

## **Cortical Gray Matter Density Increases in Patients with Bipolar Disorder**

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### **Background:**

Structural neuroimaging studies of bipolar patients have revealed cortico-limbic abnormalities, which may be related to symptom severity (depression or mania) and illness duration. However, previous findings have been inconsistent. With advances in computational image analysis, differences in gray matter density (GMD) can be examined at high spatial resolution, localizing disease effects on cortical anatomy with increased statistical power. These mapping methods may better characterize neuroanatomic changes in bipolar disorder than standard volumetric measures. Here we report initial results applying these algorithms to map gray matter abnormalities over the entire cortical surface in bipolar patients.

### **Methods:**

High-resolution T1-weighted 3D MR images and cortical pattern matching methods were used to compare GMD between 28 bipolar subjects (mean age=36.1+/-10.5; 39% female) and 28 demographically group-matched controls (mean age=35.9+/-8.5; 46% female). Scans were rigidly aligned to the ICBM stereotaxic space and maps of gray matter, white matter and CSF were created. To better align anatomy across subjects, a cortical pattern matching technique used 72 sulcal landmarks traced on each subject's cortex to constrain the nonlinear mapping of one cortex onto another in 3D space. GMD, defined as the proportion of gray matter in a small region of fixed radius (15 mm) around each cortical point, was compared across subjects at 65,536 homologous cortical locations. Group differences in GMD were mapped onto the group average cortical surface, revealing localized patterns. To correct for multiple comparisons, significance was confirmed by performing permutation tests on the area of suprathreshold statistics in the cortical surface maps.

### **Results:**

Unexpectedly, GMD was significantly increased in bipolar patients in diffuse cortical areas (*Left hemisphere:  $p=0.025$ , Right hemisphere:  $p=0.007$ , corrected*). Effects of greatest magnitude were found in bilateral cingulate and inferior parietal cortices, and left ventromedial prefrontal cortex (Figure 1). No significant decreases in GMD compared to controls were observed in any cortical location. However, within the bipolar group, GMD was inversely correlated with depression severity, measured by the Hamilton Depression Rating Scale, in cingulate cortex and diffuse areas of heteromodal association cortex (Figure 2; *L hem.:  $p=0.04$ , R hem.:  $p=0.03$ , corrected*).

**Conclusions:**

These maps visualize the pattern of cortical alterations in bipolar disorder. Patients exhibited significantly increased GMD, particularly within the medial walls of the cerebral hemispheres. Most patients in this study were lithium-treated, so these increases may reflect neurotrophic effects. GMD increases may index absolute increases in cortical thickness, decreases in cortical curvature, regional reductions in sulcal CSF, or combinations of these factors. The observed association between GMD reduction and depression severity is consistent with prior cytoarchitectural and neurophysiologic findings in bipolar patients. Further examination of interactions between medication history, symptom severity, and neuroanatomic changes may yield valuable insights into the pathophysiology of bipolar disorder.