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**Title:** Gray matter thinning in frontal and anterior cingulate cortices is associated with course of illness in adults with bipolar type I disorder

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**Abstract:** **INTRODUCTION:** Several lines of evidence implicate abnormalities in the prefrontal cortex (PFC) in patients with bipolar (BP) disorder. Previous findings have varied however, perhaps because of the inclusion of patients treated with lithium, a medication that increases cortical gray matter volume (Moore et al., 2000; *Lancet*, 7:356). Past studies have also relied on traditional volumetric methods, which may be insensitive to subtle neuroanatomic changes. **METHODS:** 34 subjects with BP type I disorder (13f, 38.1±12.0yrs) and 32 healthy subjects (13f, 38.2±13.1yrs) were scanned on a 1.5T MRI scanner. 33% of patients were unmedicated and all were free from lithium. MRI data were processed to provide a measurement of cortical gray matter thickness (Thompson et al., 2004; *NeuroImage*, 23:S2-18), and cortical pattern matching methods were used to associate homologous brain regions across subjects (Thompson et al., 2000; *Hum. Br. Mapp.* 9:81-92). Spatially normalized thickness maps were analyzed to assess illness effects while controlling for age, sex and medication. Based on our *a priori* hypotheses regarding specific brain regions that might be affected in BP disorder, permutation testing was conducted in PFC and anterior cingulate subregions, defined by Brodmann areas (Rasser et al., 2005; *NeuroImage*, 26:941-51). Associations with clinical demographics were assessed using correlation analyses. **RESULTS:** Relative to healthy subjects, patients showed overall significant decreases in cortical thickness in both left ( $p=0.045$ ) and right ( $p=0.006$ ) hemispheres. Frontal lobe thinning in patients was localized to bilateral orbitofrontal (BA11,  $p<0.01$ ), right ventrolateral (BA47,  $p=0.03$ ), left superior frontal (BA10,  $p=0.049$ ) and left anterior cingulate cortices (BA32,  $p=0.047$ ). No areas of thicker cortex were found in patients relative to healthy subjects. Significant inverse associations were found within these regions with duration of illness, prior number of depressions and duration of time between illness onset and initiation of treatment with medication ( $p<0.05$ ). **DISCUSSION:** This is the first brain mapping study to examine illness effects in a patient sample free from lithium, a medication that has significant confounding effects on gray matter. We found thinning in anterior cingulate cortex, and ventrolateral and ventromedial PFC, brain regions which are critical in the modulation of attention, motivation, and emotion. Inverse association between thickness in these regions and prior course of illness variables suggest cumulative thinning may occur as a result of this illness, and pharmacological treatment could protect against such thinning.

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