Targeting Cognition in Schizophrenia Research: From Etiology to Treatment

Over the past 20 years, a plethora of resources have been aimed at characterizing and treating the cognitive impairments of schizophrenia. This activity is reflected in the exponential increase in scientific publications related to cognition in schizophrenia (1). As a result of these efforts, cognitive impairment is now considered a core symptom of the disorder. Of crucial importance is the influence of cognitive impairment in predicting patients' functional adaptation. Cognitive impairment appears to be a major predictive factor in determining a patient's ability to cope successfully with everyday activities, including vocation, social networks, and living independently (2). For this reason, efforts are being made to develop treatments aimed at enhancing cognition, as well as to identify the underlying etiopathogenic mechanisms of cognitive impairment. In this issue of the *Journal*, two articles address this trend in schizophrenia research.

"In addition to the search for cognition-enhancing compounds that enhance neural systems with specificity, will drugs need to be developed that are specific to etiology?"

In a pragmatic and clinically oriented open-label trial, Davidson et al. (3) tested the cognition-enhancing properties of four second-generation antipsychotics—amisulpride, olanzapine, quetiapine, and ziprasidone—as well as the most commonly prescribed first-generation antipsychotic—haloperidol, administered at low doses. This trial enabled the researchers to test the efficacy of haloperidol on cognitive deficits without the motor and speed impairments in cognitive performance that it often causes at higher doses. The study found enhanced cognitive performance after 6 months of treatment and no overall difference in the degree of improvement among the five drugs. While these results are consistent with those of the Clinical Trials of Antipsychotic Intervention Effectiveness (CATIE) in chronically ill patients (4), this study used haloperidol instead of perphenazine and extended the findings to patients with first-episode schizophrenia.

The investigators present convincing arguments that neither the use of an open-label design nor study dropouts biased the results. Despite the low doses of haloperidol, the use of a test battery heavily weighted toward tests of speed may have influenced the results. Slower responses are scored as cognitive deficiencies in executive function and working memory. An editorial published in the February 2008 issue of the *Journal* highlighting the results of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) collaborative project spoke to the need for standardized cognitive tests that better distinguish the different facets of cognitive dysfunction in schizophrenia (5).

The results of the Davidson et al. study have important implications for the clinical management of cognitive deficits in schizophrenia. They also allude to the disadvantages and cost-effectiveness, or lack thereof, of using second-generation antipsychotics for the therapeutic goal of enhancing cognitive performance. As the authors point out, the process of finding a new drug with cognition-enhancing properties would require the development of new compounds focusing on cognitive impairments rather than merely using drugs that have been successful in ameliorating psychotic symptoms.

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There are three factors to consider when thinking about these data. The first has to do with practice effects (6). Certainly, longer intervals (like the 6 months in the Davidson et al. study) may attenuate practice effects but not entirely eliminate them. For instance, verbal learning tests repeated at 2-year intervals demonstrate a practice effect of 0.22 effect size units (the mean difference between the two tests divided by the pooled standard deviation), an effect similar to that observed with drug treatment (7). Procedural or implicit learning may show effects of earlier exposure to the test that are especially long lived. Second, the different binding profiles of the drugs used in this study, at receptors known to influence neurocognition (including the D_1, D_2, M_1, and 5-HT_{2A} receptors), might in principle make it seem improbable that all would engender similar degrees of cognitive improvement, yet they do. Third, if one assumes that a cognition-enhancing agent should also enhance cognition in at least some healthy comparison subjects (e.g., in the elderly or in individuals carrying a specific genotype), there is little evidence to suggest that a class of drugs with high D_2 receptor antagonist activity could improve cognition.

Nevertheless, it is important to appreciate that D_2 antagonists have profound restorative effects on the neurocognitive underpinnings and circuitry of psychiatric symptoms, including abnormal salience in delusions, semantic misprocessing in speech disorganization, and misattribution in hallucinations (8–10). Thus, understanding how the first- and second-generation D_2 antagonists succeed and how they fail in reversing specific types of information processing abnormalities in relatively dissociable neural systems may provide an important lead in understanding pathogenesis in schizophrenia.

In a second study reported in this issue, Brown et al. (11), in line with their previous research on the associated risk of schizophrenia and increased serological levels of influenza and toxoplasma antibodies (12, 13), go a step further in trying to demonstrate an etiopathogenic mechanism underlying executive dysfunction in schizophrenia. In a research area where studies focusing on descriptions of impaired cognition have been the rule instead of studies aimed at finding etiological mechanisms, this is one of the first studies to look at prenatal exposure to infection as an etiologic mechanism of cognitive dysfunction in schizophrenia. Using prospective data from a well-characterized population-based birth cohort, Brown et al. found an association between serologically documented maternal infection with influenza and toxoplasmosis and executive dysfunction in people who have schizophrenia. The acquisition of biomarkers documenting the prenatal exposure to infection is doubtless a robust strength supporting the finding, but the small sample of only eight infected schizophrenia patients who underwent executive evaluation (and a small, albeit exquisitely well matched, comparison group) and the lack of an infected comparison group are limitations that future research should address to replicate this finding.

Prenatal exposure to infection with *Toxoplasma gondii* is associated with immediate and delayed cognitive sequelae in children: microcephaly, low IQ, and bilateral deafness (14). Given that the parasite that causes the infection cannot cross the placenta, it is assumed that elevated maternal IgG antibody to toxoplasma is the agent that damages the developing fetal brain (13). How antibody titers selectively disrupt frontal-type executive functions is an unresolved question. Moreover, it is unknown whether higher IgG toxoplasma antibody levels are related to the severity of executive dysfunction as a possible surrogate of the effect of IgG antibody on the brain. Little is known about the consequences of maternal influenza infection in human fetal development. As findings in experimental animals suggest (15), prospective cohort studies should address the question of what the neurodevelopmental consequences are in offspring of mothers who have been exposed to influenza infection during pregnancy. In that respect, a recent study (16) has linked general cognitive abnormalities (as reflected in IQ) in children exposed in utero to influenza who later developed schizophrenia in contradistinction to exposed children who did not develop schizophrenia. Again, future research

should aid in distinguishing between cognitive consequences of prenatal exposure to infections, such as toxoplasmosis and influenza, and specifically schizophrenia-related changes. In addition, as may have been expected, cognitive sequelae of exposure to infection in this schizophrenia sample are complex. For instance, premorbid cognitive ability (measured with the Wide Range Achievement Test–3) was higher in the exposed than in the nonexposed case subjects.

To summarize, Brown et al. demonstrated that exposed case subjects had poorer executive function. This is not only interesting in and of itself, it also raises questions about the nature of the pathology, its selectivity or predilection for a presumptively prefrontal neural system (versus the alternative notion that the tests showing impairment were simply those most psychometrically sensitive), and whether a specific etiology shapes the cognitive target. What would be the implications for the treatment of schizophrenia patients who had prenatal exposure to infection? Should they be treated in a different way than those not exposed? Thus, in addition to the search for cognition-enhancing compounds that enhance neural systems with specificity, will drugs need to be developed that are specific to etiology? Economic hard times notwithstanding, these are million-dollar questions that the field faces.

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