

Biological Psychiatry

A Journal of Psychiatric Neuroscience and Therapeutics

IN THIS ISSUE-JULY 15TH

Altered Patterns of Gene Expression in Schizophrenia and Bipolar Disorder

Using microarray gene expression, **Shao and Vawter** (pages 89–97) studied the prefrontal cortex in individuals with schizophrenia and bipolar disorder and found 78 genes, representing genes involved in nervous system development and cell death, which displayed differential expression compared to controls. Three genes, AGXT2L1, SLC1A2, and TU3A, were highly expressed in brain and might be targets of antipsychotic medication. Better understanding of the neurobiology of the shared genes, which may represent a shared molecular profile for both disorders, will offer a window into discovery of common brain mechanism(s) that might lead to more effective core treatments.

Yang et al. (pages 98–103) implicate *Chitinase 3-like 1* (CHI3L1), a cellular survival gene, in the vulnerability to a relatively mild form of schizophrenia. Their work suggests a functional mechanism through which a marker, rs10399805, in the gene promoter may increase CHI3L1 expression as reported in several post-mortem schizophrenia studies. This mechanism may involve a milder illness, as carriers of the risk variant had less positive symptoms and relatively spared cognitive performance when compared with other schizophrenia patients.

Genetic mapping studies have identified the gene for G protein receptor kinase 3 (GRK3) as a possible susceptibility gene for bipolar disorder. A mutation (P5) in this gene, which plays an important role in regulating receptor signaling, was previously shown to be associated with bipolar disorder. **Zhou et al.** (pages 104–110) now show that this mutation increases the expression of the GRK3 gene in brain, suggesting abnormalities in receptor desensitization in bipolar disorder.

Brain Structures in Schizophrenia

For many years, the cerebellum has been viewed as a brain region primarily dedicated to coordinating motor activity. In their review, **Andreasen and Pierson** (pages 81–88) discuss new evidence that has emerged which indicates that the cerebellum may play a key role in cognitive functions as well. Recent data also implicate the cerebellum in schizophrenia. This review highlights the importance of this new view of the cerebellum for understanding schizophrenia.

The basal ganglia are brain structures involved in regulating movement, cognition and psychiatric processes. Using magnetic resonance imaging (MRI), **Mamah et al.** (pages 111–120) found similar alterations in basal ganglia size and shape in individuals with schizophrenia and their unaffected siblings. The similarity of the findings in patients and their healthy, medication-free sib-

lings indicates that heritable factors contribute to altered basal ganglia structure in schizophrenia.

Genetic Heterogeneity in Schizophrenia

Latent class analysis is one statistical approach for estimating the clustering of subjects into groups. In their study of 270 Irish families, **Fanous et al.** (pages 121–127) suggest that their subjects clustered into the following groups: bipolar, schizoaffective, mania, schizomania, deficit syndrome, and core schizophrenia. When they divided the affected individuals in their study using this approach, four regions of the chromosome became associated with the risk for these syndromes that were not implicated when traditional diagnostic schema were employed.

Endophenotypes are traits that can be measured that are intermediate between the genotype and the clinical diagnosis, or phenotype. **Aukes et al.** (pages 128–136) report that 5 of 13 investigated endophenotypes for schizophrenia show moderate (37%–54%) heritability. Two of these endophenotypes, sensorimotor gating and openness, showed evidence of a simple dominant mode of genetic transmission. These data raise questions about the utility of some commonly used approaches for studying the genetics of schizophrenia.

Variation in the catechol-O-methyltransferase (*COMT*) gene has been associated with cognitive function. **Barnett et al.** (pages 137–144) combined data from previous studies to determine the strength of the association of *COMT* genotype and performance on a number of cognitive tests. Their meta-analysis provides evidence of a modest association between *COMT* genotype and IQ, but no significant association with performance on several other tests (Trail Making task, verbal recall, verbal fluency, n-back task, and Wisconsin Card Sorting Test). This analysis raises questions about the interpretation of reported associations between genotype and cognitive performance.

Pharmacologic Tests of Receptor Occupancy

Using animal models, **Samaha et al.** (pages 145–152) show that transient antipsychotic treatment is more efficacious over time than continuous treatment (CT). CT was linked to greater elevations in dopamine D2 receptor number and behavioral dopamine supersensitivity. These findings challenge the assumption that high levels of receptor occupancy by antipsychotics must be maintained continuously in order to maintain efficacy.

Van Laere et al. (pages 153–161) used positron emission tomography (PET) to characterize the dose-related occupancy of γ -aminobutyric acid-A (GABA_A) receptors by TPA023B, a novel, high-affinity selective activator of the α_2 , α_3 - and α_5 -, but not α_1 -GABA_A receptor subtypes. The authors found that a single 1.5

mg. dose produced high levels of receptor occupancy (52% 5 hours after dosing and 46% 25 hours after dosing).

Abnormal Reward Learning in Bipolar Disorder

Bipolar disorder has been linked to abnormal reward processing. **Pizzagalli *et al.*** (pages 162–168) used a probabilistic reward task to test whether individuals with bipolar disorder, particularly

those with residual anhedonic symptoms, show reduced reward learning. As hypothesized, euthymic subjects with bipolar disorder were characterized by impairments in adjusting behavior as a function of prior reinforcement history. These findings offer initial insights about the potential source of dysfunctional reward processing in bipolar disorder.