In this Issue

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A brief summary of the articles appearing in this issue of *Biological Psychiatry*.

Schizophrenia: Genetic, Molecular, and Cellular Findings

Recently, the discovery of several novel genes for schizophrenia has provided a solid basis on which to investigate its biological foundations. Here, **Ottis *et al.*** (pages 604–610) report that one of these genes, disrupted-in-schizophrenia 1 (*DISC1*), when aggregated as a protein, can segregate with another schizophrenia candidate protein, dysbindin, that previously has not been directly linked to the DISC1 pathway. These investigations suggest that schizophrenia pathology of different, independently identified genes may converge on the protein level.

Schizophrenia susceptibility has been previously linked to neurodevelopmental processes involving tyrosine phosphorylation-mediated signaling. **Takahashi *et al***. (pages 626–635) performed genetic, behavioral, and postmortem mouse and human studies that implicate the *PTPRA* gene, which encodes protein tyrosine phosphatase RPTPα, in schizophrenia. This convergent evidence linking RPTPα to schizophrenia may represent a potential novel avenue for therapeutic exploration, particularly the tyrosine kinases c-Src and Fyn.

Identifying the location of ErbB4, the receptor mediating the biological effects of neuregulin-1, is essential for understanding how this pathway regulates neuronal network activity and behaviors, and its association with psychiatric disorders. **Neddens *et al.*** (pages 636–645) analyzed the cellular and subcellular distribution of ErbB4 in neurons of the frontal cortex of five species. They found that ErbB4 expression is evident in a subset of interneurons, but undetectable in pyramidal neurons of the frontal cortex, validating the use of rodents to study the biological functions of ErbB4.

Sodhi *et al.* (pages 646–654) measured the expression of glutamatergic transcripts in two populations of laser-captured cells from the medial dorsal thalamus in postmortem brains of individuals with schizophrenia and psychiatrically healthy controls. They detected reduced glutamatergic gene expression in schizophrenia, specifically in the large medial dorsal cells, which are mostly glutamatergic relay neurons projecting to the prefrontal cortex. These findings indicate that glutamatergic innervation is dysfunctional in the thalamocortical circuitry in schizophrenia.

Buizer-Voskamp *et al.* (pages 655–662) investigated the involvement of large genomic deletions and duplications in Dutch schizophrenia patients and healthy controls. They observed significantly more genomic deletions, but not duplications, in patients compared to controls. A subsequent systematic literature search for genomic and cytogenetic variants reported in schizophrenia patients helps highlight potential chromosomal regions of interest.

The major histocompatibility complex (MHC) region plays a central role in the immune system and has been implicated in the development of schizophrenia. **Agartz *et al.*** (pages 696–698) investigated associations between gene variants across the MHC region and brain structure in patients with severe mental illness and healthy controls. They report significant associations in schizophrenia spectrum disorder patients between common gene markers in the MHC region and cerebral ventricular volume, adding evidence to potential immune system involvement in schizophrenia pathology.

Sensory Dysfunction in Schizophrenia

In a study of patients with schizophrenia, **Leitman *et al.*** (pages 611–618) report that deficits in perceiving social intent of speech as conveyed by vocal intonation (prosody) hinge on abnormal processing of elementary auditory features within and between temporolimbic and inferior-frontal brain circuits. These findings illustrate the interplay between sensory and higher-order cognitive dysfunction in schizophrenia, suggesting that remediation targeting auditory perceptual abilities may improve social communication and function.

Schizophrenia: Cytokine Levels

Miller *et al.* (pages 663–671) performed a 40-study meta-analysis of cytokine levels in schizophrenia, considering effects of clinical status and antipsychotic treatment. They found that blood levels of interleukin (IL)-1β, IL-6, and transforming growth factor-β appeared to be state-related markers for acute exacerbations of psychosis, whereas IL-12, interferon-γ, tumor necrosis factor-α, and soluble IL-2 receptor appeared to be trait markers. Although these results could provide the basis for future hypothesis testing, most studies did not control for potential confounding factors such as body mass index and smoking.

Structural Imaging in Schizophrenia

Brain abnormalities are present in individuals with schizophrenia at disease onset, but the progression of these abnormalities over time is less clear. Using data from a longitudinal study of patients with first-episode schizophrenia and controls, **Andreasen *et al.*** (pages 672–679) report that progressive brain change occurs in schizophrenia, affects both gray matter and white matter, is most severe during the early stages of the illness, and occurs only in a subset of patients. Thus, measuring the severity of progressive brain change may offer a promising new avenue for phenotype definition in genetic studies of schizophrenia.

Phillips *et al.* (pages 680–689) used a novel structural and diffusion tensor imaging method to assess the integrity of superficial white matter between schizophrenia patients and their relatives and community comparison subjects and their relatives. Compared to controls, patients showed reduced superficial white matter integrity across both hemispheres. Further, integrity of superficial white matter was shown to vary in accordance with relatedness to a schizophrenia patient in both hemispheres indicating disease-related genetic factors.

Clinical Staging Model for Psychiatry?

A new approach to understanding severe mental disorders is to adopt a clinical staging model, which defines disease progression along a continuum of severity. **Wood *et al.*** (pages 619–625) review the evidence for such a model in psychotic disorders, with a focus on neuroimaging data. Overall, they report that the main predictions of the model are supported, although a number of other contributing factors still need to be accounted for.

Metabolic Effects of Brain Stimulation

Binkofski *et al.* (pages 690–695) demonstrate that cerebral energy consumption induced by transcranial direct current stimulation increases systemic glucose uptake and reduces stress axes activity in healthy male volunteers. This finding demonstrates that transcranial brain stimulation not only evokes alterations in local neuronal processes but also clearly influences downstream metabolic systems regulated by the brain, and suggests that it may serve as a promising non-pharmacological therapy option for metabolic disturbances in a number of neuropsychiatric diseases.

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