
Keith H. Nuechterlein1,2, Trevor W. Robbins3, and Haim Einat4

1Departments of Psychiatry and Psychology, University of California, Los Angeles, 300 UCLA Medical Plaza, Room 2251, Los Angeles, CA 90095-6968; 2Cambridge University; 3College of Pharmacy, University of Minnesota, Duluth

At the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) New Approaches Conference, a discussion group focused on directions for future research that are critical to enhancing our understanding of the distinctions among key cognitive domains that have relevance for the development of cognition-enhancing interventions. One set of recommendations emphasizes the need for examining and optimizing the psychometric properties of relevant measurement paradigms from cognitive psychology and cognitive neuroscience. This step is critical to translating many notable advances in these basic fields into measures that would be appropriate for clinical trials. A second set of recommendations focuses on key directions for the development and application of animal models of cognitive processes that would greatly aid the discovery and preclinical testing of potential cognition-enhancing agents. As part of this process, the group noted several existing animal paradigms that have particular promise as measures in the key cognitive domains in schizophrenia identified by the MATRICS Neurocognition Committee.

Key words: neurocognition/clinical trials/behavioral neuroscience

Introduction

As part of the process of developing a Consensus Cognitive Battery to be used in clinical trials of potential cognitive enhancers for schizophrenia,1 the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Neurocognition Committee examined the existing literature on cognitive deficits in schizophrenia to identify the key separable dimensions. This critical evaluation of the empirical literature emphasized factor-analytic studies of cognitive performance in patients with schizophrenia as a means of identifying dimensions that are independent or only weakly intercorrelated.2 Six replicable cognitive dimensions were found that were judged appropriate for inclusion in a Consensus Cognitive Battery for clinical trials: speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, and reasoning and problem solving. One other replicable dimension, verbal comprehension, was judged inappropriate for a clinical trials battery, because it indexes a static cognitive ability that is unlikely to be sensitive to pharmacological intervention. Subsequent discussion at the first MATRICS consensus conference led to the addition of social cognition as a seventh domain for the clinical trials battery. Its emergence in the scientific literature on schizophrenia was too recent to have representative measures included in factor-analytic studies, yet several lines of evidence suggest that it is a key domain for intervention studies. These 7 cognitive domains then became the basic structure of the MATRICS Consensus Cognitive Battery for clinical trials.2 The selection of individual measures within each domain was based on reliability and validity criteria appropriate for measuring cognitive change in schizophrenia within clinical trials.3

Starting from this background, a discussion group at the MATRICS New Approaches Conference focused on several core issues that had become evident in the process of attempting to distinguish major separable cognitive domains in schizophrenia and selecting measures of these domains. During the earlier deliberations of the MATRICS Neurocognition Committee, certain gaps in the available data were identified that tended to limit the incorporation of recent, very promising paradigms from cognitive psychology and cognitive neuroscience.
into cognitive batteries for clinical trials. Thus, some discussion focused on strategies for filling these gaps. A second major theme of the discussion concerned directions for further development of animal models of the processes in these same key cognitive domains. Because early stages in the development of new cognition-enhancing agents for schizophrenia are dependent on the availability of appropriate animal models of the basic cognitive processes, certain directions within behavioral neuroscience need to be given priority to facilitate successful drug development. This summary focuses on the major recommendations that emerged from the initial discussion group and the presentation of its findings to the larger audience on the second day of the New Approaches Conference.

Psychometric Properties of Paradigms From Cognitive Psychology and Cognitive Neuroscience

Major advances in basic cognitive psychology (basic behavioral research on cognition) and cognitive neuroscience (research on the neural and physiological roots of cognition) have been made in recent years.4-7 These advances have included both new conceptual distinctions and associated measurement paradigms that have substantial potential to influence our understanding of cognitive deficits in schizophrenia and to refine efforts to develop new pharmacological agents to reverse these deficits. In considering the adoption of several of these paradigms for the MATRICS Consensus Cognitive Battery for clinical trials, the MATRICS Neurocognition Committee found that the lack of standardized versions of the paradigms and absence of sufficient psychometric data typically precluded their inclusion at this juncture. Specifically, promising cognitive paradigms from cognitive psychology and cognitive neuroscience had sometimes already been applied to schizophrenia patients, but limited or no data were available on their test-retest reliability, repeatability (absence of practice effects or availability of parallel forms), ceiling and floor effects, and relationship to functional outcome. Because these aspects of test reliability and validity are critical to the evaluation of cognitive change in clinical trials, the newer paradigms often did not emerge as the strongest current tests within a cognitive domain for clinical trials purposes.

This situation is understandable, given that the first priority in the development of new paradigms in cognitive psychology and cognitive neuroscience is usually the study of distinctive elementary cognitive and neural processes in normal individuals. An emphasis on mean effects in normal individuals does not lead naturally to a focus on the psychometric properties that are critical to the use of cognitive paradigms to measure differences between individuals and cognitive changes with repeated measurement. Even the initial application of such promising paradigms to schizophrenia does not typically emphasize evaluation of these psychometric properties, as the first stage of clinical research application usually focuses on establishing the utility of the new paradigm to make a contribution to understanding the nature of the cognitive deficits of the modal patient with schizophrenia.

To remedy this situation for the future, our discussion group recommended that certain specific research directions be given greater priority. First, for paradigms with promise for application to schizophrenia, collaborations between cognitive neuroscientists and experts in psychometrics should be encouraged. Clinical investigators will often be a critical component of these teams to allow the effective application of promising paradigms to samples of schizophrenia patients. The primary measures from the paradigm should be evaluated for short-term test-retest reliability (e.g., 2 to 4 weeks), repeatability without ceiling or floor effects, and relationship to functional outcome.

An iterative process should be expected during the psychometric evaluation of such promising new paradigms, as it is likely that the initial test version will not have optimal psychometric properties for clinical trials. As the parameters of the basic paradigm are manipulated to improve the psychometric properties of a measure, it will be critical to evaluate whether the intended cognitive process continues to be isolated by the new version of the measure. For example, certain manipulations to bring task difficulty into an optimal psychometric range might shift the specific cognitive process that is demanded to complete the task. This careful attention to maintaining the focus on the same cognitive process while adjusting the psychometric properties of a task applies to animal as well as human paradigms. Thus, thoughtful interactions between cognitive scientists and experts in psychometrics will be needed to ensure that psychometrically improved measures continue to partition the cognitive processes in the same fashion as the original versions.

Pharmacological Dissociation of Cognitive Processes

The identification of separable cognitive domains within schizophrenia to date has primarily depended on cross-sectional studies of patients that employed large neurocognitive test batteries. While the relative independence of performance at a cross-sectional point in schizophrenia patients is a critical form of evidence for separable cognitive domains, this type of evidence does not directly address whether changes in these cognitive domains within individual patients tend to occur together or independently. In particular, these cross-sectional data do not address the extent to which pharmacological agents that target certain receptors have an impact on cognitive domains very selectively or affect a number of domains. Administration of a cognitive-enhancing agent can address whether certain cognitive domains change together.
over time while others remain unchanged in response to this agent. Evidence that certain pharmacological interventions result in changes in several cognitive domains, but not in other domains, would suggest a pharmacological dissociation of certain groups of cognitive processes. This type of pharmacological separation of cognitive processes may be partially distinct from the separation of cognitive domains in cross-sectional factor-analytic studies of cognitive performance in schizophrenia.

While evidence of the pharmacological disassociation of cognitive processes will arise naturally from clinical trials of potential cognitive enhancers in schizophrenia patients, this discussion group also recommended that increased attention be paid to such studies using animal models. While some animal models of cognition allow multiple cognitive processes to be assessed within a single study, many studies focus on measures of pharmacological response in a single cognitive domain. Increased use of measures from multiple cognitive domains within the same study would help to clarify which cognitive changes tend to occur together and how these linked changes vary with the receptor targets of various pharmacological agents.

Available Animal Models for the Key Cognitive Domains in Schizophrenia

Animal models are available for several of the cognitive domains that were identified as key for schizophrenia, while animal models may need to be developed for certain other domains. The discussion group identified the domains of working memory, attention/vigilance, and speed of processing as those in which animal models that are clearly appropriate for preclinical drug development work are already available. In working memory, delayed matching-to-sample and delayed nonmatching-to-sample tasks were viewed as very appropriate parallels to human working memory tasks. For attention/vigilance, the 5-choice serial reaction time task and other models of processes in Continuous Performance Test–like tasks are examples of appropriate parallels to the cognitive domain identified in schizophrenia patients. Simple reaction time tasks and some indexes of the 5-choice serial reaction time task may be useful animal models of the speed of processing dimension in schizophrenia patients.

Two other cognitive domains chosen by the MATRICS Neurocognition Committee as key for schizophrenia do have existing animal analogues that may parallel the human measures reasonably well. For visual learning and memory, novel object recognition tasks involve many of the same basic processes. Animal models that involve learning the spatial placement of rewards and which require longer memory periods than typical working memory tasks would be expected to require additional active retrieval processes that are characteristic of many human visual learning and memory tasks. The group also noted that drug discovery efforts could profit from increased use of animal paradigms that make a distinction between recollective and familiarity based memory. Recollective or episodic memory requires that an event be recalled with associations to specific concurrent features (place, time, etc.) and a sequential organization, whereas familiarity-based memory requires only the ability to determine that a stimulus has been experienced previously through a vague sense of familiarity. For the domain of reasoning and problem solving, the particular test chosen for the MATRICS Consensus Cognitive Battery is the Mazes subtest from the Neuropsychological Assessment Battery. While many animal maze tests focus on responses to immediate cues that do not involve reasoning and problem solving, these cognitive processes could be modeled by animal maze paradigms that entail the application of a rule across trials or rule-based switching across trials. The set-shifting aspects of reasoning and problem solving are well modeled by attentional set-shifting paradigms and by intradimensional versus extradimensional shift paradigms. Ironically, the group noted that the most popular human set-shifting tests, such as the Wisconsin Card Sorting Test, were eliminated from the MATRICS Consensus Cognitive Battery due to dramatic practice effects that are less evident in the animal analogues.

For these domains with available animal models, the discussion group suggested that I focus for further development should be the clarification of whether the same subcomponents of a domain are being measured at the animal and human level. Taking working memory as an example, Baddeley's conceptual model distinguishes mental manipulation of information (central executive functions) from maintenance of information (slave store functions), and schizophrenia may involve more impairment in one aspect than the other. In the test selected to represent verbal working memory for the MATRICS Consensus Cognitive Battery, a letter–number span, substantial demand on manipulation of information is involved. On the other hand, delayed matching-to-sample tasks in animal studies often require mainly short-term maintenance of information. Thus, despite the fact that the human and animal measures are both considered to be working memory tasks, their emphasis on different component processes might lead to somewhat different pharmacological response.

The example of emphasis on different component processes in human and animal measures within a cognitive domain was viewed as a contributor to a more general limitation in current knowledge that affects successful drug development. Namely, the extent to which pharmacological response using an animal model of a cognitive domain is predictive of human response in the same cognitive domain using the same agent is often less than one would expect or desire. Systematic work to improve the degree to which pharmacological response in an animal model predicts human response in the same cognitive
domain was viewed as a high priority, as this correspondence is fundamental to moving successfully from preclinical to clinical trials of potential cognitive-enhancing agents. Incentives for focused interactions and collaborations between relevant experts in human cognition and behavioral neuroscience were viewed as necessary to move this knowledge base forward.

Cognitive Domains Without Readily Available Animal Models

The discussion group viewed verbal learning and memory and social cognition as the 2 key cognitive domains that do not have clear analogues in animal models at this time. For verbal learning and memory, the emphasis on use of language prevents any close parallels in lower animals. However, the group suggested that animal models of visual/spatial learning and memory may serve as adequate preclinical tests of agents with the potential for success in improving verbal learning and memory in schizophrenia. Despite the partial separation of verbal and visual learning and memory deficits in schizophrenia, many investigators believe that these abnormalities are attributable to the components of neural circuits that are common to these domains rather than those that are content specific. Any attempt to find drugs that target verbal learning and memory preferentially would require animal models for left hemisphere functions, to the extent that lateralized learning functions can be isolated in animal species that are appropriate for drug discovery efforts. Certain differentiations in declarative memory may require nonhuman primate models.

Animal models that involve various aspects of social interaction are already available. However, it is not immediately clear how typical aspects of human social cognition correspond to the social interaction processes these animal models assess. Thus, some initial work may be needed to consider which of the available animal measures best index human processes such as emotion perception and managing of emotional responses that are central to deficits in schizophrenia.

Summary

This summary has focused on recommendations for future research that would allow greater incorporation of basic cognitive paradigms into clinical trials research, strengthen bridges between relevant animal and human paradigms, and aid identification of the key separable cognitive domains at human and animal levels. Examining and optimizing the psychometric properties of promising paradigms from cognitive psychology and cognitive neuroscience were recognized as an essential step in translating these paradigms into measures appropriate for clinical trials. This process will require careful attention to the discrete cognitive processes that are being distinguished, to avoid changing the measured process while optimizing psychometric properties. High-priority directions for the development of animal models of cognitive processes were discussed, with emphasis on the steps that would aid the discovery and preclinical testing of potential cognition-enhancing agents. Several existing animal paradigms were identified that have promise as measures of the key cognitive domains in schizophrenia. A high priority was recommended for research to identify parallel animal and human cognitive paradigms that would allow the prediction of human pharmacological response from animal pharmacological response within the same cognitive domain.

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