

Mark A. Geyer
Gerhard Gross *Editors*

Novel Antischizophrenia Treatments

Handbook of Experimental Pharmacology

Volume 213

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Novel Antischizophrenia Treatments

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ISSN 0171-2004

ISBN 978-3-642-25757-5

DOI 10.1007/978-3-642-25758-2

Springer Heidelberg New York Dordrecht London

ISSN 1865-0325 (electronic)

ISBN 978-3-642-25758-2 (eBook)

Library of Congress Control Number: 2012947033

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Preface

Six decades after the serendipitous discovery of chlorpromazine as an antipsychotic and four decades after the launch of clozapine, the first atypical or second-generation antipsychotic, psychopharmacology has arrived at an important crossroad. Revealing the different modes of action of available antipsychotics on biochemical, electrophysiologic, neuroanatomic, and behavioral grounds has not only helped to develop new medications with improved tolerability but also contributed to our understanding of mechanisms relevant for psychosis in general and schizophrenia and bipolar disorder in particular. It is remarkable in this context the extent to which such research has moved towards using imaging techniques and more empirical clinical assessments. Although research targeted at specific receptors and pathways of antipsychotic drug action has extended our knowledge considerably, it remains true that all currently approved antipsychotic drugs share one common mechanism, i.e., dopamine D₂ receptor antagonism. There is still uncertainty as to whether first- and second-generation antipsychotics can really be separated and if the assumed progress exemplified by newer compounds is sufficient to survive the challenges of evidence-based medicine. Although the use of antipsychotics has become safer, adverse metabolic and cardiac effects remain as major issues in the clinic and in the development of new agents. It became clear that all clinically used antipsychotic medications are effective in treating positive symptoms, but certainly not for negative symptoms and also not for the core cognitive deficits that have been widely neglected in research in the time between Kraepelin and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative.

The efforts to develop antipsychotics based on D₂ receptor antagonism in combination with effects on other receptors (with or without intention) have remained the focus of the last two decades. It is clear that pharmacological research and pharmaceutical development must now focus on complementary or even alternative mechanisms of action to address unmet medical needs, i.e., poorly treated domains of schizophrenia, improved acceptance by patients, better adherence to medication, safety in psychoses in demented patients, and avoiding cardiac and metabolic adverse effects. The first completely novel mechanisms evolving

from our insights into the pathophysiology of psychotic disorders, especially the role of glutamatergic mechanisms in schizophrenia, are now under development, and further principles are on the horizon. This situation, in many respects similar to that when the initial second-generation antipsychotics became available, can be rewarding for all. Preclinical and clinical researchers now have the opportunity to confirm their hypotheses and the pharmaceutical industry may be able to develop really novel classes of therapeutics.

When we were approached by the publishers of the Handbook of Experimental Pharmacology to prepare a new volume on antipsychotics, our intention was to capture both the accumulated preclinical and clinical knowledge about current antipsychotics as well as prospects for new and potentially more specific antischizophrenia principles. These efforts should be based on the pathophysiology of the diseases and the affected neurotransmitter systems. Since preclinical research on antipsychotic compounds is only reliable when intimately linked through translational aspects to clinical results, we decided to include clinical science as well. It turned out that that this endeavor could not be covered by a single volume. We thank the editorial board and the publishers for supporting our decision to prepare two volumes: Current Antipsychotics and Novel Antischizophrenia Treatments. These topics cannot really be separated from one another and should be seen as a composite entity despite the somewhat arbitrary separation of contributions into two volumes. The continuing challenges of developing improved and safer antipsychotic medications remain of concern and are discussed in the first volume. The new opportunities for the field to develop and license adjunctive treatments for the negative symptoms and cognitive deficits that are treated inadequately by existing compounds have been incentivized recently and provide the focus for the second volume. We hope these collective contributions will facilitate the development of improved treatments for the full range of symptomatology seen in the group of schizophrenias and other major psychotic disorders.

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Clinical Instruments to Evaluate and Guide Treatment in Schizophrenia

Stephen R. Marder

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Abstract Treatment research in schizophrenia is focused on the development of pharmacological agents that are effective for improving community functioning and decreasing disability. As a result of this recent focus, there has been substantial activity for developing instruments that can measure functioning as well as the psychopathological domains that are related to functioning. Issues in selecting measures of real-world functioning include ensuring that the instrument measures the full range of possible outcomes and differentiating symptoms from functioning. For many treatment studies it is unrealistic to expect a change in actual functioning. Most treatment trials are too brief to permit subjects to change their level of vocational or social functioning. In addition, real-world functioning is influenced by factors such as an individual's financial status or the availability of community services. This has led to the use of functional capacity measures which monitor an individual's ability to perform functionally meaningful tasks even if they do not complete these tasks. Attention has also focused on interview-based measures of cognition and negative symptoms. Both of these psychopathological domains are related to functioning and both are the focus of drug development.

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Recent drug development has focused on the development of agents that target domains of psychopathology that may lead to improved functioning. This focus contrasts with the development of first and second-generation antipsychotics; these drugs were considered effective when they treated psychotic symptoms such as auditory hallucinations, suspiciousness, delusions, and disorganized behaviors. Treating these symptoms was important for reducing suffering and for allowing many patients to live in their communities. On the other hand, these agents had relatively modest effects on the ability of patients to function in their communities. This new focus on functioning has led to the development of new instruments for measuring functioning as well as the psychopathological domains that appear to be related to impaired functioning. This review will discuss the challenges that instrument developers have faced in designing these new instruments as well as the current state of the field. The measurement of typical psychopathology—particularly psychosis will not be discussed. The measurement of cognition and social cognition is discussed in the review by Keefe and Harvey (2012) Cognitive deficits in schizophrenia. In: Geyer MA, Gross G, Eds. In: Novel antischizophrenia treatments. Handbook of experimental pharmacology. Springer, Heidelberg.

Keywords Schizophrenia • Functional outcome • Disability • Cognition • Negative symptoms

1 Functioning as an Outcome in Clinical Trials

Schizophrenia is associated with substantial disability in a number of important areas. A survey in Australia found that 77.5% of people with schizophrenia were unemployed (which included not having a job, being a student, or carrying out home duties) (Castle and Morgan 2008). The same survey found that 35.5% of patients had dysfunctions in their abilities for self-care, 50% were impaired in their participation in household activities, and 61.2% were impaired in their ability to socialize. It is important to note that there is not a typical person with schizophrenia. Although a high proportion of patients have some disability, a substantial number function at a very high level with professional work accomplishments and successful family lives. Moreover, when patients receive adequate treatment and rehabilitation, they are frequently able to show substantial improvement. Therefore, it is important that measures of functioning in schizophrenia clinical trials monitor the full range of possible outcomes in areas such as work and social relationships. As noted below, some instruments may have good sensitivity to change at lower levels of functioning and can measure changes in basic activities like dressing or bathing. However, these measures may not be sensitive to changes in functioning at work or school.

Since functioning is a complex construct, it is also important to note that it is related to multiple factors including many that are not related to the illness. Communities or families can provide resources that affect social and educational accomplishments. A recent study found that different psychopathological domains can affect different

functional domains (Leifker et al. 2009). Social outcomes were related to affective blunting and passive-apathetic social withdrawal; residential outcomes were related to everyday living skills, psychotic symptoms, and lack of spontaneity. This observation suggests that the best functional target in an intervention study may be a particular domain rather than a global measure of functioning.

A number of instruments have been proposed over the years to measure functioning in schizophrenia. The *Global Assessment of Functioning (GAF)* (American Psychiatric Association 1994) is commonly used in both clinical and research settings. The instrument gives a single global score from 1 to 100 (where 100 is the best functioning) for a patient's symptomatic, social, and functional state. Since raters often give weight to symptoms over social and work functioning, there is uncertainty as to what is being measured. This uncertainty has led to attempts to divide the rating into meaningful components. For example, the GAF used by the Veteran's Administration Mental Illness Research, Education, and Clinical Center (MIRECC) (Niv et al. 2007) measures occupational functioning, social functioning, and symptom severity on three subscales. Each has a 100-point scale with anchors. Each of the three scales has been shown to have good predictive and concurrent validity.

The *Quality of Life Scale (QLS)* (Heinrichs et al. 1984) or Heinrichs-Carpenter Scale is among the most commonly used functional measures in schizophrenia research. Using a 21-item structured interview, functioning is assessed in four domains: intrapsychic functioning, interpersonal relations, instrumental roles, and common objects and activities.

The *Independent Living Skills Survey (ILSS)* (Wallace et al. 2000) measures skills in appearance, clothing, personal hygiene, care of possessions, food preparation, health preparation, money management, transportation, leisure and community, and job skills. The scale is very useful for patients with severe impairments since most of the items measure very basic functions. The *Birchwood Social Functioning Scale* (Schneider and Struening 1983) (*SFS*) assesses a wider range of functioning than the ILSS. It assesses domains including social engagement, interpersonal communication, pro-social activities, recreation, independence-competence, independence-performance, and employment. The *Specific Levels of Functioning Scale* (Schneider and Struening 1983) (*SLOF*) is a survey that is administered to a caseworker or a caregiver of a schizophrenia patient. It assesses six domains: physical functioning, personal care skills, interpersonal relationships, social acceptability, activities of community living, and work skills. A recent study (Bowie et al. 2007) compared self-ratings with ratings by case managers and found that the case manager's ratings were more associated with performance on functional capacity measures. The Social Behavior Schedule (Wykes and Sturt 1986) (*SBS*) is used to assess social functioning in individuals with psychiatric illnesses who depend on psychiatric services. The scale is administered to an informant. The Life Skills Profile (Rosen et al. 1989) (*LSP*) assesses self-care, nonturbulence, social contact, communication, and responsibility by interviewing available informants.

Since the measurement of functioning is fraught with complications and assumptions, it has been problematic for the field to reach a consensus as to the most effective methods for measuring this construct in clinical trials. A recent NIMH process named VALERO for Validation of Every Day Real-World Outcomes used

the RAND Appropriateness Method to evaluate these and other instruments according to predetermined criteria (Leifker et al. 2011). These criteria included reliability; convergence with neuropsychological tests and functional capacity measures; sensitivity to change; practicality and tolerability; usefulness for multiple informants; relationship with symptom measures; and comprehensiveness of assessment. Scales were evaluated in the categories—everyday living, social functioning, and hybrids. The QLS, the SLOF, the SBS, the SFS, the ILSS, and the LSP were selected for a validation study that was recently completed (Harvey et al. 2011). The findings indicated that the SLOF was the best functional measure for clinical trials in schizophrenia.

2 Functional Capacity

Clinical trials of schizophrenia treatments are seldom long enough to affect functional domains such as work, education, and social functioning. Moreover, success in these domains is often affected by financial opportunities and other factors that cannot be controlled in a clinical trial. This limitation has led researchers to develop functional capacity measures that monitor whether people are able to carry out functionally meaningful activities even if they do not perform these activities in their everyday lives. Functional capacity has been defined as the ability to perform critical, everyday living skills in controlled, observational settings (Harvey and Velligan 2011). Measuring functional capacity usually requires that subjects actually perform tasks in a laboratory setting. Tasks can range from basic self-care to managing social situations.

The importance of functional capacity was demonstrated in the NIMH Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) process which focused on facilitating the development of drugs for improving cognition in schizophrenia. During the MATRICS process, a representative from the US Food and Drug Administration (FDA) informed the field that improved performance on a neuropsychological test would not be sufficient to approve a drug. Improvement would need to be demonstrated on measures that were more clearly linked to improved functioning (Buchanan et al. 2005). Discussions with FDA representatives indicated that functional capacities could fill this role.

Although the original MATRICS process did not carry out a systematic review of available functional capacity measures, the group did include measures in the initial validation study (Green et al. 2008). A small group recommended two functional capacity measures: the *University of California at San Diego Performance-Based Skills Assessment (UPSA)* and the *Maryland Assessment of Social Competence (MASC)*. The UPSA (Patterson et al. 2001) uses standardized role-play situations to evaluate five domains: Household Chores; Communication; Finance; Transportation; and Planning Recreational Activities. For example, finance skills are evaluated by having patients pay bills and transportation skills are evaluated by having the person plan a trip to a zoo using public transportation.

A brief version of the UPSA measures finance and communication. The MASC (Bellack et al. 2006) evaluates a subject's performance in simulated social interactions. The individual's performance is recorded and scored at a later time.

Both tests were administered to schizophrenia subjects at baseline ($n = 176$) and 4 weeks later ($n = 167$) along with interview-based measures of cognition (described below) and a battery of cognitive tests (Green et al. 2008). All of the measures showed good test-retest reliability. The two functional capacity measures—UPSA and MASC were more strongly related to the cognition battery than the interview-based measures. Since the main function of the measure is to provide a more face-valid test of cognition, this relationship to the battery is probably the most important criteria. All four instruments showed modest relations to functioning. The UPSA showed some ceiling effects that resulted from the inclusion of a medication management component. Overall, this study did support the use of functional capacity measures as co-primary measures for studies of cognition enhancers.

A more recent process named MATRICS-CT (for co-primary and translation) used the RAND Appropriateness Method to evaluate both functional capacity measures and interview-based measures of cognition. As with the original MATRICS process, measures were nominated and a database was developed that compared each instrument to pre-established selection criteria. A diverse panel of experts used the database to select the measures that would be included in a validation study. The selected instruments for a validation study (which was termed the Validation of Intermediate Measures or VIN study) included the UPSA as well as the following two measures:

The Independent Living Scales (ILS) (Loeb 1996) evaluates memory/orientation, managing money, managing home and transportation, health and safety, and social adjustment. It requires subjects to solve problems, show knowledge, or carry out a task.

The Test of Adaptive Behavior in Schizophrenia (TABS) (Velligan et al. 2007) evaluates daily function in the following areas: medication management, supplying an empty bathroom, shopping skills, organizing a clothes closet, and work and productivity. Social skills are observed and scored.

The VIM study found that both the UPSA and the ILS had test-retest reliabilities above 0.70 indicating that they were acceptable (Green et al. 2011). The TABS and the UPSA had reasonable correlations of $r = 0.61$ and 0.67 respectively with cognition scores (using the MATRICS Consensus Cognitive Battery or MCCB). Shorter versions of the measures also had acceptable test-retest reliability as well as similar (but mostly lower) correlations with the MCCB. The Committee that administered the trial considered the UPSA to be the leading measure. For shorter forms, the TABS and UPSA instruments appeared to have advantages.

The MATRICS CT process is also addressing the challenges of international trials. In using functional capacity measures there is a concern that the tasks that are used in these measures will fail to translate into different cultures. For example, the UPSA's evaluation of skills in using public transportation may not translate in rural India or China where public transportation is sparse. This issue of cultural adaptability was evaluated in a recent study that surveyed clinical researchers at 31 sites in 8 countries (Velligan et al. 2010). The study found substantial challenges in

India, China, and Mexico. In addition, there were problems across countries when studies occurred in rural areas. Approaches to these translation problems are being addressed in a recently initiated validation study in India.

Taken together, these processes indicate important advances in tools for evaluating the abilities of people to function in their community life. At this time, researchers who are planning trials of innovative, pharmacological, and psychosocial interventions have a selection of instruments that have been carefully evaluated in validation studies. It is unlikely that there will be a single functional capacity scale that will be used for all studies in schizophrenia. Rather, the level of impairment of the study population, the domains of functioning that are being addressed, and the time and resources available will determine the favored instrument.

3 Interview-Based Measures of Cognition

The MATRICS process also explored interview-based (in contrast to performance-based) measures of cognition as potential co-primary outcome measures for trials of cognition-enhancing interventions. Interviews can be carried out with patients who describe their own perception of their cognition and how it affects their daily lives as well as informants who can be relatives or caretakers. The informants provide information based on their observations of the patient. There are some concerns regarding an individual's ability to assess his or her own cognitive abilities and how they compare to those of others, as well as an informant's ability to determine whether impairments in functioning are related to impairments in cognition or other symptom domains. In addition, studies suggest that clinical assessment of cognition with rating scales may provide poor estimates of actual cognitive impairment when measured with neuropsychological tests (Harvey et al. 2001). However, there may be additional value in assessing cognition using these other perspectives. If new interventions improve cognition, it will be important to understand how patients experience this improvement since it may help clinicians to assess if the treatment is effective. Moreover, as mentioned above, the interview-based assessments could be a co-primary outcome measure for registration trials.

As noted above, a number of interview-based measures have been evaluated recently. The *Schizophrenia Cognition Rating Scale (ScoRS)* is an 18-item instrument that assesses attention, memory, reasoning and problem solving, working memory, language production, and motor skills (Keefe et al. 2006). Ratings are obtained from a patient, an informant familiar with the patient, and an interviewer who carried out the ratings. The strongest relationships with neuropsychological performance test and functional outcome were with the ratings from the interviewer followed by the informant. This finding suggests that interview-based ratings are more likely to be useful when an informant is available. In the MATRICS validation study (Green et al. 2008), the SCORS showed good test-retest reliability. However, the relation to cognitive performance was not as strong as the relation of the functional capacity measures.

The Clinical Global Impression of Cognition in Schizophrenia (CGI-CogS) (Ventura et al. 2010) is a 38-item scale that evaluates each of the seven MATRICS domains—Working Memory, Attention/Vigilance, Verbal Learning and Memory, Visual Learning and Memory, Reasoning and Problem Solving, Speed of Processing, and Social Cognition. Each item is evaluated from three sources: the patient, a caregiver, and all available sources. It also includes a global cognition item—GAF-CogS—which uses a 100-point scale and parallels the GAF. The instrument shows moderate correlations with functioning and cognition (Subotnik et al. 2006). The scores for patients, caregivers, and the composite were moderately correlated with cognition. However, the correlations were not as high as the UPSA.

The Cognitive Assessment Interview (CAI) used Classical Test Theory (CTT) and Item Response Theory (IRT) to derive an instrument using data from studies of the CGI-CogS and the SCoRS (Ventura et al. 2010). The result is a scale with ten items that assess all of the MATRICS domains with the exception of visual learning. A trained rater uses information obtained from both the patient and an informant. The CAI was among the instruments included in the VIM study (Kee et al. 2009). It showed lower correlations with cognitive performance as measured by the MCCB when compared with the performance-based measures.

4 Negative Symptoms

According to an NIMH consensus meeting, the domains of negative symptoms include blunted affect, alogia, asociality, anhedonia, and avolition (Kirkpatrick et al. 2006). A number of instruments are available for clinical trials, with some instruments failing to measure all of the domains and other instruments including items that are probably not a component of the negative symptoms construct.

The Schedule for the Assessment of Negative Symptoms (SANS) (Andreasen 1983) is a widely used interview-based-scale that measures all five negative symptoms domains. It also includes inappropriate affect, attentional impairment, and poverty of content of speech which probably should not be included in negative symptom instruments. In addition, some of the apathy items measure an individual's social encounters rather than their interest in social encounters. The actual amount of social activity may be determined by factors that are not related to negative symptoms. Nevertheless, the instrument has shown itself to be a scale with excellent reliability and validity.

The Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) was developed as an instrument for assessing multiple symptom domains in schizophrenia, with a particular emphasis on positive and negative symptoms. Using a semi-structured interview and well-described anchors, it has been widely used in clinical trials. The original negative symptom domain included seven symptoms: passive withdrawal, emotional withdrawal, blunted affect, lack of spontaneity, poor rapport, difficulty in abstraction, and stereotyped thinking. These factors are able to measure the expressive components of negative symptoms including blunted affect and alogia, but provide very limited coverage of asociality, anhedonia, and avolition.

A number of investigators (Lindenmayer et al. 1994; Marder et al. 1997) have studied the structure of the PANSS and have proposed a negative symptom factor that also include passive social withdrawal, active/apathetic social withdrawal, and motor retardation. These models did not include items such as difficulty in abstract thinking and stereotyped thinking. These revisions of the PANSS have clear advantages as tools for measuring negative symptoms in clinical trials.

The Negative Symptom Assessment Scale (Axelrod et al. 1994) was developed to assess multiple domains of negative symptoms. Although originally developed as a 25-item scale, a briefer 16-item instrument, the NSA-16, retains its psychometric properties (Axelrod et al. 1993) and is the version that is most commonly used in clinical trials. An important advantage of the NSA-16 is that for the asociality-avolition component it more carefully differentiates between the actual negative symptom and the person's behavior. For example, it measures reduced sense of purpose and reduced social drive which determine a person's behavior. A recent study (Velligan et al. 2009) found that changes in the NSA-16 were related to changes in functioning in schizophrenia patients.

Two other instruments are currently under development. Both include all of the domains from the NIMH consensus meeting. An NIMH multisite group known as the Collaboration to Advance Negative Symptom Assessment in Schizophrenia (CANSAS) is developing the Clinical Assessment Interview for Negative Symptoms (CAINS) using a data-driven process (Blanchard et al. 2010). The second instrument, the Brief Negative Symptom Scale is similar, but will likely be briefer than the CAINS. A recent report (Kirkpatrick et al. 2010) indicates that it has very good psychometric properties.

5 Summary

This chapter has focused on clinical instruments that will support a new era of therapeutics research. The overall goal is to improve the quality of life and functioning of individuals with schizophrenia. The instruments can measure either functioning itself or symptom domains—negative symptoms and cognitive impairment—that are related to functioning. Readers should also consult the chapter on cognition which focuses on basic cognition and social cognition as clinical endpoints.

Acknowledgements This work was supported by the Desert Pacific MIRECC.

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Cognitive Impairment in Schizophrenia

Richard S.E. Keefe and Philip D. Harvey

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Abstract Cognitive functioning is moderately to severely impaired in patients with schizophrenia. This impairment is the prime driver of the significant disabilities in occupational, social, and economic functioning in patients with schizophrenia and an important treatment target. The profile of deficits in schizophrenia includes many of the most important aspects of human cognition: attention, memory, reasoning,

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and processing speed. While various efforts are under way to identify specific aspects of neurocognition that may lie closest to the neurobiological etiology and pathophysiology of the illness, and may provide relevant convergence with animal models of cognition, standard neuropsychological measures continue to demonstrate the greatest sensitivity to functionally relevant cognitive impairment.

The effects of antipsychotic medications on cognition in schizophrenia and first-episode psychosis appear to be minimal. Important work on the effects of add-on pharmacologic treatments is ongoing. Very few of the studies completed to date have had sufficient statistical power to generate firm conclusions; recent studies examining novel add-on treatments have produced some encouraging findings. Cognitive remediation programs have generated considerable interest as these methods are far less costly than pharmacologic treatment and are likely to be safer. A growing consensus suggests that these interventions produce modest gains for patients with schizophrenia, but the efficacy of the various methods used has not been empirically investigated.

Keywords Cognition • Neurocognition • Neuropsychology • Cognitive neuroscience • Memory • Attention • Processing speed • Executive functioning • Social cognition • Cognitive remediation • Enhancement

1 Cognitive Impairment in Schizophrenia and Its Clinical Relevance

1.1 Cognition in the Diagnosis of Schizophrenia

Cognitive impairment associated with schizophrenia is now viewed as a potential psychopharmacological target for treatment (Hyman and Fenton 2003). Although cognition is not a formal part of the current diagnostic criteria for schizophrenia, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR (American Psychiatric Association 2000) includes seven references to cognitive dysfunction in the description of the disorder. Diagnostic and scientific experts increasingly have expressed the idea that neurocognitive impairment is a core feature of the illness and not simply the result of the symptoms or the current treatments of schizophrenia. It is likely that the fifth edition of DSM will include cognition as a domain that will need to be evaluated by clinicians in the course of a diagnostic assessment (Keefe and Fenton 2007; Barch and Keefe 2010).

1.2 Cognitive Deficits Are Found in Almost All Patients with Schizophrenia

Severely impaired performance on cognitive tests is the strongest evidence for the importance of cognitive deficits in schizophrenia. In several cognitive domains,

the average cognitive impairment in schizophrenia can reach two standard deviations below the healthy control mean (Harvey and Keefe 1997; Heinrichs and Zakzanis 1998; Saykin et al. 1991; Keefe et al. 2011a). Although approximately 27% of patients with schizophrenia (and 85% of the general population) are not rated as “impaired” by clinical neuropsychological assessment (Palmer et al. 1997), these patients tend to have the highest levels of premorbid functioning (Kremen et al. 2000) and demonstrate cognitive functioning that is considerably below what would be expected of them based on their premorbid levels and the education level of their parents. Up to 98% of patients with schizophrenia perform more poorly on cognitive tests than would be predicted by their parents’ education level (Keefe et al. 2005). In addition, comparisons of monozygotic twins discordant for schizophrenia suggest that almost all affected twins perform worse than their unaffected twin on cognitive tests (Goldberg et al. 1990). Therefore, it is likely that almost all patients with schizophrenia are functioning below the level that would be expected in the absence of the illness.

1.3 Cognitive Impairment Is Not Caused by Psychotic Symptoms

Neurocognitive ability is not strongly correlated with severity of psychotic symptoms in patients with schizophrenia (Addington et al. 1991; Keefe and Harvey 2008; Bilder et al. 1985). Although some exceptions exist, such as isolated reports of significant correlations of positive symptoms with working memory (Strauss 1993; Bressi et al. 1996; Carter et al. 1996), source monitoring (Keefe et al. 2002), and auditory distractibility (Walker and Lewine 1988), the overall trend is for general neurocognitive impairment not to be correlated with positive symptoms. This low correlation across various patient samples, including first-episode (Mohamed et al. 1999), chronic (Addington et al. 1991), and elderly (Tamlyn et al. 1992; Davidson et al. 1995) patients, and confirmed in 1,331 patients assessed at entrance into the CATIE schizophrenia trial (Keefe et al. 2006a), suggests that positive symptoms are clearly not the sole cause of the cognitive impairment found in patients with schizophrenia. However, there are some reasonable caveats to these data. First, patients who are too psychotic to be tested are of course never included in empirical studies assessing the relationship between cognition and psychosis severity. Second, it is possible that patients with more preserved cognitive performance may be more articulate about their psychotic symptoms, causing higher scores on symptom rating scales, and thus reducing the detection of any true relationship between cognitive impairment and psychosis. Finally, most of the studies that have assessed cognition have focused on standardized measures of neuropsychological function. As described later, the identification of the true relation between cognitive impairment and psychosis may require more specific assessments of the processes that lead to these symptoms (Keefe et al. 2011b; Kraus et al. 2009; Krishnan et al. 2011a, 2011b).

1.4 Cognitive Impairment Is an Important Cause of Functional Disability and Related Outcomes in Schizophrenia

Cognition has been firmly established as a predictor of real-world community functioning (Green 1996) as well as the ability to perform everyday living skills in assessment settings (Evans et al. 2003; Patterson et al. 2001). All of the key neurocognitive constructs have demonstrated significant relationships to elements of functional outcome and to manifest effect sizes in the medium range in cross-sectional (Green et al. 2000; Nuechterlein et al. 2004) and longitudinal follow-up studies (Malla et al. 2002).

1.4.1 Employment

Ratings of work behavior/performance are related to baseline scores on cognitive tests in schizophrenia. For example, improvement in patient work performance in a 6-month work rehabilitation program was predicted by baseline performance on various cognitive tests (Bell and Bryson 2001). Patients enrolled in school full-time or holding competitive employment show superior performance across measures of working memory, sustained attention, problem solving, and episodic memory when compared with unemployed patients (Lysaker and Bell 1995; McGurk and Meltzer 2000); neurocognitive performance plays a more important role than clinical symptoms in the ability of patients with schizophrenia to work (McGurk et al. 2003).

1.4.2 Independence in Residential Functioning

Cognitive impairments and associated deficits in the ability to perform everyday living skills (referred to as functional capacity) are highly related to the ability to live independently. Residential independence can be predicted with considerable accuracy by performance-based measures (Mausbach et al. 2008). The aspect of functioning that differed most substantially between samples of schizophrenia patients that performed near the mean of healthy controls and those who were more impaired was independent residential status (Leung et al. 2008). These data suggest that perhaps the most significant impact of neurocognitive impairment is a patient's ability to find and maintain adequate independent living.

1.4.3 Quality of Life

Reductions in quality of life are strongly associated with cognitive impairment. The relationship between subjective experience and social functioning has been shown to be mediated by executive functioning (Brekke et al. 2001). The long-term effects

of impaired neurocognition on quality of life in patients with schizophrenia are quite substantial. While cognitive impairment is a key component of reduced quality of life in schizophrenia, it is not the entire story as the severity of positive and negative symptoms is also a significant contributor (Mohamed et al. 2008).

1.4.4 Relapse Prevention

Cognitive functions have been shown to be associated with medication adherence and are the strongest predictors of patients' ability to manage medications (Jeste et al. 2003; Fenton et al. 1997). Cognitive deficits contribute to patterns of medication mismanagement that are associated with poor adherence and risk of relapse (Jarboe and Schwartz 1999). In one study, memory impairment was the best predictor of partial compliance (Donohoe et al. 2001). Patients performing poorly in medication management tests also had poor global scores on a dementia inventory (Patterson et al. 2002).

1.4.5 Medical Comorbidity

Neurocognitive impairment is also related to medical comorbidities in schizophrenia. Deficits in executive functions such as planning directly affect patients' ability to seek treatment for medical problems. In elderly patients with schizophrenia, cognitive and functional impairments predicted the later incidence of new-onset medical problems, whereas medical problems did not predict the subsequent worsening of cognitive and self-care deficits (Friedman 2002). Inability of patients with schizophrenia to reduce damaging habits such as smoking has been correlated with deficits in memory and attention (Buchanan et al. 1994; George et al. 2000) and is a likely determinant of the substantial increase in cardiac morbidity and mortality in this population. Cognitive impairments may thus directly effect new-onset medical problems in people with schizophrenia.

1.4.6 Costs

Cognitive impairment is also a major factor in the costs (direct and indirect) associated with schizophrenia (Sevy and Davidson 1995). Factors leading to the increased cost include loss of ability for self-care, level of inpatient and outpatient care needed, and loss of productivity for patients as well as caregivers.

1.5 The Profile of Cognitive Impairment in Schizophrenia

Neurocognitive tests often assess more than one domain of functioning, and many tests do not fit neatly into a single domain. Thus, descriptions of the profile of cognitive deficits in schizophrenia have varied across literature reviews. The opinion

of a group of experts who served on the Neurocognition Subcommittee for the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project (<http://www.matrics.ucla.edu>) is that the most important domains of cognitive deficit in schizophrenia are working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving, speed of processing, and social cognition (Green et al. 2004). As described later, the outcome measure derived by this group has been approved by the Psychiatry Division of the Food and Drug Administration as the gold standard for registration trials targeting cognition in schizophrenia (Buchanan et al. 2005; Buchanan et al. 2011a). Since this organization of the domains of cognition is particularly relevant for treatment studies emphasized in this volume, these domains are described later. Alternative views have also been considered (Reichenberg et al. 2009). In addition, recent data have supported the hypothesis that perception may not only be impaired in schizophrenia, but may mediate some of the higher level cognitive deficits, such as working memory performance. However, any serious review of this literature suggests that the profile of cognitive deficits and level of performance in patients with schizophrenia include almost no aspect of cognition that is similar to those in healthy control subjects (Dias et al. 2011). This profile contrasts with the cognitive performance of patients with other psychotic disorders such as bipolar disorder, which suggests near-normal performance in the reasoning and problem solving or social cognition domains of the MATRICS battery (Burdick et al. 2011).

1.5.1 Vigilance and Attention

Vigilance refers to the ability to maintain attention over time. Impairments in vigilance can result in difficulty following social conversations and an inability to follow important instructions; simple activities such as reading or watching television become labored or impossible. Vigilance deficits in patients with schizophrenia are related to various aspects of outcome, including social deficits, community functioning, and skills acquisition (Green 1996; Green et al. 2000).

1.5.2 Verbal Learning and Memory

The abilities involved in memory functioning include learning new information, retaining newly learned information over time, and recognizing previously presented material. In general, patients show larger deficits in learning than in retention. The tests used to measure learning typically involve the ability to learn lists of words or written passages. Much empirical evidence points to severe verbal memory impairments in schizophrenia (Aleman et al. 1999). There is a clear connection between verbal memory impairments and social deficits in patients with schizophrenia, including both real-world functioning (Green 1996) and performance on social competence tests (McClure et al. 2007).

1.5.3 Visual Learning and Memory

Because visual information is not as easily expressed as verbal information, fewer tests sensitive to the deficits of schizophrenia have been developed, and this area of cognitive function has generally been found not to be as impaired as verbal memory (Heinrichs and Zakzanis 1998). Visual memory has been found to correlate modestly with employment status (Gold et al. 2003), job tenure (Gold et al. 2002), psychosocial rehabilitation success (Mueser et al. 1991), social functioning (Dickerson et al. 1999), quality of life ratings (Buchanan et al. 1994), and strongly with functional capacity (Twamley et al. 2003). Other studies have reported no significant correlations (Addington and Addington 1998, 2000; Ertuğrul and Uluğ 2002; Velligan et al. 2000).

1.5.4 Reasoning and Problem Solving

Although there are many tests of reasoning and problem solving, the most well known and most frequently used in schizophrenia research is the Wisconsin Card Sorting Test (WCST). The very poor performance of patients with schizophrenia on the WCST and the reduced activity of the dorsolateral prefrontal cortex during performance of this test (Goldberg et al. 1987; Weinberger 1987) led to widespread pursuit of the hypothesis of frontal hypoactivation in schizophrenia. It is important to note, however, that performance on the WCST reflects a variety of cognitive functions and is not a pure measure of executive functions (Keefe 1995). The rules of society and the workplace change regularly, and success in these arenas is often measured by one's ability to adapt to changes. Patients with schizophrenia who are impaired on measures of executive functions have difficulty adapting to the rapidly changing world around them.

1.5.5 Speed of Processing

Many neurocognitive tests require subjects to process information rapidly and can be compromised by impairments in processing speed. Standard examples of this type of task are the coding tasks, which have been found to demonstrate the most severe deficits in schizophrenia (Dickinson et al. 2007). This aspect of cognitive impairment is relatively nonspecific and has been found to correlate with a variety of clinically important features of schizophrenia, such as daily life activities (Evans et al. 2003), job tenure (Gold et al. 2002), and independent living status (Brekke et al. 1997). Reduced processing speed can impair the ability to keep in step with the task-oriented jobs that are frequently held by patients with schizophrenia. Increased response latency in social settings may hamper social relationships.

1.5.6 Working Memory

Working memory has been described by various authors as a core component of the cognitive impairment in schizophrenia (Brekke et al. 1997; Goldman-Rakic 1994; Keefe 2000) and is related to functional outcomes such as employment status (Lysaker and Bell 1995) and job tenure (Gold et al. 2003). Much of the clinical relevance of working memory deficits in schizophrenia comes from strong correlations that working memory measures have with a variety of other cognitive domains impaired in schizophrenia, such as attention, planning, memory (Silver et al. 2003), and intelligence (Keefe 2000), as well as the advanced understanding of the neuroanatomy of working memory functions in human and nonhuman primates. This neuroanatomical work has suggested that neural circuitry that includes prefrontal cortical regions mediates aspects of working memory functions (Baddeley 1992; Callicott et al. 1999) and that this circuitry may be impaired in schizophrenia (Baddeley 1992; Goldman-Rakic 1987).

1.5.7 Social Cognition

Theory-of-mind skills and social and emotion perception and recognition have been the general focus of the literature on social cognition in schizophrenia. Theory of mind is the ability to infer another's intentions and/or to represent the mental states of others. Individuals with schizophrenia perform poorly on measures of theory-of-mind abilities (Tan et al. 2005; Corcoran et al. 1995; Drury et al. 1998). Facial affect recognition and social cue perception are the two general areas into which studies of social perception in schizophrenia can be broken down. Reviews of the literature on facial affect recognition (Sarfati et al. 1997; Morrison et al. 1988; Penn et al. 1997) suggest that individuals with schizophrenia have stable deficits on tests of facial affect perception and that perception of negative emotions and fear may be particularly impaired (Addington and Addington 2000; Penn et al. 1997; Pinkham et al. 2011; Edwards et al. 2001). Tests of social cue perception use more dynamic stimuli that require multiple sensory modalities, such as watching people interacting. Patients with schizophrenia show consistent impairments on these tasks (Gaebel and Wölwer 1992; Bell et al. 1997). Social cognition is related to social impairments in schizophrenia, even after controlling for performance on neurocognitive tasks (Corrigan et al. 1990; Trumbetta and Mueser 2001). Path models have suggested that the relations between social cognition and functional outcomes are complex, but that social cognition may explain more of the direct variance in social functioning than other aspect of cognitive performance (Penn et al. 1996).

1.6 Cognitive Impairment Precedes the Onset of Psychosis

Various methods for assessing the relationship between premorbid cognitive impairment and later psychotic disorders have suggested that young people destined

to develop schizophrenia are modestly impaired on cognitive measures. However, these deficits tend to be quite mild (Brekke et al. 2007) and their ability to help predict psychotic disorders is under question. In a special circumstance, the longitudinal follow-up of individuals who manifest prodromal symptoms (Reichenberg et al. 2010), deficits on standard neuropsychological tests that are present at the time of the development of the prodrome discriminate cases who go on to develop psychosis from those who do not. However, impairment on these measures was not able to contribute to the prediction of psychosis beyond clinical measures implemented in the study.

Early work completed in the U.K. (Seidman et al. 2010) and Sweden (Jones et al. 1994) suggested that children who went on to develop schizophrenia as adults differed significantly from the general population in a wide range of cognitive and behavioral domains. Similar findings were generated from a population-based study that investigated the risk of schizophrenia in the United States. Scores from grades 4, 8, and 11 on the Iowa Tests for 70 children who later developed schizophrenia suggested that those children who later developed schizophrenia, test scores dropped significantly between grades 8 and 11, corresponding with the onset of puberty (David et al. 1997).

In Israel, a study of all adolescents between the ages of 16 and 17 years suggested that cognitive functions are significantly impaired in those adolescents who are later hospitalized for schizophrenia. These deficits thus precede the onset of psychosis in young people destined to develop schizophrenia, and, along with social isolation and organizational ability, cognitive deficits are a significant predictor of which young people will eventually develop a psychotic disorder (Fuller et al. 2002). However, the mean level of performance of this group, at about the 35th percentile of the overall population, does not allow for a very strong predictive signal on a case-by-case basis. In the young people who later experienced a first episode of schizophrenia, their cognitive results in the prodrome suggested that most of the cognitive impairment of schizophrenia occurs prior to the first psychotic episode (Davidson et al. 1999).

Recent work from the Dunedin study in New Zealand, which tracked the cognitive and mental health of a large group of individuals in a single geographical location, suggests that a subtle pattern of cognitive changes over early childhood may predict schizophrenia compared to depression and no illness (Brekke et al. 2007). In this study, children aged 7–13 who developed adult schizophrenia exhibited cognitive impairments that emerged early and remain stable on tests of verbal and visual knowledge acquisition, reasoning, and conceptualization. They also demonstrated developmental cognitive growth that was slower relative to healthy comparison subjects on tests indexing processing speed, attention, visual–spatial problem solving ability, and working memory. These two premorbid cognitive patterns were not observed in children who later developed recurrent depression. The authors concluded that the origins of schizophrenia include two interrelated developmental processes evident from childhood to early adolescence. Children who will grow up to develop adult schizophrenia enter primary school

struggling with verbal reasoning and lag further behind their peers in working memory, attention, and processing speed as they get older.

Prospective studies have suggested that cognitive impairment is manifest in individuals who are identified as being at “ultra-high” risk (Caspi et al. 2003) for schizophrenia by virtue of their family history of schizophrenia and/or the manifestation of mild signs and symptoms consistent with the prodromal symptoms of schizophrenia (Yung and McGorry 1996; Brewer et al. 2003). Some aspects of cognitive and perceptual performance in ultra-high risk individuals have been found to predict which individuals will develop psychotic symptoms such as olfactory impairment (Yung and McGorry 1996), verbal memory impairment (Hawkins et al. 2004), and attentional impairment (Brewer et al. 2005). Data combined from the seven sites of the North American Prodromal Longitudinal Study (NAPLS) consortium indicate that poorer scores on an overall composite score of several tests provided the most sensitive measure that differentiated those high-risk children who would develop psychosis from those who would not, and worse verbal memory scores predicted a briefer time to psychosis in those who developed schizophrenia (Reichenberg et al. 2010). However, when regression models were used, a clinical cluster of genetic risk for schizophrenia with recent deterioration in functioning, higher levels of unusual thought content, higher levels of suspicion/paranoia, greater social impairment, and a history of substance abuse predicted psychosis best (Keefe et al. 2006b) and cognitive measures did not contribute additionally beyond the clinical measures.

One of the important limitations of the work completed to date has been a reliance upon the assessment of cognition in schizophrenia and at-risk states with measures designed to measure intelligence or brain damage that may not be sensitive to the specific neural circuitry impairments underlying schizophrenia. Methodologies investigating the specific cognitive and neurobiological processes that may underlie and possibly precede the conversion to psychosis are likely to yield greater risk prediction specificity. Human perception, thought, and action—the basic elements of maintaining reality—are based upon a hierarchical process that conjoins memory and external stimuli, which has been referred to as learning-dependent predictive perception (Cannon et al. 2008; Keefe et al. 2011b). It has been hypothesized that perturbations of the circuitry underlying learning-dependent predictive perception may contribute to risk for developing schizophrenia and thus early detection of risk may be more successful with tasks specifically designed to test memory-prediction function (Krishnan et al. 2011a; Keefe et al. 2011c; Kraus et al. 2009).

1.7 Assessment of Cognition in Schizophrenia Treatment Studies

As listed in Table 3, multisite trials present a large number of challenges that need to be met for cognitive data to be collected reliably and efficiently (Keefe and Kraus 2009). Sites and testers must be trained and certified on the test battery and related

Table 1 MATRICS consensus cognitive battery (MCCB)

Domain	Tests
Speed of processing	<ul style="list-style-type: none"> • Category fluency • BACS symbol coding • Trail making A
Attention/vigilance	<ul style="list-style-type: none"> • Continuous performance test (identical pairs version)
Working memory	<ul style="list-style-type: none"> • Letter–number span • WMS-III spatial span
Verbal learning	<ul style="list-style-type: none"> • Hopkins verbal learning test-R
Visual learning	<ul style="list-style-type: none"> • Brief visuospatial memory test-R
Reasoning and problem solving	<ul style="list-style-type: none"> • NAB mazes
Social cognition	<ul style="list-style-type: none"> • MSCEIT managing emotions

procedures. Data review processes must be established, followed, and maintained throughout the course of the study. Plans must be in place for adding replacement testers or new sites during the study. Test selection must address the scientific hypotheses of the investigators yet be efficient to implement without excessive missing data. Finally, the data analytic plan should focus on a single or small number of outcome measures to reduce statistical errors and avoid reduced statistical power.

1.7.1 Registration (Phase III) Trials

The primary product of the MATRICS project was a battery of tests that could be used across treatment studies. This battery, the MATRICS Consensus Cognitive Battery (MCCB), was vetted by a panel of experts in schizophrenia, cognition and clinical trials, validated (Nuechterlein et al. 2008), and normed for ease of use (Kern et al. 2008). This battery of tests was chosen on the basis that these tests were in the key domains of cognition in schizophrenia, had excellent psychometric properties, relations to functional outcomes, were practical for use in clinical trials, and were not burdensome for patients (Nuechterlein et al. 2008). The battery includes ten tests of cognition in seven domains (see Table 1). It was accepted by the US Food and Drug Agency (FDA) as the primary endpoint for registration trials of cognition in schizophrenia (Sevy and Davidson 1995; Buchanan et al. 2005). In multisite government and industry clinical trials, the MCCB has demonstrated sensitivity to cognitive deficits in all domains, excellent test–retest reliability, small practice effects, and is strongly correlated with measures of functional capacity (Buchanan et al. 2011a, b; Keefe et al. 2011a). See Fig. 1. To date, translations have been made available in over 15 languages.

1.8 Early Phase Trials

While the MCCB has been established as the gold standard for schizophrenia registration trials, it is possible that earlier phase work may benefit from the use

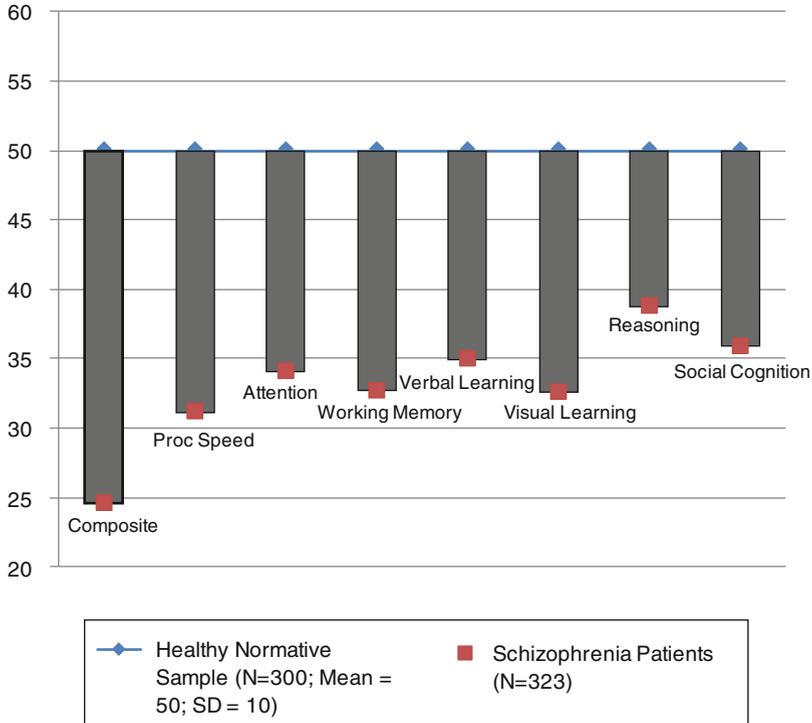


Fig. 1 Severity and profile of cognitive impairment in schizophrenia using the MATRICS consensus cognitive battery (Keefe et al. 2011a). Reprinted with permission

of measures that assess cognition in a manner that is closer to the actual neurobiological circuits that mediate cognitive function. To meet the need for more precise assessment instruments for measuring changes in specific cognitive functions in treatment studies, cognitive neuroscience methods with known linkages to specific brain systems, and to some extent their biochemistry, provide a logical alternative assessment strategy for identifying specific cognitive impairments to be targeted in schizophrenia treatment trials. These methods can potentially distinguish specific cognitive deficits from generalized deficits that are well assessed by neuropsychological testing. For instance, while list-learning tests may assess memory in a manner that is clinically relevant and correlated with important functional skills, the development of a treatment for memory impairment may need a more sensitive task that better reflects the biological processes involved in the acquisition and storage of representations (Table 2).

A large variety of such tests are available in the cognitive neuroscience literature, many of which have been utilized in schizophrenia research (Carter and Barch 2007; Carter et al. 2008). In order to expedite the use of these tests for early phase drug development, the National Institute of Mental Health sponsored a series of meetings and funding sources called the Cognitive Neuroscience Treatment

Table 2 Concerns for schizophrenia cognitive enhancement clinical trials using standard neuropsychological tests^a

Rater training and certification is essential

- Are testers qualified?
 - Excluding unqualified testers
 - Educating testers prior to certification
- Are the necessary procedures supported by sponsors?
- Is the importance of these procedures acknowledged by site investigators?

Data review processes

- When cognition is the primary outcome measure, all data reviewed centrally
- Less intensive data review is risky and must include random checks throughout trial

Intervention during a trial

- Prior to study initiation, procedures must be in place for adding testers and sites

Task considerations for clinical trials

- Increased task complexity can increase missing data rate
- Simplify instructions for testers and patients

Additional concerns with computerized tests

- Automatized procedures can hide problems indigenous to schizophrenia clinical trials

^aModified from Keefe and Harvey (2008)

Table 3 Criteria for selecting which cognitive constructs and mechanisms should be used for cognition treatment studies in schizophrenia

(a)	Construct validity and link to cognitive mechanisms
(b)	Link to neural circuit
(c)	Link to neural systems through pharmacology
(d)	Availability of animal model
(e)	Amenable for use in human neuroimaging
(f)	Evidence of impairment in schizophrenia
(g)	Linked to functional outcome in schizophrenia
(h)	Good psychometric characteristics
(i)	Multisite implementation potential

Research to Improve Cognition in Schizophrenia (CTNRICS). One hundred and forty one academic and industry experts in basic cognitive neuroscience, cognitive research in schizophrenia, and treatment of schizophrenia were surveyed to determine the most important criteria for selecting which cognitive constructs and mechanisms should be used for cognition treatment studies in schizophrenia. The most highly rated criteria are listed in Table 3. A subset of the tests that met these criteria has been further developed for early phase trials including the following tests assessing four cognitive constructs:

- Goal maintenance: The Dot Probe Expectancy Task (DPX), a variation on the Expectancy AX-CPT
- Relational encoding and retrieval: The Relational and Item Specific Encoding Task (RISE)
- Gain control: The Contrast–Contrast Effect Task (CCE)
- Visual Integration: The Jitter Orientation Visual Integration Task (JOVI)

These tests are available for download by researchers and clinical trialists at (<http://cntrics.ucdavis.edu/>).

One of the critical issues associated with sophisticated cognitive neuroscience tests is whether these tests will manifest the substantial and consistent correlations seen between standard neuropsychological tests and indices of everyday functioning. One of the reasons that these standard tests may be so strongly correlated with everyday functioning is because that they are so global and nonspecific. It should be noted that individuals with highly localized lesions in focal brain regions often manifest levels of everyday disability that are less than those seen in schizophrenia. It is entirely possible that these sophisticated tests will be highly sensitive to focal brain functioning and only modestly sensitive to disability. If this is found, then their use for early stage research would have to be carefully considered. As described later, the goal of treatment of cognition, as currently conceptualized, is to reduce disability. If task performance is uncorrelated with disability, then it seems implausible to think that improving performance would reduce disability.

1.9 Functional Capacity

A new development in the last decade of study of cognition and functioning in schizophrenia is that of direct measurement of the abilities that are required to succeed in critical functional domains. Based on the idea that what one can do (i.e., competence or capacity) constrains what one will do (everyday functional performance), these assessments have been developed to measure the skills that underlie functioning. This area of research has led to findings suggesting that functional capacity measures are highly correlated with cognitive test performance and may be more proximal than cognitive abilities to everyday outcomes. This relationship seems logical. If one is interested in whether someone can pay their bills, should the predictive assessment require the patient to manage money, write checks, and make bank deposits, or should they be asked to connect 25 dots as fast as they can?

1.9.1 Domains of Functional Capacity Assessment

Functional capacity assessments have been developed to measure everyday living skills, social skills, vocational skills, and medication management. While a review of these instruments could fill this entire chapter, some highlights are presented and more details are available in Harvey et al. (2007). These measures are inherently performance based. As a result, their psychometric characteristics can be measured (e.g., test-retest reliability, floor and ceiling effects). At the same time, as a performance-based assessment, practice effects can occur and other factors that affect the validity of performance-based assessment, such as motivation and environmental settings, can also require consideration.

The original focus of functional capacity measures in schizophrenia was on social skills; these assessments are still routinely performed. Recently, everyday living skills have been a particular focus of research and several of these assessments have been developed and validated. The UCSD Performance-based Skills Assessment

(UPSA) (Patterson et al. 2001) is the most widely used. This assessment has 5 or 6 subtests depending on the version and measures finances, comprehension and planning, communication, transportation, and household management. In the second edition of the UPSA, the UPSA-II, medication management was added. A short two-subtest version has also been developed. The UPSA has been shown to be quite consistently and substantially correlated with cognitive performance; across 11 published studies to date the correlation is consistently about $r = 0.63$. The test-retest reliability and practice effects of the UPSA seem similar to those seen in standard neuropsychological tests. UPSA scores predict residential independence quite effectively. In a comparative study of several different short and long forms of different functional capacity measures (Green et al. 2011), the UPSA was most highly convergent with performance on the MCCB and also the most user friendly in terms of complexity, duration, and ease of administration.

There are some issues in the interpretation of functional capacity assessments as compared to neuropsychological tests and these issues arise when both types of measures are used as treatment outcomes as described later. Neuropsychological tests are designed to measure the entire range of human cognitive functioning and are not designed to be specifically targeted at the prediction of any particularly functional skills. As a result, there is a wide range of scores on these tests and, because of the way that they are designed, only about 0.1% or less of the healthy population attain perfect scores and hence show ceiling effects. In contrast, functional capacity measures are intrinsically aimed at disability. Because the successful performance of everyday living skills is very common in the healthy adult population, a valid functional capacity test would have a large proportion of healthy people passing with 100% correct. As people with schizophrenia show an extraordinary prevalence of disability in domains where the healthy population typically achieves success without a problem, the distribution of scores across the two populations would not be expected to be equivalently normal. The uncommon nondisabled individual with schizophrenia would also be expected to perform extremely well on these tests. Thus, relatively higher scores on functional capacity measures may occur in people with schizophrenia. This issue does not arise as often with tests from the neuropsychology tradition. Similar to the discussion earlier, disability is not a treatment target in individuals who are not disabled. Thus, someone who is living independently, paying his/her own expenses, and otherwise managing their everyday functioning would be expected to get a high score on a disability-related skills measure and not to be a candidate for a treatment aimed at disability reduction.

2 Treatments for Cognitive Impairment in Schizophrenia

As of this writing, there are no pharmacologic or behavioral treatments that have received regulatory approval. Other chapters in this volume address the many important advances that hold promise for the eventual development of a treatment

for cognition in schizophrenia. In this chapter, we will review the literature on the effects of antipsychotics on cognition and discuss methodology for cognitive enhancement studies.

2.1 Antipsychotic Effects on Cognition

The effects of antipsychotic medications on cognition remain controversial. Several early studies and meta-analyses (Swartz et al. 2003; Davis et al. 2003; Rosenheck et al. 2003) suggested that second-generation antipsychotic treatment may provide greater neurocognitive benefit to schizophrenia patients than first-generation, “typical” antipsychotics. These effects extended even to first-episode patients who had not had previous antipsychotic treatment (Keefe et al. 2004; Harvey et al. 2005). However, many of these studies had substantial methodological limitations or flaws, such as small sample sizes, short duration of treatment, no comparator or a comparator of relatively high doses of first-generation antipsychotic treatment, and inattention to important clinical factors such as the relationship of cognitive improvement with symptom change, anticholinergic treatment, and change in extrapyramidal symptoms (Swartz et al. 2003; Davis et al. 2003; Rosenheck et al. 2003; Stroup et al. 2006). The CATIE study enabled an examination of these issues in a large sample of patients (Keefe et al. 2007a). Despite unprecedented statistical power in 817 patients randomized to a single first-generation antipsychotic, perphenazine, and the four second-generation antipsychotics available at the time (olanzapine, quetiapine, risperidone, and ziprasidone), there were no significant differences in the treatments after 2 months of treatment, which was the primary analysis endpoint. All groups showed a small benefit over time, but the magnitude of the benefit was viewed as consistent with the small practice and/or placebo effects found with the test battery utilized (Keefe et al. 2007b). Surprisingly, in exploratory analyses, the first-generation antipsychotic perphenazine demonstrated greater improvement than two of the second-generation antipsychotics in the 303 (37% of those assessed in the 2-month analyses) patients who continued on the same treatment for 18 months.

These results were unexpected and controversial (Kraemer and Frank 2010). In comparison to previous studies, at least 60% of patients in the CATIE trial reported being on atypical antipsychotic treatment prior to randomization, which was substantially higher than in many of the earlier studies completed when treatment with second-generation antipsychotics was less common. However, more recent studies on patients with first-episode psychosis and minimal or no previous antipsychotic treatment confirm these results. A comparison of olanzapine, quetiapine, and risperidone in first-episode patients using the identical neurocognitive test battery the CATIE trial produced very similar results, with all treatments having a very modest effect on cognition (Van Putten et al. 1991). Perhaps the most relevant study in this area was the European Union First Episode Schizophrenia Trial (EUFEST), a comparison of

open-label haloperidol (1–4 mg/day), amisulpride (200–800 mg/day), olanzapine (5–20 mg/day), quetiapine (200–750 mg/day), or ziprasidone (40–160 mg/day). This trial produced similar results with no differences between treatments, even in antipsychotic-naïve patients (Sweet et al. 2000). However, all groups showed a modest improvement. These improvements were only slightly stronger than practice effects, and demonstrated a relation to clinical symptom change, suggesting that first-episode patients may demonstrate some overall cognitive benefit related to overall clinical improvement. However, recent studies of completely antipsychotic-naïve patients suggest that while standard neuropsychological measures may demonstrate little change with treatment, other more specific measures of cognitive neuroscience processes such as speeded saccadic latencies to visual targets are normalized by risperidone but not haloperidol treatment (Reilly et al. 2006). Follow-up studies utilizing cognitive neuroscience tasks across specific cognitive domains may yield useful insights as was observed with the CATIE trials.

Overall, these data suggest that in current treatment settings, the impact of antipsychotic medications on neurocognition varies little on average, with minimal benefit for most treatments. The nature of these trials cannot exclude the possibility that some individual patients experience benefits while others worsen, possibly differentially across medications, but do suggest that there is no specific medication to which a switch would ensure benefit.

2.2 Pharmacological Augmentation as a Cognitive Enhancement Strategy

Pharmacological augmentation as a treatment strategy is consistent with best practices for the treatment of other illnesses. For instance, the treatment of hypertension and heart disease typically involves multiple medications with different targets, such as diuretics, ACE inhibitors, and calcium channel blockers. In schizophrenia, the analogous treatment might include atypical antipsychotic medications, treatments for negative symptoms, and treatments for cognitive deficits. Based on the history of FDA evaluation of treatments for cognitive and functional deficits in dementia, a model strategy for the development of cognitive enhancing treatments for schizophrenia has been advanced and endorsed. As a result of the MATRICS initiative, a unique collaboration between the FDA, the National Institute of Mental Health (NIMH), academia, and the pharmaceutical industry and a consensus regarding the acceptable methods for conducting a registration trial were developed (Sevy and Davidson 1995) and modified (Buchanan et al. 2005). There are several critical features of this design.

2.2.1 Clinical Stability

The FDA has long been concerned that new treatments that improve cognition do so directly, rather than by reducing the severity of other features of the illness. Thus, a

treatment that improves cognition must do so in the absence of improvements in other illness features, such as psychosis. Since FDA has thus far taken the position that simultaneous changes in illness features (cognition and psychosis) that are not statistically correlated may be related, only patients who are clinically stable can participate. This screening criterion was initially defined as a moderate or less (<4) severity rating on selected PANSS positive scale items at both screening and baseline (Sevy and Davidson 1995), but has recently been revised to allow patients who receive a score of 5 on the PANSS positive items (Buchanan et al. 2005). Also, there can be no hospitalization for psychiatric illness for at least 8 weeks prior to screening.

2.2.2 Treatment Stability

This is defined by no major change in antipsychotic medications for at least 6 weeks prior to screening.

2.2.3 No Medications That Can Influence Cognitive Functioning

This is defined by no treatment with anticholinergics, amphetamines, or L-DOPA.

2.2.4 Treatment Duration

At least some of the pivotal trials must have a 6-month treatment duration. This requirement is based on the idea that treatment effects must be durable and is influenced by concerns that the benefit of certain treatments may not persist over time. However some evidence indicates that cognitive enhancing treatments in people with schizophrenia can have benefits that occur within minutes to hours (Carter and Barch 2007).

2.2.5 Co-primary Measure

The FDA required a “co-primary” in cognitive enhancement studies in dementia. This requirement was designed to ensure that changes in cognition on a performance-based test led to a clinically meaningful change in everyday functioning. In the context of, for instance, cholinesterase inhibitor treatment of dementia, this requirement makes sense because none of the treatments approved by the FDA actually led to immediate improvements in functioning, but rather treatments were deemed successful for suspending the otherwise inexorable decline seen in Alzheimer’s disease.

Similarly, a co-primary measure has been required for schizophrenia cognitive enhancement trials. However, there is little evidence that any of the currently

available co-primary measures have the potential to be sensitive to treatment-related changes in performance. The existence of this FDA requirement led to a comprehensive collaborative study, funded by grants from the pharmaceutical industry to the Foundation for the National Institute of Mental Health (F-NIMH), which was recently completed, presented to the public, and is now published. The results of that study (Green et al. 2011) indicated that performance-based measures of functional capacity were clearly superior to interview-based assessments of cognitive functioning in terms of their convergence with the MCCB. It needs to be stressed that this was a cross-sectional validation study and not a treatment outcomes study.

2.3 Results of Cognitive Enhancement Efforts to Date

Several cognitive enhancement treatment research programs with a wide variety of treatment mechanisms are under way. Very recent data from Phase II trials suggest that some compounds may have promise for improving cognition in schizophrenia, but none of these compounds have been approved for actual use in patients. Some of these studies have been completed with negative results (Keefe et al. 2011c). While a full discussion of the reasons for the negative results would be speculative and premature, one of the major issues that may be important is that of possible interfering effects of antipsychotic medications. A single abnormal neurotransmitter system is unlikely to lead to the widespread impairments seen, but it is quite likely that single-transmitter interventions could be interfered with by the blocking effects of antipsychotic medications. Most importantly, however, many of the studies completed to date have been seriously underpowered to detect true treatment effects. A recent review of all studies completed as of June 1, 2011 (Keefe et al. 2011c) suggested that none of the studies above had sufficient power to detect a medium ($d = 0.5$) effect size, which would require 71 subjects per group assuming the primary outcome measure has excellent test-retest reliability ($ICC = -0.90$) as with the MCCB composite score (Keefe et al. 2011a). Several studies had sufficient power to detect a large ($d = 0.8$) effect.

2.4 Cognitive Remediation as a Platform for Pharmacologic Studies

While broad-ranging initiatives are ongoing to refine our understanding of the mechanisms of cognitive improvement in schizophrenia, an additional area of consideration is the relatively impoverished cognitive lives of patients who enroll in pharmacologic enhancement studies. It is possible that many of these experimental pharmacologic interventions will be of only minimal benefit when patients are evaluated in the context of their habitual low level of cognitive stimulation.

Part of the explanation for why clinical trials testing the efficacy of cognitive-enhancing medications have so far been largely unsuccessful may be that patients in these trials are not provided with substantive opportunity to utilize the cognitive benefit that they may have acquired during the drug treatment study. Thus, analogous to the need for physical exercise in an individual who takes steroids to increase muscle mass, schizophrenia patients in pharmacological intervention trials may require systematic cognitive training to “exercise” any newfound cognitive potential that they may have acquired from drug treatment (Keefe et al. 2011d).

Cognitive remediation may provide an excellent platform for enriching the cognitive environment of patients engaged in pharmacologic trials to improve cognition. Several studies and meta-analysis suggest that cognitive remediation produces medium effect size improvements in cognitive performance and, when combined with psychiatric rehabilitation, also improves functional outcomes (McGurk et al. 2007a, b). Additionally, patients find these programs to be enjoyable and engaging, and they have been linked with increases in participant self-esteem (Wykes et al. 1999). Ongoing treatment with cognitive remediation may thus provide schizophrenia patients with the necessary cognitive enrichment and motivation to demonstrate the true potential of effective cognitive enhancement with pharmacologic intervention. Recent work suggests that these methods are feasible in clinical trials even at sites without cognitive remediation experience (Keefe et al. 2012).

3 Conclusions

Cognitive functioning is moderately to severely impaired in patients with schizophrenia. This impairment is the prime driver of the significant disabilities in occupational, social, and economic functioning in patients with schizophrenia. The profile of deficits in schizophrenia includes many of the most important aspects of human cognition: attention, memory, reasoning, and processing speed. While various efforts are under way to identify specific aspects of neurocognition that may lie closest to the neurobiological etiology and pathophysiology of the illness, and may provide relevant convergence with animal models of cognition, standard neuropsychological measures continue to demonstrate the greatest sensitivity to functionally relevant cognitive impairment. These measures have been the primary outcome measures in treatment studies, as exemplified by the MCCB.

There have been several prominent negative treatment trials, including large-scale studies examining the effects of antipsychotic medications on cognition in schizophrenia and first-episode psychosis. There have also been a number of prominent negative studies of add-on treatments, although very few of these studies have had sufficient statistical power to generate firm conclusions. In addition, a few recent studies examining novel add-on treatments have produced some encouraging findings. Ongoing work aims to produce more specific cognitive neuroscience measures that may be more sensitive targets for pharmacologic intervention.

Cognitive remediation programs have generated considerable interest as these methods are far less costly than pharmacologic treatment and are likely to be safer. A growing consensus suggests that these interventions produce modest gains for patients with schizophrenia, but the efficacy of the various methods used has not been empirically investigated. An additional consideration for cognitive remediation methods is that they may serve as an excellent platform of cognitive enrichment in trials of pharmacologic treatment to generate the cognitive activity that may be necessary to register pharmacologic benefit.

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