VBM detection of Volumetric Abnormalities in Bipolar Disorder

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Background: Neuromorphometric abnormalities are known to occur in bipolar disorder (BD). In particular, structural MRI studies employing manual segmentation approaches have reported abnormalities of grey matter volume in the prefrontal cortex (including orbital and anterior cingulate cortex), amygdala, hippocampal subiculum and ventral striatum (reviewed in Strakowski, et. al.) in BD. These structures share extensive anatomical connections with each other and form part of a network that plays major roles in regulating emotional experience and expression. Recent anatomical studies in humans demonstrate that these regions also share abundant, monosynaptic connections with the posterior cingulate and the superior temporal cortices (Price, et. al.), raising the possibility that these structures may additionally contain structural abnormalities in BD. The current study utilized voxel based morphometry (VBM) to determine if volumetric abnormalities within these structures could be detected in BD without hand segmentation. VBM is a viable alternative to hand segmentation in regions without clear anatomical landmarks, and also offers the advantage of being free from rater bias. This is the first report of a VBM study distinguishing between medicated and unmedicated BD subjects, a vital distinction considering the established neurotrophic effects of mood stabilizers used to treat BD (reviewed in Gray, et. al.).

Methods: Subjects aged 19 to 60 years who were healthy (n=65; 46 female; mean age 38) or had bipolar disorder (n=36; 26 female; mean age 39) were imaged using one of two GE 3T MRI scanners, running an MP-RAGE pulse sequence optimized for tissue contrast resolution. Images were acquired at a resolution of 0.9x0.9x1.2mm. Non-brain tissues were removed from the images, using a combination of the FSL tool BET (FMRIB, Oxford, UK) and manual editing, then images were segmented into gray matter (GM), white matter (WM), and CSF using the FSL tool FAST. Images were then spatially normalized to a skull stripped template using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London). Both and affine and non-linear transformation were calculated, using a 25mm cutoff, and 16 iterations of the nonlinear optimization algorithm (Ashburner, et. al.). Regularization was used to constrain large non-linear warps. The regularization parameter was varied, with a very heavy amount of regularization resulting in less distortion of the cortical surface (Wilke, et. al.) and medium regularization resulting in more accurate normalization of structures which are morphometrically similar across subjects (such as subcortical structures) (Salmond, et. al.). In order to examine absolute volume, images undergoing nonlinear normalization were modulated by the Jacobian determinant of the transformation matrix, so that intensity at each voxel would reflect the absolute amount of GM or WM present. Images normalized using only affine transformations were left unmodulated, to reflect concentration of gray matter. Images were then smoothed using a 12mm FWHM Gaussian smoothing kernel. GM images were compared using an AnCova, with age, gender, and scanner modeled as nuisance variables. For *a priori* regions of posterior cingulate, lateral orbital cortex, superior temporal cortex, and limbic system, results are reported for voxels significant at $p<0.0001$ uncorrected for multiple comparisons.

Results: In gray matter, a volumetric reduction was evident in unmedicated BD subjects as compared to medicated subjects in the posterior cingulate/retrosplenial cortex in all normalization routines (most significant in affine, peak voxel -10, -58, 10, T=4.12, Figure 1a). In affine and very heavy regularized normalizations, the unmedicated subjects exhibited reduced gray matter in the same region as compared to the healthy subjects (most significant in affine, peak voxel -10, -56, 8, T=3.86). When affine transformations were applied, reduced gray matter in the medicated BD subjects as compared to healthy controls was observed in the lateral orbital cortex (peak voxel -40, 25, -6, T=3.61, Figure 1b). Across all normalization routines, a reduction in superior temporal gyrus was seen in the unmedicated BD subjects when compared to the healthy controls (most significant in medium regularization, peak voxel -48, -49, 23; T=4.10). When a nonlinear transformation was applied with medium or very heavy regularization, a bilateral reduction in GM of the posterior cingulate adjacent to the parahippocampal gyrus was seen in unmedicated BD subjects as compared to healthy controls (most significant in medium regularization; left: -18, -35, 7; T=3.67, right: 24, -33, 7; T=3.51, Figure 1c).

Discussion: Voxel based morphometry offers an alternative to hand segmentation, as it examines the gray matter and white matter content at each voxel. When nonlinear normalization is applied, superior alignment of structures which are morphologicaly similar across subjects is seen (Salmond, et. al.), consistent with our finding in the uniform portion of the posterior cingulate adjacent to the parahippocampal gyrus. It has been suggested that affine or heavy regularized normalization should result in less distortion of gyral morphology and more accurate results in cortex and structures morphologically discordant across subjects (Wilke et. al.), a result consistent with our findings in lateral orbital cortex and regions of the posterior cingulate with more complex gyral morphology. The reductions in gray matter of the lateral orbital cortex is consistent with the functional and histopathological abnormalities reported previously in BD (Strakowski, et. al.). Reductions in posterior cingulate and superior temporal cortex support the theory of emotional dysregulation by a network encompassing these structures and projecting to prefrontal and limbic regions (Price, et. al.).

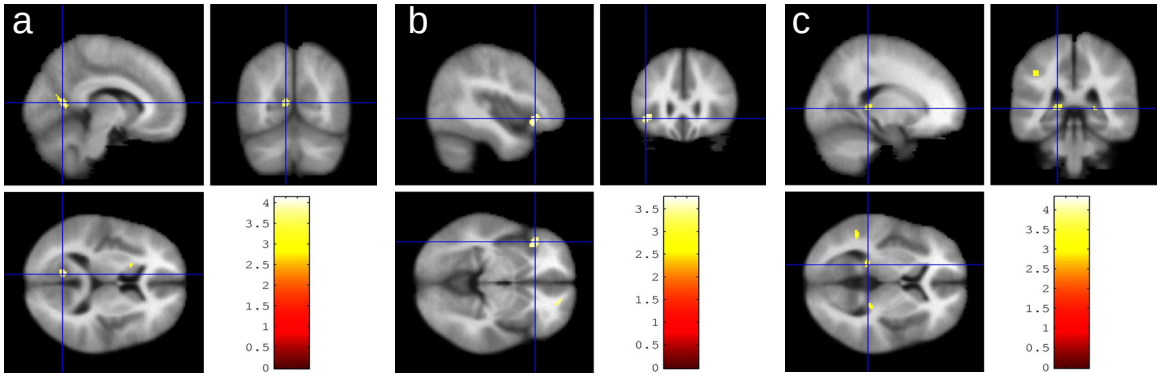

Figure 1: T-maps of areas of reduced gray matter in a) unmedicated BD subjects as compared to medicated BD subjects in posterior cingulate, b) medicated BD subjects as compared to healthy controls in the lateral orbital cortex, and c) unmedicated BD subjects as compared to healthy controls in posterior cingulate adjacent to the parahippocampal gyrus.

References:

Ashburner et. al., Hum Brain Mapp. 1999; 7(4):254-66.
Gray, et. al., J. Clin. Psych. 2003; 64 Suppl 5, 3-17.
Price, et. al., Society for Neuroscience Annual Meeting, 2004.
Salmond, et. al., Neuroimage. 2002; 17:507-12.
Strakowski, S.M., et. al., Molecular Psychiatry, Epub ahead of print; 2004.
Wilke, et. al., Neuroimage. 2003; 20:330-43.