Structural Brain Changes in Patients with Bipolar Disorder and Their Unaffected First Degree Relatives

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OBJECTIVE

- Bipolar disorder (BD) is a highly impairing mental illness which is associated with structural brain abnormalities.
- Metaanalytic studies revealed that structural changes in BD include lateral ventricle enlargement, increased rates of deep white matter hyperintensities, volumetric decrease in bilateral anterior cingulate cortex, inferior frontal cortex, insular cortex and volumetric increase in globus pallidus.
- Neuroanatomical abnormalities in BD may represent inherent risk factors or may emerge as a result of burden of illness, medication effects, or confounding conditions.
- Especially lithium is associated with volumetric increases in ventromedial prefrontal cortex, anterior cingulate cortex, limbic and paralimbic structures.
- Focusing on unaffected relatives may help to distinguish biological risk factors without the confounding effects of burden of illness or medication.
- Previous studies reported larger left insular cortex, inferior frontal gyrus; left caudate nucleus, left cerebellum volumes; smaller gray matter density in the left thalamus; smaller gray matter volumes in the left hippocampus and parahippocampal gyrus; and thicker right hippocampus in unaffected first-degree relatives of BD patients than in healthy controls.
- In this study, we hypothesized structural differences in euthymic BD patients, their unaffected first degree relatives (UAR) and healthy controls in order to identify a structural endophenotype for bipolar disorder using voxel based morphometry.

METHODS

- Euthymic patients with DSM IV bipolar disorder (N=27), their unaffected first degree relatives (UAR; N=24), and age- and sex- matched healthy controls with no personal or family history of psychopathology (N=22) were included in the study.
- BD patients were euthymic for at least 6 months and did not have any other Axis I psychiatric disorders.
- All participants underwent staining for 1.5T Philips Achieva MR scanner (Philips Medical Systems, Cleveland, OH).
- After standard preprocessing of T1-weighted 3D images (smoothing with a Gaussian Kernel of 12 mm FWHM), VBM analyses were performed using SPM8. Two sample T tests were used to search for gray matter differences between bipolar subjects and healthy controls, UAR and healthy controls, and bipolar subjects and UAR.

RESULTS

- Seventy-five percent of the UAR were siblings.
- Mean duration of euthymia for bipolar subjects was 23.7 (+7.9) months. Bipolar subjects had increased volume in left thalamus in comparison to controls (T=4.7, p<0.05, FWE corrected).
- Right inferior frontal gyrus volume was larger in both bipolar subjects and in UAR than in controls (p<0.001, unc.).
- Bipolar subjects had increased volume in bilateral thalamus, right anterior cingulate cortex, and left occipital cortex in comparison to controls (p<0.001, unc.).
- UAR had decreased volume in posterior cingulate cortex in comparison to controls (p<0.001, unc.).
- Bipolar subjects had increased volume in bilateral occipital cortex in comparison to UAR (p<0.001 unc.).

CONCLUSIONS

- Consistent with a recent replication-design study by Hajek et al. (2013), these findings suggest that larger right inferior frontal gyrus volume might be a potential candidate for structural endophenotype in bipolar disorder.
- Right inferior frontal cortex is involved in several tasks which are relevant to BD, including response inhibition, task set switching, memory and sustained attention. Impaired response inhibition is a neurocognitive endophenotype candidate for BD.
- Lithium treatment may also have potential neurotoxic effects on thimic and paralimbic regions in bipolar subjects.

SELECTED REFERENCES


Table 1. Demographic and clinical variables.

<table>
<thead>
<tr>
<th></th>
<th>BD patients (N=27)</th>
<th>UARs (N=24)</th>
<th>Controls (N=22)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>36.3(9.5)</td>
<td>32.1(11.3)</td>
<td>33.6(9.3)</td>
<td>F(2,77)=4.4, p=0.3</td>
</tr>
<tr>
<td>Gender (N, %)</td>
<td>20(76.9)</td>
<td>13(54)</td>
<td>16(72)</td>
<td>H=8.08, df=2, p=0.07</td>
</tr>
<tr>
<td>Years of education (mean, SD)</td>
<td>12.92(16.3)</td>
<td>9.15(3.3)</td>
<td>14.2(3.7)</td>
<td>F(2,77)=4.8, p=0.06</td>
</tr>
<tr>
<td>Age of onset (mean, SD)</td>
<td>36.1(7.9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of episodes</td>
<td>4.7(3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>Number of months unwell (mean, SD)</td>
<td>14.9(22.6)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Duration of euthymia (months, mean, SD)</td>
<td>23.7(15.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HAM-D score (mean, SD)</td>
<td>1.3(1.4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>YMRS score (mean, SD)</td>
<td>0.6(0.9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>Current lithium use (N, %)</td>
<td>18(67)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>Lithium use in the past (N, %)</td>
<td>6(22)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>Current antipsychotic use (N, %)</td>
<td>14(47)</td>
<td>-</td>
<td>-</td>
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</table>

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