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New Opportunities in the Treatment of Cognitive Impairments Associated With Schizophrenia

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Abstract
The cognitive deficits so characteristic of patients with schizophrenia are largely responsible for the poor functional outcome apparent in this patient population and are not ameliorated by existing antipsychotic drugs. The critical unmet need for treatments for the cognitive impairments associated with schizophrenia has been addressed in a series of federally funded initiatives, beginning with Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and continuing with Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS). As reviewed here, these programs have set the stage for an expansion of basic and clinical cognitive neuroscience research to support the discovery and development of cotreatments to be used in conjunction with antipsychotic medications in the treatment of specific cognitive deficits in patients with schizophrenia.

Keywords
Schizophrenia, MATRICS, TURNS, CNTRICS, cognition, CIAS

The group of schizophrenias has long been among the most challenging mental disorders to understand and treat. The advent of antipsychotic drugs in the 1950s brought about a revolution in the care and treatment of patients with schizophrenia, profoundly reducing the number of patients who are chronically institutionalized. Nevertheless, the functional outcome of patients treated effectively with antipsychotic medications remains far less than adequate, with few patients achieving successful reintegration into the workplace and society. Cognitive impairments are present at the onset of the illness, persist throughout the lifespan, are strongly associated with poor outcome and functional disability, and are largely refractory to treatment. The focus of the present review is on initiatives that have evolved over the past several years with the goal of rectifying this critically important unmet clinical need. These initiatives have paved the way for psychological and neuroscientific investigations that could revolutionize treatment strategies in the care of patients with schizophrenia.

MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia
Cognitive deficits have been long recognized as core characteristics of the group of schizophrenia disorders and are largely responsible for the functional disability apparent in this patient population (Green, 1996). It has become clear that the cognitive deficits so characteristic of patients with schizophrenia have not been ameliorated by existing antipsychotic drugs. Although many antipsychotic treatments have been identified and marketed, the cognitive deficits remain and most individuals with schizophrenia are burdened by significant psychosocial deficits. Only a small percentage of antipsychotic-treated patients with schizophrenia achieve full employment and independent living. Strong evidence that cognitive deficits are critical contributors to the typically poor functional outcome in schizophrenia has emerged (Green, 1996). For several decades, the U.S. Food and Drug Administration (FDA) has licensed drugs for use in schizophrenia only if they reduce the positive symptoms of psychosis (i.e., are antipsychotics). In effect, the FDA has operated from the implicit assumption that a single drug should treat the entire disorder instead of specific compounds treating specific clinical problems. This requirement precluded the development of drugs having therapeutic effects.
that were limited to amelioration of the cognitive impairments associated with schizophrenia (sometimes abbreviated CIAS). Instead, attempts to improve the efficacy of treatments for such impairments focused on combining multiple actions in the same molecule. Thus, industry sought more complex drugs having multiple mechanisms of action in order to treat both the positive symptoms and the cognitive deficits.

This approach forced the field away from specific pharmacological tools that impacted specific molecular targets toward less specific drugs with complex mechanisms and multiple unwanted effects. At a time when the fields of psychology and neuroscience were bringing new levels of sophistication to our understanding of the substrates of separable aspects of cognitive function, our efforts at intervention in the cognitive functions of patients were becoming progressively less specific. Once this critical bottleneck limiting the development of treatments for the cognitive impairments associated with schizophrenia was identified (Fenton, Stover, & Insel, 2003), the United States National Institute of Mental Health (NIMH) initiated the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program. MATRICS developed a broad consensus as to how cognitive deficits could be assessed and treated (Marder & Fenton, 2004), enabling the FDA to consider registering compounds intended to treat these deficits in schizophrenia, independently of treating psychosis per se.

The MATRICS initiative consisted of a systematic series of six conferences designed to build consensus opinions spanning governmental, academic, and industrial sectors. In just 2 years, the MATRICS group established agreement between these different constituencies in critically important areas. In the first meeting, a neurocognition working group determined the domains of cognition deemed most relevant in schizophrenia: working memory, attention/vigilance, verbal learning and memory, visual learning and memory, speed of processing, reasoning and problem solving, and social cognition (see Green & Nuechterlein, 2004; Nuechterlein et al., 2004). It is noteworthy that the domain of social cognition was included in this list not on the basis of an extensive supporting literature, as was the case for the other six domains of cognition, but by virtue of a clear consensus among the MATRICS participants that the psychosocial disabilities so pervasive in schizophrenia patients are powerful impediments to functional recovery and are relatively specific to this disorder compared to other cognitive disorders (see Green, Oliver, Crawley, Penn & Silverstein, 2005). In the second MATRICS meeting, a diverse group of psychopharmacologists identified the most intriguing molecular targets, promising compounds, relevant human test measures, and potentially predictive animal models for use in the discovery of treatments that target basic mechanisms related to complex cognitive operations (Geyer & Tamminga, 2004a, 2004b). In the third meeting, MATRICS established a MATRICS Consensus Cognitive Battery (MCCB) for clinical trials (see www.matrics.ucla.edu; Green et al., 2004) and described the processes required for assessment of cognition as a clinical endpoint (Buchanan et al., 2005). In follow-up work by the leaders of MATRICS, the MCCB was refined using empirical comparisons of alternative versions and assessed for its psychometric properties in an additional NIMH-funded program. Subsequently, MATRICS leaders developed a nonprofit entity to make the MCCB, which drew upon a variety of established psychological test instruments, available as a package (see www.matricsinc.org). In a fourth meeting, MATRICS published extensive discussions regarding the development of a research agenda that would foster improved methods for the discovery, validation, and assessment of procognitive cotreatments for schizophrenia (see Geyer, 2005; Geyer & Heissen, 2005). As a result of MATRICS, the FDA appears ready to consider registering drugs for the treatment of cognitive impairments associated with schizophrenia, either as global treatments for cognition or as specific treatments for the separate domains of cognition identified by MATRICS as being affected in those with the disorder. Hence, multiple new indications for use in patients with schizophrenia are now clinical targets for the pharmaceutical industry. A key to the success of the entire MATRICS program was the enlightened willingness of NIMH to provide the leadership and support for the partnership between industry and academia that were essential to the consensus-building process.

It is relevant here to note that the willingness of the FDA and NIMH to consider using a strategy of licensing cotreatments for specific aspects of a diagnostic entity has broad implications for psychiatric drug development and treatment. In part, this approach reflects the considerable complexity of disorders such as schizophrenia, which likely have a variety of etiologies. Although there are always concerns regarding interactions between different drugs when using cotreatment strategies, the reality is that most patients with schizophrenia are treated routinely with multiple psychopharmacological medications. This movement away from requiring that all aspects of a complex disorder be treated with a single medication may further enable clinicians to personalize treatment by utilizing more specific compounds targeting specific complaints and domains of function. Of course, such optimism assumes that pharmaceutical companies will be successful in identifying and developing specific treatments for the specific cognitive impairments that a particular patient exhibits. It also assumes that clinicians will be able to identify specific profiles of impairments and assess the efficacy of cotreatments. Such changes in drug development and prescribing practices will not evolve rapidly, especially considering the intrinsic complexity of assessing cognitive functions. Nevertheless, the MATRICS model is in keeping with the growing recognition that few psychiatric symptoms are unique to any given diagnostic entity and that more dimensional characterizations of psychiatric patients may provide better guides to treatment strategies. Since many stakeholders are already discussing the potential value of adopting a MATRICS-like approach to revising treatments for other psychiatric disorders, the MATRICS program may have influences far beyond the treatment of schizophrenia.
TURN S: Treatment Units for Research on Neurocognition in Schizophrenia

It is important to emphasize that the model developed by MATRICS and approved by the FDA involves the use of cognitive enhancers to be administered as cotreatments in schizophrenia patients who are already on stable regimens of antipsychotic medications. The consensus was that cognitive deficits, and their amelioration, simply could not be assessed accurately in patients experiencing hallucinations and other disruptive psychotic symptoms. Given the novelty of this treatment approach involving the addition of a cognitive enhancer to continuing treatment with an antipsychotic drug, NIMH funded another substantial project called Treatment Units for Research on Neurocognition in Schizophrenia (TURN S). This multisite clinical-trials network sought to implement the MATRICS clinical-trial design using the MCC B assessment tools (see www.turns.ucla.edu; Stover, Brady, & Marder, 2007). The TURN S Project was charged with selecting potential cognitive-enhancing agents and developed a network of academic sites in order to evaluate potential efficacy of novel agents in proof-of-concept trials (Buchanan, Freedman, Javitt, Abi-Dargham, & Lieberman, 2007). Some of the TURN S studies are still ongoing under the auspices of the Treatment and Evaluation Network for Trials in Schizophrenia (TENETS) network, although the clinical network is no longer receiving federal support. To date, no clearly efficacious agent has been identified by TURN S, although it should be recognized that this field is still in its infancy.

It can be argued that TURN S was an overly ambitious program that underestimated the scope of work required and the complexity of dealing with the intellectual property implications of partnerships between industry, government, and multiple academic institutions. Since federal funding was involved, there were intrinsic constraints against utilizing the more developed expertise of the pharmaceutical industry in guiding the selection of candidate compounds and optimizing the designs of clinical trials. Funding limitations also constrained the sample sizes and therefore the power of the TURN S studies. The concern remaining is that some might feel that the failure of TURN S to demonstrate the efficacy of a procognitive cotreatment indicates that such treatments will be difficult to discover. Given how little fundamental research has been directed at validating potential treatments for cognitive impairments associated with schizophrenia, it should not be surprising that the few candidate compounds tested to date, mostly in small trials involving relatively few patients, have not met with success. A more protracted effort based on more targeted basic neuroscience research will be required to satisfy this critical unmet need in the treatment of schizophrenia patients.

Additional Post-MATRICS Initiatives in the United States

Another continuing effort spawned from MATRICS is the MATRICS-CT (for co-primary selection and translation of the MCC B; see www.matrics.ucla.edu/matrics-ct). MATRICS-CT is supported by a partnership of pharmaceutical companies to address the need for measures of functioning and functional capacity (Stover et al., 2007). In MATRICS meetings, the FDA indicated that improvement on neuropsychological tests alone would be insufficient for approval of a treatment for cognitive impairments in schizophrenia. Rather, measured cognitive improvement should be accompanied by improvement on a measure of functioning or at least the patient’s perception of improved cognition. The FDA did not require confirmation of improvement in community functioning but indicated the need for improvement in a measure that had more face validity (i.e., improvement on a measure that appears to be relevant to function) than a neuropsychological task. Given the lack of consensus regarding instruments for measuring functioning that can be used in relatively brief clinical trials, MATRICS-CT is working to develop such a consensus. This emphasis on a demonstration of treatment-induced improvement in functional outcome reflects the fundamental rationale for MATRICS, insofar as the focus on ameliorating cognitive deficits was driven by the evidence indicating that psychosocial disabilities were attributable in large part to impaired cognition. In addition, MATRICS-CT is translating and validating the MCC B for use with additional languages, in recognition of the international nature of drug discovery and development in psychiatric disorders. Another initiative (the NIMH Initiative Regarding Treatment for Negative Symptoms) is using the MATRICS consensus-building model to address the inadequate treatment of negative symptoms in schizophrenia (i.e., those symptoms that reflect an absence of normal behavior, such as apathy, lack of pleasure, or social withdrawal), with the aim of developing more sensitive instruments for measuring this symptom domain (see Stover et al., 2007).

European Initiatives

In Europe, the European Commission has approved funding to be provided by a combination of governmental and pharmaceutical industry funds and directed specifically to the improvement of preclinical–clinical translation via partnerships between industry and academia under a program called Novel Methods leading to New Medications in Depression and Schizophrenia (NewMeds) as part of Europe’s Innovative Medicines Initiative (see imi.europa.eu/documents_en.html). Approximately €10 million will involve projects focusing on psychiatric drug discovery, including a substantial focus on drugs to treat the cognitive impairments associated with schizophrenia. Included within this effort are plans to assess empirically the possible interactions between pharmacological treatment of cognitive deficits and the application of cognitive training programs. One concern raised during MATRICS was that the effects of pharmacological cognitive enhancers might not yield changes in functional outcome, or even surrogate (i.e., laboratory-based) measures of outcome, in the absence of some form of concomitant cognitive training. Another practical issue being addressed in this initiative, as well as by
independent groups, is the development of formal comparisons between the MCCB and other cognitive-test batteries. Although currently considered the standard that the FDA will expect for licensing compounds for treating cognitive impairments, the MCCB is seen by some to be limited by the fact that it takes a substantial amount of time, is not computerized, and is not particularly conducive to cross-species comparisons. Clinical assessment tools that cannot be predicted by or translated from preclinical tests in animals considerably constrain the drug discovery process. As with the original MATRICS effort in the United States, an encouraging and critically important aspect of this initiative is the openness of European governments to support, and the pharmaceutical companies to participate in, cooperative efforts involving multiple companies and multiple academic institutions.

**CNTRICS: Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia**

A subsequent program that is still ongoing, Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS), is designed to bring the modern tools and concepts of cognitive neuroscience to bear upon the assessment of cognitive impairments in schizophrenia and the efficacy of pharmacotherapeutics in ameliorating them (see cntrics.ucdavis.edu). The CNTRICS initiative was born of discussions during MATRICS about the desirability of utilizing tasks and tools derived from cognitive neuroscience to supplement the MCCB (Carter & Barch, 2007; Carter et al., 2008; Stover et al., 2007). This supplementation could involve the use of additional physiological and behavioral measures, such as event-related potentials (i.e., changes in brain waves elicited by sensory stimuli), prepulse inhibition of startle (i.e., a simple laboratory measure of sensory filtering that reflects the difficulties in inhibiting irrelevant responses), or functional imaging technologies (Green et al., 2009). The goal of CNTRICS is to integrate the tools and constructs of cognitive neuroscience to enhance our ability to translate basic research in animals into clinical studies in patients in order to facilitate the discovery and development of treatments that target cognitive impairments in schizophrenia.

As is true in all psychiatric drug discovery (Geyer & Markou, 2002), an emphasis on understanding the neurobiology underlying cognitive constructs is required for the development of novel treatments for cognitive impairments. Such work will depend on the coordinated use of both animal and human measures to identify and validate novel molecular targets for cognitive deficits (Floresco, Geyer, Gold, & Grace, 2005; Hagan & Jones, 2005). Because MATRICS needed to produce a consensus-based cognitive battery quickly, it necessarily focused on extensively studied tasks having demonstrated reliability, as well as considerations of how faithfully the measures assessed the cognitive domains that are impaired in patients. Measures derived from cognitive neuroscience were considered, but many were not included primarily because their measurement properties had yet to be established. The CNTRICS project grew out of the final MATRICS meeting, where the potential benefits of using tasks and tools from cognitive neuroscience were broadly acknowledged (see Geyer, 2005). These benefits include: (a) the use of fine-grained tasks that measure discrete cognitive processes; (b) the ability to design tasks that distinguish between specific cognitive deficits and poor performance due to generalized deficits resulting from sedation, low motivation, poor test-taking skills, and so on; and (c) the ability to link cognitive deficits to specific neural systems using animal models, neuropsychological or psychophysiological tests, and functional imaging (Barch et al., 2009). Measuring the function of specific cognitive systems that are linked to specific neural systems using a cognitive neuroscience approach offers unique advantages, especially for translational research (see Carter & Barch, 2008; Carter et al., 2008).

CNTRICS acknowledges the practical realities inherent in clinical trials, such as the need for efficient and standardized tasks having good psychometric properties. The idea is to adapt tasks being used in academic settings, which typically are long and frequently modified, for use in clinical settings. Clearly, some of these tasks will be burdened with technological requirements beyond the scope of larger clinical trials but still may be valuable for Phase II trials that are so critical to a company’s decision to make a major investment in costly Phase III trials with a potential new drug. A related reality being addressed in CNTRICS is the value of developing biomarkers reflecting the underlying neural systems in addition to measures of behavior. The use of simultaneous measures of behavior and brain function may help determine when and even why new drugs are or are not working. Further, biomarker measures may eventually provide important information about individual differences in neural function that may determine who will respond in what way to which type of medication, supporting the move toward personalized medicine. CNTRICS has developed an ambitious agenda, to bring new sophisticated tests to bear upon assessments of clinical efficacy. The critical need for tests having construct validity for the cognitive impairments troubling our patients is undeniable. It must be recognized, however, that the process envisioned by CNTRICS is a slow one. CNTRICS is not focused on utilizing tasks that have already been developed and may have some degree of established validity in the context of biomarkers or efficacy signals. The worthy goal of CNTRICS is to foster the development, adaptation, and validation of new tasks being used largely in academic settings and to streamline them for use in the clinic. Since such a process will take years to evolve, it may be difficult for the field to be sufficiently patient, given the pressures for industry to see tangible proof-of-principle studies in order to invest further in treatments for cognitive impairments associated with schizophrenia.

The need to identify and develop cross-species tools with which to predict and evaluate novel treatments of cognitive impairments associated with schizophrenia is evident (Floresco et al., 2005; Hagan & Jones, 2005). Due to the
absence of any treatments known to ameliorate the cognitive deficits in schizophrenia, preclinical drug discovery programs have difficulty assessing the predictive validity of the many cognitive tests available (Floresco et al., 2005). As a result, current efforts are based primarily on our understanding of the theoretical constructs and neurobiology related to cognition. A subgroup of TURNS began to address this need by surveying a number of experts in the field regarding the appropriate approaches to evaluating rodent and primate tests of each of the cognitive domains identified by MATRICS (see www.turns.ucla.edu; Young & Geyer, 2007). Many groups are exploring translational paradigms that have construct validity for the assessment of cognitive impairments in schizophrenia and may be applicable across species. The preclinical models ranked in the TURNS survey are now being used by pharmaceutical companies to guide their preclinical drug discovery and validation programs. More recently, Young and colleagues have provided an extensive critical review of the available animal tasks that best relate specifically to the constructs and tasks assessed by the MCCB (Young, Powell, Risbrough, Marston, & Geyer, 2009). Future meetings of the CNTRICS program will constitute the first formal effort to develop some consensus about what preclinical tests will be optimal for predicting the clinical efficacy of pharmacological treatments for cognitive impairments in schizophrenia.

As discussed briefly at the last of the MATRICS meetings (Floresco et al., 2005), the drug discovery process will depend essentially on the development and validation of preclinical tests having construct and predictive validity across species for the several domains of cognitive impairments associated with schizophrenia. Construct-valid cognitive tests are typically complex and relatively time-consuming and costly to conduct. Hence, the overall task of creating a useful preclinical test battery for cognitive impairments in schizophrenia is enormous. Most of the extant literature relevant to tasks that might be included in a preclinical test battery derives from models related to the cognitive impairments seen in disorders such as Alzheimer’s, not schizophrenia. Many believe that the scope of work required to develop useful preclinical screening tests for cognitive enhancers is such that coordinated collaborations among multiple pharmaceutical companies and many academic laboratories will be critically important. Although the development of a collaborative preclinical trials network for cognitive impairments in schizophrenia was suggested by the MATRICS group (Floresco et al., 2005), it is difficult for industry to share data and work openly with academia. Some such collaborative efforts appear to have been initiated successfully by the NewMeds program begun in the European Community (discussed previously). There is not yet a safe harbor in the United States for such an effort would be highly recommended and could have a significant impact.

**Implications for Psychological Science**

MATRICS has altered the environment for drug discovery for schizophrenia in substantial ways. The products of MATRICS and CNTRICS have the potential to provide evidence for efficacy in the early phases of clinical drug testing. The availability of validated measures of the specific cognitive deficits seen in schizophrenia could enable Phase II trials to identify the particular cognitive target affected most strongly by selective pharmacological interventions. Hence, Phase III trials targeting specific cognitive functions could be designed with increased confidence, power, and efficiency. Furthermore, CNTRICS’ focus on using homologous animal and human paradigms during the drug discovery and validation process should enhance translational predictions of efficacy. Thus, pharmaceutical companies and academic laboratories alike now have the incentive to pursue the development of compounds with specific pharmacological actions on systems known to modulate separable domains of cognition. In concert, cognitive psychologists and behavioral neuroscientists now have renewed enthusiasm to refine our understanding of the neural substrates of particular cognitive processes. Within these academic communities, the most immediate consequence of the MATRICS initiative has been the renewed hope that improvements in our fundamental understanding of the neurobiology of cognition may potentially be translated into improved treatments that could actually be developed and marketed and thereby become available to treat patients with schizophrenia.

**Recommended Reading**

Green, M.F. (1996). (See References). The classic review that established the importance of cognitive deficits in the poor functional outcome associated with schizophrenia despite the efficacy of antipsychotics in treating positive symptoms.


Young, J.W., Powell, S.B., Risbrough, V.B., Marston, H.M., & Geyer, M.A. (2009). (See References). A recent and very extensive review that critically evaluates the applicability of many animal models to the cognitive constructs and tasks used in the MATRICS cognitive test battery for clinical assessments.

**Declaration of Conflicting Interests**

The author declared that he had no conflicts of interest with respect to his authorship or the publication of this article.

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