IN THIS ISSUE

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

CNTRICS II: Developing Biomarkers

Carter *et al.* (pages 7–12) describe the results of the second phase of the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) meetings, in which, through a consensus-passed process, issues related to the use, interpretation, and development of imaging and transcranial magnetic stimulation (TMS) biomarkers for use in treatment development were identified and evaluated. A detailed set of criteria were also specified in order to guide the future development of imaging biomarkers for use in treatment development for impaired cognition in schizophrenia and other serious mental and developmental disorders. Future directions for the development of imaging biomarker measures through the CNTRICS process are discussed.

The first phase of the CNTRICS initiative focused on the identification of cognitive constructs from human and animal neuroscience that were relevant to understanding cognitive deficits in schizophrenia, as well as promising task paradigms that could be used to assess these constructs behaviorally. The current phase of CNTRICS has the goal of expanding this initial work by including measures of brain function that can augment these behavioral tasks as biomarkers to be used in drug development processing. Here, **Barch and Mathalon** (pages 13–18) review many of the psychometric issues that need to be addressed in regards to the development and inclusion of such methods in the drug development process.

TMS is a neuropsychiatric tool that can serve as a useful method to better understand the neurobiology of cognitive function, behavior, and emotional processing. In their review, **McClintock *et al.*** (pages 19–27) examine the utility of TMS as a means of measuring neocortical function in neuropsychiatric disorders in general, and schizophrenia in particular, for the CNTRICS initiative.

Event-related potentials (ERPs) have been used for decades to characterize cognitive deficits in schizophrenia and other psychiatric disorders. Could they be used as biomarkers of these deficits in the development and implementation of new treatments for disordered cognition? **Luck *et al***. (pages 28–34) describe the consensus opinion resulting from the CNTRICS II meeting which examined this possibility. They review several promising aspects of ERPs as well as preliminary studies in which ERPs have proven useful, for example, by predicting which patients will benefit from a given medication.

Schizophrenia Genetics: Cognition, Immunity, and Diabetes

Patients with schizophrenia often have strong cognitive deficits. The underlying mechanisms remain elusive but correlations to immunity responses have been documented. **Håvik *et al.*** (pages 35–42) hypothesized that immunity-related pathways are important for cognition-linked neuronal activities in brain. Using three independent case-control samples, they found a strong genetic association to *CSMD1* and *CSMD2*, two complement-control-related genes, suggesting that immunity genes have an alternative role in dysregulation of neuronal networks in schizophrenia.

A previous genome scan of Taiwanese schizophrenia families suggested linkage to chromosome 10q22.3. Aiming to find candidate genes in this region, **Liu *et al.*** (pages 51–58) used a multipronged approach and identified four susceptibility genes, *ANXA7*, *PPP3CB*, *DNAJC9*, and *ZMYND17*, that were associated with schizophrenia patients with deficits in sustained attention and executive function.

Patients with schizophrenia and their relatives are at an increased risk for type 2 diabetes compared to the general population, but the reasons for this co-morbidity have been unclear. **Hansen *et al.*** (pages 59–63) genotyped risk variants of type 2 diabetes in patients with schizophrenia and healthy controls, and in a second replication sample, and found an association with one at-risk allele located in *TCF7L2*. This finding suggests the increased incidence of type 2 diabetes among schizophrenia patients and relatives results from heritable factors that are common to both disorders.

Functional Connectivity and Neuroimaging in Schizophrenia

Cole *et al.* (pages 43–50) used resting state functional connectivity magnetic resonance imaging (MRI) to attempt to identify sources of individual differences in psychopathology. They identified a dorsolateral prefrontal cortex region with global dysconnectivity in patients with schizophrenia, compared to control subjects. Consistent with their hypothesis, they found that this region's dysconnectivity is highly variable, and that this variability correlates with multiple symptom domains of schizophrenia.

Schizophrenia affects one's capacity to adaptively regulate thoughts and behavior, a capacity termed cognitive control. **Fornito *et al.*** (pages 64–72) used novel brain imaging techniques to identify alterations of frontoparietal regions involved in cognitive control, and show that these are superimposed on a more widespread and generalized abnormality of brain network function. These findings provide important new insights into how large-scale brain networks are affected by schizophrenia under different cognitive demands.

Disturbances of cognitive control have been associated with impaired functional specialization within the lateral prefrontal cortex (LPFC). Using functional MRI (fMRI) with an action selection task, **Barbalat *et al.*** (pages 73–80) demonstrated that the effective connectivity within the rostro-caudal axis of the LPFC is impaired in schizophrenia compared to controls, providing evidence of a top-down functional disconnection within the LPFC in this disorder.

Individuals with schizophrenia show impaired emotion processing, but their unaffected siblings also display behavioral impairments in emotion processing. Using fMRI, **van Buuren *et al.*** (pages 81–87) examined brain activation in unaffected siblings and healthy controls during the viewing of emotional and neutral pictures. They report hyperactivity in the siblings during the emotional pictures within areas important in emotion processing, including the amygdala, hippocampus and medial prefrontal cortex, supporting the notion that emotion processing is abnormal in subjects genetically at risk for schizophrenia.

It is well-established that schizophrenia is associated with structural brain abnormalities, but whether these progress over time remains unclear. **Olabi *et al.*** (pages 88–96) conducted a systematic review of longitudinal region-of-interest structural MRI studies. Subjects with schizophrenia showed significantly greater decreases over time in whole brain volume, whole brain gray matter, frontal gray and white matter, parietal white matter, and temporal white matter volume, as well as larger increases in lateral ventricular volume, than healthy control subjects.

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Bimodal Distribution of Polyunsaturated Fatty Acids

There is conflicting evidence of whether polyunsaturated fatty acids (PUFA) in red blood cells are bimodally distributed in schizophrenia. Here, **Bentsen *et al.*** (pages 97–105) show that schizophrenia and schizoaffective disorder can be divided in two, according to blood levels of PUFA. One third of patients constituted a low-PUFA group who had levels at one fifth of those in high-PUFA patients and healthy controls, which did not differ. Alpha-tocopherol was predictive of PUFA, but not smoking, gender, antipsychotic medication or diet.