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Voxel-based morphometry in affected and unaffected offspring of bipolar parents

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Purpose of the study: Little is known about which of the many neuroanatomical abnormalities found in patients with bipolar disorder (BD) meet criteria for endophenotype. Recent review of MRI studies conducted in individuals genetically at-risk for BD showed that abnormalities in gray matter (GM) volume represent potential candidate biological risk factors (endophenotype) for BD. In order to test whether regional GM volumes represent an endophenotype for BD, we performed voxel-based morphometry (VBM) in unaffected and affected (with bipolar or unipolar disorder) offspring of bipolar patients.

Methods used: We included 20 unaffected, 15 affected offspring of bipolar parents and 18 healthy controls matched by sex and age. Participants were between 15 and 25 years old and were interviewed using Schedule for affective disorders and schizophrenia-lifetime version (SADS-L). MRI structural images were acquired using a 1.5-T Siemens scanner. VBM analyses were conducted using SPM5 package, executed in Matlab 7.3. Between-group statistical comparisons of mean GM volumes were performed with the general linear model with total whole-brain volume and age as covariates. Resulting statistics (F values) at each voxel were transformed to Z scores and displayed in a glass brain into standard MNI space at a threshold of $Z = 3.32$ and an extent threshold of 25 voxels. Statistical significance was set at $p < 0.001$, uncorrected for multiple comparisons and subsequently family-wise error (FWE) correction for multiple comparisons in regions emerging from whole-brain analyses was used ($p < 0.05$).

Summary of results: VBM analysis for all groups has shown significant differences in GM volume in the right cerebellar hemisphere ($F_{max} = 10.62$, $Z = 3.61$, uncorrected $p < 0.001$, $x = 30$, $y = -74$, $z = -56$, lower semilunar lobule, cluster size: 39 voxels) and the right parahippocampal gyrus ($F_{max} = 10.51$, $Z = 3.59$, uncorrected $p < 0.001$, $x = 20$, $y = -20$, $z = -34$, BA 28, cluster size: 32 voxels). In the subsequent comparisons between groups (unpaired t test) increased GM volume in unaffected offspring compared to controls in the same areas was detected (right cerebellar hemisphere: $t_{max} = 4.56$, $Z = 4.14$, uncorrected $p < 0.001$, $x = 30$, $y = -74$, $z = -56$, cluster size: 165 voxels; right parahippocampal gyrus: $t_{max} = 4.40$, $Z = 4.01$, uncorrected $p < 0.001$, $x = 20$, $y = -20$, $z = -34$, cluster size: 103 voxels). These findings, however, did not survive correction for multiple comparisons (FWE, $p > 0.05$). No significant differences in GM volumes were found in case of affected offspring.

Conclusions: We found an increased gray matter volume in the right cerebellar hemisphere and the right parahippocampal gyrus in unaffected offspring of bipolar parents compared to control subjects. These findings, however, did not survive correction for multiple comparisons and therefore we suppose that regional gray matter volumes did not meet criteria for endophenotype of bipolar disorder.

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