

Approaching a Consensus Cognitive Battery for Clinical Trials in Schizophrenia: The NIMH-MATRICES Conference to Select Cognitive Domains and Test Criteria

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To stimulate the development of new drugs for the cognitive deficits of schizophrenia, the National Institute of Mental Health (NIMH) established the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative. This article presents an overview of decisions from the first MATRICS consensus conference. The goals of the meeting were to 1) identify the cognitive domains that should be represented in a consensus cognitive battery and 2) prioritize key criteria for selection of tests for the battery. Seven cognitive domains were selected based on a review of the literature and input from experts: working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving, speed of processing, and social cognition. Based on discussions at this meeting, five criteria were considered essential for test selection: good test-retest reliability, high utility as a repeated measure, relationship to functional outcome, potential response to pharmacologic agents, and practicality/tolerability. The results from this meeting constitute the initial steps for reaching a consensus cognitive battery for clinical trials in schizophrenia.

Key Words: Cognition, cognitive assessment, cognitive enhancement, neurocognition, psychopharmacology, schizophrenia

The study of cognitive deficits in schizophrenia is expanding rapidly: over the decade of the 1990s, the annual publication rate for studies of cognition in schizophrenia increased roughly fivefold (Gold and Green in press; Hyman and Fenton 2003). Impressive growth in publication rate can be expected in new areas of exploration, but the topic of cognition of schizophrenia is neither new nor has it depended on recently developed technologies. One key reason for the rapid growth in this area is that cognitive deficits in schizophrenia are increasingly viewed as influencing functional outcome and, hence, targets for intervention. As such, the cognitive deficits of schizophrenia are now viewed as potential treatment targets for psychopharmacology (Green and Nuechterlein 1999; Hyman and Fenton 2003). Despite the desirability of interventions that target these deficits, no standards exist for evaluating drugs to treat the cognitive deficits in schizophrenia, and no drug has

been approved for this purpose. This situation presents a formidable disincentive for drug manufacturers to expend resources to develop an intervention, lest the U.S. Food and Drug Administration (FDA) not sanction their methodology. To stimulate the development of drugs to treat the cognitive deficits of schizophrenia, to clarify requirements for regulatory approval, and to facilitate the development of appropriate methods for collecting data to present to the FDA when requesting regulatory approval for such drugs, the National Institute of Mental Health (NIMH) established the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative. The MATRICS contract was awarded to UCLA in September 2002 (S.R. Marder, principal investigator; M.F. Green, Co-Principal Investigator).

This article presents an overview of selected topics from the first MATRICS consensus conference, "Identifying Cognitive Targets and Establishing Criteria for Test Selection," held in Potomac, Maryland, on April 14 and 15, 2003. This meeting constituted the initial steps in deciding on a consensus cognitive battery for clinical trials in schizophrenia. The absence of a standardized set of measures for cognitive deficits has been one of the obstacles to receiving regulatory acceptance. Although pharmaceutical companies have been using a variety of batteries to assess the cognitive effects of their compounds, there is a concern on the part of the FDA that acceptance of one of these instruments would give an undue advantage to a single company. The FDA prefers that a clinical end point for drug approval and labeling be widely accepted by the scientific community, rather than the product of a single company's research program.

The meeting was organized by the MATRICS Neurocognition Committee (K.H. Nuechterlein and M.F. Green, co-chairs), whose primary task is to oversee the process of selecting the NIMH-MATRICES consensus cognitive battery for use in clinical trials. Members of the Neurocognition Committee, who are among the authors of this report, represent academic, government, and consumer perspectives on the selection process. A complete list of the members and their affiliations is provided at

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Received February 2, 2004; revised April 27, 2004; accepted June 16, 2004.

the end of the paper. This report provides a rationale for the MATRICS contract and summarizes key decisions that were made at the meeting.

Background and Rationale for MATRICS

Cognitive deficits in this context refer to a wide range of performance deficits in areas such as attention, memory, speeded responses, or problem solving. A cognitive deficit reflects a disturbance in one of these underlying cognitive processes that may, or may not, be detected by standard clinical instruments or informal clinical observation but can be detected by appropriately designed cognitive performance tasks. The rationale for the psychopharmacologic treatment of cognition in schizophrenia rests on a few premises that have received substantial empirical support. One premise is that the cognitive deficits of schizophrenia are a core feature of the illness. A core feature means that the cognitive performance deficits are not simply the result of the symptoms, nor of the current treatments of schizophrenia. Instead, these deficits represent a fundamental aspect of the illness. Indeed, if the cognitive performance deficits were only a result of the clinical symptoms of schizophrenia or were only the side effects of current treatments, then it would make little sense to target cognition separately.

Evidence that cognitive deficits are core features of schizophrenia comes from various sources (Braff 1993; Gold and Green, *in press*; Goldberg and Green 2002; Nuechterlein and Dawson 1984; Nuechterlein et al 1994). First, many patients demonstrate clear cognitive impairments before the onset of psychotic symptoms and before the start of other clinical features (Cornblatt et al 1992; Davidson et al 1999; Mednick et al 1987; Nuechterlein 1983). Second, a subgroup of the first-degree relatives of schizophrenic patients who have no evidence of psychosis also demonstrate a pattern of cognitive impairments that is similar to that found in schizophrenia (Asarnow et al 2002; Cannon et al 1994; Green et al 1997), suggesting that certain cognitive deficits are likely to be components of genetic vulnerability to schizophrenia. Third, on some measures of cognition, the level of impairment shown by patients during a psychotic episode is similar to that seen in the same patients when their symptoms are under control or when they are in full remission (Finkelstein et al 1997; Nuechterlein et al 1998). Hence, cognitive impairment may occur independently, and even in the absence of clinical symptoms of schizophrenia. Fourth, the correlations between psychotic symptom severity and measures of cognitive performance are typically near zero (Bildler et al 2000; Goldberg et al 1993; Mohamed et al 1999). The findings are mixed for disorganized symptoms with some studies, but not others, reporting relationships (Mohamed et al 1999; Perry and Braff 1994; Spitzer 1997). Cognitive performance tends to be more related to negative symptoms, although the magnitude of the cross-sectional correlations is not very large (about 15% of the variance). Although the magnitude of cross-sectional correlations is modest, it is entirely possible that the relationships are stronger when within-subject change is considered. In addition, certain aspects of the negative syndrome that are not easily assessed on interview (e.g., motivation) may be more closely linked to cognitive performance. Fifth, the types of cognitive deficits seen in schizophrenia, although variable from person to person, tend to fit a typical profile that differs from the pattern of deficits seen in dementia (Welsh et al 1992), bipolar disorder (Fleck et al 2001; van Gorp et al 1998), and depression (Zakzanis et al 1998). This pattern can be seen in recent-onset, as well as chronic, patients

(Saykin et al 1991, 1994). Finally, both first- and second-generation antipsychotic treatments have marked effects on the psychotic symptoms of the illness, but their effects on cognition are much smaller, with the second-generation medications generally showing cognitive advantages (Blyler and Gold 2000; Cassens et al 1990; Harvey and Keefe 2001). This discrepancy between clinical and cognitive effects suggests that the antipsychotic medications act on different neural systems from those that underlie the cognitive impairments.

A second premise, one that is related to the idea that these deficits are a core feature, is that cognitive deficits are relatively common in schizophrenia. Estimates of the number of patients with cognitive deficits naturally depend on the performance cut-offs that are used. One influential study estimated that 90% of patients have clinically meaningful deficits in at least one cognitive domain and that 75% have deficits in at least two, the criterion for "impairment" in this study (Palmer et al 1997). Even these relatively high rates may be underestimates of the frequency of cognitive impairment in schizophrenia. Almost all schizophrenia patients are performing at a level below what would be expected in the absence of illness, based on, for example, the performance of patients' unaffected monozygotic twins on cognitive tests (Goldberg et al 1990).

A third key premise for targeting cognition in the treatment of schizophrenia is that the cognitive deficits are related to the daily functioning of patients, and these relationships are generally stronger than those between psychotic symptoms and functional outcome. Across studies, cognitive deficits show highly consistent relationships to various types of functional outcomes, including community functioning and the ability to acquire skills in psychosocial rehabilitation (Green 1996; Green et al 2000). These relationships for individual cognitive domains are usually moderate in strength, although relationships with large effects are possible (e.g., 20%-50% of the variance in outcome explained), especially when multiple cognitive domains are considered (Green et al 2000). Although most of the evidence supports cross-sectional relationships, recent studies have typically (although not always) found similar relationships with prospective studies in which cognitive deficits predict later functional status (Bryson and Bell 2003; Fujii and Wylie 2003; Gold et al 2002; Norman et al 1999).

A fourth premise is that patients' performance on cognitive tasks can be improved through psychopharmacologic treatment. The evidence for this comes from two sources. One is that newer antipsychotic medications have cognitive benefits when compared with conventional antipsychotic medications (Harvey and Keefe 2001; Keefe et al 1999; Meltzer and McGurk 1999). The benefits of newer versus older medications may depend on the dosage of the conventional medication, so it is not clear at this time whether the differences represent true pro-cognitive effects or reduced cognitive liability of the newer medications (Carpenter and Gold 2002; Green et al 2002; Harvey and Keefe 2001). Another source of evidence supporting efforts in this area comes from novel intervention approaches (e.g., glutamatergic, serotonergic, and dopaminergic agents) that have shown promise for cognitive enhancement in schizophrenia (Goff et al 1996; Stone et al 2003; Sumiyoshi et al 2001; Tsai et al 1998), in animal models (Castner et al 2000), or nonclinical samples (Luciana et al 1998). The large body of literature demonstrating brain structural abnormalities in schizophrenia and long-standing problems in neural connectivity also suggests limits on the magnitude of improvement we might expect from psychopharmacologic interventions. Although there is no expectation that medications will

completely surmount problems caused by structural abnormalities, it is reasonable to assume that novel drugs could generate more efficient use of the neural systems.

These premises and the related lines of evidence provide a context in which the cognitive deficits in schizophrenia become logical and desirable treatment targets; however, the FDA has thus far not allowed any claims to be made about a drug's effects on cognitive deficits in schizophrenia. Instead, the FDA and NIMH are seeking an unbiased assessment from experts in the field to reach a consensus on standards of measurement for cognition and clinical trial design. The NIMH has used its convening authority to start the process of establishing standards in this area by initiating the MATRICS contract.

Overview of MATRICS

The MATRICS contract has four main goals: 1) to promote development of novel compounds to enhance cognition in schizophrenia, 2) to catalyze regulatory acceptance of cognition in schizophrenia as a target for drug approval, 3) to help focus the economic research power of industry on a neglected clinical target, and 4) to identify promising compounds and support proof of concept trials for cognition in schizophrenia.

To accomplish these goals, MATRICS is coordinating a series of six consensus conferences in 2003 and 2004. More information on these meetings, including the slides and transcripts from the presentations, can be found on the MATRICS Web site (www.matrics.ucla.edu).

The first steps in the process of developing a consensus cognitive battery were to 1) identify the cognitive domains that should be represented in the battery and 2) prioritize criteria by which tests were to be selected for inclusion in the battery. These two topics were the focus of the first consensus conference, which was organized by the MATRICS Neurocognition Committee.

In preparation for this first consensus meeting, the MATRICS Neurocognition Committee selected experts in the following areas: cognitive performance deficits in schizophrenia, cognitive science, neuropharmacology, clinical trials methodology, psychometrics/test development, and biostatistics. These experts were invited to participate in a preconference survey and to attend the consensus conference. Of 73 experts who were invited, 65 agreed to participate in the April 2003 meeting. Of these, 62 took the preconference survey, as did 6 members of the Neurocognition Committee, yielding a total of 68 interviews.

Selecting Separable Cognitive Domains

To reach agreement on the number of separable cognitive domains in schizophrenia that should be represented in a cognitive battery to evaluate effects of new drugs on cognition in schizophrenia, a subgroup of the Neurocognition Committee was formed. This subgroup, which consisted of Keith Nuechterlein (chair), Deanna Barch, James Gold, Terry Goldberg, Michael Green, and Robert Heaton, evaluated the empirical evidence for separable cognitive performance factors in schizophrenia.

To maximize the utility of examining various cognitive domains within clinical trials in schizophrenia, this subgroup sought to identify dimensions of cognitive performance that have been implicated in schizophrenia and are relatively independent of each other. To obtain initial guidance from large-scale studies of neuropsychological performance in normal samples, factor analytic studies of well-established instruments such as the Wechsler Adult Intelligence Scale —III (WAIS-III) and Wechsler

Memory Scale —III (WMS-III) were examined (Tulsky and Price 2003). Then all known exploratory and confirmatory factor analytic studies of cognitive performance in schizophrenia were examined, including both published and as yet unpublished analyses, to obtain maximal breadth of sampling.

Thirteen factor analytic studies of cognitive performance in schizophrenia, with samples ranging from 34 to 209, were scrutinized. To select factors that replicated across several studies, the review of the factor analyses emphasized the cognitive constructs that were being indexed by the loadings of test scores, regardless of the name for the factor selected by the investigators. Furthermore, in instances in which the distinctiveness of dimensions was in question, additional probe factor analyses were completed with relevant data sets that were available to this Neurocognition Committee subgroup. Because the intent was to develop a consensus cognitive performance battery to be used in clinical trials of promising pro-cognitive agents for schizophrenia, consideration was also given to the potential for "pharmacologic sensitivity." For example, general verbal ability was found to be a replicable cognitive factor but was not included as a domain in the cognitive battery because of its marked resistance to change (Lezak 1995).

The degree of similarity of factor content across samples was considerable, particularly given that sample size limitations for some of the studies would be expected to result in increased variability of factor structure. The subgroup of the Neurocognition Committee concluded that six separable factors had been replicated in multiple studies of schizophrenic patients and were appropriate for the consensus cognitive battery for clinical trials:

1. Working memory
2. Attention/vigilance
3. Verbal learning and memory
4. Visual learning and memory
5. Reasoning and problem solving
6. Speed of processing

When these six factors were presented at the consensus meeting in April 2003, several participants expressed concern about the omission of social cognition from the list of domains. Social cognition is defined in various ways and broadly refers to the mental operations underlying social and emotional interactions, including the human ability and capacity to perceive the intentions and dispositions of others (Brothers 1990). Social cognition had not been proposed as one of the domains by the Neurocognition Committee because this domain was not represented in factor analytic studies because it has only relatively recently been introduced into the empirical literature on schizophrenia. Furthermore, measures of social cognition in schizophrenia have not yet achieved standardization across investigative groups. Nevertheless, initial data suggest that social cognition is closely related to functional outcome and may be an intervening variable between basic (nonsocial) cognition and outcome. Neuroimaging studies also suggest that certain measures of social cognition, such as perception of affect expressed in faces, may have a distinctive neural substrate from at least some of the systems that support the cognitive domains described earlier (Hariri et al 2000; Pinkham et al 2003; Pizzagalli et al 2002; Whalen et al 1998). Thus, based on feedback at the consensus meeting, the Neurocognition Committee added social cognition as one of the domains to be represented in the battery, yielding a total of seven domains.

The derivation of factors in this manner is likely to yield somewhat broad domains that could be subdivided even further

Table 1. Ranking of Test Qualities by 68 Experts for the MATRICS Meeting, April 2003

Test Qualities	Median Rank	First-Place Votes ^a
High immediate test–retest reliability	3	17
Good coverage of individual cognitive constructs	3	17
Comparable alternative forms	3	1
Clear relationship to functional outcome	4	13
Strong internal consistency of individual scales	5	6
Well-established norms for general population	5	0
Highly interpretable overall summary score	7	6
Clear relationship to known neural systems	7	5
Clear relationship to clinical symptoms	8	0

Median rank: 1 = most important; 9 = least important. MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative.

^aNot including 3 surveys: 2 experts gave ties, and 1 abstained

with refined measures. Indeed, much of the cognitive neuroscience research in schizophrenia attempts to parse cognitive deficits into the smallest meaningful units. For the purposes of MATRICS and clinical trial studies, however, it was seen as an advantage to select a relatively small number of cognitive domains that are derived from performance tests that can be administered within a relatively short, easily administered battery.

Criteria for Selection of Tests

To aid in the selection of essential criteria for tests to be included in the consensus cognitive battery, invited experts were asked to rate the importance of various test qualities as part of the preconference survey. Table 1 shows the rankings by the 68 surveyed experts of nine test qualities. Based on the ratings from the experts, as well as presentations and discussions at the conference on psychometrics, biostatistics, and outcome assessment, the Neurocognition Committee decided that five criteria would be prioritized for test selection:

1. Test–retest reliability
2. High utility as a repeated measure
3. Relationship to functional outcome
4. Potential changeability in response to pharmacologic agents
5. Tolerability and practicality

1. Test–Retest Reliability

Test–retest reliability was the highest rated test criterion among the surveyed experts, and a presentation by Helena Kraemer of Stanford University reinforced the importance of short-term test–retest reliability for end points in clinical trials, because this property is critical for detecting changes with treatment. Test–retest reliability translates directly into statistical power; as test–retest reliability decreases for any given measure, a larger sample size is required to detect the same amount of change (Kraemer 1991).

2. High Utility as a Repeated Measure

It is possible for a test to have excellent test–retest reliability but still be inappropriate for trials that require several repeat administrations. This criterion of utility as a repeated measure includes two separate considerations. First, it would be desirable to select measures that do not have a substantial practice effect, when possible. Second, if measures do show a practice effect, it is important that the improvement in performance with repeated

administrations not be so large that the mean performance at follow-up approaches ceiling and has reduced variability, because this situation makes it difficult to detect treatment effects. Tests with potentially large practice effects include memory tests that use the same lists of words and problem-solving tests that involve learning a particular strategy. Sometimes such tests have alternative forms, which generally prevent performance from reaching ceiling; however, alternate forms are not perfectly equivalent, which may introduce a new source of variability (form-to-form variability) and a potential drop in test–retest reliability. Consequently, there would be a further reduction of power and a further reduction of effect size in detecting treatment effects. Thus, evaluation of this criterion involves the need to balance these various considerations.

3. Relationship to Functional Outcome

As mentioned earlier, the relationship between cognitive deficits and functional outcome is a key part of the rationale for MATRICS. The importance of the relationship between cognitive change and functional outcome change was also emphasized by Thomas Laughren from the FDA in his presentation at the consensus conference (transcripts available at www.matrics.ucla.edu). Before granting a claim of cognitive effects to a drug, the FDA may expect to see evidence that improvements on cognitive performance measures will be mirrored by improvements in a measure of everyday functioning. Hence, clinical trials that will be used as a basis for an indication for treating cognitive deficits in schizophrenia may involve co-primary end points, one for cognitive performance and one to indicate functional status. (A MATRICS consensus conference in April 2004 was dedicated to clinical trial methodology for studies of cognition in schizophrenia.) For the purposes of evaluating cognitive tests for the consensus battery, priority will be given to tests that have demonstrated a relationship to some aspect of functional outcome, including community functioning or success in psychosocial rehabilitation. Because different settings place different types of demands on cognitive processing, the relationships between cognition and functional outcome may vary across situations, such that certain cognitive deficits are needed for certain types of daily activities (Bryson and Bell 2003). Little effort has been made to identify specific linkages between cognition and particular demands of different settings. Hence, for the purposes of evaluating and selecting tests, the committee did not specify a particular type of functional outcome.

The possibility that a cognitively enhancing drug may be required to demonstrate change on a functional outcome measure presented a dilemma for the experts at the MATRICS meeting. On one hand, it was seen as desirable to demonstrate changes on measures that clinicians can easily understand and that are face valid indicators of patient improvement; however, there was concern expressed that changes in functional outcome are an indirect and unreliable index of improvements in cognition. Improvements in cognition might take a long time to translate into functional improvements (perhaps 6–12 months). In addition, any such changes in functioning would heavily depend on factors that are typically beyond the control of clinical trial studies, including availability of psychosocial rehabilitation, social support networks, and local school and vocational opportunities. One possible resolution to this dilemma might be to use standardized tests of “functional capacity,” which specifically assess whether an individual has the capacity for performing key tasks of daily living (e.g., preparing a meal, taking mass transportation, managing medications, demonstrating social competence). Assessments of functional capacity are simulated

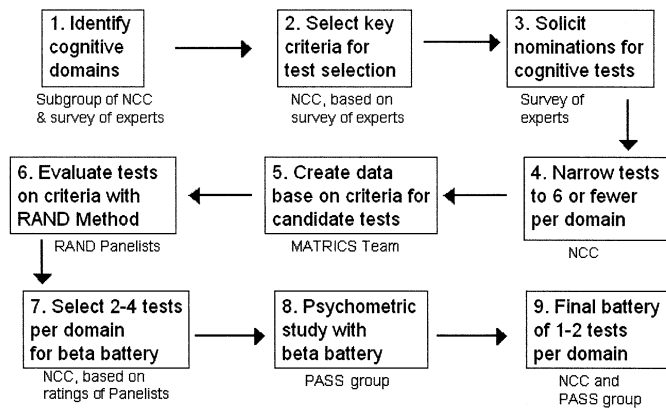


Figure 1. Steps to National Institute of Mental Health MATRICS Consensus Battery. MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative; NCC: MATRICS Neurocognition Committee; PASS, MATRICS Psychometric and Standardization Study.

activities, conducted in the clinic, not the community (Bellack et al 1994; Patterson et al 2001). Although such assessments do not guarantee that an individual actually performs the tasks in the community, they are less influenced by intervening variables and may be appropriate for clinical trials of cognitive enhancing agents.

4. Potential Response to Pharmacologic Agents

Tests may have good test–retest reliability, high utility as repeated measures, and even be associated with functional outcome, but still not be suitable for psychopharmacologic clinical trials. Tests that are otherwise useful may assess constructs that are unlikely to change with drug treatments. As noted earlier, measures of verbal ability (e.g., vocabulary, fund of general information) were not considered for the consensus battery mainly because general verbal ability is quite stable, even with head injury, and would be unlikely to change with a pro-cognitive drug. Because there is currently no clearly successful drug to normalize cognitive deficits in schizophrenia, we do not know which cognitive abilities will change with future pro-cognitive agents. Thus, the suggestion at this juncture is to give priority to measures of abilities that have shown to be sensitive to differences between first- and second-generation antipsychotic medications or that have shown a response with novel agents (e.g., d-cycloserine, d-serine, tandospirone).

5. Tolerability and Practicality

The Neurocognition Committee decided that it was important to include ratings of tolerability (the experience of the test from the patient's point of view) and practicality (the experience from the experimenter's point of view). One concern about developing a consensus cognitive battery with seven domains is that it could become too long for convenient use in clinical trials. There is an inherent trade-off in length of the battery: in general, longer batteries will provide more reliable measurement of the separate cognitive domains. On the other hand, if the cognitive battery is too long and perceived by patients as burdensome, it increases the chances that patients will drop out of studies prematurely. Hence, one aim of including this as an essential criterion was to limit the total length of the test battery by prioritizing more efficient methods of testing each cognitive domain. Tolerability refers both to the length of the test and to any feature of a test that would make it more or less pleasant for patients, such as an unusual degree of difficulty or excessive repetitiveness. This

quality needs to be inferred from the description of test procedures, because subjective response to tests is rarely systematically assessed. Practicality includes consideration of any particular difficulties in test setup, staff training, administration, and scoring that would create a burden for an experimenter (e.g., tests that have unusual equipment requirements or scoring procedures that make it difficult to establish reliability.)

Next Steps

The steps for reaching a consensus cognitive battery are shown in Figure 1. Following the MATRICS meeting in April 2003, the Neurocognition Committee discussed each of the roughly 90 neurocognitive tests that were nominated as measures within one of the seven cognitive domains and narrowed the number of tests to six or fewer per domain (a total of 36 tests). The MATRICS staff systematically conducted a comprehensive review of the literature bearing on the performance of each of these 36 tests across each of the five criteria for test selection (materials provided at www.matrics.ucla.edu). This comprehensive review constituted the database for a RAND Panel meeting held in September 2003. At the RAND Panel meeting, 14 experts selected by the Neurocognition Committee used the RAND Panel Method (Fitch et al 2001) to rate each of the candidate tests on each of the essential criteria. This RAND Panel process and the resulting selection of a “beta” version of the consensus cognitive battery will be described in our next report. This beta version of the battery will still be overinclusive, and an initial MATRICS study will directly compare the tests on their psychometric properties and on their relationships to functional outcome to select 1–2 tests in each domain for the final NIMH consensus cognitive battery for clinical trials. Once the final battery is selected, it is expected to become a standard instrument for clinical trials of cognitive enhancing agents in schizophrenia. A final MATRICS meeting (to be held in September 2004) will be devoted to discussing approaches to refine future versions of the consensus battery by incorporating developments in cognitive science and cognitive neuroscience.

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The conference “Identifying Cognitive Targets and Establishing Criteria for Test Selection” was supported by MH22006 Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS; SRM, MFG).

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