

Cognitive Neuroscience and Schizophrenia: Translational Research in Need of a Translator

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It has now been more than half a century since the discovery of neuroleptic medications as a treatment for schizophrenia. Their discovery marked the beginning of the biological revolution in psychiatry. An understanding of their mechanisms of action promised to shed light on the pathophysiologic processes that are fundamental to schizophrenia. Furthermore, their efficacy in treating some of the most dramatic symptoms of schizophrenia (including hallucinations and delusions) raised the promise that additional pharmacologic agents could be discovered to treat the other, equally debilitating disturbances associated with the illness—loss of affect and cognitive disorganization. Unfortunately, neither set of promises has been fully met. Although we have learned much about neurobiological disturbances associated with schizophrenia, we remain in the dark about the etiology and basic pathophysiology of this illness. At the same time, although there have been refinements in antipsychotic medication, for the most part these have addressed the side effects of earlier agents, and little progress has been made in treating the other disturbances associated with this illness. Most important among these is cognitive dysfunction—a treatment-refractory hallmark symptom of schizophrenia, that may be the primary contributor to loss of social and occupational function (1). Cognitive dysfunction can be clinically dissociated from the emotional and motivation disturbances associated with schizophrenia (2) and has been found to be one of the most disabling dimensions of the illness, closely associated with inability to work and need for structured living (3).

Recognizing the need for medications targeted at the cognitive deficits in schizophrenia, in 2002 the National Institutes of Health sponsored the MATRICS Initiative (Measurement and Treatment Research to Improve Cognition in Schizophrenia). The goal of this initiative, led by Steve Marder, Keith Nuechterlein, and Michael Green at the University of California—Los Angeles and overseen by Wayne Fenton and Ellen Stover at the National Institute of Mental Health (NIMH), was to identify and standardize a battery of clinical instruments for assessing cognition in clinical trials of schizophrenia. An important purpose of this effort was to collaborate with the Food and Drug Administration (FDA) in sanctioning the use of such instruments as targets for the development and approval of new pharmacologic agents that improve cognitive function in schizophrenia. This effort represented an unprecedented collaboration between basic and clinical scientists in academia, the pharmaceutical industry, NIMH, and FDA. With remarkable speed, the initiative produced the MATRICS Consensus Cognitive Battery (MCCB) (4), released in 2006, and had an instantaneous impact on pharmacologic research in schizophrenia.

The MCCB was a landmark development, representing the first time that a measure of improvement in cognitive function in

schizophrenia was recognized by the FDA as a legitimate indication, unto itself, for the development of pharmacologic agents. Toward this end, two important factors governed the inclusion of specific instruments in the MCCB: psychometric validation and clinical practicality. That is, each instrument must provide a robust and reproducible measure of the dimension of cognitive function for which it was targeted, and its administration must be practical and reliable in a clinical setting. These requirements naturally favored the inclusion of standard neuropsychologic instruments that had been vetted by decades of intense evaluation and use in clinical settings.

For these same reasons, however, most of the neuropsychologic instruments included in the MCCB are based on psychological theory and behavioral testing methods from the 1960s that have changed little since that time. During the intervening 4 decades, there have been revolutions in basic research on human cognition and its neural underpinnings, marked by the emergence of cognitive psychology in the early 1970s and cognitive neuroscience in the late 1980s. Research in these fields has produced major advances in the precision with which cognitive processes can be measured and related to underlying neural mechanisms using modern electrophysiologic and neuroimaging techniques.

Unfortunately, however, these developments in basic science have seen little translation into clinical research or practice. As the authors of the MATRICS battery dutifully noted, a “priority for future research will be to subject these new instruments—emerging from basic cognitive neuroscientific research—to rigorous psychometric testing, and translate the most promising of these into clinically useful instruments that may provide improved sensitivity for the evaluation of cognitive functioning in schizophrenia.” This is the focus of the NIMH sponsored Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS; <http://cntrics.ucdavis.edu/index.shtml>) and the subject of this special issue.

Both scientific and sociological obstacles have impeded the translation of advances in cognitive psychology and cognitive neuroscience to clinical research and practice. Scientifically, instruments emerging from behavioral and cognitive neuroscience laboratories are not always suitable “off the shelf” for clinical application: they may not be sufficiently robust to produce reliable results in clinical populations while having sufficient sensitivity to detect changes in clinical state necessary to assess the effects of treatment. They may also lack practicality, involving procedures that are too long or too complex to be performed by patients with psychiatric illness or relying on apparatus or procedures that require specialized training to administer. Although in many instances it may be possible to overcome these obstacles, doing so also faces sociological challenges. On one hand, the basic scientists responsible for developing these measures often are not interested in, nor are they rewarded for, translating these paradigms into clinically useful instruments (tenure is rarely given for methods development). On the other hand, the clinical researchers and practitioners who could make productive use of such instruments rarely have the relevant training in behavioral and neuroscientific

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methods to pursue such work. In other words, translational research in cognitive neuroscience is in need of a translator.

This is the express purpose of CNTRICS: to provide mechanisms for, incentives that motivate, and instructive examples of the translation of modern cognitive psychological and cognitive neuroscientific measures into clinically useful instruments. Under the leadership of Cameron Carter at the University of California, Davis and Deanna Barch at Washington University, and the guidance of Robert Heiassen at the NIMH, three international meetings have been planned to initiate this effort. These are sponsored by the NIMH and designed to sustain the collaborative momentum built by the MATRICS Initiative, engaging basic and clinical scientists from academic and industry laboratories, as well as representatives from the NIMH and FDA. The goal of these meetings is to generate consensus on three critical issues: which cognitive processes and corresponding neural mechanisms are most important to target (first meeting), what steps must be taken to adapt methods for studying these to use in clinical settings (second meeting), and what specific tasks and neuroscientific methods measure the relevant cognitive processes and are suitable for such adaptation (third meeting). The overview article by Carter *et al.* in this special issue (pages 4–10) describes the agendas for each of these three meetings in greater detail, as well as future directions for the CNTRICS initiative. The remaining articles report on the significant progress that was made at the first of these meetings, held in February 2007 in Washington, DC, and focusing on the selection of cognitive systems to be targeted.

Over the past 5 years, the NIMH has increasingly focused on translating neuroscience discoveries to solve problems in public health. In some areas, this has meant understanding the developmental expression of candidate genes or the search for new molecular targets, a translational task that can be accomplished through traditional research grant mechanisms. Translating breakthroughs in cognitive neuroscience is a greater challenge, requiring NIMH to exert its convening authority to bridge the sociological and intellectual gaps among the academic world of cognitive science, the regulatory constraints of the FDA and industry, and the needs of clinical investigators working with acutely ill patients. The goal is ambitious: to redefine schizophrenia as a cognitive disorder, with psychosis as a late and potentially preventable consequence. If CNTRICS can identify cognitive markers of schizophrenia that precede and predict psychosis, this effort could transform our approach to the treatment of schizophre-

nia from ameliorative antipsychotic medications to the development of preemptive interventions that could forestall or even prevent psychosis. With the encouragement of the National Mental Health Advisory Council and the leadership of NIMH program staff, and especially Robert Heiassen, CNTRICS is already on its way to transforming the next generation of research studies of schizophrenia.

The CNTRICS Initiative represents the second milestone in a bold new mission for the field of schizophrenia research. The MATRICS Initiative broke ground by establishing improvements in cognition as a legitimate target for drug development and by establishing the precedent of consensus measures for the field. CNTRICS now seeks to modernize the instruments used to assess cognitive processes and the neural mechanisms on which they rely. Success in this effort will yield many important dividends, including progress in our understanding of the pathophysiology of schizophrenia and the generation of more refined methods for diagnosis and treatment of schizophrenia, including the development and approval of new drugs. These efforts promise also to have an impact on other domains of psychiatric research by providing a new generation of methods for studying cognitive disturbances in illnesses such as depression, bipolar disorder, and attentional-deficit disorder. We applaud the vision and commitment of the many investigators who have worked to move this effort forward and eagerly anticipate the progress their work will bring.

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