New Approaches to Measurement and Treatment Research to Improve Cognition in Schizophrenia

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This special issue of Schizophrenia Bulletin includes a set of review articles derived from the sixth and final meeting of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program (www.matrics.ucla.edu). MATRICS was initiated by the National Institute of Mental Health (NIMH) in order to identify and remedy barriers to the development and evaluation of drugs targeting the specific treatment of cognitive deficits in schizophrenia. The NIMH awarded the MATRICS contract to the University of California, Los Angeles (UCLA; Drs. Stephen Marder and Michael Green, co-principal investigators), in 2002.

MATRICS was designed to achieve broad academic and industry consensus regarding the nature of cognitive impairments in schizophrenia and how they might best be assessed and treated. Over the course of 2 years, MATRICS brought together the relevant stakeholders to build a consensus and establish a clear path that would enable the U.S. Food and Drug Administration (FDA) to consider registering compounds intended to treat cognitive deficits in schizophrenia, independently of treating psychosis per se. The modal use of such compounds likely would be as cotreatments in schizophrenia patients already stably treated with antipsychotic medications.

The MATRICS Neurocognition Committee organized the first 2-day MATRICS consensus meeting in April 2003 and identified 7 critical domains of cognition in which deficits are evident in patients with schizophrenia. The MATRICS Neuropharmacology Committee Meeting, held at the National Institutes of Health (NIH) in June 2003, brought together clinicians and psychopharmacologists from academia and industry to identify the most promising molecular targets, compounds, human test measures, and animal models for use in the pursuit of treatments that target the basic mechanisms related to complex cognitive operations. The papers derived from that meeting are assembled in a special issue of Psychopharmacology. The third MATRICS conference used the RAND consensus process to develop suggestions for the optimal neurocognitive tests and resulted in the beta version of the MATRICS Consensus Cognitive Battery for Clinical Trials (see www.matrics.ucla.edu). The fourth MATRICS meeting was the NIMH–Industry Collaboration Meeting held at NIMH in January 2004. The fifth was the FDA/NIMH joint meeting on the assessment of cognition as an end point in clinical trials and was held at NIH in April 2004. The conclusions from this conference are summarized by Buchanan et al. In sum, the MATRICS conferences included participants from the NIMH, NIH, and FDA, as well as academic and industry representatives, and were very effective in establishing a broad consensus regarding the appropriate criteria and opportunities for discovering and evaluating cotreatments for the cognitive impairments in schizophrenia.

Once the primary consensus-building goals of MATRICS were accomplished, the final MATRICS meeting was designed to look forward and develop a research agenda that would foster the theme “New Approaches to Assessing and Improving Cognition in Schizophrenia.” This meeting was organized by the MATRICS New Approaches Committee, listed in table 1, and was held at the Bolger...
Center (Potomac, Md.) in September 2004. Approximately 120 individuals from academia, industry, and government participated in this 2-day meeting, which began with 5 formal presentations and a series of 8 breakout groups on the first day. Each breakout group was charged with the task of identifying the key priorities for future research programs to advance the preclinical and clinical science relevant to identifying and evaluating treatments for cognitive deficits in schizophrenia. On the second day, each of the breakout group’s priorities were presented and discussed by the entire group of meeting participants. Transcripts of the slide presentations and summary discussions from the meeting are available on the MATRICS website.

Introductory presentations at the meeting addressed the goals for the conference, including what the NIMH hoped to learn from the participants in terms of the new research programs needed to capitalize on the opportunities presented by breakthroughs in the registration possibilities for pro-cognitive cotreatments in schizophrenia. These presentations were given by Dr. Steven Marder, principal investigator of the MATRICS program at UCLA; Dr. Wayne Fenton, who led the MATRICS effort from NIMH together with Dr. Ellen Stover; and Dr. Thomas R. Insel, the director of NIMH. The transcripts of these presentations are provided on the MATRICS website.

Five formal presentations then provided the background to the challenge of developing an effective research program. The original slides and transcripts are available on the MATRICS website, and each presentation is presented as an essay in this issue. The paper by Dr. Cameron Carter reflected months of preparatory discussions from within the MATRICS New Approaches Committee. It presents the case for a needed paradigm shift involving the application of new approaches derived from experimental cognitive psychology and cognitive neuroscience to complement the traditional neuropsychological approaches that provided the basis for the MATRICS clinical test battery. Such a paradigm shift is seen as critical to the development and validation of cross-species methods that are essential to support the effort to discover new molecular entities and validate their efficacy first in predictive animal models, then in human proof-of-concept studies, and finally in extensive clinical trials.

Dr. Alan Breier, of Eli Lilly and Company, then presented a summary of the future research needs from the perspective of the key clinical challenges facing the pharmaceutical industry as it engages in the actual clinical development of cognition-enhancing agents in schizophrenia. He emphasizes the needs for validated biomarkers, especially markers that are amenable to translational studies across species, and the essential collaborations among academia, industry, NIH, and regulatory agencies that have characterized the MATRICS effort to date.

Dr. John Jonides then described the power and desirability of using a top-down approach involving sophisticated imaging methods and cognitive paradigms to specify the component processes that are disturbed in psychiatric disorders such as schizophrenia. The essay by Jonides and Nee illustrates that we already possess many of the tools needed to develop a more neurobiologically informed understanding of the nature and potential treatments of the cognitive deficits in schizophrenia.

Dr. Jim Hagan, of GlaxoSmithKline, reviewed the MATRICS-inspired needs of the pharmaceutical industry from the perspective of the preclinical drug discovery and selection process. The extensive review by Hagan and Jones emphasizes the challenges associated with mapping existing animal model paradigms onto the 7 cognitive domains identified by the MATRICS program. Although some domains are not tractable to cross-species work (e.g., verbal learning and memory), opportunities are evident in most of the relevant domains of interest. Hagan and Jones note that it will be critical to develop empirical evidence in human proof-of-concept trials of efficacious agents that can then be used as positive controls in validating predictive animal models. Again, the need for collaborations between preclinical and clinical researchers and paradigms is identified as critical to the future success of the research program.

The final formal presentation, by Dr. Trevor Robbins of the University of Cambridge, described a bottom-up approach to cross-species examinations of cognitive processes and their modification by pharmacological treatments. This article examines the challenges—and opportunities—for...
the future research program from the perspective of animal model development by illustrating the value and feasibility of designing analogous animal and human tests to maximize their predictive and construct validity.

Based on the challenges summarized in these introductory presentations, the remainder of the meeting focused on discussion groups. Separate breakout groups addressed topics that were necessarily divided somewhat arbitrarily in order to cover the wide range of issues. Each breakout group was asked to identify 3 to 5 priorities for new research needed to advance each area. Two co-leaders and several key participants were invited to lead each group; other participants in the meeting were free to participate fully in the groups of their choice. On the second day of the meeting, the key issues and priorities identified by each of the groups were presented by the co-leaders and then opened for discussion by the entire group of meeting participants. The slides, transcripts of the presentations, and transcripts of the subsequent discussions are available on the MATRICS website (see www.matrics.ucla.edu).

Five essays in this special issue summarize the majority of these breakout group discussions. Two groups examined the need to develop new biomarkers that could track the efficacy of cognitive treatments in schizophrenia, as summarized in a single article by Cho et al. These groups identified several needs for further validation of biomarkers based on either functional neuroimaging or electrophysiological methodologies, including assessment of test-retest reliability and pharmacological responsiveness. Potential biomarkers based on positron emission tomography or psychophysiology, although better studied pharmacologically, were acknowledged but not discussed extensively. The essay by Nuechterlein et al. summarizes group discussions regarding issues related to distinguishing separable domains of cognition in both human and animal studies. Two sets of recommendations are presented concerning research to evaluate the psychometric properties of available measures and studies designed to develop and validate animal models that will enable the discovery and preclinical testing of potential cognition-enhancing agents.

The review by Barch identifies several specific priorities for the research needed to better understand how cognitive dysfunction in schizophrenia may be related to, influenced by, or lead to disturbances in emotion, motivation, and stress. In particular, research examining the influences of pharmacological treatments on motivation and the hedonic processing of affectively laden stimuli is critically needed. Green et al. review the equally complex issues surrounding research on deficits in social cognition in schizophrenia, emphasizing that such work is in its infancy and must be approached from a variety of perspectives in an interdisciplinary manner. Strategies are discussed to address the difficulties inherent in defining relevant constructs and relating studies in animals to those in humans.

Finally, in keeping with the fundamental theme of translational science that emerged in the conference, Floresco et al. review the discussions of the breakout group charged with establishing priorities for the development of predictive animal models for assessing treatment effects on cognition in schizophrenia. Validation of appropriate animal models is essential to the discovery of new compounds and requires close collaboration with the clinical studies that are needed to identify compounds having known efficacy to serve as positive controls, preferably using human paradigms that can be readily mimicked in animals. One explicit suggestion is that existing data regarding the effects of nonproprietary compounds in various relevant animal paradigms be assembled into a shared database. More broadly, the group urges that a mini MATRICS-style workshop involving both academic and industrial scientists be convened to draft the key elements of a research program and suggests that a preclinical trials network of laboratories is urgently needed to develop and evaluate potential models.

Overall, the New Approaches Conference identified and specified important priorities to guide the development of further research in this newly incentivized arena of drug discovery for treatments of cognitive deficits in schizophrenia. The opportunities presented by the prospect of using specific treatments for specific cognitive problems in patients with schizophrenia were spawned by a deliberate consensus-building effort that brought together key stakeholders from academia, industry, and government. One of the pervasive sentiments expressed at the MATRICS New Approaches Conference and in the essays assembled in this special issue is that the realization of these opportunities will similarly depend on cross-fertilizations from multiple disciplines based on close coordination of preclinical and clinical efforts in both academia and industry.

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References

