Cognitive Deficits in Patients With Schizophrenia: Effects and Treatment

Richard S. E. Keefe, Ph.D.

The average patient with schizophrenia performs on cognitive tests at the lowest 5% to 10% of the general population. Cognitive impairments impact patients on virtually every aspect of functioning, interfere with patients' ability to engage in real-world tasks, and affect long-term outcome. Therefore, cognitive deficits should be included in the diagnostic criteria for schizophrenia. Clinicians need to focus treatment options on helping patients to regain premorbid levels of cognitive functioning.

(J Clin Psychiatry 2007;68[suppl 14]:8–13)

Cognitive deficits appear to be present in patients with schizophrenia early in the course of the illness. A classic demonstration by Saykin et al.[1] showed that, on cognitive test domains, unmedicated patients with either first-episode or chronic schizophrenia performed approximately 2 standard deviations below healthy controls (Figure 1). Wilk et al.[2] confirmed this cognitive performance level on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which has a mean of 100 and standard deviation of 15, like an IQ test. These findings suggest that the average patient with schizophrenia performs so poorly on cognitive tests, he or she would likely receive a RBANS score of about 70 to 75. This range of scores is similar to the threshold of pervasive developmental disorder, otherwise known as mental retardation for IQ tests.

Because cognitive deficits can interfere with an individual's ability to engage in real-world tasks, difficulty with task engagement may be a key impairment found in patients with schizophrenia. Cognitive deficits are widely suggested as a core feature of schizophrenia and affect long-term outcomes.[3–5] Therefore, inclusion of cognitive deficits in the diagnostic criteria for schizophrenia could aid clinicians dealing with diagnostic challenges. Clinicians need to focus treatment options on helping patients to regain premorbid levels of cognitive functioning.

SYMPTOM DIMENSIONS AND NEUROCOGNITIVE DOMAINS

Clinicians often reasonably wonder whether cognitive deficits in patients with schizophrenia are a result of positive symptoms. The idea is that, because patients with schizophrenia experience hallucinations and delusions, these patients cannot reliably engage with cognitive tests. However, empirical data[5] suggest that delusions and hallucinations do not affect cognition test performance. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project,[5] patients with chronic schizophrenia were assessed with a 90-minute battery of cognitive tests at baseline, and 91.2% of subjects provided neurocognitive data that were quantifiable and clinically meaningful. No statistically significant correlations were found between positive symptoms and cognition in any of the 5 domains of testing; correlations with positive symptom severity were near zero ($r < 0.08$). Negative symptom severity was slightly correlated with neurocognitive deficits ($r = 0.13–0.27$). Investigators concluded that positive symptoms do not cause cognitive deficits in schizophrenia and neurocognitive tests can be performed in most patients with schizophrenia.

Functional Outcome

Cognition is related to functioning. For example, a review[6] of studies of functioning and neurocognitive

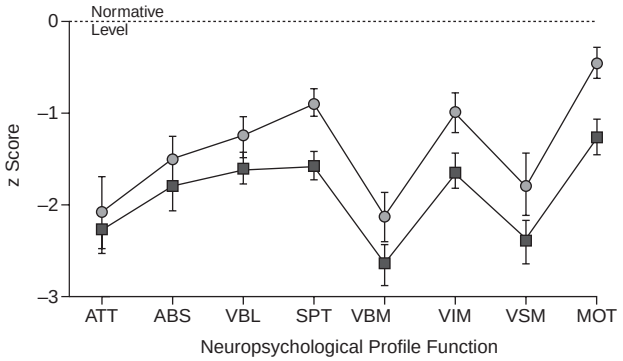
From the Department of Psychiatry and Behavioral Sciences, Duke University, Durham, N.C.

This article is derived from the teleconference series "Raising the Bar in Schizophrenia by Treating to Remission," which was held in July and August 2007 and supported by an educational grant from Janssen, L.P., administered by Ortho-McNeil Janssen Scientific Affairs, LLC.

Dr. Keefe is a consultant for Bristol-Myers Squibb, Cephalon, Dainippon Sumitomo Pharma, Eli Lilly, Forest, Gabriel, GlaxoSmithKline, Johnson & Johnson, Lundbeck, Memory, Merck, Orexigen, Otsuka, Pfizer, Repligen, Saegis, Sanofi-Aventis, and Xenoport; has received grant/research support from AstraZeneca, Eli Lilly, and Pfizer; is a member of the speakers/advisory boards for Abbott, AstraZeneca, Eli Lilly, Memory, Pfizer, Saegis, and Sanofi-Aventis; and has received royalties from Brief Assessment of Cognition (BACS), and MATRICS Battery (BACS Symbol Coding).

Corresponding author and reprints: Richard S. E. Keefe, Ph.D., Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Box 3270, Durham, NC 27710 (e-mail: richard.keefe@duke.edu).

Figure 1. Neuropsychological Profile for Drug-Naive First-Episode and Previously Treated Patients[a]



[a]Reprinted with permission from Saykin et al.[1] Neuropsychological profile (± SEM) for neuroleptic-naive patients with first-episode schizophrenia (circles, N = 37) and previously treated patients (squares, N = 65) relative to healthy controls (dashed line, N = 131).
Abbreviations: ABS = abstraction-flexibility, ATT = attention vigilance, MOT = fine manual motor functions, SPT = spatial organization, VBL = verbal intelligence and language function, VBM = verbal memory and learning, VIM = visual memory, VSM = speeded visual-motor processing and attention.

measures found that all forms of functional outcome were related to verbal memory. Social problem solving and skill acquisition were associated with vigilance. Community functioning was predicted by executive function, as tested by card sorting. This review also found that functional outcome was not significantly affected by psychotic symptoms. A subsequent meta-analysis by Green et al.[7] showed that although the individual cognitive domains verbal memory, card sorting, and vigilance had a medium effect on functional outcome ($p < .0001$), the composite score had a large effect.

The work of Green et al.[8] for the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative, established by the National Institute of Mental Health, identified the following 7 domains as separable for use in a cognitive battery for clinical trials: attention or vigilance, reasoning and problem solving, speed of processing, social cognition, verbal learning and memory, visual learning and memory, and working memory. Studying how patients with schizophrenia perform in these cognitive domains may help to predict long-term functional outcomes.

RECOGNIZING COGNITIVE DEFICITS IN SCHIZOPHRENIA

Patients With Schizophrenia Compared With Healthy Controls

Cognitive decline is ubiquitous in schizophrenia. Although cognitive performance in schizophrenia is generally about 2 standard deviations below that of healthy controls,[1,2] some people with schizophrenia perform in the average and even above-average range. Palmer et al.[9] classified 27% of individuals with schizophrenia as neuropsychologically normal. However, many of these people with schizophrenia may have had higher levels of premorbid cognitive functioning.[3] For example, if a young person with strong cognitive abilities was on his or her way to medical school or law school at the onset of schizophrenia, he or she would be very likely to have a decline in cognitive function. This premorbidly gifted individual may then perform at the same cognitive level as an average healthy control.[3]

Antecedent Factors and Level of Cognition

Antecedent factors, such as parents' level of education and premorbid IQ estimates, affect patients' current cognitive levels. Controls whose mothers and fathers had high levels of education performed much better on cognitive tests than those whose parents had low levels of education.[10] However, 98.1% of patients with schizophrenia scored lower on cognitive tests than their premorbid intellectual functioning and parental education levels would have predicted,[10] suggesting that almost all patients with schizophrenia are likely to perform worse in cognitive ability than they would have had they never developed the illness.

DEFINITIONS OF COGNITIVE IMPAIRMENT

DSM-IV-TR Diagnostic Criteria

If cognitive deficits are ubiquitous across patients with schizophrenia, why is cognition not part of the criteria for schizophrenia in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)?[11] Although the DSM-IV-TR description of characteristics of schizophrenia mentions cognitive dysfunction, the diagnostic criteria do not require cognitive impairment. Given that cognitive deficits in patients with schizophrenia are more predictive of functional outcome than psychotic symptoms,[6] cognitive impairment deserves a place in the formal diagnostic criteria.

Potential Diagnostic Criteria

If cognitive impairment were to be included in the criteria for schizophrenia, a consensus definition and measurement would be needed. One way to define cognitive impairment would be by using a definitive cognitive test that patients would take to measure performance. However, there is no such test currently available, and it may be unrealistic to expect formal cognitive testing to be available and practical in every psychiatric setting.[12] Formal cognitive testing can take up to several hours to

Table 1. Improvements in Specific Aspects of Cognition in 20 Studies in Which Cognitive Changes Were Reported in Patients With Schizophrenia Following Novel Antipsychotic Treatment[a]

Cognitive Construct	Effect Size (Cohen's d)[b]
Immediate memory	0.13
Secondary memory	0.39
Vigilance	0.39
Executive functions	0.18
Visuo-motor skills	0.27
Verbal fluency	0.43
Spatial functions	0.20

[a]Reprinted with permission from Harvey and Keefe.[14]
[b]Values represent average improvement as measured by changes from baseline in standard deviations: figures are weighted for the study group size in each study and collapsed across all newer medications.

administer and would, therefore, stress the normal resources of typical mental health centers. In addition, some cognitive performance is affected by educational factors and socioeconomic status, and so formal testing is not always the most useful or feasible option.

An alternative to formal cognitive testing is clinical judgment.[12] The psychiatrist who is making a diagnosis may be required to determine whether or not a patient has cognitive impairment, but clinicians who see patients for only a brief visit are not able to make good judgments about cognitive ability. Caregivers and relatives can be invaluable in informing psychiatrists as to whether or not cognitive impairment negatively affects a patient's daily life.[13] However, some patients may not have available informants.

Another possible way to formalize a cognitive impairment requirement in the schizophrenia criteria is to determine whether or not a patient's level of cognition has declined from premorbid levels. Decline can be determined by comparing current cognitive functioning to the expected cognitive levels based on patient educational background, familial background, and socioeconomic status.[12]

EFFECT OF TREATMENT ON COGNITION

Cognition may improve with antipsychotic treatment. A 2001 review[14] of the available 20 studies suggested that, while the research provided initial support for improved performance on cognitive tests with atypical antipsychotic medications, the studies had methodological problems that limited the reliability of this conclusion. Many of the patient samples were small and did not accurately represent most patients with schizophrenia. In addition, these studies never truly addressed whether cognitive improvement was secondary to other symptom improvement or merely an effect of switching from the typical antipsychotics (often at high doses) and the anticholinergic treatments that usually accompanied them. Furthermore, the cognitive improvements in these studies were modest, averaging about a quarter of a standard deviation (Table 1).

The CATIE Project

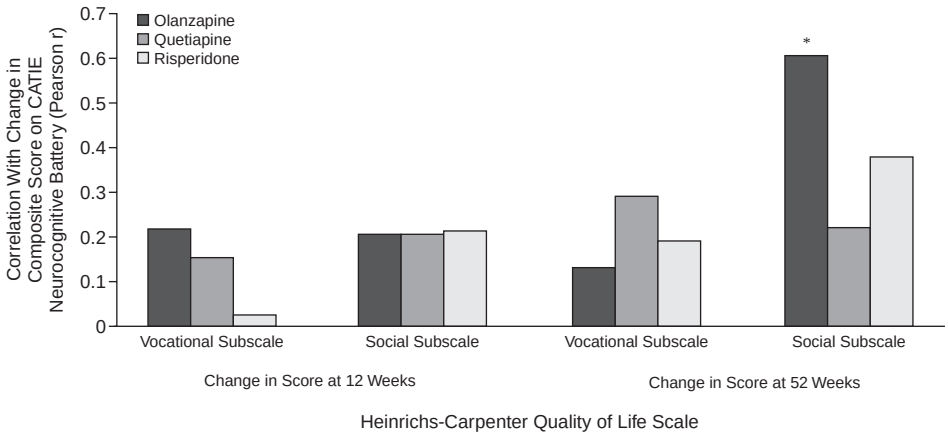
One of the ways in which these methodological issues were addressed was through the CATIE project,[4,5,15] which was considered an all-comer trial (N = 1460), because patients were not excluded based on comorbid psychiatric or medical conditions. The point of such a varied trial sample was to obtain generalizability and genuinely reflect the larger population of patients with schizophrenia. The 5 medications compared in the CATIE project were olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine. Perphenazine was chosen as the representative of the class of typical antipsychotics, and it was not administered at a high dose. The primary outcome measure from the CATIE project was all-cause discontinuation. This study was not actually designed to assess cognitive benefit or worsening; however, because cognitive assessments were made at baseline and 2-month follow-up—817 subjects completed neurocognitive testing at both time points—the results afford an opportunity to examine the effects of these medications in a large sample. The 5 cognitive domains examined in the study were processing speed, reasoning, working memory, verbal memory, and vigilance. A composite score was derived from these 5 domains.

All of the medications in the CATIE study[15] resulted in cognitive improvement from baseline; however, that improvement was small. One of the benefits of having a large sample size was the resulting statistical power to determine group differences; no significant group differences were found, either between cognitive domains or between drugs. After 2 months, the improvement levels were as follows: olanzapine ($p < .002$), perphenazine ($p < .001$), quetiapine ($p < .001$), risperidone ($p < .001$), and ziprasidone ($p < .06$); results at 6 months were similar. At 18 months, cognitive improvement was greatest in the perphenazine group. Thus, although previous research[14] with methodological limitations had indicated that atypical antipsychotics best aid cognition in patients with schizophrenia, data from the CATIE study showed that 4 atypical antipsychotics and 1 typical antipsychotic produced similar improvement in cognition. An additional finding was that adding anticholinergic agents during the first 2 months of treatment resulted in cognitive worsening.

Clinical Significance

If the cognitive improvements resulting from antipsychotic treatment are small, do they have any clinical significance? While the CATIE study[15] found that neurocognitive improvement did not predict a longer time to treatment discontinuation, another study[16] of early phase

Figure 2. Partial Pearson Correlations Between Change in CATIE Neurocognitive Battery Composite Score and Change in Functional Outcome Measures From Baseline to Weeks 12 and 52, Controlling for Baseline CATIE Composite Score and PANSS Total Score[a]



[a]Reprinted with permission from Keefe et al.[16]
*p < .01.
Abbreviations: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness, PANSS = Positive and Negative Syndrome Scale.

schizophrenia, in which patients took olanzapine, quetiapine, or risperidone, showed that the amount of cognitive change was related to changes in functional outcomes at 52 weeks. A correlation was found between change in cognition and change in functioning that occurred independently of type of treatment (Figure 2). These findings suggest that patients who experience cognitive improvement, even if modest, may experience improved clinical outcomes.

CHANGES IN ATTENTION DURING PRACTICE-RELATED LEARNING

A key cognitive impairment in patients with schizophrenia is changes in attention during practice-related learning, which can affect one's ability to perform real-world tasks. Posner and Rothbart[17] identified 3 stages of practice-related learning: the cognitive stage, the associative stage, and the autonomous stage. These 3 stages describe how tasks are learned, made more efficient through practice, and eventually experienced as effortless.

The cognitive stage of practice-related learning involves discerning how to perform a given task. People tend not to perform as well at the early stages of a new task as they do once the task has become familiar. The cognitive stage of practice-related learning applies not only to laboratory performance but to job performance, relationship performance, and the performance of many real-world activities. The second stage of practice-related learning is the associative stage, during which actions become engrained and more efficient through practice and the development of mental associations between complex activity and simpler thoughts. In the autonomous stage, performing the task or activity becomes less directly subject to cognitive control and distracting influences. At this stage, a task can sometimes be experienced as effortless or automatic. People with schizophrenia often do not experience the autonomous stage, even during the simplest of activities.

TASK DIFFICULTY AND ENGAGEMENT

A fluctuating relationship exists between task difficulty and a person's engagement with the task.[18] For example, a very easy task does not require full cognitive engagement, but more difficult tasks require effort and greater engagement. If a task is too difficult, one can become disengaged altogether. Likewise, if a task is too easy, it also will not hold one's attention.

Pupillometers have been used to study how people engage with tasks of varying complexity. As a person becomes more engaged with a task, the pupils dilate. A study by Granholm et al.[19] showed that healthy controls (N = 32) and patients with schizophrenia (N = 24) performed similarly if a task was very easy. Each group showed the same amount of pupillary response and therefore the same level of engagement. However, as the task became more difficult, healthy controls became more engaged, whereas patients with schizophrenia became less engaged to the point where some patients could not complete the task. The difficulty level was increased again, at which point some of the healthy controls became disengaged and the patients with schizophrenia became even more disengaged. These

findings suggest that task engagement may be a crucial determinant as to whether or not patients will perform cognition-related tasks well.

Consequences of Disengagement in Patients With Schizophrenia

Disengagement has some direct relevance to the clinical status of patients with schizophrenia. Patients who are unable to engage in tasks have great difficulty with social interactions and intimacy. Simply speaking to another person may be a task that is too difficult. Occupational and educational activities, even menial jobs, may also be almost impossible for patients with schizophrenia if their level of engagement is low due to cognitive deficits. If patients repeatedly interact with the outside world and repeatedly feel a sense of failure because of their cognitive difficulties, they will disengage from external life. This disengagement may lead to reduced self-esteem, reduced self-efficacy, and an increased sense of hopelessness.

Unfortunately, as patients disengage from tasks because of cognitive difficulties and then from the outside world in general, they also tend to disengage from their doctors and family members. Disengagement threatens the treatment alliance and treatment adherence.[18] Patients who do not engage in the complexities of everyday life have trouble engaging with those who are giving them instructions concerning their medications, and thus those patients have great difficulty adhering to treatment. As a result, disengaged patients with schizophrenia are at a high risk for frequent relapses.

An empirical question is whether disengagement precedes schizophrenia onset. It may be the case that, in the early stages of schizophrenia, patients begin to disengage from tasks owing to cognitive difficulty, then disengage from the external world, and then begin to engage with their internal experiences, which can lead to psychotic delusions and hallucinations.

CONCLUSION

If impairment in cognition and task engagement is a core feature of schizophrenia, then treatment should focus on improving these impairments. It appears as though the choice of an antipsychotic has minimal overall impact on cognition, although individual patient responses may vary. However, if older antipsychotics are dosed too high, cognition may worsen. Adjunctive treatments may also worsen cognition. Clinicians should try to help patients regain as many of their cognitive abilities as possible, which may in turn enhance their functioning. Cognitive deficits should become a part of the formal diagnostic criteria for schizophrenia, and treatments that provide greater improvement in cognitive abilities of patients with schizophrenia than the current agents should be developed.

Drug names: olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

REFERENCES

1. Saykin AJ, Shtasel DL, Gur RE, et al. Neuropsychological deficits in neuroleptic naive patients with first episode schizophrenia. Arch Gen Psychiatry 1994;51:124–131
2. Wilk CM, Gold JM, Humber K, et al. Brief cognitive assessment in schizophrenia: normative data for the Repeatable Battery for the Assessment of Neuropsychological Status. Schizophr Res 2004;70:175–186
3. Kremen WS, Seidman LJ, Faraone SV, et al. The paradox of normal neuropsychological function in schizophrenia. J Abnorm Psychol 2000;109:743–752
4. Keefe RS, Mohs RC, Bilder RM, et al. Neurocognitive assessment in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project schizophrenia trial: development, methodology, and rationale. Schizophr Bull 2003;29:45–55
5. Keefe RS, Bilder RM, Harvey PD, et al. Baseline neurocognitive deficits in the CATIE schizophrenia trial. Neuropsychopharmacology 2006;31:2033–2046
6. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 1996;153:321–330
7. Green MF, Kern RS, Braff DL, et al. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr Bull 2000;26:119–136
8. Green MF, Nuechterlein KH, Gold JM, et al. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. Biol Psychiatry 2004;56:301–307
9. Palmer BW, Heaton RK, Paulsen JS, et al. Is it possible to be schizophrenic yet neuropsychologically normal? Neuropsychology 1997;11:437–446
10. Keefe RS, Eesley CE, Poe MP. Defining a cognitive function decrement in schizophrenia. Biol Psychiatry 2005;57:688–691
11. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
12. Keefe RS, Fenton WS. How should DSM-V criteria for schizophrenia include cognitive impairment? Schizophr Bull 2007;33:912–920
13. Keefe RSE, Poe M, Walker TM, et al. The Schizophrenia Cognition Rating Scale: an interview-based assessment and its relationship to cognition, real-world functioning, and functional capacity. Am J Psychiatry 2006;163: 426–432
14. Harvey PD, Keefe RS. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am J Psychiatry 2001;158:176–184
15. Keefe RS, Bilder RM, Davis SM, et al. Neurocognitive

effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. Arch Gen Psychiatry 2007;64:633–647
16. Keefe RS, Sweeney JA, Gu H, et al. Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. Am J Psychiatry 2007;164:1061–1071
17. Posner MI, Rothbart MK. Attention, self-regulation, and consciousness. Philos Trans R Soc Lond B Biol Sci 1998;353:1915–1927
18. Keefe RSE. Missing the sweet spot: disengagement in schizophrenia. Psychiatry 2006;3:36–41
19. Granholm E, Morris SK, Sarkin AJ, et al. Pupillary responses index overload of working memory resources in schizophrenia. J Abnorm Psychol 1997;106: 458–467