Pharmacological Treatment of Cognition in Schizophrenia: An Idea Whose Method Has Come

In writing a commentary on the three articles in this issue generated by the MATRICS project (the Measurement and Treatment Research to Improve Cognition in Schizophrenia, an initiative of the National Institute of Mental Health [NIMH]), we find ourselves in a unique position: We are almost the only psychologists in the field of cognition and schizophrenia who are not authors of reports on this enormous collaborative effort—one that has led to a sea change in the integration of neurocognition and clinical trials. However, both of us, along with many others, were nevertheless part of the process, as consultants in early stages on test selection and as developers of specific measures that were included in the final assessment battery. The number of early participants as well as the extensive list of authors is a clear indication of the involvement of the overall field in the MATRICS process.

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Developing a method to evaluate the efficacy of treatments that target cognitive impairment in schizophrenia has been a timely and critical task, especially given that the central role of cognition in long-term disability has become increasingly apparent. This achievement is all the more remarkable in light of the contentiousness characterizing previous attempts among neuropsychologists to establish a representative (and practical, meaning "brief") assessment battery. Prior to the MATRICS initiative, we had no agreed-upon standardized way of measuring change in cognition in response to treatment, one consequence of which was that findings often could not be compared across studies. For example, in the recent past, it was not uncommon for the results of one antipsychotic clinical trial to show no effects on memory while another showed notable improvement. Closer inspection of the reports, however, often revealed that a much easier memory test was used in the study that showed improvement, leading to the question of whether differential memory effects between studies were due to different medication properties or to psychometric confounders. This type of problem greatly compromised interpretation of findings across treatments. The MATRICS initiative has provided a solution to this problem by developing a common test battery to be used across clinical trials, thus holding measure variance constant while varying treatment.

In the world of clinical practice, an equally challenging issue has been to ascertain the role of cognition—and hence of improved cognition—in the course of illness, in the lives of our patients, and in our patients' prognosis in the real world. As a result of the efforts of some of the central participants in the MATRICS project, particularly Drs. Green and Nuechterlein, the research and clinical worlds are now interacting and jointly recognizing that cognition is an important component of schizophrenia and of successful everyday functioning for patients with the disorder. Improving cognition has thus been increasingly viewed as perhaps the best way to reduce the long-term functional disability so characteristic of schizophrenia. The MATRICS initiative has provided a significant initial step for developing an assessment method and a regulatory pathway

that will allow medications to be tested for efficacy in improving cognition and reducing disability in schizophrenia (1).

The three articles appearing in this issue clearly show the amount of effort that went into this project and the care with which it was carried out. The first article, by Nuechterlein et al., describes the initial test selection and validation process. More than 90 tests were nominated by the field as a whole; this pool was narrowed through an expert review process to 36 measures, of which a RAND panel selected 20 to constitute the beta battery that was tested with schizophrenia patients. Each measure in the beta battery was evaluated for reliability and temporal stability to generate a final battery of 10 tests, representing seven cognitive domains, referred to as the MATRICS Consensus Cognitive Battery (MCCB).

The next step, as reported by Kern et al. in the second of three articles, was to co-norm and standardize the 10 MCCB measures. Co-norming, which refers to establishing normative data simultaneously for all measures in the MCCB using a single representative sample, represents a distinct advance in the field, where the use of norms has until now been very uneven. As indicated in the report, based on the findings of this study, the default scoring option in the MCCB computer scoring program produces data for adults controlled for age and gender.

The third article, by Green et al., is concerned with the implications of cognitive impairment for real-world functioning. This study represents an extension of the MATRICS initiative in response to the requirement by the U.S. Food and Drug Administration (FDA) that for a drug to be accepted as a cognition-enhancing agent, change must also be demonstrated on a coprimary measure, that is, a measure considered functionally meaningful. The FDA position reflects the questions about the significance of cognitive change in the real world often asked by clinicians. Although assessments of function in everyday living are important, they are only in the early stages of development. Green et al. evaluate the coprimary potential of four relatively new measures—two measures of functional capacity and two interview-based measures of cognition. This study is critically important from a scientific perspective since it represents the first attempt to examine comprehensive correlations between a cognitive assessment battery and measures of real-world social and daily living. The results were complex and interesting, and they highlight the amount of work remaining to be done in the newly emergent area of functional outcome. On the one hand, cognitive performance related well to the two functional capacity measures, and relatively lower correlations were observed with the interview-based measures of cognition. On the other hand, both the functional and interview measures showed lower-than-expected associations with established measures of real-world functioning. The authors conclude that on the basis of these findings, any of the four coprimary measures evaluated appear acceptable for use in clinical trials, but there is no one measure sufficiently strong to be recommended for this purpose. The Green et al. report will likely fuel a new generation of functional outcome studies focusing on the development and refinement of measures of functional capacity, which in turn will lead to major advancements in clinical trial and research methodology.

Multiple constituencies will benefit from the results of the MATRICS process. One of these is the scientific community. The fact that a consensus battery was developed and validated means that clinical neuropsychologists were able to shed their (probably deserved) reputation as a group whose primary focus was on “my favorite tests” and work collaboratively to achieve consensus about something aimed at a larger, greater good. As early as the first MATRICS meeting, consensus on the important domains, albeit not on all of the individual tests, was actually achieved by the meeting’s close. NIMH will benefit from the MATRICS results as well. The fact that the goals of the MATRICS project were achieved and that we now have available a consensus battery for testing cognition

underscores the good judgment that went into starting this process in the first place as well as funding it with a large-scale, long-term contract.

Pharmaceutical companies will also benefit from the MATRICS project: Now "all" they have to do is to develop a drug that enhances cognition—they will no longer have to convince the FDA of the merits of their assessments as well as the merits of their compound. Similarly, the FDA will benefit because it will no longer have to rely on testimony from consultants as to the best way to assess the outcomes of interest. Likely this will result in faster, fairer decisions on claims for indications associated with cognition and functional deficits in schizophrenia.

It is clear, however, that the major beneficiaries of MATRICS process will be our patients. They are the ones with disability, poverty, and social isolation, the ones whose quality of life suffers because of cognitive impairments and the negative assumptions made about those who are not employed, self-sufficient, or independent. Moreover, it is not just people with schizophrenia who will benefit when these treatments are developed. It has been increasingly recognized that patients with bipolar disorder and major depression have cognitive impairments that persist when their symptoms are in remission. The availability of a regulatory pathway and a means of assessing cognitive outcomes makes it more likely that reduction of disability in affective disorders will become a focus of treatment as well.

MATRICS is still a process and not a closed book. The three articles in this issue represent only the first phase of the MATRICS project. Additional follow-up work is now being done, including translation of the MCCB into other languages and, in response to findings of the Green et al. article, a major effort directed toward the development of change-sensitive and practical coprimary measures. The MCCB will also serve as a reference point for later research on the basic underpinnings of the cognitive processes measured by the battery. Such developments could lead to more targeted treatment-development research. One of the best possible future outcomes of the MATRICS process would be for it to spur similar efforts to understand the neurobiological substrates underlying cognitive impairment in schizophrenia, including advancement of assessment measures, understanding of the biological underpinnings of cognition, and development of targeted interventions. A major goal of this research would then be to understand the different (or overlapping) causes of cognitive impairment in schizophrenia, affective disorders, and other forms of severe mental illness.

Reference

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