Schizophrenia but not Bipolar Adolescent Offspring Show Developmentally Mediated Deficits in Prefrontal Structure and Function

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Introduction: Schizophrenia and bipolar disorder may be characterized and differentiated by patterns of neurodevelopment[1]. Adolescent offspring of patients are at higher risk (HR) for developing psychiatric symptoms[2] and are therefore an important group in whom to assess impaired neurodevelopment in brain and behavior. The prefrontal cortex is a central cortical region implicated in schizophrenia[3], but not in bipolar disorder. Therefore, understanding the pattern of structural and functional development of this region during adolescence may be crucial toward understanding varying pathways of risk in each disorder[4]. In this study we cross-sectionally assess changes in frontal gray matter, and performance on spatial working memory during adolescence in age- and gender matched adolescent offspring of schizophrenia and bipolar patients. We hypothesized that relative to controls (HC), schizophrenia (HRS)-but not bipolar (HRB) offspring would show developmentally related deficits in frontal structure and function, specifically relating to accelerated gray matter loss and a failure of function.

Methods: Three age and gender matched groups HC, HRS and HRB (n=12 in each, age range 11.5-19.5 years, mean age=14.5 yrs; 5 males) gave informed consent. Frontal structure was assessed with optimized voxel-based morphometry[5]. Frontal function was assessed using a delayed spatial working memory task[6] with larger error indicating poorer working memory. T_1-weighted SPGR images (124 coronal slices, 1.5 mm thickness, TE=5 msec, TR=25msec, acquisition matrix=256x192, FOV=24 cm, flip angle 40^0) were acquired using a GE 1.5T whole body scanner (GE Medical Systems, Milwaukee, Wisconsin). Voxel-based analyses was conducted using a region of interest mask for Brodmann areas 9 & 46[7], with statistical thresholding confined to voxels within the mask. Developmental trends were addressed cross-sectionally with intra-group median splits by age, cleaving groups into younger (age<15 yrs) and older adolescents.

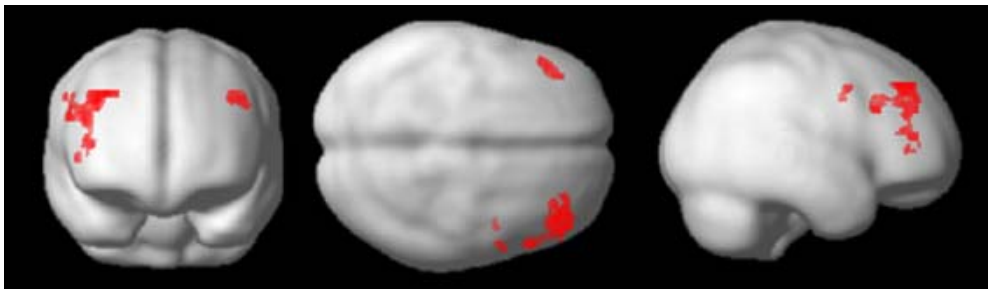

Figure1: Grey matter density reductions in frontal cortex in older HRS relative to their younger counterparts are rendered in three surface views (see text for details).

Results: MRI data were analyzed in a Group (HC, HRB, HRS) x Age (Young vs. Old) factorial design with gender as covariate. Separate contrasts (Young > Old) were employed to assess intra-group changes in gray matter density from the younger to older groups. Significantly, only $HRS_{(Younger > Older)}$ showed bilateral clusters in frontal cortex. Three peaks were observed: a) mni: 43 45 32, $p_{FDR\text{-}corr} < 0.04$, $t_{29}=4.45$, k=1652 voxels; b) mni: -45 32 39, $p_{FDR\text{-}corr} < 0.048$, $t_{29}=3.55$, k=294 voxels; c) mni: 58 6 41, $p_{FDR\text{-}corr} < 0.048$, $t_{29}=3.54$, k=73 voxels. Significant clusters for this contrast are depicted in Figure 1. In addition, both HRS sub-groups showed decrements in performance in spatial working memory relative to HC and HRB ($p<.05$, Fig 2).

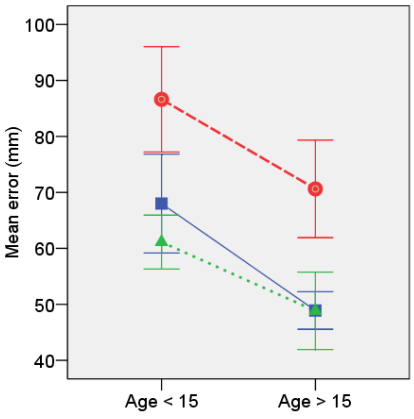

Figure2**:** Spatial working memory in HRS (red), HRB (blue) and HC (green). Error bars are 95% confidence intervals.

Discussion: These results are preliminary, yet are suggestive of accelerated decreases in gray matter density in HRS that occur in conjunction with impairments in prefrontal function that exist through adolescence. The gray matter deficits are consistent with the hypothesized model of exaggerated pruning in schizophrenia[8] suggesting particular vulnerability of the frontal cortex in risk for the illness. The enduring deficits in spatial working memory provide evidence for the behavioral expression of these structural deficits indicating convergence between these biomarkers of risk for schizophrenia. Our ongoing efforts are assessing these trends longitudinally in schizophrenia offspring and cross-sectionally in larger cohorts of bipolar offspring using functional and structural MRI and MR spectroscopy.

References: [1]R. M. Murray, P. Sham, J. Van Os et al., *Schizophr Res* 71 (2-3), 405 (2004). [2]M. S. Keshavan, V. A. Diwadkar, D. M. Montrose et al., *Schiz Res* 79, 45 (2005). [3]D. A. Lewis and P. Levitt, *Annual Review of Neuroscience* 25, 409 (2002). [4]M. S. Keshavan, V A Diwadkar, and D. R. Rosenberg, *Epidemiologia e Psichiatria Sociale* 14, 188 (2005). [5]C. D. Good, I. S. Johnsrude, J. Ashburner et al., *NeuroImage* 14, 21 (2001). [6]P. S. Goldman-Rakic, *Biological Psychiatry* 46 (5), 650 (1999). [7]J. A. Maldjian, P. J. Laurienti, R. A. Kraft et al., *Neuroimage* 19 (3), 1233 (2003). [8]M S Keshavan, S Anderson, and J W Pettegrew, *J Psychiatr Res* 28, 239 (1994).