., 2009; Ellison-Wright and Bullmore, 2010; Yu et al., 2010). However, bipolar individuals in these samples have been heterogeneous for presence of psychotic features.

A potentially informative distinction can be made between subtypes of bipolar disorder presenting with and without psychosis. Psychotic bipolar disorder may be more similar to schizophrenia than to bipolar disorder without psychosis (Potash, 2006). Psychotic bipolar disorder and schizophrenia co-aggregate in families and identified candidate genes predispose to both disorders. In addition, the overall neuroanatomical features of psychotic bipolar disorder, rather than bipolar disorder without psychosis, may be more similar to what is seen in schizophrenia (Strasser et al., 2005). Frazier et al. (2008) were not able to detect an overall difference in volume of amygdala in early-onset psychotic bipolar disorder and early-onset schizophrenia. However, they did find a sex-specific effect where a larger left amygdala volume was seen in bipolar males as compared to males with schizophrenia or controls and the difference was more pronounced in bipolar disorder without psychosis than in bipolar disorder with psychosis. In a study of first-episode psychosis subjects with psychotic affective disorders were observed to have a larger right amygdala than subjects with schizophrenia (Velakoulis et al., 2006). In order to shed light on this issue, we assessed whether size of amygdala differed between subjects with psychotic bipolar disorder, schizophrenia and healthy comparison subjects.

2. Methods

2.1. Subjects

Ninety-four subjects were selected from schizophrenia and bipolar disorder studies at the Division of Psychiatric Neuroimaging at Johns Hopkins University School of Medicine. The subjects were classified into three groups for neuroanatomical comparison, subjects with schizophrenia, psychotic bipolar disorder, and healthy comparison subjects. Subjects were matched such that distributions on the variables age and sex were similar across the three study groups. Healthy comparison subjects were screened for presence of mental illness using two instruments, either the MINI (Sheehan et al., 1998) and DIGS (Nurnberger et al., 1994) or the SCAN (Wing et al., 1990) and CIDI-SF (Kessler et al., 1998). Consensus diagnosis of bipolar disorder or schizophrenia was determined by a research psychiatrist and

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a research assistant using a semi-structured interview and two in-
struments, either the DIGS and MINI or SCAN and CIDI-SF. All bipolar
disorder patients had at least one episode of psychotic symptoms,
such as hallucinations or delusions in the context of an affective epi-
sode (manic or depression) in clear consciousness. All subjects with
bipolar disorder or schizophrenia were medicated. None of the sub-
jects with schizophrenia was on mood stabilizers. Potential participants
with either a lifetime history of substance dependence or current sub-
stance abuse were excluded from the study. All subjects were right-
handed (Annett, 1970). Socioeconomic status was assessed using the
Hollingshead Scale (Hollingshead, 1975).

2.2. MRI

Prior to MRI scanning, all subjects gave informed consent after the
risks and benefits of participation were explained to them. T1 weight-
ed 3D volumes were acquired using a 1.5 T Philips MR system and
MPRAGE sequence (repetition time = 13.40 ms, echo time = 4.60 ms,
flip angle = 20°, number of acquisition = 1, matrix 256 × 256), with
1-mm3 isotropic resolution across the entire cranium. Skull stripping
was performed and total intracranial volume (ICV) was calculated in
Freesurfer 3.05 (Segonne et al., 2004). Semi-automated segmentation
of amygdala was performed in MRStudio software (Jiang et al., 2006),
utilizing the LDDMM algorithm (Oishi et al., 2009) and the JHU-MNI-
SS Type II atlas (www.mristudio.org). All segmentations were manually
checked for accuracy and rerun if errors were detected. All segmenta-
tion procedures were conducted by study personnel blind to diagnosis.

2.3. Statistical analysis

Comparisons of demographic and clinical characteristics across study
groups were conducted using F-tests or t-tests for continuous variables
and x2-tests for categorical variables. Diagnostic differences among
the three groups (psychotic bipolar disorder, schizophrenia, healthy com-
parison subjects) for mean volume of amygdala were evaluated using
linear mixed models with repeated measures in SPSS 19 (2010). Amyg-
dala volume was the dependent variable and hemisphere was the re-
peated measure. Diagnostic category and sex were factors in the model
and age and total intracranial volume were included in the model as cov-
ariates. Years of education and socioeconomic status did not contribute
significantly and were not included in the final model. We first tested a
factorial model, however none of the interaction terms were statistically
significant (p > 0.1) and they did not contribute to the model. Thus, our
final model included main effects only. Post hoc comparisons of the ad-
justed means across diagnostic groups were performed using t-tests
and were Bonferroni-adjusted for multiple comparisons.

3. Results

The patient and comparison groups were not significantly different
in age, sex or total ICV (see Tables 1 and 2). Additionally, the schizo-
phrenia patient and bipolar patient groups did not differ significantly
in their duration of illness. Patients with schizophrenia had fewer
years of education on average than patients with psychotic bipolar dis-
order (t = −3.55, p = 0.0007). Conversely, patients with psychotic bipol-
ar disorder had lower mean socioeconomic status than either patients
with schizophrenia (t = 2.53, p = 0.0139) or healthy comparison sub-
jects (t = 2.26, p = 0.0270). Independent of diagnosis, a significant sex
difference was observed in amygdala bilaterally, with females having sig-
ificantly smaller volumes than males (p_{left} = 0.009, p_{right} = 0.018).
There was significant laterality of amygdala shown by repeated mea-
sures analysis, with left amygdala larger than right amygdala on average
(adjusted mean difference = 118.1 mm3, s.e. = 15.0, p < 0.001).

The unadjusted mean volume of amygdala by study group is pre-
sented in Table 2. We detected a significant main effect of diagnosis
on size of amygdala (see Fig. 1; F_{2,170} = 4.38, p = 0.014). There was

\[
\begin{array}{l|c|c|c|c|c|c|l}
\text{Characteristic} & \text{Psychotic bipolar disorder} & \text{Schizophrenia} & \text{Healthy comparison} & \text{Statistical test, p-value} \\
\text{patients (n = 36)} & \text{patients (n = 31)} & \text{subjects (n = 27)} & & \\
\hline
\text{Age, years} & 39.9 (11.1) & 41.4 (9.5) & 44.0 (15.6) & F = 0.93, p = 0.400 & \hline
\text{Males (%)} & 52.8 & 54.8 & 44.4 & x^2 = 0.09, p = 0.707 & \\
\text{Education level, years} & 14.6 (2.5) & 12.5 (2.2) & 13.7 (2.6) & F = 5.61, p = 0.005 & \\
\text{Socioeconomic status} & 3.2 (1.0) & 3.9 (1.2) & 3.8 (1.0) & F = 4.10, p = 0.020 & \\
\text{Duration of illness, years} & 17.6 (12.7) & 19.3 (11.0) & NA & t_{30} = 0.54, p = 0.593 & \\
\end{array}
\]

Abbreviations: NA, not applicable.
\(^a\) Data are given as mean (SD) except where noted.

no evidence of a sex-by-diagnosis or hemisphere-by-diagnosis interac-
tion. Pairwise comparisons showed that subjects with schizophrenia
had significantly smaller amygdala than subjects with psychotic bipolar
disorder (adjusted mean difference = 51.4 mm3, s.e. = 18.0, adjusted
p = 0.014). We detected a trend of smaller amygdala in the schizophre-
nia group as compared to the healthy control group (adjusted mean dif-
ference = 42.3 mm3, s.e. = 19.6, adjusted p = 0.096). There was no
difference in size of amygdala between the psychotic bipolar disorder and
healthy comparison groups (adjusted mean difference = 9.1 mm3,
s.e. = 18.2, adjusted p = 1.0).

4. Discussion

This study expands upon previous work comparing volume of
amygdala in patients with bipolar disorder and schizophrenia. In this
context, studying psychotic bipolar disorder is of special interest as it
has symptomatic overlap with schizophrenia (Coryell et al., 2001) as
well as potentially a shared genetic etiology (Potash et al., 2003). We
examined whether volume of amygdala was different or similar in psy-
chotic bipolar disorder and schizophrenia.

Our finding of a significant effect of diagnosis on size of amygdala
is consistent with previous studies. Specifically, we found that amygd-
ala was smaller in our schizophrenia group than in the psychotic bio-
polar disorder group. Velakoulis et al. (2006) found that first-episode
psychosis subjects with schizophrenia had larger right amygdala than
subjects with first-episode psychotic affective disorders. Frazier et al.
(2008) reported a sex-specific effect where a smaller left amygdala
volume was seen in males with first-episode schizophrenia as com-
pared to males with first-episode bipolar disorder and the difference
was more pronounced in bipolar disorder without psychosis than in
bipolar disorder with psychosis. Differences in methodology used con-
tribute to the difficulty in directly comparing our results to previous
studies. Importantly, the definition of phenotype used and the delinea-
tion of the boundaries of amygdala differed across studies. Velakoulis
et al. (2006) examined morphological differences between first-episode
schizophrenia and first-episode psychotic affective disorders, not

\[\text{Mean volume, cm}^3 (SD)\]

<table>
<thead>
<tr>
<th>Group</th>
<th>Psychotic bipolar patients (n = 36)</th>
<th>Schizophrenia patients (n = 31)</th>
<th>Healthy comparison subjects (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total intracranial volume (^a)</td>
<td>1398.1 (150.7)</td>
<td>1326.5 (166.0)</td>
<td>1396.6 (132.6)</td>
</tr>
<tr>
<td>Amygdala, total (^b)</td>
<td>2.07 (0.29)</td>
<td>1.91 (0.24)</td>
<td>2.05 (0.29)</td>
</tr>
<tr>
<td>Left</td>
<td>1.10 (0.16)</td>
<td>1.01 (0.14)</td>
<td>1.08 (0.16)</td>
</tr>
<tr>
<td>Right</td>
<td>0.97 (0.14)</td>
<td>0.90 (0.11)</td>
<td>0.96 (0.13)</td>
</tr>
</tbody>
</table>

\(^a\) Volumes are unadjusted.
\(^b\) F_{2,91} = 4.09, p = 0.13.
\(^c\) F_{2,31} = 4.38, p = 0.01.
limited to bipolar disorder. In contrast, Frazier et al. (2008) limited their analysis to the early-onset forms of schizophrenia, bipolar disorder with psychosis and bipolar disorder without psychosis. In our study, we compared patients with schizophrenia to those with psychotic bipolar disorder. For segmentation of amygdala, we utilized a semi-automated method based on the JHU-MNI-SS Type II atlas boundaries, while other studies utilized the method of Convent et al. (1999) or Filipek et al. (1994).

We also observed that females had smaller amygdala bilaterally than males, independent of diagnosis. Evidence of a sex effect on volume of amygdala from previous studies is conflicting. Some studies have found that the volume of the amygdala was smaller in women compared with men after controlling for ICV (Goldstein et al., 2001; Fjell et al., 2009), while other studies have not (Pruessner et al., 2000; Gur et al., 2002; Kim et al., 2012). Larger amygdala in men than in women may underlie well established sex differences in emotional regulation (Gur et al., 2002).

A limitation of the current study is that we did not have available a bipolar without psychosis group and so we were not able to make any comparisons to this group. Also, we did not have available information about potential confounders such as global cognitive ability. Further studies including a bipolar without psychosis comparison group and assessing additional potential confounding variables would shed further light on the relationship between psychosis and amygdala size.

Patients with bipolar disorder and schizophrenia are necessarily treated with different classes of medications. Notably, patients with bipolar disorder are commonly treated with mood stabilizers such as lithium, which has been shown to increase volume of amygdala over time (Lyoo et al., 2010). Many of our bipolar patients were treated with lithium, while none of the patients with schizophrenia were taking mood stabilizers. Antipsychotics, a standard treatment for schizophrenia, have not been shown to affect size of amygdala (Szeszko et al., 2003; Velakoulis et al., 2006). Thus, we cannot rule out the possibility that the larger amygdala in psychotic bipolar disorder may be a treatment effect rather than a disease effect. However, there are important clinical implications to either of these explanations. In the case of a disease effect, these data suggest further studies in which the disease state is better characterized than in our study. In the case of a treatment effect, these results are consistent with previous studies suggesting the possibility that treatment with lithium might lead to neurotrophic or neuroprotective effects (Bowley et al., 2002; Machado-Vieira et al., 2009). It will be important for future studies to attempt to disentangle potential medication effects from effects of disorder.

Taken together, these results suggest that change in volume of amygdala may represent a morphologic feature distinguishing bipolar disorder subjects from subjects with schizophrenia, even though psychotic symptoms can be found in both. Potential mechanisms whereby size of amygdala may change include response to chronic stress, response to medication, changes in intracellular fluid, changes in number or size of neurons and glia or changes in connective tissue (Altshuler et al., 2000; Vyas et al., 2002). While the nature of abnormalities of the amygdala in bipolar disorder and schizophrenia differ, this brain region might still be the locus of a partially shared pathophysiology between these disorders.

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Contributors
Dr. Mahon conceptualized the study, conducted analyses and drafted the manuscript. Ms. Eldridge, Crocker, Postell, Notes and Gindes aided in data analysis. Ms. King assisted with recruitment and data collection. Dr. Potash aided in interpretation of results and drafting the manuscript. Dr. Rathananther assisted in data analysis, interpretation and drafting the manuscript. Dr. Barta directed data collection and aided in conceptualization of the study, interpretation of the results and drafting the manuscript.

Conflict of interest
The authors declare no conflicts of interest.

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