White Matter Deficits Correlate with Limbic Structural Asymmetry in Pediatric Bipolar Disorder: A Diffusion Tensor Imaging Study

R. Zampolin[1], A. Papolos[6], J. Nierenberg[4], M. Hoptman[4], D.Papolos[3,5], M.L. Lipton[1,2,4]

Departments of [1]Radiology, [2]Neuroscience and [3]Psychiatry, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, USA, [4]The Center for Advanced Brain Imaging, The Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA, [5]The Juvenile Bipolar Research Foundation, Marlboro, NJ, USA, [6]Cornell University, Ithaca, NY, USA

Aim

To determine if, and if so at what loci, white matter abnormalities correlate with limbic asymmetry in pediatric bipolar patients.

Introduction

Bipolar disorder (BD) manifests in children as a severe behavioral disturbance characterized by paroxysmal outbursts of disproportionate rage separated by intervening periods of more stable mood with or without depressive symptoms. Ultra-rapid cycling is common in children with bipolar disorder as compared to adults. The characterization of BD in the pediatric population has largely been based on clinical phenotype, but characterization of the defective neural systems underlying the disorder is essential.

We recently reported limbic gray matter asymmetry using structural MRI in a cohort of patients meeting research diagnostic criteria for the pediatric bipolar core phenotype. The present study explores the potential to further delineate the neural pathways underlying the disorder by identifying loss of white matter ultrastructural integrity using DTI with measurement of fractional anisotropy (FA).

Methods

Subjects:

8 boys and 2 girls. Age range: 8-16.

Clinical Assessments:

- Neurological examination
- Standardized research-clinical evaluations
  - K-SADS, CBQ
  - YBOCS
  - OAS
  - Neuropsychology

Imaging at 1.5 Tesla:

- Structural
  - FSPGR
  - 1 mm isotropic resolution
- DTI
  - 25 independent directions
  - b = 1000
  - 5 mm slice thickness
  - FA calculated on console

Data Analysis:

- Structural
  - Automatic segmentation (grey, white, CSF) -- FSL FAST (http://www.fmrib.ox.ac.uk/fsi)
  - Manual segmentation -- Slicer
    - Amygdala, Hippocampus, Cingulate
    - Experienced raters
    - r = 0.89
- DTI
  - 2D distortion correction
  - Co-registration to MNI space
  - White matter masking
  - Voxel-based correlation analysis to identify decrease in FA associated with the volumetric assymetries
    - p<0.005 (voxel level)
    - p<0.001 (cluster level)
    - cluster size > 100 voxels

Results

Limbic Volume Asymmetry:

Structure	Laterality	Magnitude	Significance
Amygdala	R > L	6% (3-13)	p<0.001
Hippocampus	R < L	4% (3-13)	p<0.03
Cingulate	R < L	3% (1-20)	p<0.05

Voxel-based correlation analysis identified multiple loci of decreased FA associated with each structural asymmetry. Affected regions include:

- Bilateral frontal white matter
- Bilateral parietal white matter
- Right medial temporal white matter
- Inferior frontal white matter adjacent to olfactory cortex
- Bilateral parieto-occipital white matter

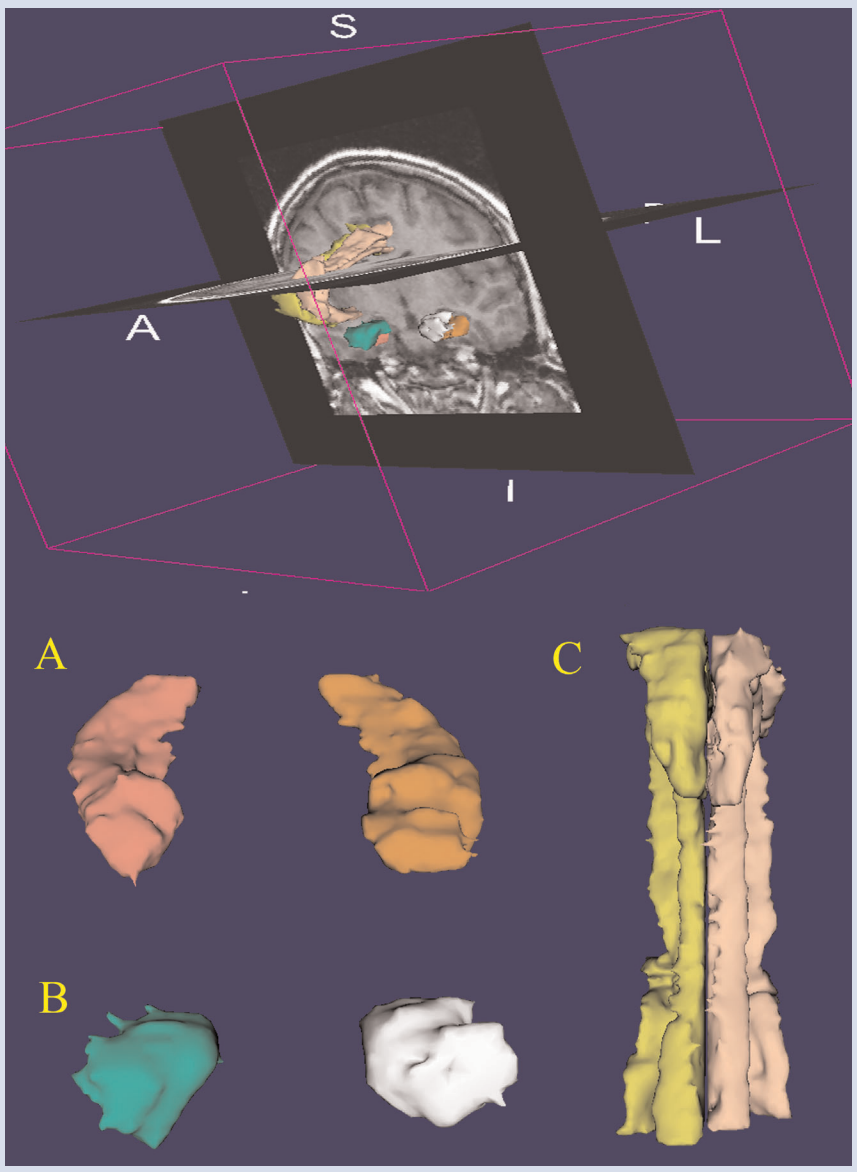

Fig 1: 3D rendering of limbic volumes. Hippocampus (a), amygdala (b) and cingulate (c) from a representative subject.

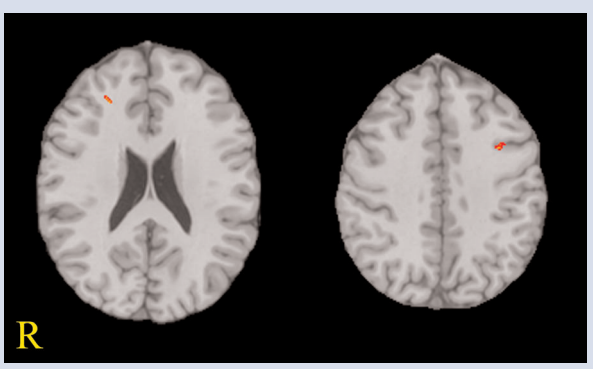

Fig 2: Decrease in FA associated with limbic asymmetry. Regions of diminished FA in frontal white matter bilaterally, correlate with asymmetry of the amygdala.

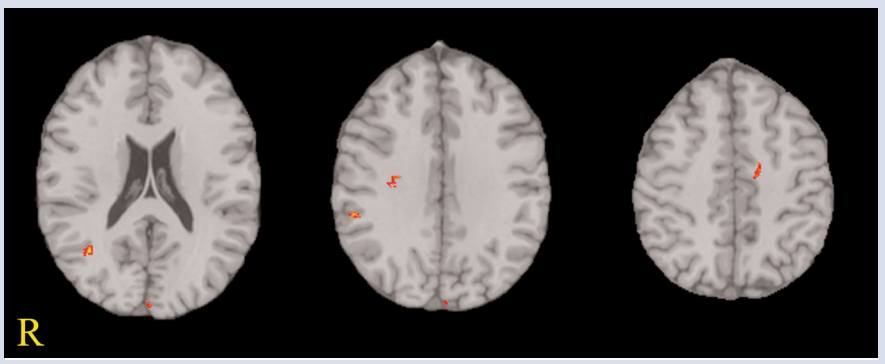

Fig 3: Decrease in FA associated with limbic asymmetry. Regions of diminished FA in bifrontal and right parietal white matter correlate with asymmetry of the hippocampus.

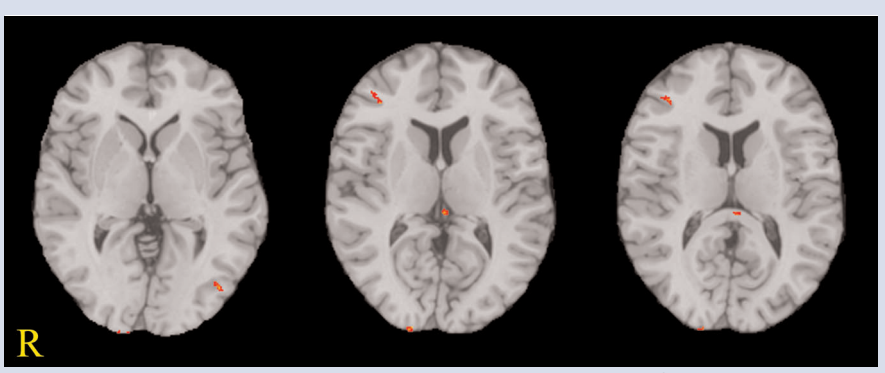

Fig 4: Decrease in FA associated with limbic asymmetry. Regions of diminished FA in right frontal white matter, splenium and bilateral parieto-occipital white matter correlate with asymmetry of the cingulate.

Discussion

- Our imaging findings identify abnormalities of brain structures that have been implicated in pediatric BD.
- Potential substrates of the dysfunctional neuropsychological domains found in children with bipolar disorder.
- Asymmetry of mesial temporal structures is similar to findings in temporal lobe epilepsy, suggesting a biological basis for the paroxysmal episodes of rage seen in these patients. Notably, anti-epiletic medications are effective in controlling BD in children.
- DTI deficits in frontal white matter implicate fronto-limbic circuits in the pathogenesis of the disorder, consistent with existing hypotheses regarding the likely brain substrates of bipolar disorder.
- Perhaps most importantly, these results indicate that specific imaging findings may be useful in psychiatric differential diagnosis. Confusion of bipolar disorder and ADHD is common. Imaging markers might ultimately provide a diagnostic tool for resolving an important clinical problem in child psychiatry.