Amygdala activation is associated with prefrontal cortical thickness in healthy subjects, but not in euthymic bipolar patients

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Introduction: Bipolar (BP) disorder is a severe chronic mental illness characterized by dramatic mood swings between mania and depression. Several lines of evidence have implicated disruptions of prefrontal cortex and amygdala, known components of an emotion regulatory network. Recent data from our group have shown such a disruption occurs during an emotion identification task in bipolar mania (Foland et al., 2008). Here, we use the same task to examine (1) if amygdala hyper-responsivity persists during euthymia, and (2) whether amygdala hyper-responsivity is associated with a reduction in prefrontal cortical (PFC) gray matter thickness, given that the PFC directly suppresses amygdala output (Hariri et al., 2000).

Methods: 18 lithium-free bipolar I euthymic subjects (8f, 36.6+/-13.0yrs) and 18 healthy subjects (8f, 36.6+/-12.8yrs) were scanned on a 3T scanner during an affective faces task for collection of fMRI data, and on a 1.5T scanner for collection of high resolution structural MRI data. During fMRI, subjects cognitively assessed an emotional target face by choosing one of two linguistic labels (cognitive evaluation condition) or matched geometric forms (control condition). Manually prescribed regions of interest (ROIs) for the left amygdala were delineated on each 1.5T scan by a trained neuroanatomist (CP), and spatially registered to subjects' 3T scans to extract percent signal change occurring during the contrast of "cognitive evaluation" versus "control". A correlation analysis between amygdala activation and cortical thickness, computed using the Eikonal fire equation (Sapiro, 2001) in conjunction with cortical pattern matching (Thompson et al., 2004), was performed along each point of the cortical surface, resulting in a color coded r value at each cortical point. Permutation testing was used to correct for multiple comparisons and to interrogate our *a priori* frontal lobe ROIs.

Results: Compared with healthy subjects, patients showed nonsignificant increases in activation of the left amygdala (0.87% versus 0.76%, p=0.291). Correlation of this activation with cortical thickness revealed negative correlations in right PFC of healthy subjects (BA9, p=0.04; BA10, p=0.07; Figure 1a). Positive correlations between amygdala activation and cortical thickness in healthy subjects were also found in left anterior cingulate (BA24, p=0.049; BA33, p=0.046) and right temporal lobe (BA20/21, $p<0.05$; Figure 1a). These patterns were reduced or not detectable in patients ($p>0.05$; Figure 1b).

Conclusions: This is the first study to demonstrate that, in healthy subjects, gray matter thickness in right PFC is negatively associated with activation level of the amygdala. Thus, the amount of gray matter volume in PFC may be directly related to this region's ability to modulate or inhibit activation in the amygdala. These findings support the concept of an emotion regulatory network in which medial PFC directly inhibits amygdala activity level (Ghashghaei & Barbas, 2002; Quirk et al., 2003; Taylor et al., 2003). This prefrontal-amygdala association was absent in bipolar subjects, who instead demonstrated no significant increases in amygdala activation relative to healthy subjects. Future studies that examine this network in medication-naïve patient populations, and in patients scanned during different mood states would be of interest.

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