Stimulating the Development of Drug Treatments to Improve Cognition in Schizophrenia

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Abstract
Cognitive impairment in schizophrenia is a core feature of the illness (i.e., not a result of clinical symptoms or drug treatments) that is related to the daily functioning of patients. Because schizophrenia is associated with poor community functioning, there is considerable interest in finding treatments to improve cognition in schizophrenia in the hopes that such improvement will yield functional benefits. Before the U.S. Food and Drug Administration could consider granting approval to any new drug for improving cognition in schizophrenia, it was first necessary to achieve consensus on the measurements and methods that would be used in clinical trials, as well as neuropharmacological targets. The U.S. National Institute of Mental Health launched an initiative to help address these obstacles to drug approval (MATRICS). This initiative has generated several additional follow-up initiatives including a clinical trial network and consensus projects for other clinical targets, such as negative symptoms. This review describes how an area that was primarily of academic interest (cognition in schizophrenia) became a focus of public health concerns and drug-development policy.
INTRODUCTION

In the past few years, we have seen a broad convergence on the problem of developing new drugs to treat cognitive impairment in schizophrenia. The effort is unusual in that it required substantial input from highly diverse entities, including academia, the pharmaceutical industry, and the federal government. Another unusual aspect of this effort is that it intended to create a pathway to approve drugs to treat a completely new clinical target. This review summarizes how cognition in schizophrenia was elevated from a limited academic consideration to a broader public health problem and how people with widely ranging expertise worked together to make it an accepted treatment goal.

SCIENTIFIC BACKGROUND

An initial question is how cognition in schizophrenia came to be viewed as an important treatment target. Three key lines of investigation have provided the rationale. First, the cognitive impairments in schizophrenia are considered to be core features of the illness. Second, the impairments are related to how well patients with schizophrenia function in daily life. Third, an emerging neuropharmacology of cognition can provide guidance for new types of medications. I briefly discuss each of these factors below.

Cognition as a Core Feature of Schizophrenia

The cognitive deficits associated with schizophrenia encompass a wide range of domains. Based on a careful literature review and consensus meetings sponsored by the National Institute of Mental Health (NIMH), several cognitive domains were selected as important to assess in all treatment studies of cognition in schizophrenia: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Nuechterlein et al. 2004). Although there is considerable variability in the pattern of deficits across subjects, there is an identified modal neurocognitive profile that...
is characterized by larger deficits (in the range of 1.5 standard deviations) in verbal learning and vigilance, and lesser impairments in visual organization abilities and vocabulary (Heinrichs & Zakzanis 1998). Other studies have supported the relatively large deficits in verbal memory compared with other domains, but the disorder is associated with impairments in nearly all domains (Saykin et al. 1991).

Cognitive impairments are relatively common in schizophrenia, with estimates that 90% of patients have clinically meaningful deficits in at least one cognitive domain and 75% have deficits in at least two (Palmer et al. 1997). Even these relatively high rates of impairment may be underestimates, and almost all schizophrenia patients may have illness-associated performance deficits, even those who perform in the normal range. Such interpretations are based on findings of consistent deficits in patients when they are compared with their unaffected monozygotic twins (Goldberg et al. 1990) or when compared with estimates of expected levels based on premorbid functioning (Kremen et al. 2000).

One of the most important conceptual developments in schizophrenia over the past two decades is that cognitive impairment has become seen as a core feature, meaning that these impairments are not secondary or derivative of other aspects of schizophrenia, such as medications or psychotic symptoms of hallucinations and delusions. Several lines of evidence indicate that cognitive deficits are core features of schizophrenia (Braff 1993, Gold 2004, Gold & Green 2004, Nuechterlein et al. 1994).

1. The time course of cognitive impairment is quite different from that of clinical symptoms. Many patients demonstrate cognitive or intellectual impairments before the onset of psychotic symptoms and other clinical features (Cornblatt et al. 1992, 1999; Davidson et al. 1999; Niendam et al. 2003; Nuechterlein 1983; Reichenberg et al. 2002).

2. Milder cognitive impairment can be detected in first-degree relatives of schizophrenic patients who have no evidence of psychosis (Asarnow et al. 2002; Cannon et al. 1994, 2000; Green et al. 1997; Kremen et al. 1994; Snitz et al. 2006). The presence of such deficits in relatives suggests that certain cognitive deficits are likely to be components of genetic vulnerability to schizophrenia.

3. The magnitude of the cognitive impairment is relatively stable across clinical state. On some cognitive measures, the level of impairment shown by patients during a psychotic episode is remarkably similar to that seen when their symptoms are under control or when they are in full remission (Finkelstein et al. 1997, Nuechterlein et al. 1998). Therefore, cognitive impairment can occur with low levels, or complete absence, of clinical symptoms of schizophrenia.

4. The cross-sectional correlations between cognitive performance and ratings of psychotic-symptom severity are typically small (Bilder et al. 2000, Goldberg et al. 1993, Heydebrand et al. 2004, Mohamed et al. 1999, Nieuwenstein et al. 2001). Although the findings for correlations with psychotic symptoms (i.e., hallucinations and delusions) are consistently small, the findings are inconsistent regarding the degree of association with disorganized symptoms (e.g., formal thought disorder), with some studies showing relationships for specific aspects of disorganization (Mohamed et al. 1999, Perry & Braff 1994, Spitzer 1997). Cognitive performance tends to be related to negative symptoms, although the magnitude of the correlations is modest (typically approximately 15% of the variance).

5. Antipsychotic medications have substantial benefits for the psychotic
symptoms of schizophrenia, but their effects on cognition are much smaller. This pattern is true for both first- and second-generation antipsychotic medications. This discrepancy between clinical and cognitive effects suggests that antipsychotic medications act on different neural systems from those that underlie the cognitive impairments. Differences in the cognitive effects of first- and second-generation medications have been reported, but these differences are rather small compared with the clinical impact of medications on psychotic symptoms (Harvey & Keefe 2001, Woodward et al. 2005). This limited effect on cognition also provides a rationale to search for other types of drugs to manage the cognitive deficits of the illness.

A related question is whether the cognitive deficits in schizophrenia are diagnostically specific. On the one hand, none of the deficits can be considered specific to schizophrenia, as they appear in other disorders as well. On the other hand, the deficits in schizophrenia are clearly distinguishable from those in dementia (Heaton et al. 1994, Zakzanis 1998). Specifically, dementia is characterized by severe deficits in memory retention, which is largely intact in schizophrenia. Cognitive impairment in mood disorders such as depression and bipolar disorder tends to be reduced in magnitude and different in pattern from that seen in schizophrenia, even when patients are out of a mood episode (Altschuler et al. 2004, Buchanan et al. 2005, Fleck et al. 2001, van Gorp et al. 1998). In contrast, the pattern and magnitude of cognitive impairment in schizoaffective disorder are not distinguishable from that of schizophrenia (Buchanan et al. 2005, Evans et al. 1999, Miller et al. 1996), suggesting that any treatment for cognition in schizophrenia is likely helpful in schizoaffective disorder as well.

Cognition and Functional Outcome

The connection between cognition and functional outcome in schizophrenia provided another key line of support for viewing cognition as a treatment target. To put this area in context, it should be emphasized that functional outcome in schizophrenia has been disappointing, to say the least (Hegarty et al. 1994, Helgason 1990, Wiersma et al. 2000). Even with the introduction of antipsychotic medications that largely control psychotic symptoms for the majority of patients, individuals with schizophrenia have considerable difficulty achieving adequate community functioning. Even in the presence of symptom management, troubles persist in activities such as finding a job, forming a network of friends, or living independently. This is why schizophrenia remains one of the largest causes of disability among all illnesses for young adults (Murray & Lopez 1996). Psychotic symptoms are not strong determinants of community functioning; if they were, controlling symptoms would be sufficient for improved outcomes. Hence, other factors must be related to community functioning. Cognitive impairment is one such determinant.

Several literature reviews have shown that, across studies, cognitive deficits have 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, 2004a). The strengths of the associations for individual cognitive domains are typically moderate, although relationships with large effects can be found when multiple cognitive domains are combined into composite scores (Green et al. 2000).

Most of the studies in the reviews have been cross-sectional, but a review of prospective studies with a minimum six-month follow-up also showed that measurement of cognitive impairment at one point in time is a reasonable predictor of later community functioning (Green et al. 2004a). Some of the studies found good associations with outcome two
to four years after baseline assessment, which is typically considered long enough to see changes in functional status (Dickerson et al. 1999, Friedman et al. 2002b, Gold et al. 2002, Robinson et al. 2004, Stirling et al. 2003).

Taken as a whole, the literature supports connections between cognition and outcome in a general sense, but there are several recurring questions regarding the specificity of the connections. One question is whether some cognitive domains are more strongly related to outcome than other cognitive domains. A second question is whether specific cognitive domains are related to a specific aspect of functioning. At this stage, we do not have good answers to either of these questions. Verbal episodic memory (Green et al. 2000) or speed of processing (Gold et al. 2002) may be particularly important for functional outcome, but at this point, it is difficult to select one domain that is particularly important to outcome. Instead, it appears that, when averaged across subjects, all the cognitive domains studies are related to functioning (Velligan et al. 2000). Similarly, it is currently difficult to draw any clear connections between specific cognitive domains and particular aspects of outcome (e.g., work versus social outcome, skill acquisition versus independent living). In fact, when specific connections are detected, they may change over time, even for the same functional activity. For example, vigilance was much more important than verbal memory in accounting for the level of work performance (12% versus 4% variance explained) in the first half of a structured vocational program (Bryson & Bell 2003). However, the pattern was reversed for the second half of the program, with verbal memory more important than vigilance (11% versus 6%), suggesting that familiarity with the tasks changed the type of cognitive demands.

The connections between cognitive performance and functioning are not diagnostically specific to schizophrenia, as similar relationships exist in neurological disorders (including multiple sclerosis and HIV infection) (Rao et al. 1991, van Gorp et al. 1999). In fact, these deficits are associated with functioning in normal aging (Moritz et al. 1995). Considerably fewer data exist for other psychiatric disorders, but the emerging findings suggest that similar relationships are present for bipolar disorder (Dickerson et al. 2004, Martinez-Aran et al. 2004). The possibility remains that distinct patterns of relationships will characterize different disorders, possibly owing to differences in the nature of the daily tasks. For example, verbal memory may be particularly important for social functioning in schizophrenia, but executive functions may be more important in bipolar disorder (Laes & Sponheim 2006).

Although the linkages between cognition and functioning are well documented at this stage, little is known about the mechanisms through which the linkages exist. Several studies are proposing and testing intermediate variables that may provide steps linking cognition and functioning (see Figure 1). If the mediating variables are included, direct connections between cognition and functioning may or may not remain. One such mediating step may be social cognition. Social cognition research in schizophrenia has explored several areas, including social perception, theory of mind, emotion processing, social knowledge, and attributional bias (Green et al. 2005, Penn et al. 1997). Several recent studies using structural equation modeling and path analysis have demonstrated that measures of social cognition (i.e., emotion perception and social perception) act as mediators between basic (nonsocial) cognition and functional outcome (Brekke et al. 2005, Sergi et al. 2006, Vauth et al. 2004). Measures of functional capacity have also been considered potential mediators. Functional capacity refers to an individual's capacity for performing key tasks of daily living, such as whether a person can maintain a social conversation, prepare a meal, take public transportation, or manage their medications (McKibbin et al. 2004). Assessments of functional capacity are simulated activities and do not rely on observing the individual in the community. Good performance on a
Figure 1
Cognition, mediating variables, and functional outcome.

functional capacity task means that a person can perform the task in the community, but it does not guarantee that he or she will perform the tasks in the community. Such tasks are likely related to both basic neurocognition and functional outcome, and hence may be key mediators (Bowie et al. 2006).

The Neuropharmacology of Cognition in Schizophrenia

The neuropharmacology of cognition was another line of research that helped provide a foundation for drug development in this area. There is considerable activity and interest, from both academia and the pharmaceutical industry, in identifying novel drugs that can improve cognition. These drug-discovery efforts often start with an intention to find drugs for dementia or mild cognitive impairment, but if there is an incentive (i.e., possibility of a new market), these efforts can be directed to other disorders with cognitive impairment, including schizophrenia.

Before considering novel drugs for improving cognition in schizophrenia, an initial question is whether such cognition-enhancing drugs already exist. For example, there have been substantial efforts to determine whether the newer (second-generation) antipsychotic medications have cognitive benefits. Studies in this literature have typically found that second-generation medications have cognitive benefits when compared with first-generation medications that act selectively at the dopamine 2 receptor (Harvey & Keefe 2001, Woodward et al. 2005). However, the size of this difference is modest (in the range of 0.2–0.4 standard deviations). Interestingly, several more recent studies tend to show smaller differences between medications than earlier studies (Keefe et al. 2006b, Purdon et al. 2000). Generally, the studies have become larger and better controlled over time, so the smaller effect sizes may be more representative. In addition, more recent studies with smaller effect sizes sometimes use lower doses of the first-generation medication. Hence, the size of the difference of cognitive effects between first- and second-generation medications may depend partly on the dosage of the first-generation medication (Green et al. 2002). If we accept that there are cognitive differences between first- and second-generation medications, the interpretation remains ambiguous. One could interpret differences either to mean that second-generation medications have cognitive benefits (above a cognitive baseline) or that first-generation medications are more cognitively impairing (Carpenter & Gold 2002). This question is currently unresolved and actively debated.

Even those who are enthusiastic about the cognitive advantages of second-generation antipsychotic medications do not think that cognitive effects of these drugs are sufficient
for meaningful improvement. After all, none of the second-generation medications was developed with cognition in mind. Hence, if they had true cognition-enhancing properties, it would be a lucky accident. There is now broad agreement that other drugs are needed to achieve meaningful gains.

We can consider drugs that were developed for dementia, as such drugs may be beneficial for schizophrenia as well. The first drugs approved for dementia stimulate acetylcholine by blocking its breakdown (i.e., acetylcholinesterase inhibitors). Among these dementia drugs, one (donepezil) has been examined in several controlled studies in schizophrenia (Erickson et al. 2005, Freudenreich et al. 2005, Friedman et al. 2002a, Tugal et al. 2004). The results are not encouraging with three studies clearly negative and one study with mixed results. Newer drugs for dementia act on different mechanisms and may provide more promising results. However, the results so far are not encouraging with three studies clearly negative and one study with mixed results. Newer drugs for dementia act on different mechanisms and may provide more promising results.

Table 1 Promising neuropharmacological targets for cognition enhancement in schizophrenia (from the MATRICS Consensus Meeting)

<table>
<thead>
<tr>
<th>Neuropharmacological target</th>
<th>Number of nominations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-7 nicotinic receptor agonists</td>
<td>31</td>
</tr>
<tr>
<td>D1 receptor agonists</td>
<td>30</td>
</tr>
<tr>
<td>AMPA glutamatergic receptor agonists</td>
<td>14</td>
</tr>
<tr>
<td>Alpha-2 adrenergic receptor agonists</td>
<td>14</td>
</tr>
<tr>
<td>NMDA glutamatergic receptor agonists</td>
<td>12</td>
</tr>
<tr>
<td>Metabotropic glutamate receptor agonists</td>
<td>12</td>
</tr>
<tr>
<td>Glycine reuptake inhibitors</td>
<td>8</td>
</tr>
<tr>
<td>M1 muscarinic receptor agonists</td>
<td>7</td>
</tr>
<tr>
<td>GABA A R subtype selective agonists</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 1 contains a tally from the experts at the consensus meeting of the most promising candidates (they were able to vote for more than one). A glance at the voting reveals the large diversity of interest in the various targets and compounds. Small-scale, and somewhat encouraging, studies have already been conducted in schizophrenia that target the glutamatergic NMDA (N-methyl-D-aspartic acid) receptor (Coyle & Tsai 2004), as well as the glutamatergic AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor (Goff et al. 2001). Enthusiasm was high for other targets, including the dopamine D1 receptor (Goldman-Rakic et al. 2004) and the alpha-7 nicotinic receptor (Martin et al. 2004), based largely on the strength of animal models. It is safe to say that there is no shortage of promising targets. Of course, the challenge is finding suitable compounds that act, ideally in a selective fashion, on these targets.

OBSTACLES TO DEVELOPING DRUGS TO IMPROVE COGNITION IN SCHIZOPHRENIA

View from the Food and Drug Administration

One of the key roles for the U.S. Food and Drug Administration (FDA) for any new claim is to decide if the clinical target is...
appropriate. In most cases, the target is a distinct disease or syndrome (e.g., depression, anxiety, schizophrenia). In some cases, the target is a nonspecific symptom, such as pain or fever. In a few cases, however, an indication (i.e., a claim) for a drug was given for treatment of a symptom specific to a disorder. This situation, which is most relevant to cognition in schizophrenia, happened twice recently in psychiatry: One drug was approved for agitation in schizophrenia (ziprasidone) and another for suicidality in schizophrenia (clozapine).

This latter situation, approving a drug for a symptom of a disorder, is complex because it raises concerns that a claim is pseudospecific, which can lead to FDA disapproval. Pseudospecificity is a key concept for FDA decision making, and it refers to a claim for a drug that is overly narrow, for example, a claim that a drug works for a subgroup of individuals with a disorder (e.g., that a drug treats depression in women) or that it works for a particular aspect of an illness (e.g., a drug specifically for the treatment of hallucinations) (Laughren 2003). The FDA views such overly narrow claims as providing an unwarranted promotional advantage for the drug. Hence, before one can start to think about drugs for cognitive impairment in schizophrenia, one confronts the possibility that efforts can be preempted by pseudospecificity, depending on the FDA’s view of cognition in schizophrenia.

There were two concerns related to pseudospecificity that, if not satisfactorily addressed, would have undermined the effort. One was whether the cognitive impairment in schizophrenia was sufficiently different from the clinical symptoms. If cognitive impairment was closely connected to psychotic symptoms, it should respond to treatments for psychotic symptoms, and drug development in this area should continue to focus on newer antipsychotic medications. If cognition and psychotic symptoms were part of the same constellation, then any claims of treating cognition would be pseudospecific. The data mentioned above indicating that cognitive impairment is a core feature of illness were convincing in this regard, and the concern was alleviated. A second concern was whether the cognitive impairment in schizophrenia is diagnostically specific to schizophrenia, or if cognitive impairment is a generic condition, similar to fever. If it was generic, then any claim for cognitive impairment in schizophrenia would be pseudospecific. The answer to this concern was more nuanced. At one level, no particular cognitive deficit is diagnostically specific because many other disorders and neurological conditions have cognitive impairment. Conversely, the pattern of cognitive impairment in schizophrenia is quite distinct from that of dementia (Buchanan et al. 2005). Because of the distinct cognitive profile and time course, in addition to presumed differences in pathophysiology of the two disorders, there was no reason to believe that cognitive impairment is generic and that drugs approved for dementia would be valuable for schizophrenia. With such concerns addressed, it was possible to move on to address other obstacles.

Challenges to Receiving FDA Approval for Cognition in Schizophrenia as a New Clinical Target

Although there is no shortage of promising approaches to enhancing cognition in schizophrenia (see Table 1), moving from promising targets to promising new drugs requires a firm commitment from the pharmaceutical industry. However, no drug has been approved by the FDA for this purpose (Marder & Fenton 2004). Several issues were identified that needed resolution before the FDA would consider approval for a drug for cognition in schizophrenia. First, there was no consensus regarding how to measure outcome. Hence, a critical prerequisite for establishing the efficacy of a procognitive agent in schizophrenia is the definition of cognition that can be used as an end point in clinical trials. The FDA had previously received
inquiries from companies that were seeking approval of potential cognition-enhancing compounds. However, the companies each used different definitions and measurements of cognition, a situation that the FDA found unacceptable. The FDA regulatory process demanded that an end point in a clinical trial not be selected for the convenience of a single company or academic group but rather reflect a broadly based consensus grounded in evidence that the measures under consideration are reliable, valid, and clinically meaningful. In essence, the situation was similar to the classic prisoner’s dilemma in that no one could receive approval for any drug until everyone first made a concession and mutually cooperated to identify a single consensus outcome measure (Marder & Fenton 2004).

There were other significant barriers to drug development for cognition in schizophrenia. For example, there was no consensus regarding the appropriate clinical trial design to evaluate drugs for treating cognitive deficits. Issues such as subject-selection criteria, phase of illness, length of the trials, and ways to manage potential drug-drug interactions were unresolved. Another obstacle was the lack of consensus regarding the best approaches for identifying promising compounds. A consensus regarding appropriate neuropharmacological targets and animal models was needed to guide screening of compounds at the preclinical stage.

The Role of NIMH in Establishing Consensus in Key Areas

In essence, there was a logjam. Cognition in schizophrenia was increasingly viewed as a serious public health problem by NIMH and clinicians owing to its relationships to outcome and its distinctiveness from psychotic symptoms. In addition, the pharmaceutical industry had considerable interest in discovering and developing cognition-enhancing drugs. However, there were obstacles that effectively prohibited any drug from receiving FDA approval. In the absence of a clear pathway for FDA approval, the pharmaceutical industry was understandably unwilling to make a substantial investment in cognition-enhancing agents for schizophrenia.

As a way to unblock this logjam, NIMH used its convening authority and launched MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia). This initiative, awarded through a competitive application process to the University of California at Los Angeles, was charged with developing a mechanism by which cognition-enhancing drugs for schizophrenia could be marketed for that purpose. The goal of MATRICS was to build a pathway that would lead to drug approval.

The mandate of MATRICS was to hold consensus meetings to decide on the methods and measures that would be used to evaluate promising new drugs so they could receive approval for cognition enhancement in schizophrenia. The expectation was that once a pathway to drug approval was constructed, the pharmaceutical industry would travel it. MATRICS sponsored consensus meetings that brought together representatives of industry, academia, and government to address the key barriers.
Measurement of Cognition for Clinical Trials: MATRICS Consensus Cognitive Battery

Because the lack of a consensus cognitive battery was a serious obstacle for the development of new drugs, an essential product of the NIMH-MATRICS Initiative was a consensus cognitive battery that would provide a standard outcome measure for all clinical trials of cognition-enhancing drugs for schizophrenia. To select the consensus cognitive battery, a thorough multistep process was generated and then carried out with oversight from the MATRICS Neurocognition Committee. Figure 2 depicts the steps in sequence and the relevant groups responsible for each step. Each step is fully described elsewhere (Green et al. 2004b, Nuechterlein & Green 2006), and a brief summary is provided here.

Step one involved the identification of cognitive domains. There was a clear message from the MATRICS consensus meetings that the battery should assess cognition at the level of individual cognitive domains, as opposed to only a cognitive summary score. Therefore, it was first necessary to determine which cognitive domains should be represented in the MATRICS battery. Although there is a large literature on the nature of cognitive deficits in schizophrenia, there had never been any consensus on how to divide the cognitive deficits into key domains. Hence, one task for MATRICS was to form a group to carefully review the literature and recommend key separable cognitive domains (Nuechterlein et al. 2004). Based on the literature review and subsequent discussions at a consensus meeting, the following domains were selected:

1. Identify cognitive domains
2. Select key criteria for test selection
3. Solicit nominations for cognitive tests
4. Narrow tests to 6 or less per domain
5. Create data base on criteria for candidate tests
6. Evaluate tests on criteria with RAND method
7. Select 2-5 tests per domain for beta battery
8. Psychometric study with beta battery
9. Final battery of 1-3 tests per domain
10. Conorming of tests on community sample
for the consensus cognitive battery: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition.

Step two involved the selection of key criteria for test selection. Based on interviews with experts about the relative importance of various criteria (Kern et al. 2004) and subsequent discussion at a consensus conference, four key criteria were selected (Green et al. 2004b).

1. **High test-retest reliability.** Test-retest reliability was the highest rated test criterion among the surveyed experts as this property is critical for detecting changes with treatment (Kern et al. 2004, Kraemer 1991).

2. **High utility as a repeated measure.** It was considered desirable to select measures that do not have a substantial practice effect, or if they do, the degree of improvement in performance with repeated administrations is not so large that performance at follow-up approaches ceiling and has reduced variability.

3. **Demonstrated relationship to functional outcome.** For evaluating candidate cognitive tests, priority was given to tests that demonstrated a relationship to some aspect of functional outcome (e.g., work and social outcome, independent living).

4. **Demonstrated tolerability and practicality.** Tolerability refers to the view of the test from the examinee’s perspective, including the length of the test, unusual degree of difficulty, or excessive repetitiveness. Practicality refers to the view of the test from the administrator’s perspective, including ease of test set-up, staff training, administration, and scoring.

Steps three and four involved the narrowing of a large number of nominated tests to a more tractable (n = 36) number that could be evaluated through a consensus method, known as the RAND Panel method (shown in steps five and six). For the RAND Panel method (Fitch et al. 2001), a large and comprehensive database for each of the 36 tests was created for each of the criteria of test selection (test-retest reliability, utility as a repeated measure, relationship to functional outcome, and practicality/tolerability). The information was sorted, tabulated, and compiled into a large database (available at [http://www.matrics.ucla.edu](http://www.matrics.ucla.edu)). This comprehensive review constituted the database for rankings at the RAND Panel. The RAND Panel comprised 14 panelists of diverse areas of expertise. The RAND panelists independently examined the database compiled in step five and rated each candidate test on each of the essential criteria. Ratings were made independently prior to an in-person meeting, and any discrepancies were resolved following discussion at the meeting. Based on ratings from the RAND Panel, the MATRICS Neurocognition Committee selected 20 tests for the beta version of the battery, with 2–5 tests per cognitive domain (step seven).

The remaining steps required a new data collection. MATRICS sponsored a five-site Psychometrics and Standardization Study (MATRICS-PASS) that was conducted in two phases. The first phase (step eight) directly compared the tests in the beta version of the battery on their psychometric properties (including test-retest and practice effects), relationships to functional outcome, and practicality/tolerability. This psychometric study included 176 schizophrenia patients tested at baseline and at a four-week follow-up. Based on the results from this study, the MATRICS Neurocognition Committee carefully compared tests within each cognitive domain and voted their ranking of tests (step nine). Based on this review of data from MATRICS-PASS, the Committee selected the tests that comprise the MATRICS Consensus Cognitive Battery (MCCB) (*Table 2*).

The second phase of MATRICS-PASS involved 300 standardization subjects tested at
Table 2  MATRICS Consensus Cognitive Battery

<table>
<thead>
<tr>
<th>Domain</th>
<th>Test</th>
</tr>
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<tbody>
<tr>
<td>Speed of processing</td>
<td>Brief Assessment of Cognition in Schizophrenia (BACS)—Symbol Coding</td>
</tr>
<tr>
<td></td>
<td>Trail Making A</td>
</tr>
<tr>
<td></td>
<td>Category Fluency (Animal Naming)</td>
</tr>
<tr>
<td></td>
<td>Trail Making A</td>
</tr>
<tr>
<td>Attention/vigilance</td>
<td>Continuous Performance Test—Identical Pairs</td>
</tr>
<tr>
<td>Working memory (nonverbal)</td>
<td>Wechsler Memory Scale (WMS)-III—Spatial Span</td>
</tr>
<tr>
<td>Working memory (verbal)</td>
<td>University of Maryland—Letter-Number Span</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>Hopkins Verbal Learning Test—Revised</td>
</tr>
<tr>
<td>Visual learning</td>
<td>Brief Visuospatial Memory Test—Revised</td>
</tr>
<tr>
<td>Reasoning and problem solving</td>
<td>Neuropsychological Assessment Battery (NAB)—Mazes</td>
</tr>
<tr>
<td>Social cognition</td>
<td>Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT)—Managing Emotions</td>
</tr>
</tbody>
</table>

the same five sites that were drawn from the community through survey-sampling methods and stratified on age, gender, and education (step ten). These data were used to establish a common metric for each of the individual tests, for the seven cognitive domains, and for the overall cognition composite score. Essentially, this final step provided conorming of the tests in the final battery, and it served as the basis for the computerized scoring system for the MCCB.

How to Establish Meaningfulness in Outcomes: The Use of Coprimary Measures

One of the most complicated, and unexpected, questions in this process was whether improvement of cognition by itself should be sufficient for FDA approval. On the surface, it might appear that if a drug improves cognition, it deserves approval for cognition improvement. The FDA, however, sometimes requires improvements in two types of clinical trial outcomes for approval, one of which is considered to be functionally meaningful. Such a requirement for improvement on two types of measures is referred to as a requirement for coprimary end points. A coprimary requirement occurs for dementia drugs in which treatment-related effects need to be observed on a cognitive measure and also a global measure of functioning.

On the one hand, improvement on a well-developed cognitive performance measure is probably the most reliable and sensitive way to determine whether a drug improves cognition. On the other hand, small but statistically significant changes on cognitive performance measures alone may not be sufficient evidence of patient improvement for drug approval. In other words, it may have insufficient face validity. Although face validity carries little weight in psychological science, it is a consideration for drug approval. This importance stems from a concern about the acceptance of a new drug by patients and prescribing clinicians. In addition, the FDA understandably wants to justify its approval decisions with easily understood evidence of patient improvement. Based on these considerations, the FDA indicated that approval of a new cognition-enhancing drug for schizophrenia would require a functionally meaningful coprimary measure. So, where does one find such a measure?

One possible coprimary measure would be an assessment of community functioning. However, change in community status, such as work and social outcome, is a distant target and having such a requirement would set a high bar for approval for several reasons. For example, we know that intervening variables (e.g., social cognition) act between measures of cognition and functional outcome (Brekke et al. 2005, Sergi et al. 2006,
Vauth et al. 2004). These intervening variables would make it more difficult to see the functional benefits of cognition-enhancing effects because any improvements would need to influence successive steps. Along these lines, improvements in cognition would be expected to take a long time to translate into functional improvements, based on the delays in improved functioning seen for intensive psychosocial interventions (Brekke et al. 1997). In addition, any changes in daily functioning would depend on nonbiological factors that are typically well beyond the control of clinical trial studies, including the availability of psychosocial rehabilitation, social support networks, local employment rates, and training opportunities. Hence, there was concern that a requirement for changes in community status as a coprimary outcome variable may be too stringent and would lead to the failure of drugs to gain approval, even if they improve cognitive performance measures. Alternative coprimary measures that might change more directly with cognitive improvement include standardized tests of functional capacity or interview-based assessments of cognition.

Functional capacity was mentioned above and refers to an individual's capacity for performing key tasks of daily living. It can be measured with tests that assess whether a person can maintain a social conversation, prepare a meal, take public transportation, or manage their medications (Bellack et al. 1994, McKibbin et al. 2004). Good performance on a measure of functional capacity does not mean that a person will perform the tasks in the community, but it does mean that the person could perform the task if he or she had the opportunity and the willingness. Because performance on measures of functional capacity does not depend on social and community factors, they are likely to occur more closely in time with treatment-related changes in underlying cognition compared with changes in community functioning.

The correlations between functional capacity measures and cognitive performance are fairly consistent and suggest a good correspondence between the underlying cognitive skills and the simulated activities (Addington & Addington 1999, Bellack et al. 1994, Klapow et al. 1997). There are fewer data to link functional capacity to community functioning. A recent study showed that measures of functional capacity act as mediating variables between cognitive performance and outcome in schizophrenia (Bowie et al. 2006), similar to the pattern mentioned above for social cognition. Hence, measures of functional capacity appear to be appropriate for clinical trials of cognition-enhancing drugs in schizophrenia because of their face validity and their pattern of correlations with cognitive performance and functional outcome.

Another possible avenue for coprimary measures is to consider interview-based assessments of cognitive abilities. This approach presents a challenge because most of the data show that individuals (healthy subjects as well as patients) are poor at estimating their own performance abilities (Dunning et al. 2004, Mortiz et al. 2004). Some recent cognitive assessment interviews have been developed for use with psychotic patients and their caregivers that might have advantages over previously used assessments. Such measures are now starting to be evaluated in studies of schizophrenia (Keefe et al. 2006a).

Figure 3 illustrates some of the concepts mentioned above (Green et al. 2004a). The coprimary measures being considered represent a middle ground in that they are presumed to be closer to the biological processes affected by drugs than community status, but also more proximal to community functioning than the performance measures.

Finding a suitable indicator that is functionally meaningful remains a huge challenge for approving drugs for cognition in schizophrenia. This area presents a daunting range of conceptual, measurement, and practical challenges (Bellack et al. 2006). To help address these challenges, NIMH has launched a new program to develop and validate measures of functioning that can be used in the
context of clinical trials with psychotic patients. This will be an area of intense activity over the next several years.

**NEXT STEPS: CLINICAL TRIALS AND CONSENSUS**

The NIMH-MATRICS Initiative generated a flurry of activities that were stimulated by the initial consensus meetings. A clinical trials network has been launched by NIMH, essentially to field-test the products of MATRICS in actual trials. Other follow-up activities have consisted of consensus meetings on a variety of specific topics, including negative symptoms of schizophrenia, social cognition in schizophrenia, standardization and psychometrics of cognitive neuroscience measures, and the development and validation of coprimary measures for clinical trials. The clinical trial network and one example of a follow-up consensus process (negative symptoms) are briefly described here.

**Pilot Clinical Trial Network**

As a way to utilize the products of MATRICS, the NIMH established a clinical trials network called Treatment Units for Research on Neuropsychology and Schizophrenia (TURNS). The network was awarded through a competitive application process. TURNS is a network of seven research sites located at academic centers that is dedicated to identifying, obtaining, and testing the efficacy of new drugs to improve cognition in schizophrenia. This network will validate the clinical trial methodology recommended by MATRICS (Buchanan et al., 2005) by conducting two or three NIMH-supported trials. The trials will be proof-of-concept studies and will be modest in size (e.g., 40–50 subjects per

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**Figure 3**

Key linkages for cognition and functional outcome. The x-axis represents a dimension running from proximal, within-subject factors to distal, social factors. The dimension also reflects differences in how sensitive the outcome measure might be to cognition-enhancing effects of drugs. The y-axis represents locations of assessments ranging from less to more ecological (e.g., the cognitive-performance laboratory to the community). Arrows on the figure show well-supported linkages, and arrows with question marks are those that are not clearly established.
One or two additional pharmacodynamic/pharmacokinetic studies will also be conducted for drugs that are earlier in development. Pharmaceutical and biotechnology companies nominate drugs that they think have promise for cognition enhancement based on available data (typically both preclinical and limited human data). TURNS investigators decide which compounds to study based on careful review of the materials submitted by the companies. After four years of NIMH support, the network should be self-sufficient with federal, foundation, or industry support for subsequent trials.

The compounds nominated for study in the TURNS network act on many of the neuropharmacological targets listed in Table 1, including alpha-7 nicotinic, D1, GABA A, and glycine. The first drug to be evaluated in TURNS is expected to be an ampakine (a positive modulator of the glutamate AMPA receptor). Interest in drugs that affect the AMPA receptor grows out of theoretical work on the basis of long-term memory and encouraging preclinical data from animal models of learning (Hampson et al. 1998, Staubli et al. 1994). A small preliminary study with a weaker ampakine administered to schizophrenia patients yielded generally encouraging results but was limited by its small sample size (Goff et al. 2001). Hence, TURNS will provide a more rigorous test (with a larger study and more potent compound) of an ampakine in schizophrenia.

TURNS was designed to be a fast track for evaluating potentially efficacious compounds. Such standing networks for clinical trials are common for testing drugs in other areas of medicine but are not typical for psychiatric disorders. Studies in psychiatry typically use a less efficient system in which each trial has its own particular set of performance sites. The first TURNS trials began in the fall of 2006.

**Negative Symptoms in Schizophrenia**

Negative symptoms in schizophrenia include features such as blunted affect, anhedonia, asociality, and reduction in speech. Typically the negative symptoms form two different clusters of symptoms: one for diminished expression (e.g., reduced facial and verbal expressivity and reduced verbal outcome) and another for anhedonia and asociality (e.g., decreased social engagement, diminished interest) (Blanchard & Cohen 2006). In some respects, negative symptoms and cognitive impairment in schizophrenia are similar: They are both relatively unresponsive to the current medications, and they are both related to functional outcome. They also have modest overlap, usually in the range of 15% shared variance. The two constructs differ in one key respect: Negative symptoms are an accepted clinical target and part of the definition of schizophrenia. But similar to cognition, negative symptoms are considered to be an unmet need for the illness that has not responded adequately to existing interventions, and there is no approved drug for negative symptoms.

To stimulate drug development for negative symptoms in schizophrenia, many of the same steps need to be taken as described above for cognitive impairment. For example, there would need to be consensus on the definition of negative symptoms, the measure of negative symptoms that would serve as an end point in clinical trials, and the type of trial design (e.g., subject selection, phase of illness, length of trial, drug interactions). The FDA has not taken a position on whether a functional coprimary measure will be required for a drug to receive a claim for treatment for negative symptoms (Bellack et al. 2006, Laughren & Levin 2006), and it is seeking additional input on this question. From the FDA’s perspective, the need for a coprimary measure is less obvious than it was for cognition because negative symptoms are an accepted and readily observed feature of schizophrenia. A reduction in negative symptoms would have more face validity and improvement in cognitive performance.

To address these issues, a series of meetings following from MATRICS were held to reach consensus on some of these issues (Kirkpatrick...
The resulting discussions were recently published in a special issue of *Schizophrenia Bulletin* (volume 32, issue 2). Aside from definitional issues, this effort has led to the development and field-testing of a new scale for negative symptoms, one designed to detect change in clinical trials. Similar to the situation with cognition, the expectation is that once a pathway for FDA approval is worked out, it will attract interest and investment from the pharmaceutical industry.

**Integration with Psychosocial Interventions**

This review discusses how cognition in schizophrenia has become an accepted target for psychopharmacological intervention. Because the focus of this chapter is on drug development, nonpharmacological interventions for cognition (such as cognitive remediation) are not mentioned. This omission should not be viewed as dualistic thinking or as a preference of one approach versus another. On the contrary, nonpharmacological intervention has been a recurring topic in the context of drug development for cognition. One reason is that recent efforts to improve cognition in schizophrenia through retraining methods have shown promise (Kurtz et al. 2001, Twamley et al. 2003, Wexler & Bell 2005). In fact, retraining methods are presently the only reliable way we have to improve cognitive performance in schizophrenia. A second reason is that, so far, the primary evidence for cognitive improvement leading to functional benefits comes from nonpharmacological approaches. For example, two groups have recently reported that cognitive retraining coupled with standard vocational rehabilitation yielded greater benefits than vocational rehabilitation alone (McGurk et al. 2005, Wexler & Bell 2005).

A final reason for considering nonpharmacological interventions in the context of drug development is the growing realization that cognition-enhancing drugs will do little good if they act in isolation. To see the full effects of drug treatments, it is likely patients will need to be actively engaged in learning or training. By analogy, the performance-enhancing drugs at the root of professional sports scandals only provide benefits to the user in the context of rigorous physical exercise and training. Similarly, the benefits of cognition-enhancing drugs likely will be seen in the context of mental exercise and training. Although it is expected that the cognition-enhancing effects of drugs will be seen on highly reliable cognition-performance measures, translation of these benefits to community functioning may require an active training and learning environment (e.g., psychosocial rehabilitation, cognitive remediation). Hence, one of the unforeseen benefits of the recent concentration on developing new drugs for cognition is likely to be a renewed focus on nonpharmacological approaches that will serve as complementary interventions.

**SUMMARY**

This review summarizes several recent developments in the area of cognition in schizophrenia and activities designed to stimulate the development of new drugs to improve cognition. Cognitive impairment in schizophrenia is common, it is a core feature of the illness, and it is a determinant of the daily functioning of patients. There has been strong interest in finding treatments to improve cognition in schizophrenia, but before a drug could be approved for this purpose, it was first necessary to achieve consensus on several key questions, including the measurements and methods that would be used in clinical trials. The NIMH launched one initiative to address obstacles to drug approval and to identify promising neuropharmacological targets (MATRICS), and it introduced a clinical trial network (TURNS) to field-test the products of MATRICS in trials in this area. Other initiatives are underway for other clinical targets, including negative symptoms. This chapter describes how developments in experimental psychopathology have moved and expanded
the view of cognition in schizophrenia to be seen as a separate aspect of illness from clinical symptoms, a determinant of functional outcome, a target for intervention, a focus of public health concerns, and finally an area of drug development.

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Errata

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