for a schizophrenia spectrum disorder in parents of childhood-onset patients was 4.9 times greater than for parents of adult-onset patients. These data are consistent with the hypothesis that a childhood-onset of schizophrenia is due, at least in part, to a greater genetic diathesis for the disorder.

### Brain Imaging I

**Thursday, May 11, 2:30 PM–5:00 PM**  
**Location:** New Orleans  
**Chair:** Robert M. Cohen

#### 42. THE CONTRIBUTION OF ORBITOFRONTAL CORTEX TO EPISODIC MEMORY IMPAIRMENT IN OCD


(1) Dept. of Psychiatry and (2) Radiology, Massachusetts General Hospital/Harvard Medical School, Charlestown, MA 02129; (3) Dept. of Psychology, Harvard University, Cambridge, MA

Biological studies of obsessive-compulsive disorder (OCD) provide consistent evidence of dysfunction in orbitofrontal cortex (OFC). We have used the California Verbal Learning Test (CVLT) in behavioral studies to examine episodic memory in OCD. In two separate investigations, we found that OCD patients failed to spontaneously apply semantic organizational strategies during encoding and this led to problems in delayed recall. We will present new data from a PET study in normal subjects examining the neural systems underlying semantic organization using a verbal memory paradigm patterned after the CVLT. Eight normal subjects listened to lists of 24 words, in three conditions: 1) Unrelated: words were semantically unrelated; 2) Spontaneous: words were related in four semantic categories, and subjects were not instructed of this beforehand; 3) Directed: same as (2) but subjects were explicitly instructed to notice the relationships and use them to improve memory. Behavioral data included a Semantic Clustering score, measuring active regrouping of words into semantic categories during recall. In a graded PET contrast (Directed > Spontaneous > Unrelated), two distinct activations were found in left inferior prefrontal cortex and left dorsolateral prefrontal cortex. Correlation analyses in the Spontaneous condition indicated that blood flow in OFC during encoding predicted the use of semantic clustering strategies during immediate recall. These results indicate that OFC plays a role in episodic memory by supporting the mobilization of effective strategic processes, mediated in other regions of PFC. Disruptions in learning strategies in OCD are likely related to OFC dysfunction.

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#### 43. MRI ANALYSIS OF CHILDREN AT RISK FOR BIPOLAR DISORDER


The University of Cincinnati College of Medicine, Cincinnati, OH 45267-0559

Studies of adults with bipolar disorder suggest abnormalities in the neuroanatomic pathways thought to modulate mood. To our knowledge, there have been no studies examining these neuroanatomic structures in children at risk for bipolar disorder. We hypothesized that compared with healthy volunteers, children with a parent with bipolar disorder (high-risk) would exhibit abnormalities in brain regions that regulate mood. Children (ages 8–12 years) with at least one parent with bipolar disorder (N = 17) and children of healthy parents without any DSM-IV Axis I disorder (N = 13), matched for age, sex, socioeconomic status, handedness, and Tanner stage, were assessed using the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS). Parents were evaluated using the Structured Clinical Interview for DSM-IV (SCID-P). Contiguous 1 mm axial T1-weighted MRI slices were obtained using a GE 1.5 Tesla scanner. Morphometric analyses were performed by raters blind to subject diagnosis. Regions of interest (ROIs) included whole brain, hippocampus, amygdala, thalamus, striatum, globus pallidus, cerebellum, and prefrontal cortex.

MANCOVA adjusting for Tanner stage and education revealed the high-risk children demonstrated significantly different overall ROI volumes as compared to the healthy volunteers (Wilks lambda = 0.51, F(7,19) = 2.6, p = 0.05). The differences between groups in hippocampal volumes contributed the only large effect size (f = 0.6) and hippocampal volumes were larger in high-risk children than in volunteers.

Our results suggest that children at risk for bipolar disorder may have neuroanatomic abnormalities similar to those found in adults with bipolar disorder, suggesting that these abnormalities may be present prior to the onset of bipolar disorder. We are continuing to collect data in effort to increase power so that additional differences in structural volumes may be detected.

#### 44. REDUCED LEFT HESCHL’S GYRUS VOLUME IN SCHIZOTYPAL PERSONALITY DISORDER


Harvard Medical School/Brockton VA Medical Center, Department of Psychiatry, Brockton, MA 02401

Schizotypal personality disorder (SPD) shares the same genetic diathesis as the schizophrenia spectrum disorders, yet persons with SPD are not psychotic and generally have not been prescribed neuroleptics. Therefore, they may represent an ideal group to study the underlying structural abnormalities in the spectrum disorders. Previously we showed SPD subjects to have enlarged CSF volumes, parahippocampal asymmetry, and reduced left superior temporal gyrus (STG) gray matter volumes compared with normal control subjects. The STG consists anatomically of the anterior pole, Heschl’s gyrus (primary auditory sensory cortex) and planum temporale (auditory unimodal association cortex). In order to better define this STG abnormality, we examined Heschl’s gyrus and planum temporale in an extended group of subjects. **Subjects:** SPD subjects were all right-handed males (N = 24) and age-matched within 3 years to the comparison subjects (N = 23), with no difference in IQ, years of education or parental socio-economic status. SPD subjects did have lower socioeconomic status. **Image processing:** The STG was manually drawn on the acquired coronal images consisting of 124 slices. To correct for the effects of head tilt, the images were realigned and resampled to form a new set of images with over 200 slices and isotropic voxels. The drawings were edited as necessary and the boundaries were extended to their anterior and posterior most extent with high interrater reliability (intraclass r > 0.99). The effect of brain volume on region size was accounted for using a regression procedure. The resultant residual volume for left Heschl’s gyrus was not normally
distributed and Mann-Whitney U statistics were used. There was no difference in volume of the total intracranial contents. The SPD subjects showed a 21% reduction in left Heschl’s gyrus volume, but no difference in right Heschl or planum temporale volume or Heschl or planum asymmetry. These findings suggest that the reduced left STG finding may be, in part, due to the volume reduction of Heschl’s gyrus. This is intriguing as Heschl’s gyrus participates in early processing of auditory stimuli (tones) and is consistent with the finding of abnormal P300 amplitude in a similar group of SPD subjects.

45. GENDER DIFFERENCES IN AGING EFFECT ON THE 5-HT1A RECEPTOR WITH [11C-CARBONYL]WAY100635 PET


Departments of Radiology and Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213

The effects of age on serotonergic function have been implicated in aging changes in human mood and behaviors. Large reductions in 5-HT2A receptor density with normal aging have been documented. However, the influence of age on 5-HT1A receptors is less well-characterized in vitro, and selective PET ligands have not been previously available.

Dynamic PET imaging (60 min) was performed in 16 healthy subjects (7 M, 9 F: ages 21–80 yrs) following injection of 8–15 mCi [11C-carbonyl] WAY100635 using an ECAT HR+ tomograph in 3D. Time-activity data were generated from MR-guided regions of interest, and binding potential (BP) values determined from a reference tissue model using cerebellar data as reference. Regional BP values were corrected for partial volume effects.

There were significant inverse correlations (*p ≤ 0.05) between age and BP in several cortical regions in men but not in women. These included lateral orbitofrontal cortex [Brodmann area (BA) 47]: r = −0.87*, r = −0.08; subgenual cingulate (BA 10): r = −0.89*, r = −0.23; pregenual cingulate (BA 32): r = −0.80*, r = +0.06; hippocampus: r = −0.88*, r = −0.16; occipital r = −0.92*, r = −0.32; in men and women, respectively. A similar trend (p = 0.09) was observed in the region of the dorsal raphe nucleus in men (r = −0.68), with no significant age effect in women (r = +0.16).

Preliminary data support gender differences in the effect of age on the 5-HT1A receptor, with aging reductions in binding observed in men only. This may contribute to differential vulnerability of men and women to aging changes in mood, cognition and serotonergerically-mediated behaviors, such as sleep.

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46. APOE E4 MAY MODULATE WHITE MATTER MICROSTRUCTURE IN THE ELDERLY

D.T. Crandall (1), N. Pomara (1), S.J. Choi (1), G. Johnson (2), K.O. Lim (1)

(1) Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY 10962; (2) New York University, New York, NY 10016

Patients with Alzheimer’s disease (AD) reveal patterns of reduced frontal and posterior glucose metabolism that correlate with atrophy in the corresponding regions of the corpus callosum, suggestive of cortical disconnection. Individuals at genetic risk for AD, who have the apolipoprotein E epsilon 4 allele (apoE E4+), show similar patterns of reduced cortical metabolism, indicating possible white matter involvement. Fractional anisotropy (FA), a measure derived from diffusion tensor imaging (DTI), quantifies the directionality and relative coherence of white matter fiber tracts. In healthy individuals, reduced FA in the anterior corpus callosum has been associated with advancing age. This pilot study examined whether age-related changes in FA might be modulated by the apoE E4 allele. Two age-matched groups of cognitively intact elderly subjects (age range: 61.1–75.6; 13 apoE E4+ (2 homozygous); 14 apoE E4−) underwent a DTI scan. Regression analyses were performed separately by group with age as a predictor of FA in three cortical white matter regions. Results showed group differences in the relationship between age and white matter microstructural organization (i.e., FA). In the apoE E4− subjects, increasing age was significantly associated with decreased FA (i.e., worse fiber organization) in the anterior corpus callosum, the posterior corpus callosum, and the parietal white matter. In contrast, age was a predictor of FA only in the anterior corpus callosum of the apoE E4+ subjects. These preliminary findings suggest the apoE E4 allele may modulate white matter microstructural changes in individuals at risk for AD. DTI may be useful in the early detection of AD neuropathology.

47. STRIATAL D2 RECEPTOR BLOCKADE PREDICTED EPS WITH NOVEL ANTIPSYCHOTICS: A [123I] IBZM SPECT

J. Tauscher (1,2), B. Kufferle (1), C. Barnas (1), P. Fischer (1), S. Tauscher-Wisniewski (2), S. Asenbaum (3), T. Brücke (3), S. Kasper (1)

(1) Department of General Psychiatry, University of Vienna, Vienna, Austria A-1090; (2) PET Centre, The Clarke Institute of Psychiatry, CAMH, Toronto, ON, Canada M5T 1R8; (3) Department of Clinical Neurology, University of Vienna, Vienna, Austria A-1090

Extrapyramidal symptoms (EPS) are common with conventional antipsychotics and have been related to extensive blockade of striatal dopamine-2 (D2) receptors. Clozapine and other novel antipsychotic substances with lower in vitro affinity for these receptors showed lower EPS risk.

We present a SPECT study in 71 patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder. We investigated, whether striatal D2 receptor occupancy predicted the occurrence of EPS. [123I] Iodobenzamide (IBZM) and SPECT were used for visualisation of D2 receptors. Striatal tracer binding was compared to an age-corrected value obtained in untreated healthy controls to calculate receptor occupancy. EPS were rated according to the Simpson-Angus-Scale (SAS). EPS were judged to be relevant, if (1) the SAS score was 5; or (2) anticholinergic comedication was required. Patients received antipsychotic monotherapy for at least 14 days with amisulpride (n = 2), clozapine (n = 6), haloperidol (n = 10), olanzapine (n = 6), quetiapine (n = 4), risperidone (n = 14), sertraline (n = 13), or zotepine (n = 16).

The striatal D2 receptor occupancy ranged from 20% to almost saturation. The lowest occupancy was seen with quetiapine and clozapine, and the highest with haloperidol. The 23 patients (32%) experiencing EPS displayed higher mean striatal D2 receptor occupancy (77%) than those without relevant EPS (61%; student’s t-test: t = 3.14, p = .003). We found a weak but positive correlation between the percentage of striatal D2 receptor occupancy and the SAS score (Pearson R = .28; p = .02), despite 18 patients (25%) received anticholinergics. In summary, the striatal D2 receptor occupancy measured with [123I] IBZM SPECT predicted the occurrence of EPS.