

Cognitive deficits and functional outcome in schizophrenia

Christopher R Bowie
Philip D Harvey

Mount Sinai School of Medicine,
New York, NY, USA

Abstract: Cognitive dysfunction is a core feature of schizophrenia. Deficits are moderate to severe across several domains, including attention, working memory, verbal learning and memory, and executive functions. These deficits pre-date the onset of frank psychosis and are stable throughout the course of the illness in most patients. Over the past decade, the focus on these deficits has increased dramatically with the recognition that they are consistently the best predictor of functional outcomes across outcome domains and patient samples. Recent treatment studies, both pharmacological and behavioral, suggest that cognitive deficits are malleable. Other research calls into question the meaningfulness of cognitive change in schizophrenia. In this article, we review cognitive deficits in schizophrenia and focus on their treatment and relationship to functional outcome.

Keywords: cognition, schizophrenia, outcome, functional skills

The importance of understanding and treating cognitive dysfunction in schizophrenia is underscored by the relative lack of treatment success in most aspects of functional status, despite successful treatment of positive and negative symptoms. For example, Hegarty et al (1994), in a review of 100 years of outcomes literature from the late 1800s through the 1980s, found essentially no improvement in independent living status in schizophrenia. Most patients now live outside of institutional settings, but their residential and personal status is usually not truly independent. They often rely on financial assistance and clinical support for a range of areas, from work to basic living skills. Even when patients are living in the community, they are still unlikely to succeed in interpersonal relationships, maintain full-time employment, have a stable relationship, or have children.

The question arises: why, despite improved psychological and pharmacological treatments for schizophrenia, do functional deficits persist? A number of studies since the early 1990s have found that cognitive deficits are the best predictor of functional status across a number of outcome domains and patient characteristics (see Green 1996 and Green et al 2000 for reviews). Thus, the need to treat these impairments has become a priority for the field. Studies of emerging mechanisms for treating cognitive impairments suggest that they are somewhat modifiable through both pharmacological and psychological intervention. This review will present an overview of the cognitive profile of schizophrenia, review previous treatments of cognitive deficits, and outline the future of research on cognition and function in schizophrenia.

Profile of cognitive impairments in schizophrenia

Cognitive deficits are now considered a central feature of schizophrenia. Impairments in some domains are present before the emergence of the hallmark positive symptoms of the illness (Davidson et al 1999; Cornblatt et al 1999) and moderate to severe impairments across most cognitive domains are detectable at the time of the first episode (Bilder et al

Correspondence: Christopher R Bowie
Department of Psychiatry, Mount Sinai
School of Medicine, 1425 Madison Ave,
4th Floor, Box 1230, New York,
NY 10029, USA
Tel +1 718 584 9000 x3861
Fax +1 212 860 3945
Email christopher.bowie@mssm.edu

2000; Saykin et al 1994) and appear stable from emergence of the first episode until middle age (Rund 1998).

Schizophrenia is associated with impairments across a number of cognitive domains. The breadth of this impairment has led some to conclude that it is a disease with a global profile of neuropsychological impairment (Blanchard and Neale 1994; Dickinson et al 2004). Some evidence, however, suggests that there are discrete domains of cognitive impairment. For example, Bilder and colleagues (2002) found mild to moderate deficits in attention, verbal fluency, working memory, and processing speed, with superimposed severe deficits in declarative verbal memory and executive functioning. Other work suggests that discrete cognitive domains have differential correlates with symptom and functional domains. The argument over generalized or specific impairments is clouded by the fact that there is not a clear neuropsychological signature of schizophrenia. That is, most schizophrenia patients demonstrate at least some cognitive impairment, but, like other aspects of the illness, the severity and breadth of these impairments vary across patients. A rather unique feature of cognitive deficits, as compared to other characteristics of schizophrenia, is that they remain relatively stable within the same patient over time; they are generally consistent in severity and topography across changes in a patient's clinical status (Harvey et al 1990). Below, the types of impairments are described in detail.

General intelligence

Patients with schizophrenia have, as a group, lower Intelligence Quotient (IQ) scores than the general population. This difference is evident prior to the first episode of psychosis, with patients on the schizophrenia spectrum showing poorer performance on general IQ and non-verbal reasoning in particular (Reichenberg et al 2006). As young as age 8, poor performance on the Coding subtest of the Wechsler Intelligence Scale for Children, which is a measure of processing speed, distinguishes individuals who later develop schizophrenia spectrum disorders from those who do not (Sorensen et al 2006). Further evidence suggests that patients not only have lower IQ prior to and at first episode, but declines in IQ occur after the diagnosis (Seidman et al 2006). Even in schizophrenia patients who have seemingly normal cognitive skills, based on the rank of their scores in the population distribution, might still be impaired when considering their performance relative to their expected performance from expected IQ (Reichenberg et al 2005). Further, when matched to healthy control subjects on full

scale IQ score, patients with schizophrenia still evidence impairment in specific neuropsychological domains not traditionally assessed with standardized IQ batteries (Wilk et al 2005).

Attention

Impaired attention is considered a primary cognitive deficit in schizophrenia. Individuals who are genetically predisposed to schizophrenia have poor ability to maintain their attention even prior to the first psychotic episode (Cornblatt et al 1985). By the time patients experience their first episode of psychosis, attentional impairments are typically present and of moderate severity (Caspi et al 2003).

Working memory

There is increasing evidence that working memory dysfunction, particularly verbal working memory, is a core cognitive deficit in schizophrenia. Working memory can be conceptualized as the ability to maintain and manipulate informative stimuli. As opposed to simple attention span, this skill carries more of a "cognitive load" due to the additional demands of manipulating the information. The information must be held on-line for processing, but does not necessarily transfer to long-term storage, unlike episodic memory. Verbal memory impairments are quite common and often moderate to severe in magnitude in schizophrenia (Gold et al 1997; McGurk et al 2004). Moreover, these deficits are not simply an artifact of an inability to encode the information, as observed in attentional impairments (Stone et al 1998). Spatial working memory deficits are also commonly found in schizophrenia. These tasks often require the subject to maintain the spatial location of visual information while performing interference tasks. Even minimal demands beyond attentional capacity result in deficiencies in schizophrenia patients (Seidman et al 1994). As opposed to spatial working memory, an alternative form of non-verbal working memory known as object working memory reveals deficits in schizophrenia patients that are an artifact of perceptual deficits rather than problems with the working memory system (Tek et al 2002). This difficulty encoding and then arranging information can make it difficult for schizophrenia patients to handle social and interpersonal situations that require attention to multiple streams of information.

Verbal fluency

Patients with schizophrenia have difficulties producing speech on demand. Verbal fluency tests assess their ability to produce

words from a specific phonological or semantic category. These tests reveal both poor storage of verbal information (Kerns et al 1999) as well as inefficient retrieval of information from semantic networks (Aloia et al 1996; Goldberg et al 1998). Information that is stored is not always retrieved as a result of this inability to properly access semantic networks (Joyce et al 1996). Not surprisingly, deficits in verbal fluency are associated with poor interpersonal functioning (Addington and Addington 2000) and community functions (Rempfer et al 2003).

Verbal learning and memory

Poor learning and retention of verbal information is a hallmark cognitive impairment in schizophrenia. Along with executive functioning deficits, impaired ability to encode and retain verbally presented information is one of the most consistent findings across research studies. These deficits tend to be more severe than other cognitive ability domains (Saykin et al 1991; Saykin et al 1994). Like many other neuropsychiatric illnesses (and normal aging), and distinct from dementing conditions, the pattern of deficits in schizophrenia tends to be reduced rates of learning over multiple exposure trials and poor recall of learned information, while encoding of the information appears spared as evidenced by intact recognition of the target stimuli from distractors (Harvey et al 2002; Bowie et al 2004). However, some patients with a chronic course of illness and substantial functional impairments do show deficits in recognition memory along with a global pattern of profound cognitive impairments and deteriorating functional skills (Bowie et al 2004). Verbal memory performance predicts success in various forms of verbal therapy (Smith et al 1999) and is associated with social, adaptive, and occupational success (Green et al 2000).

Executive functioning

Executive functions encompass a wide range of cognitive processes that ultimately result in purposeful, goal-directed behavior. Studies using formal neuropsychological instruments have found that many schizophrenia patients have difficulties with most or all of these component processes. For example, patients have a difficult time forming a conceptual framework to understand ambiguous stimuli (Haut et al 1996). If a concept is understood, schizophrenia patients have trouble adapting to changes in the environment that require different behavioral responses (Koren et al 1998; Pantelis et al 1999). This tendency toward inflexible thinking is found in a number of studies and is highly correlated with

occupational difficulties (Lysaker et al 1995). Another component of executive functioning often found to be impaired in schizophrenia is planning (Goldberg et al 1990; Pantelis et al 1997; Bustini et al 1999). Perhaps because they encompass so many sub-component processes, the executive functioning tasks are consistently among the best predictors of functional performance. Self-care, social, interpersonal, community, and occupational functions are all associated with executive functioning in schizophrenia (Lysaker et al 1995; Velligan et al 2000; McGurk et al 2003; Evans et al 2004). Importantly, executive functions are also associated with treatment success. Impairments in this domain are associated with less engagement in therapy (McKee et al 1997), medication compliance (Robinson et al 2002; Jeste et al 2003), and longer hospital stays (Jackson et al 2001).

Treatment of cognitive deficits in schizophrenia

As mentioned above, the traditional characteristic signs and symptoms of psychosis are less stable than cognitive impairments. They tend to fluctuate naturally throughout the course and have been found to be more treatment responsive. Conventional antipsychotic medications conferred little benefit across cognitive domains (Mishara and Goldberg 2004) and often result in extrapyramidal side effects, requiring anticholinergic treatment that impairs memory (Strauss et al 1990). The emergence of second generation (atypical) antipsychotic medications resulted in several publications that observed cognitive improvements with atypical antipsychotic treatment (for an early review, see Keefe and McEvoy 2001). These changes were greater than placebo and the conventional antipsychotic medications and found in a number of cognitive domains. Several of these studies, however, were methodologically limited. A review by Harvey and Keefe (2001) noted several methodological shortcomings and calculated only modest effect sizes for improvements across atypical multiple antipsychotic medications and cognitive domains. While these improvements were statistically significant, the severe cognitive impairment found in most schizophrenia patients brings their clinical meaningfulness into question.

Recently, more methodologically sound (ie, double-blind randomized trials) have found support for greater cognitive improvement in schizophrenia patients on atypical antipsychotic medications as compared to either baseline or continued treatment with conventional antipsychotic medications (Bilder et al 2002; Keefe et al 2004; Harvey et al

2003, 2004a, 2004b, 2005). No notable differences in cognitive improvement have been found in studies directly comparing atypical antipsychotic medications, with the exception of clozapine, which tends to result in improved motor functions but not other cognitive domains (Bilder et al 2002).

Although these cognitive improvements are modest, they are promising in that they provide some initial evidence of the malleability of the characteristic of schizophrenia that is the best predictor of functional disability. With this notion, several attempts have been made to augment antipsychotic treatment with adjunctive cognitive enhancing medications such as guanfacine (Friedman et al 2002), acetylcholinesterase inhibitors (Friedman et al 2003; Stryker et al 2003; Tugal et al 2004; Erickson et al 2005), glycine (Goff et al 1999), stimulants (Barch et al 2005), and serotonergic agents (Friedman et al 2005). To date, they have had very limited, if any, success in producing cognitive improvements. However, the search for new compounds designed specifically for cognitive enhancement in schizophrenia continues to be a promising area for future research. For example, early studies demonstrate the promise for nicotinic agents to enhance attention and working memory (Smith et al 2006). As more rigorous trials with these and other agents are conducted, it will be more clear whether cognitive deficits can be normalized in schizophrenia and how this affects functional outcomes.

Behavioral treatment of cognitive deficits

Although fewer studies have been funded or published, behavioral approaches to treating cognitive deficits in schizophrenia have produced very promising results. These strategies include training on computerized tasks similar to existing cognitive tests, teaching new learning strategies, training on novel tasks, and/or performing tasks repetitively. A drawback of these strategies is that they tend to be labor intensive, and expensive. While they have been criticized for lack of external validity, recent evidence suggests that treatment of specific cognitive domains can result in symptom improvement and positive vocational outcomes (McGurk et al 2005; Wexler and Bell, 2005). Another potential area for mediation is that of social cognitive deficits, which are thought to link cognitive deficits and real world functional deficits. Choi and Kwon (2006) demonstrated the malleability of social cognitive deficits with a trial of social cognition enhancement training. Translation to real world functional improvements would be a major step forward for the field.

Combined with pharmacological treatment, these behavioral approaches might represent the best chance for improving or normalizing cognition in schizophrenia. The effects of cognitive improvements in the real world, however, are still unknown.

Implications for real world performance

Realistic optimism has emerged in the treatment of schizophrenia with the identification of malleable correlates of functional outcomes. In the US, improving cognition has been targeted as a priority in the field with the MATRICS initiative (Marder et al 2004), which fosters a collaboration between the National Institute of Mental Health, pharmaceutical industries, and Food and Drug Administration. This commendable effort to streamline the process of drug development for treating cognitive impairments in schizophrenia has moved forward quickly. However, it is important to note the limitations one can anticipate in treating cognitive impairments. Although zero-order correlations between cognitive impairments and functional deficits have been well-replicated, fewer studies have examined causal models. Lack of research in this area is, in part, due to the fact that cognitive deficits do not tend to improve, thus making the search for predictors of change difficult. Applying path analytic techniques, we recently (Bowie et al 2006) examined relationships between symptoms, cognition, functional skills, and functional performance in the real world. These last two domains are an important distinction, because there is likely to be a difference between what one is able to do (skills) and what one actually does in the real world (performance), which is limited by a number of internal and external factors such as motivation and stigma. We replicated the finding that cognitive deficits are associated with real world functional performance, but the path to these outcome domains is mediated by a person's functional skill level. That is, cognitive performance predicted scores on a performance-based measure of skills, and it is these skills that account for the variance in functional outcomes such as work skills, community activities, and interpersonal functions. Cognition is not a direct predictor of outcomes. Further, negative symptoms and depression are associated with real world performance independent of cognitive performance. These findings suggest that cognitive enhancement, while an important treatment goal, will not be sufficient for improving real world outcomes. To evaluate the meaningfulness of cognitive change, it is important to look at its correlation with

more proximal measures of functioning, such as these performance-based assessments, which remove the multitude of internal and external factors that confound assessment of real world performance. Further, any attempts to engender real world improvements will need to take a comprehensive treatment strategy that targets skill acquisition and treatment of negative and affective symptoms.

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