Cognitive Impairment in Schizophrenia

Richard S.E. Keefe and Philip D. Harvey

Contents

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,

R.S.E. Keefe (✉)
Duke University Medical Center, Durham, NC 27710, USA
e-mail: richard.keefe@duke.edu

P.D. Harvey
University of Miami Miller School of Medicine, Miami, FL 33136, USA
e-mail: philipdharvey1@cs.com

M.A. Geyer and G. Gross (eds.), *Novel Antischizophrenia Treatments*,
Handbook of Experimental Pharmacology 213,
DOI 10.1007/978-3-642-25758-2_2,

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	• Category fluency • BACS symbol coding • Trail making A
Attention/vigilance	• Continuous performance test (identical pairs version)
Working memory	• Letter–number span • WMS-III spatial span
Verbal learning	• Hopkins verbal learning test-R
Visual learning	• Brief visuospatial memory test-R
Reasoning and problem solving	• NAB mazes
Social cognition	• 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

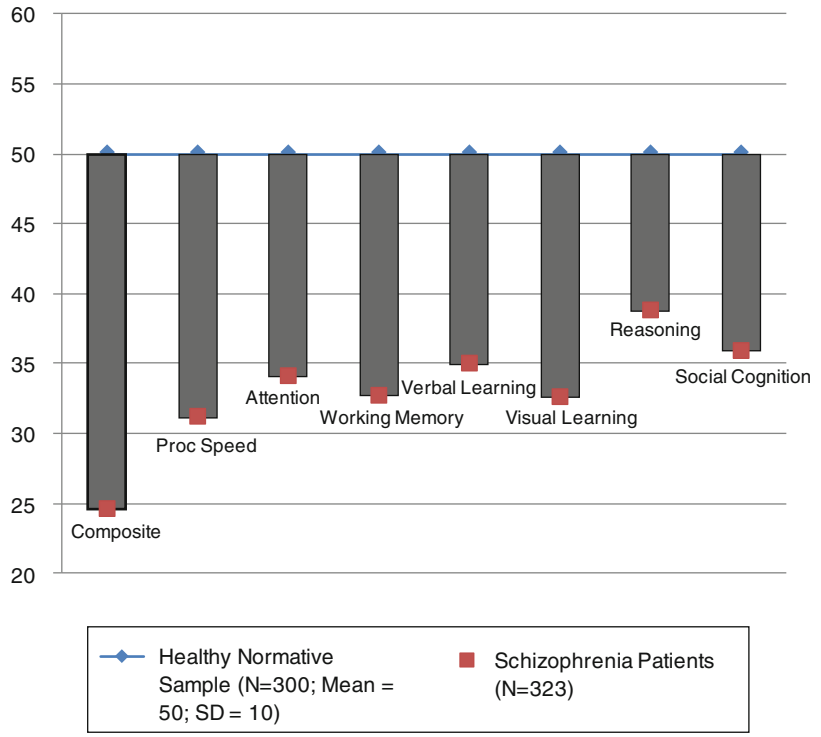

Fig. 1 Severity and profile of cognitive impairment in schizophrenia using the MATRICS consensus cognitive battery (Keefe et al. 2011a). Reprinted with permission

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

[a]Modified 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 blockading 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.

References

Addington J, Addington D (1998) Facial affect recognition and information processing in schizophrenia and bipolar disorder. Schizophr Res 32:171–181

Addington J, Addington D (2000) Neurocognitive and social functioning in schizophrenia: a 2.5 year follow-up study. Schizophr Res 44:47–56

Addington J, Addington D, Maticka-Tyndale E (1991) Cognitive functioning and positive and negative symptoms in schizophrenia. Schizophr Res 5:123–134

Aleman A, Hijman R, de Haan EH, Kahn RS (1999) Memory impairment in schizophrenia: a meta-analysis. Am J Psychiatry 156:1358–1366

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders DSM-IV-TR, Text Revision 4th edn. American Psychiatric Association, Washington, DC, ISBN 0-89042-024-6

Baddeley A (1992) Working memory. Science 255:556–559, Review

Barch DM, Keefe RSE (2010) Anticipating DSM-V: Opportunities and challenges for cognition and psychosis. Schizophr Bull 36:43–47

Bell MD, Bryson G (2001) Work rehabilitation in schizophrenia: does cognitive impairment limit improvement? Schizophr Bull 27:269–279

Bell MD, Greig TC, Kaplan E, Bryson G (1997) Wisconsin Card Sorting Test dimensions in schizophrenia: factorial, predictive, and divergent validity. J Clin Exp Neuropsychol 19:933–941

Bilder RM, Mukherjee S, Rieder RO, Pandurangi AK (1985) Symptomatic and neuropsychological components of defect states. Schizophr Bull 11:409–419

Brekke JS, Long JD, Nesbitt N, Sobel E (1997) The impact of service characteristics on functional outcomes from community support programs for persons with schizophrenia: a growth curve analysis. J Consult Clin Psychol 65:464–475

Brekke JS, Kohrt B, Green MF (2001) Neuropsychological functioning as a moderator of the relationship between psychosocial functioning and the subjective experience of self and life in schizophrenia. Schizophr Bull 27:697–708

Brekke JS, Hoe M, Long J, Green MF (2007) How neurocognition and social cognition influence functional change during community-based psychosocial rehabilitation for individuals with schizophrenia. Schizophr Bull 33:1247–1256

Bressi S, Miele L, Bressi C et al (1996) Deficit of central executive component of working memory in schizophrenia. New Trends Exp Clin Psychiatry 12:243–252

Brewer WJ, Wood SJ, McGorry PD, Francey SM, Phillips LJ, Yung AR, Anderson V, Copolov DL, Singh B, Velakoulis D, Pantelis C (2003) Impairment of olfactory identification ability in individuals at ultra-high risk for psychosis who later develop schizophrenia. Am J Psychiatry 160:1790–1794

Brewer WJ, Francey SM, Wood SJ, Jackson HJ, Pantelis C, Phillips LJ, Yung AR, Anderson VA, McGorry PD (2005) Memory impairments identified in people at ultra-high risk for psychosis who later develop first episode psychosis. Am J Psychiatry 162:71–78

Buchanan RW, Holstein C, Breier A (1994) The comparative efficacy and long-term effect of clozapine treatment on neuropsychological test performance. Biol Psychiatry 36:717–725

Buchanan RW, Davis M, Goff D, Green MF, Keefe RS, Leon AC, Nuechterlein KH, Laughren T, Levine R, Stover E, Fenton W, Marder SR (2005) A summary of the FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia. Schizophr Bull 31:5–19

Buchanan RW, Keefe RS, Umbricht D, Green MF, Laughren T, Marder SR (2011a) The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive-enhancing drugs: What do we know 5 years later? Schizophr Bull 37:1209–1017

Buchanan RW, Keefe RS, Lieberman JA, Barch DM, Csernansky JG, Goff DC, Gold JM, Green MF, Jarskog LF, Javitt DC, Kimhy D, Kraus MS, McEvoy JP, Mesholam-Gately RI, Seidman LJ, Ball MP, McMahon RP, Kern RS, Robinson J, Marder SR (2011b) A randomized clinical trial of MK-0777 for the treatment of cognitive impairments in people with schizophrenia. Biol Psychiatry 69:442–449

Burdick KE, Goldberg TE, Cornblatt BA, Keefe RS, Gopin CB, Derosse P, Braga RJ, Malhotra AK (2011) The MATRICS consensus cognitive battery in patients with bipolar I disorder. Neuropsychopharmacology 36:1587–1592

Callicott JH, Mattay VS, Bertolino A, Finn K, Coppola R, Frank JA, Goldberg TE, Weinberger DR (1999) Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. Cereb Cortex 9:20–26

Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, Seidman LJ, Perkins D, Tsuang M, McGlashan T, Heinssen R (2008) Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch Gen Psychiatry 65:28–37

Carter CS, Barch DM (2007) Cognitive neuroscience-based approaches to measuring and improving treatment effects on cognition in schizophrenia: the CNTRICS initiative. Schizophr Bull 33:1131–1137

Carter C, Robertson L, Nordahl T, Chaderjian M, Kraft L, O'Shora-Celaya L (1996) Spatial working memory deficits and their relationship to negative symptoms in unmedicated schizophrenia patients. Biol Psychiatry 40:930–932

Carter CS, Barch DM, Buchanan RW, Bullmore E, Krystal JH, Cohen J, Geyer M, Green M, Nuechterlein KH, Robbins T, Silverstein S, Smith EE, Strauss M, Wykes T, Heinssen R (2008) Identifying cognitive mechanisms targeted for treatment development in schizophrenia: An overview of the first meeting of the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia Initiative. Biol Psychiatry 64:4–10

Caspi A, Reichenberg A, Weiser M, Rabinowitz J, Kaplan Z, Knobler H, Davidson-Sagi N, Davidson M (2003) Cognitive performance in schizophrenia patients assessed before and following the first psychotic episode. Schizophr Res 65:87–94

Corcoran R, Mercer G, Frith CD (1995) Schizophrenia, symptomatology and social inference: investigating "theory of mind" in people with schizophrenia. Schizophr Res 17:5–13

Corrigan PW, Liberman RP, Engel JD (1990) From noncompliance to collaboration in the treatment of schizophrenia. Hosp Commun Psychiatry 41:1203–1211

David AS, Malmberg A, Brandt L, Allebeck P, Lewis G (1997) IQ and risk for schizophrenia: A population-based cohort study. Psychol Med 27:1311–1323

Davidson M, Harvey PD, Powchik P, Parrella M, White L, Knobler HY, Losonczy MF, Keefe RS, Frecska E (1995) Severity of symptoms in chronically institutionalized geriatric schizophrenic patients. Am J Psychiatry 152:197–207

Davidson M, Reichenberg A, Rabinowitz J, Weiser M, Kaplan Z, Mark M (1999) Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. Am J Psychiatry 156:1328–1335

Davis SM, Koch GG, Davis CE, LaVange LM (2003) Statistical approaches to effectiveness measurement and outcome-driven re-randomizations in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies. Schizophr Bull 29:73–80

Dias EC, Butler PD, Hoptman MJ, Javitt DC (2011) Early sensory contributions to contextual encoding deficits in schizophrenia. Arch Gen Psychiatry 68:654–664
Dickerson F, Boronow JJ, Ringel N, Parente F (1999) Social functioning and neurocognitive deficits in outpatients with schizophrenia: A 2-year follow-up. Schizophr Res 37:13–20
Dickinson D, Ramsey ME, Gold JM (2007) Overlooking the obvious: A meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. Arch Gen Psychiatry 64:532–542
Donohoe G, Owens N, O'Donnell C, Burke T, Moore L, Tobin A, O'Callaghan E (2001) Predictors of compliance with neuroleptic medication among inpatients with schizophrenia: A discriminant function analysis. Eur Psychiatry 16:293–298
Drury VM, Robinson EJ, Birchwood M (1998) Theory of mind skills during an acute episode of psychosis and following recovery. Psychol Med 28:1101–1112
Edwards J, Pattison PE, Jackson HJ, Wales RJ (2001) Facial affect and affective prosody recognition in first-episode schizophrenia. Schizophr Res 48:235–253
Ertuğrul A, Uluğ B (2002) The influence of neurocognitive deficits and symptoms on disability in schizophrenia. Acta Psychiatr Scand 105:196–201
Evans JD, Heaton RK, Paulsen JS, Palmer BW, Patterson T, Jeste DV (2003) The relationship of neuropsychological abilities to specific domains of functional capacity in older schizophrenic patients. Biol Psychiatry 53:422–430
Fenton WS, Blyler CR, Heinssen RK (1997) Determinants of medication compliance in schizophrenia: empirical and clinical findings. Schizophr Bull 23:637–651
Friedman L (2002) Psychoanalysis: practice and technique. J Am Psychoanal Assoc 50:727–732
Fuller R, Nopoulos P, Arndt S, O'Leary D, Ho BC, Andreasen NC (2002) Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. Am J Psychiatry 159:1183–1189
Gaebel W, Wölwer W (1992) Facial expression and emotional face recognition in schizophrenia and depression. Eur Arch Psychiatry Clin Neurosci 242:46–52
George TP, Ziedonis DM, Feingold A, Pepper WT, Satterburg CA, Winkel J, Rounsaville BJ, Kosten TR (2000) Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. Am J Psychiatry 157:1835–1842
Gold JM, Goldberg RW, McNary SW, Dixon LB, Lehman AF (2002) Cognitive correlates of job tenure among patients with severe mental illness. Am J Psychiatry 159:1395–1402
Gold JM, Wilk CM, McMahon RP, Buchanan RW, Luck SJ (2003) Working memory for visual features and conjunctions in schizophrenia. J Abnorm Psychol 112:61–71
Goldberg TE, Weinberger DR, Berman KF, Pliskin NH, Podd MH (1987) Further evidence for dementia of the prefrontal type in schizophrenia? A controlled study of teaching the Wisconsin Card Sorting Test. Arch Gen Psychiatry 44:1008–1014
Goldberg TE, Ragland JD, Torrey EF, Gold JM, Bigelow LB, Weinberger DR (1990) Neuropsychological assessment of monozygotic twins discordant for schizophrenia. Arch Gen Psychiatry 47:1066–1072
Goldman-Rakic PS (1987) Circuitry of the frontal association cortex and its relevance to dementia. Arch Gerontol Geriatr 6:299–309
Goldman-Rakic PS (1994) Working memory dysfunction in schizophrenia. J Neuropsychiatry Clin Neurosci 6:348–357
Green MF (1996) What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 153:321–330
Green MF, Kern RS, Braff DL, Mintz J (2000) Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr Bull 26:119–136, Review
Green MF, Nuechterlein KH, Gold JM, Barch DM, Cohen J, Essock S, Fenton WS, Frese F, Goldberg TE, Heaton RK, Keefe RSE, Kern RS, Kraemer H, Stover E, Weinberger DR, Zalcman S, Marder SR (2004) Approaching a consensus cognitive battery for clinical trials in schizophrenia: The NIMH-MATRICS conference to select cognitive domains and test criteria. Biol Psychiatry 56:301–307
Green MF, Schooler NR, Kern RS, Frese FJ, Granberry W, Harvey PD, Karson CN, Peters N, Stewart M, Seidman LJ, Sonnenberg J, Stone WS, Walling D, Stover E, Marder SR (2011)

Evaluation of functionally meaningful measures for clinical trials of cognition enhancement in schizophrenia. Am J Psychiatry 168:400–407
Harvey PD, Keefe RSE (1997) Cognitive impairment in schizophrenia and implications of atypical neuroleptic treatment. CNS Spectrums 2:1–11
Harvey PD, Rabinowitz J, Eerdekens M, Davidson M (2005) Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. Am J Psychiatry 162:1888–1895
Harvey PD, Velligan DI, Bellack AS (2007) Performance-based measures of functional skills: usefulness in clinical treatment studies. Schizophr Bull 33:1138–1148
Hawkins KA, Addington J, Keefe RS, Christensen B, Perkins DO, Zipursky R, Woods SW, Miller TJ, Marquez E, Breier A, McGlashan TH (2004) Neuropsychological status of subjects at high risk for a first episode of psychosis. Schizophr Res 67:115–122
Heaton RK, Pendleton MG (1981) Use of Neuropsychological tests to predict adult patients' everyday functioning. J Consult Clin Psychol 49:807–821
Heinrichs RW, Zakzanis KK (1998) Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12:426–445
Hyman SE, Fenton WS (2003) Medicine. What are the right targets for psychopharmacology? Science 299:350–351
Jarboe KS, Schwartz SK (1999) The relationship between medication noncompliance and cognitive function in patients with schizophrenia. J Am Psychiatr Nurses Assoc 5:S2–S8
Jeste SD, Patterson TL, Palmer BW, Dolder CR, Goldman S, Jeste DV (2003) Cognitive predictors of medication adherence among middle-aged and older outpatients with schizophrenia. Schizophr Res 63:49–58
Jones P, Rodgers B, Murray R, Marmot M (1994) Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 344:1398–1402
Keefe RSE (1995) The contribution of neuropsychology to psychiatry. Am J Psychiatry 152:6–15
Keefe RSE (2000) Working memory dysfunction and its relevance in schizophrenia. In: Sharma T, Harvey PD (eds) Cognition in schizophrenia: characteristics, correlates, and treatment. Oxford University Press, Oxford, pp 16–49
Keefe RSE, Fenton WS (2007) How should DSM-V criteria for schizophrenia include cognitive impairment? Schizophr Bull 33:912–920
Keefe RSE, Harvey PD (2008) Implementation considerations for multi-site clinical trials with cognitive neuroscience tasks. Schizophr Bull 34:656–663
Keefe RSE, Kraus MS (2009) Measuring memory-prediction errors and their consequences in youth at risk for schizophrenia. Ann Acad Med Sing 38:414–416
Keefe RSE, Arnold MC, Bayen UJ, McEvoy JP, Wilson WH (2002) Source monitoring deficits for self-generated stimuli in schizophrenia: Multinomial modeling of data from three sources. Schizophr Res 57:51–67
Keefe RSE, Seidman LJ, Christensen BK, Hamer RM, Sharma T, Sitskoorn MM, Lewine RR, Yurgelun-Todd DA, Gur RC, Tohen M, Tollefson GD, Sanger TM, Lieberman JA (2004) Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: A randomized double-blind trial of olanzapine versus low-doses of haloperidol. Am J Psychiatry 161:985–99
Keefe RSE, Eesley CE, Poe M (2005) Defining a cognitive function decrement in schizophrenia. Biol Psychiatry 57:688–691
Keefe RSE, Bilder RM, Harvey PD, Sm D, Palmer BW, Gold JM, Meltzer HY, Green MF, Miller DD, Canive JM, Adler LW, Manschreck TC, Swartz M, Rosenheck R, Perkins DO, Walker TM, Stroup TS, McEvoy JP, Lieberman JA (2006a) Baseline neurocognitive deficits in the CATIE schizophrenia trial. Neuropsychopharmacology 31:2033–2046
Keefe RSE, Perkins DO, Gu H, Zipursky RB, Christensen BK, Lieberman JA (2006b) A longitudinal study of neurocognitive function in individuals at-risk for psychosis. Schizophr Res 88:26–35
Keefe RSE, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM, Meltzer HY, Green MF, Capuano G, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Davis CE, Hasiao JK, Lieberman JA, CATIE Investigators, Neurocognitive Working Group (2007a)

Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. Arch Gen Psychiatry 64:633–647

Keefe RSE, Malhotra AK, Meltzer H, Kane JM, Buchanan RW, Murthy A, Sovel M, Li C, Goldman R (2007b) Efficacy and safety of donepezil in patients with schizophrenia or schizoaffective disorder: Significant placebo/practice effects in a 12-week, randomized, double-blind, placebo-controlled trial. Neuropsychopharmacology 33:1217–1228

Keefe RSE, Fox KH, Harvey PD, Cucchiaro J, Siu C, Loebel A (2011a) Characteristics of the MATRICS consensus cognitive battery in a 29 site antipsychotic schizophrenia clinical trial. Schizophr Res 125:161–168

Keefe RSE, Kraus MS, Krishnan RR (2011b) Failures in learning-dependent predictive perception as the key cognitive vulnerability to psychosis in schizophrenia. Neuropsychopharmacology 36:367–380

Keefe R, Buchanan R, Marder S et al (2011c) Clinical trials of potential cognitive-enhancing drugs in schizophrenia: What have we learned so far? Annual Meeting of NCDEU, Boca Raton, FL

Keefe RSE, Vinogradov S, Medalia A, Silverstein SM, Bell MD, Dickinson D, Ventura J, Marder SR, Stroup TS (2011d) Report from the Working Group Conference on multi-site trial design for cognitive remediation in schizophrenia. Schizophr Bull 37:1057–1065

Keefe RSE, Vinogradov S, Medalia A, Buckley PF, Caroff SN, d'Souza DC, Harvey PD, Graham KA, Hamer RM, Marder SM, Miller DD, Olson SJ, Patel JK, Velligan D, Walker TM, Haim AJ, Stroup TS (2012) Feasibility and pilot efficacy results from the multi-site Cognitive Remediation in the Schizophrenia Trials Network (CRSTN) study. J Clin Psychiatry 73: 1016–1022

Kern RS, Nuechterlein KH, Green MF, Baade LE, Fenton WS, Gold JM, Keefe RS, Mesholam-Gately R, Mintz J, Seidman LJ, Stover E, Marder SR (2008) The MATRICS consensus cognitive battery: Part 2. Co-norming and standardization. Am J Psychiatry 165:214–220

Kraemer HC, Frank E (2010) Evaluation of comparative treatment trials: assessing clinical benefits and risks for patients, rather than statistical effects on measures. J Am Med Assoc 304:683–684

Kraus MS, Keefe RSE, Krishnan RK (2009) Memory-prediction errors and their consequences in schizophrenia. Neuropsychol Rev 19:336–352

Kremen WS, Seidman LJ, Faraone SV, Toomey R, Tsuang MT (2000) The paradox of normal neuropsychological function in schizophrenia. J Abnorm Psychol 109:743–752

Krishnan RR, Fivaz M, Kraus M, Keefe RSE (2011a) Hierarchical temporal processing deficit model of reality distortion and psychoses. Mol Psychiatry 16:129–144

Krishnan RR, Kraus MS, Keefe RSE (2011b) Comprehensive model of how reality distortion and symptoms occur in schizophrenia. Could impairment in learning-dependent predictive perception account for the manifestations of schizophrenia? Psychiatry Clin Neurosci 65:305–317

Leung WW, Bowi CR, Harvey PD (2008) Functional implications of neuropsychological normality and symptom remission in older outpatients diagnosed with schizophrenia: A cross-sectional study. J Int Neuropsychol Soc 14:479–488

Lysaker P, Bell M (1995) Work rehabilitation and improvements in insight in schizophrenia. J Nerv Ment Dis 183:103–106

Malla AK, Norman RM, Manchanda R, Townsend L (2002) Symptoms, cognition, treatment adherence and functional outcome in first-episode psychosis. Psychol Med 32:1109–1119

Mausbach BT, Bowie CR, Harvey PD, Twamley EW, Goldman SR, Jeste DV, Patterson TL (2008) Usefulness of the UCSD performance-based skills assessment (UPSA) for predicting residential independence in patients with chronic schizophrenia. J Psychiatr Res 42:320–327

McClure MM, Bowie CR, Patterson TL, Heaton RK, Weaver C, Anderson H, Harvey PD (2007) Correlations of functional capacity and neuropsychological performance in older patients with schizophrenia: evidence for specificity of relationships? Schizophr Res 89:330–338

McGurk SR, Meltzer HY (2000) The role of cognition in vocational functioning in schizophrenia. Schizophr Res 45:175–184

McGurk SR, Mueser KT, Harvey PD, LaPuglia R, Marder J (2003) Cognitive and symptom predictors of work outcomes for clients with schizophrenia in supported employment. Psychiatr Serv 54:1129–1135

McGurk SR, Mueser KT, Feldman K, Wolfe R, Pascaris A (2007a) Cognitive training for supported employment: 2–3 year outcomes of a randomized controlled trial. Am J Psychiatry 164:437–441

McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT (2007b) A meta-analysis of cognitive remediation in schizophrenia. Am J Psychiatry 164:1791–1802

Mohamed S, Paulsen JS, O'Leary D, Arndt S, Andreasen N (1999) Generalized cognitive deficits in schizophrenia: A study of first-episode patients. Arch Gen Psychiatry 56:749–754

Mohamed S, Rosenheck R, Swartz M, Stroup S, Lieberman JA, Keefe RS (2008) Relationship of cognition and psychopathology to functional impairment in schizophrenia. Am J Psychiatry 165:978–987

Morrison RL, Bellack AS, Mueser KT (1988) Deficits in facial-affect recognition and schizophrenia. Schizophr Bull 14:67–83, Review

Mueser KT, Bellack AS, Douglas MS, Wade JH (1991) Prediction of social skill acquisition in schizophrenic and major affective disorder patients from memory and symptomatology. Psychiatry Res 37:281–296

Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK (2004) Identification of separable cognitive factors in schizophrenia. Schizophr Res 72:29–39, Review

Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, Essock S, Fenton WS, Frese FJ III, Gold JM, Goldberg T, Heaton RK, Keefe RS, Kraemer H, Mesholam-Gately R, Seidman LJ, Stover E, Weinberger DR, Young AS, Zalcman S, Marder SR (2008) The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. Am J Psychiatry 165:203–213

Palmer BW, Heaton RK, Paulsen JS, Kuck J, Braff D, Harris MJ, Zisook S, Jeste DV (1997) Is it possible to be schizophrenic yet neuropsychologically normal? Neuropsychology 11:437–446

Patterson TL, Goldman S, McKibbin CL, Hughs T, Jeste DV (2001) UCSD Performance-Based Skills Assessment: development of a new measure of everyday functioning for severely mentally ill adults. Schizophr Bull 27:235–245

Patterson TL, Lacro J, McKibbin CL, Moscona S, Hughs T, Jeste DV (2002) Medication management ability assessment: results from a performance-based measure in older outpatients with schizophrenia. J Clin Psychopharmacol 22:11–19

Penn DL, Spaulding W, Reed D, Sullivan M (1996) The relationship of social cognition to ward behavior in chronic schizophrenia. Schizophr Res 20:327–335

Penn DL, Corrigan PW, Bentall RP, Racenstein JM, Newman L (1997) Social cognition in schizophrenia. Psychol Bull 121:114–132

Pinkham AE, Loughead J, Ruparel K, Overton E, Gur RE, Gur RC (2011) Abnormal modulation of amygdala activity in schizophrenia in response to direct- and averted-gaze threat-related facial expressions. Am J Psychiatry 168:293–301

Reichenberg A, Harvey PD, Bowie CR, Mojtabai R, Rabinowitz J, Heaton RK, Bromet E (2009) Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. Schizophr Bull 35:1022–1029

Reichenberg A, Caspi A, Harrington H, Houts R, Keefe RS, Murray RM, Poulton R, Moffitt TE (2010) Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: A 30-year study. Am J Psychiatry 167:160–169

Reilly JL, Harris MSH, Keshavan MS, Sweeney JA (2006) Adverse effects of risperidone on spatial working memory in first-episode schizophrenia. Arch Gen Psychiatry 63:1189–1197

Rosenheck R, Doyle J, Leslie D, Fontana A (2003) Changing environments and alternative perspectives in evaluating the cost-effectiveness of new antipsychotic drugs. Schizophr Bull 29:81–93

Sarfati Y, Hardy-Bayle MC, Nadel J et al (1997) Attribution of mental states to others by schizophrenic patients. Cogn Neuropsychiatr 2:1–17

Saykin AJ, Gur RC, Gur RE, Mozley PD, Mozley LH, Resnick SM, Kester DB, Stafiniak P (1991) Neuropsychological function in schizophrenia. Selective impairment in memory and learning. Arch Gen Psychiatry 48:618–624

Seidman LJ, Giuliano AJ, Meyer EC, Addington J, Cadenhead KS, Cannon TD, McGlashan TH, Perkins DO, Tsuang MT, Walker EF, Woods SW, Bearden CE, Christensen BK, Hawkins K, Heaton R, Keefe RS, Heinssen R, Cornblatt BA, North American Prodrome Longitudinal Study (NAPLS) Group (2010) Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis. Arch Gen Psychiatry 67:578–588

Sevy S, Davidson M (1995) The cost of cognitive impairment in schizophrenia. Schizophr Res 17:1–3

Silver H, Feldman P, Bilker W, Gur RC (2003) Working memory deficit as a core neuropsychological dysfunction in schizophrenia. Am J Psychiatry 160:1809–1816

Strauss ME (1993) Relations of symptoms to cognitive deficits in schizophrenia. Schizophr Bull 19:215–231, Review

Stroup TS, Lieberman JA, McEvoy JP, Swartz MS, Davis SM, Rosenheck RA, Perkins DO, Keefe RS, Davis CE, Severe J, Hsiao JK, Investigators CATIE (2006) Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia after discontinuing a previous atypical antipsychotic. Am J Psychiatry 13:611–622

Swartz MS, Perkins DO, Stroup TS, McEvoy JP, Nieri JM, Haak DC (2003) Assessing clinical and functional outcomes in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial. Schizophr Bull 29:33–43

Sweet RA, Pollock BG, Mulsant BH, Rosen J, Sorisio D, Kirshner M, Henteleff R, DeMichele MA (2000) Pharmacologic Profile of Perphenazine's Metabolites. J Clin Psychopharmacol 20:181–187

Tamlyn D, McKenna PJ, Mortimer AM, Lund CE, Hammond S, Baddeley AD (1992) Memory impairment in schizophrenia: Its extent, affiliations and neuropsychological character. Psychol Med 22:101–115

Tan HY, Choo WC, Fones CS, Chee MW (2005) fMRI study of maintenance and manipulation processes within working memory in first-episode schizophrenia. Am J Psychiatry 162:1849–1858

Trumbetta SL, Mueser KT (2001) Social functioning and its relationship to cognitive deficits over the course of schizophrenia. In: Keefe RSE, McEvoy JP (eds) Negative Symptom and Cognitive Deficit Treatment Response in Schizophrenia. American Psychiatric Association, Washington, DC, pp 33–67

Twamley EW, Doshi RR, Nayak GV, Palmer BW, Golshan S, Heaton RK, Patterson TL, Jeste DV (2003) Generalized cognitive impairments, ability to perform everyday tasks, and level of independence in community living situations of older patients with psychosis. Am J Psychiatry 159:2013–2020

Van Putten T, Marder SR, Wirshing WC, Aravagiri M, Chabert N (1991) Neuroleptic plasma levels. Schizophr Bull 17:197–216

Velligan DI, Bow-Thomas CC, Mahurin RK, Miller AL, Halgunseth LC (2000) Do specific neurocognitive deficits predict specific domains of community function in schizophrenia? J Nerv Ment Dis 188:518–524

Walker E, Lewine RJ (1988) The positive/negative symptom distinction in schizophrenia. Validity and etiological relevance. Schizophr Res 1:315–328

Weinberger DR (1987) Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 44:660–669

Wykes T, Reeder C, Corner J, Williams C, Everitt B (1999) The effects of neurocognitive remediation on executive processing in patients with schizophrenia. Schizophr Bull 25:291–307

Yung AR, McGorry PD (1996) The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr Bull 22:353–370

http://www.springer.com/978-3-642-25757-5

Novel Antischizophrenia Treatments
Geyer, M.A.; Gross, G. (Eds.)
2012, X, 458 p., Hardcover
ISBN: 978-3-642-25757-5