

Increased brain volumes and cortical surface area in adolescents and young adults at increased genetic risk for Bipolar Affective Disorder

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Background: Characterization of brain morphometry in young people at elevated genetic risk for Bipolar Affective Disorder (BPD) may illuminate brain regions important in the development of the disorder and identify potential endophenotypes for studies of specific genetic risk factors. The handful of existing small studies of brain volume in this population have had inconsistent findings. No studies to date in this population have reported surface area and cortical thickness independently of volume, although these aspects of cortical morphometry have been demonstrated as related to different genetic factors (Panizzon et al, *Cereb Cortex* 2009).

Methods:

Subjects: Data were obtained from adolescents and young adults aged 12-30 participating in an ongoing longitudinal international study of individuals at elevated risk for bipolar disorder. Participants were classified as at-risk (AR-BD) if they were a child or sibling of a proband with confirmed DSM-IV diagnosis of BP-I, BP-II, or schizoaffective disorder (SAD), bipolar type. Control subjects (HC) had no parent or sibling with BPD, schizophrenia, SAD, major depression, substance abuse, or psychiatric hospitalization. Past or current treatment with a psychotropic medication or psychiatric diagnosis except for BP were not exclusions for either AR-BD or HC. DSM-IV diagnoses were determined using the DIGS, FIGS (Nurnberger et al, *Arch Gen Psych* 1994) and medical records in subjects over 22-30 and the K-SADS (Kaufmann et al, *JAACAP* 1997) in subjects between 12-21. IQ was measured using the WASI (Wechsler 1991). As our sample included a higher proportion of younger subjects in the AR-BD group, a subset of AR-BD and HC matched pairwise on sex and age (\leq one year difference within pair) was also created to further test whether age was contributing to group differences.

Image acquisition and analysis: T1-weighted anatomic 3DTFE 1mm isotropic images were obtained using the same protocol and 3-T Phillips Achieva scanner. Segmentation, parcellation and measurement of brain volumes, cortical surface area, and cortical thickness were performed using Freesurfer, a well-validated automated method (Fischl et al *Cereb Cortex* 2004). Scans were visually inspected and excluded for significant motion artifact, anatomical abnormalities or poor segmentation after image processing. Regions of interest (ROIs) included gray matter (GM), white matter (WM), hippocampus, and amygdala volumes. Volume, cortical thickness, and surface area were measured for the cortical bilateral insula and anterior cingulate regions. ROIs were chosen based on the extensive literature regarding their involvement in BPD. **Statistical analysis:** Brain morphometric features were compared between AR-BD and HC groups using ANCOVA with sex and age as co-variables. Age and IQ were compared using independent t-tests.

Results:

Demographics: Participants in the full sample included 85 AR-BD (31 male, mean age 21.2 yrs \pm 4.9, range 12-31, mean IQ 117.1 \pm 9.9) and 84 HC (31 male, 22.6 yrs \pm 3.5, range 13-30, IQ 117.9 \pm 11.2). IQ was not available on 35 subjects. The pair-matched subset included 114 subjects (42 male, 22.7yrs, \pm 4.0). Diagnostic information was available for 145 subjects; 36 AR-BD and 15 HC had a psychiatric diagnosis; of these 23 AR-BD and 10 HC had been diagnosed with a non-BP affective disorder.

Morphometric measures: AR-BP had significantly greater volumes for GM ($p < 0.001$), WM ($p = 0.014$) and left hippocampus ($p = 0.05$); right hippocampus and amygdala were not different. Cortical volumes and surface area were also larger (see Table). In all cases where differences were present AR-BD were greater than HC. Sex and age were significant contributors and retained in all analyses. Results were similar in the pair-matched subgroup except that L hippocampus was no longer different and age had a decreased contribution to variance.

Region	Volume	Surface Area	Cortical Thickness
Total Cortex	F = 18.6, p = 0.00	F = 12.6, p = 0.00	F = 0.53, p = 0.57
Anterior cingulate Left	F = 8.5, p = 0.00	F = 6.27, p = 0.01	F = 0.18, p = 0.89
Right	F = 7.7, p = 0.01	F = 8.63, p = 0.00	F = 0.97, p = 0.33
Insula Left	F = 7.3, p = 0.01	F = 6.04, p = 0.02	F = 0.47, p = 0.49
Right	F = 4.9, p = 0.03	F = 4.02, p = 0.05	F = 0.84, p = 0.36

Discussion: These preliminary results from a large sample of adolescents and young adults at increased genetic risk for BPD show overall brain volumes to be increased, including total cortical volume. Increased volume has been previously reported in the left insula (Kempton et al, *J Neurosci* 2009). Cortical thickness does not differ between groups, indicating the changes in brain volume may be related to the observed greater surface area in the AR-BP group. This suggests that surface area may be a useful endophenotype for genetic studies of BPAD. Future work will include more detailed examination of ROIs and effects of diagnostic status and medication.