# ENIGMA Bipolar disorder working group findings from 1,747 cases and 2,615 controls

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**Introduction:**

The pattern of effects on the brain in bipolar disorder (BP) has proven heterogeneous, and volumetric comparisons of brain structures theorized to be involved in the pathophysiology of BP have yielded mixed results. In order to investigate sources of uncertainty, we have formed an international collaboration for the study of BP as part of the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Consortium (Stein et al., 2012). The ultimate goal of our effort is identifying neuroimaging biomarkers suitable for genetic analysis of BP and thereby illuminating novel biological pathways of the disease and advancing research domain criterion-based diagnostics for mood disorders. Our current specific aims are to identify the most sensitive and specific neuroimaging biomarkers for distinguishing BP cases from controls and examine and characterize sources of heterogeneity in brain imaging volumetric indices. ENIGMA is based on the simple principle, long acknowledged for clinical trials, that there is simply no substitute for a very large sample size in discriminating effects of moderate size but crucial clinical importance.

In this initial ENIGMA-Bipolar effort, we perform the largest ever study of subcortical brain volumes in BP cases and healthy controls, based on re-analysis of MRI scans from a total of 4362 participants.

**Methods:**

The ENIGMA Bipolar disorder working group brings together structural MRI brain scans from 20 sites around the world. In total, data from 4362 subjects including 1,747 cases and 2,615 healthy controls were available for analysis. All images were processed using automated, validated segmentation software packages: FSL FIRST (Patenaude et al., 2011) or FreeSurfer (Fischl et al., 2002). Our primary focus was on the mean volumetric differences between BP cases and healthy controls in seven subcortical brain structures: nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus as well as ventricular volume and total intracranial volume (ICV). Within each sample, we used a multiple linear regression framework to quantify the differences between BP patients and healthy controls, while accounting for age, sex, and differences in head size (ICV) as covariates.

**Results:**

We found that BP cases have significantly reduced volumes of the hippocampus ($d = -0.22 \pm 0.049$; $P = 6.62 \times 10^{-6}$), thalamus ($d = -0.15 \pm 0.051$; $P = 3.2 \times 10^{-3}$), and amygdala ($d = -0.14 \pm 0.043$; $P = 9.4 \times 10^{-4}$). In addition, we found that BP cases have significantly larger lateral ventricles ($d = 0.29 \pm 0.066$; $P = 1.29 \times 10^{-5}$) than healthy controls. None of the other five structures were significantly different between BP cases and controls using a Bonferroni corrected significance threshold $p^* < 0.05/9 = 5.5 \times 10^{-3}$ (Figure 1).

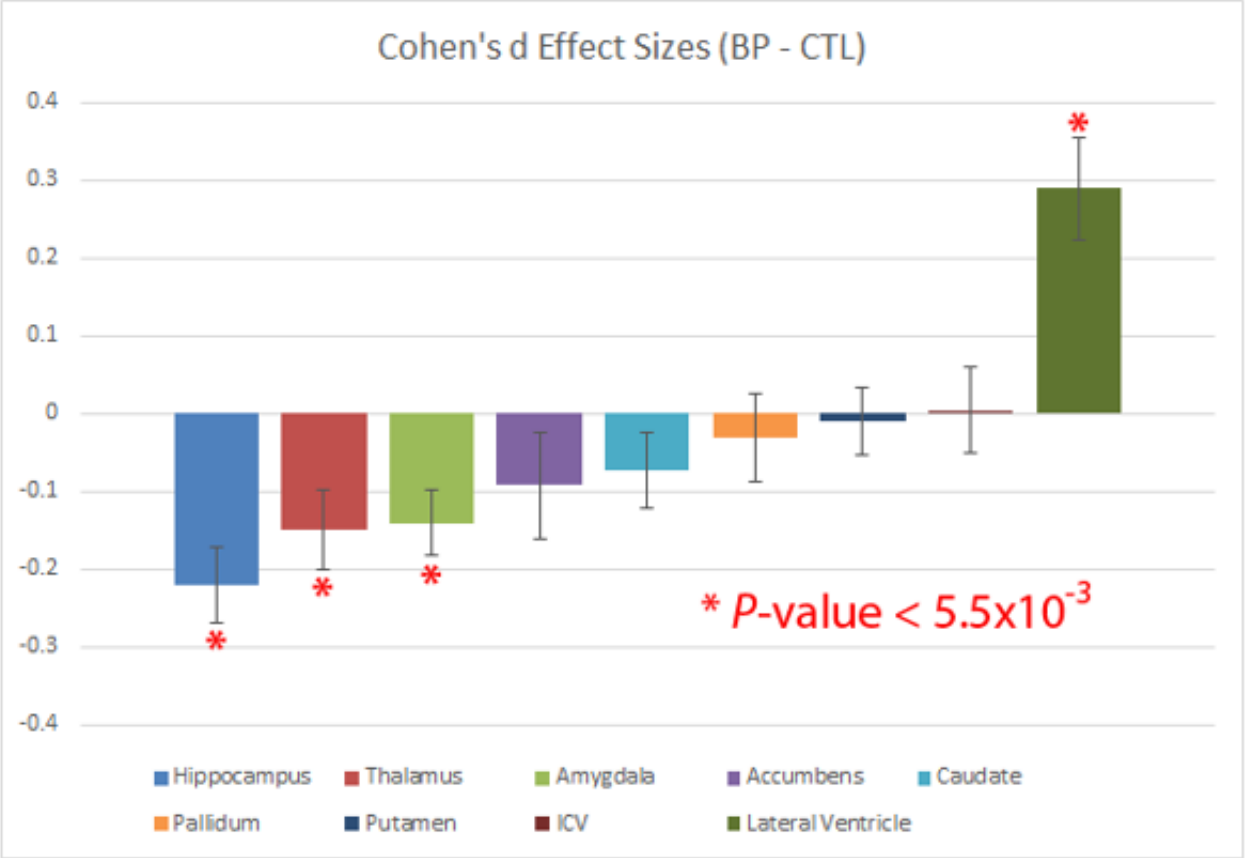


**Figure 1.** Effect sizes for the volumetric differences between bipolar disorder (BP) cases and controls (CTL), after accounting for age, sex, and intracranial volume.

**Conclusions:**

Here we performed the largest ever study of neuroimaging measures in BP, enabling robust estimates of brain structure abnormalities. We found that patients with BP have significantly enlarged ventricles, which is the most consistently reported finding in the BP literature (Fears et al., 2014; Hallahan et al., 2010; McDonald et al., 2004; Kempton et al., 2008; Arnone et al., 2009; Rimol et al., 2010). In addition, we show that patients with BP have significantly reduced hippocampus, amygdala, and thalamus volumes, findings which have not been consistently shown in previous reports. Future project will look at cortical differences between BP patients and healthy controls.

**Disorders of the Nervous System:**

Mood and Anxiety Disorders

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