Cognitive Impairment and Functional Outcome in Schizophrenia and Bipolar Disorder

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A considerable amount of evidence supports the relationship between cognitive impairment and functional outcomes in schizophrenia. Cognitive impairment is considered a core feature of schizophrenia that includes problems in speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. These deficits can also serve as an endophenotype for the illness in studies of genetics. Cognition is considered a reasonable treatment target in individuals with schizophrenia, partly because cognitive deficits contribute to poor functional outcomes. Similarly, evidence is beginning to emerge that cognitive impairment may also be a core feature of bipolar disorder. In addition, cognitive deficits adversely affect functional outcomes in bipolar disorder. This evidence suggests that cognition can be considered a reasonable target for intervention in both schizophrenia and bipolar disorder.

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A considerable body of literature exists concerning the relationship between cognitive impairment and poor functional outcomes in schizophrenia, but there is much less literature about cognition in bipolar disorder. However, a comparison of the evidence on the role of cognitive impairment in the two illnesses raises the possibility that cognition may be a reasonable treatment target in bipolar disorder as well as schizophrenia, since improving cognition may lead to improved functional outcomes for individuals with these disorders. Treating impaired cognition could lead to distinct personal and public health advantages.

SCHIZOPHRENIA

Key cognitive domains have been identified for schizophrenia: speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition.[1] The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus process, established by the National Institute of Mental Health (NIMH),[2,3] identified the key cognitive domains for schizophrenia and developed the MATRICS Consensus Cognitive Battery (Table 1).[4] These tests were selected on the basis of their test-retest reliability, their use as a repeated measure, their relationship to functional outcome, their practicality in terms of administration, and their acceptance by the people taking the tests.[5]

Cognitive impairment in schizophrenia is considered a core feature of the illness. As a core feature, cognitive deficits are not considered to be the result of the symptoms of schizophrenia or of the treatment of the illness with antipsychotic medication. Instead, they are relatively stable across clinical state changes, present before the onset of clinical symptoms, and may be seen in attenuated form in unaffected first-degree relatives of probands with schizophrenia.[6,7]

A clear discrepancy exists between the clinical and cognitive effects of both first- and second-generation antipsychotic medications. These medications have a greater effect on psychotic symptoms than on cognition. Many cognitive performance deficits are fairly stable even as patients go in and out of psychotic episode. For example, a study[6] of neuroleptic-naive and neuroleptic-withdrawn patients with schizophrenia showed that performance on a test of vigilance was nearly unchanged in spite of improvements in positive and negative symptoms. The same study also showed that the nonschizophrenic siblings of patients with schizophrenia made significantly more errors ($p = .05$) on a measure of vigilance (the continuous

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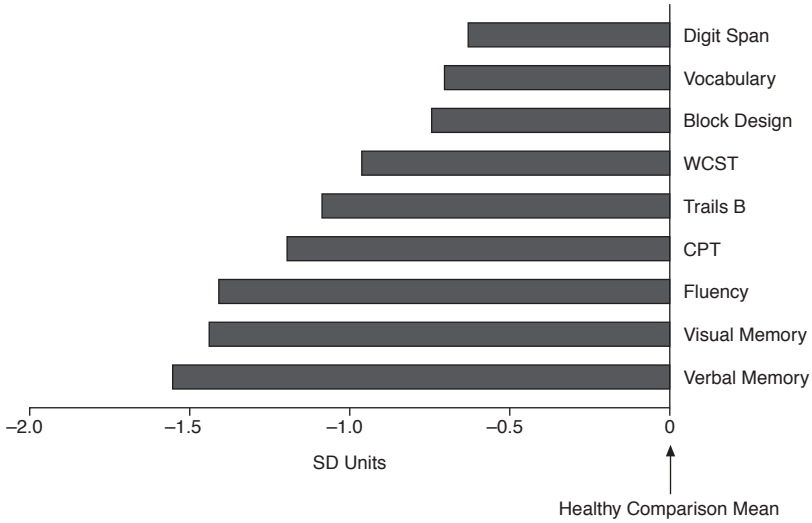
Table 1. MATRICS Consensus Cognitive Battery of Tests[a]

Cognitive Domain	Test
Speed of processing	Category Fluency Brief Assessment of Cognition in Schizophrenia (BACS), Symbol-Coding Trail Making A
Attention/vigilance	Continuous Performance Test, Identical Pairs (CPT-IP)
Working memory	Verbal: University of Maryland, Letter/Number Span Nonverbal: Wechsler Memory Scale (WMS) III Spatial Span
Verbal learning	Hopkins Verbal Learning Test (HVLT) Revised
Visual learning	Brief Visuospatial Memory Test (BVMT) Revised
Reasoning and problem solving	Neuropsychological Assessment Battery (NAB) Mazes
Social cognition	Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) Managing Emotions

[a]Based on Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS).[4]

Figure 1. Characteristic Profile of Cognitive Impairments in Schizophrenia[a]



[a]Data from Heinrichs and Zakzanis.[8] The graph shows the difference between the mean healthy control sample (0) and the number of standard deviations characteristic of patients with schizophrenia.
Abbreviations: CPT = Continuous Performance Test; Trails B = Trail Making Test, Part B; WCST = Wisconsin Card Sorting Test.

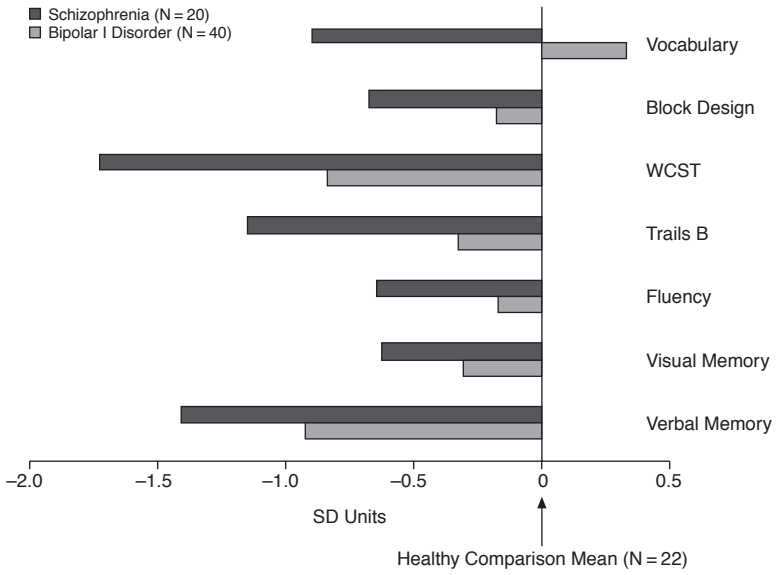
performance test) than did healthy controls, showing evidence for cognitive impairment in unaffected first-degree relatives.

Cognitive impairment can also be considered a core feature of schizophrenia because it is relatively stable across the life span. Gold's review[7] showed that cognitive impairment was present before the emergence of psychotic symptoms and the cross-sectional correlations with psychotic symptoms and cognitive impairment were fairly low, indicating that hallucinations and delusions do not correlate with cognitive deficits. Starting with onset of illness to late adulthood, relative stability of cognitive impairment is assumed.[7] In late adulthood, some patients may show an accelerated decline in cognitive function, but from onset to about age 65 years it is considered to be a relatively stable impairment in most patients.

Lastly, schizophrenia has a modal profile. People with schizophrenia have characteristic impairments across cognitive measures, although there are variations from person to person. A meta-analysis[8] of 204 studies that compared performance on standard neurocognitive tests in 7420 people with schizophrenia and 5865 healthy controls showed varying degrees of deficit in all ability domains in people with schizophrenia and a modal profile comprised of large cognitive impairments in memory, attention, and executive functions, and relatively smaller impairment in old learning, vocabulary, and visual perceptual skills (Figure 1).

The deficits can serve as endophenotypes for the genetics of schizophrenia because they show characteristics that are associated with genetic vulnerability to the illness.[6] The focus on *endophenotypes* (as opposed to the clinical

Figure 2. Neurocognitive Function in Euthymic Bipolar Patients and Clinically Stable Schizophrenia Patients[a]



[a]Data from Altshuler et al.[13] The vertical line at 0 indicates the mean score of healthy control subjects.
Abbreviations: Trails B = Trail Making Test, Part B; WCST = Wisconsin Card Sorting Test.

phenotype) is increasingly common in studies of genetics of psychiatric disorders. An endophenotype is viewed as a feature of illness that underlies the clinical disorder, has a simpler genetic architecture, and is closer to the genome than the clinical disorder. For example, if cognitive impairments are present in first-degree relatives who do not have schizophrenia and if they are stable in and out of psychotic episode, they are not tightly linked to the clinical symptoms. Instead, they appear to reflect predisposition and may be valuable endophenotypes for the genetics of schizophrenia.[6]

Cognitive deficits contribute to poor functional outcomes. Difficulties maintaining work and social connections, living independently, and acquiring skills in rehabilitation programs form a large component of the disability of schizophrenia and correlate well with cognitive impairments. A review[9] of studies that had a minimum 6-month follow-up period and assessed some aspect of community outcomes, such as job performance, job tenure, and social relations, showed that cognitive deficits correlate well cross-sectionally and also predict how well a patient will function in the future. These connections were medium in size for specific domains, but large for summary scores in which several domains were combined.[10] The relationships were stronger between cognitive impairment and functional outcome than they were between psychotic symptoms and functional outcome.[11] There was a particularly strong connection between cognitive deficits and the ease with which individuals acquired skills as they progressed through their skills training and rehabilitation.[9] Partly because cognitive impairments have an impact on the effectiveness of skills training and rehabilitation and correlate well with poor functional outcomes, cognitive deficits have been suggested as treatment targets in schizophrenia.

Several lines of evidence have led to the recognition that cognition should be considered an important treatment target. This evidence includes (1) that cognitive deficits are a core feature of schizophrenia and may be associated with genetic vulnerability to the illness, (2) that research on the neuropharmacology of cognition has increased,[12] and (3) that there is a relationship between cognitive deficits and poor functional outcomes. If new treatments can successfully improve cognition, it is hoped that they may also have a distinct public health advantage and reduce the disability of schizophrenia.

BIPOLAR DISORDER

Much less information is available on cognition in bipolar disorder, but there are some notable similarities to data in schizophrenia. The existing data suggest that impairments in some cognitive domains may serve as endophenotypes for bipolar disorder, at least for a subgroup of patients, and might be linked to community functioning.

The cognitive impairments in bipolar disorder tend to be smaller and in a subset of the domains that are affected in schizophrenia. Altshuler and colleagues[13] compared neurocognitive function in clinically stable men with bipolar I disorder or schizophrenia versus healthy control subjects (Figure 2). Using a battery of neurocognitive tests, they examined domains including executive

functioning, verbal memory, visual memory, procedural learning, visuoconstructive ability, and language functions. The patients with schizophrenia showed cognitive impairment across most domains compared with control subjects. Patients with bipolar disorder exhibited impairments in several domains but not all, and the impairments were smaller than those seen in schizophrenia. In the case of vocabulary, the patients with bipolar I disorder performed slightly better than the controls.

The relatively small group differences between patients with bipolar disorder and healthy controls raises the question whether there are distinct neurocognitive subgroups of patients with bipolar disorder.[13] The individual data from the Wisconsin Card Sorting Test (a measure of executive functions) yielded a bimodal distribution of scores, suggesting there may be two subgroups of bipolar patients: one with normal performance and one with impaired executive function. However, results for verbal memory, another test in which bipolar patients scored particularly poorly, showed a normal (not bimodal) distribution. Previous research[14] suggested that poor performance associated with alcohol dependence might account for a bimodal distribution, but that finding was not replicated in the study by Altshuler and colleagues.[13] In schizophrenia, it is unknown whether there are meaningful subgroups of people with impairments in particular cognitive domains. Such subgroups may be harder to find because the deficits are larger and include a broader range of domains.

Similar to deficits seen in schizophrenia, cognitive impairment has been suggested to be present before the onset of bipolar disorder, to exist outside of mood episodes, and to be present in first-degree relatives. Hence, cognitive impairment could be considered a core feature of bipolar disorder in general, or perhaps of a subgroup of patients. Studies[15,16] of large national samples of people entering the army have shown mixed results about whether cognitive impairment begins before the onset of illness. For example, one study[15] examined cognitive measures in apparently healthy men and women drafted into the army in Israel who later developed nonpsychotic bipolar disorder, schizophrenia, or schizoaffective disorder. People who developed schizophrenia showed substantial premorbid deficits on all intellectual and behavioral measures and on measures of reading and reading comprehension, but people who developed nonpsychotic bipolar disorder did not differ substantially on any measure compared with matched controls. In contrast to this finding, a study[16] of a Finnish cohort of men who were entering the draft shows a very different picture. Premorbid intellectual functioning was examined from results in arithmetic, verbal, and visuospatial reasoning tests taken when the subjects were about 20 years old, and the risk for developing all types of bipolar disorder (psychotic and nonpsychotic), schizophrenia, or other psychoses was calculated using information from the Finnish Hospital Discharge Register. Increased risk for all 3 categories was associated with poor performance on the visuospatial reasoning test, but the greatest risk occurred in bipolar disorder. The odds ratios indicating the difference in risk of illness between the lowest and highest of 9 performance categories were 34.65 for bipolar disorder, 13.76 for schizophrenia, and 4.28 for other psychoses.

Another reason to consider cognitive impairment as a core feature of bipolar disorder is that it can be found in first-degree relatives.[13] A study[17] compared intelligence, attention, visuospatial skills, language, learning and memory, and problem solving in a very unusual sample: 7 pairs of monozygotic twins discordant for bipolar disorder and 7 monozygotic pairs of healthy controls, twins in which neither twin had bipolar disorder. Across working and episodic memory measures, unaffected twins from the bipolar-discordant pairs tended to do worse than twins from the healthy pairs. Hence, this small sample suggests that impairment in overall verbal learning and retrieval functions might be a risk indicator for bipolar disorder, similar to that found in schizophrenia.

Although the evidence is limited,[13,15–17] it supports cognitive impairment as a core feature of and a potential endophenotype for bipolar disorder. A review by Glahn and colleagues[18] suggested some criteria for establishing valid endophenotypes for bipolar affective disorder. They concluded that there is sufficient evidence in the domains of executive function, working memory, and verbal learning to show that these deficits are heritable, are associated with illness, occur outside of mood disorders, and are present in first-degree relatives (Table 2). Hence, the available evidence suggests that cognitive impairment could serve as a reasonable endophenotype for both schizophrenia and bipolar disorder.

A remaining question is whether cognitive deficits in bipolar disorder are related to functional outcomes, as they are in schizophrenia. Only a few studies on this topic have been conducted in bipolar disorder. One study[19] examined employment status in 117 outpatients with bipolar I and bipolar II disorder and found a statistically significant stepwise relationship between a total score on a brief cognitive battery (The Repeatable Battery for the Assessment of Neuropsychological Status) and work status of no work, part-time work, or full-time work. A Spanish study[20] of 40 euthymic bipolar outpatients examined the relationship between cognitive impairment and psychosocial functioning. Initially, premorbid IQ, attention, verbal learning and memory, and frontal executive function were compared in euthymic bipolar patients and healthy controls. The patients performed worse on several measures of executive function and memory. Measures of working memory and episodic memory were statistically significantly associated with psychosocial functioning in the patients. These 2 studies suggest that in bipolar disorder, cognitive impairment is related to poor functional out-

Table 2. Cognition as an Endophenotype for Bipolar Disorder[a]

	Criteria for Valid Endophenotype			
Cognitive Domain	Highly Heritable	Associated With Illness	Independent of Clinical State[b]	Present in Relatives
General intelligence	Yes	No	…	…
Processing speed	Yes	Yes	Yes	Unknown
Sustained attention	Yes	Yes	Yes	Unknown
Executive function/working memory[c]	Yes	Yes	Yes	Yes
Verbal learning[c]	Yes	Yes	Yes	Yes
Visual learning	Yes	Unknown	Unknown	Unknown

[a]Adapted with permission from Glahn et al.[18]
[b]Evidence for impairment during symptom remission.
[c]Evidence for valid endophenotype.
Symbol: … = data unavailable.

comes. Further, the sizes of the correlations between cognitive domain impairments and functional outcomes in people with bipolar disorder were comparable (i.e., medium effect sizes) with those seen in schizophrenia.

In summary, cognitive impairments exist in bipolar disorder and may be particularly notable in certain domains, including memory and executive function. The impairments occur outside of manic episode, but the possibility remains that they may be related to some subclinical phenomenon. At this point, it is not yet clear whether these impairments characterize a subgroup of bipolar patients. The findings are mixed regarding the existence of cognitive impairments before the onset of illness, but results are more consistent in showing cognitive impairments in unaffected relatives of people with bipolar disorder. Because cognitive impairment can be considered a core feature of bipolar disorder, it may serve as an endophenotype for bipolar disorder. Although the evidence is stronger in schizophrenia, cognitive impairments also hinder people with bipolar disorder in navigating their world. Because cognitive impairment appears to be a core feature and because it appears to be related to outcome, it can be considered a rational treatment target in bipolar disorder.

CONCLUSION

In considering the evidence for the findings on cognitive impairment in schizophrenia and bipolar disorder, the confidence in the conclusions is proportionate to the size of the empirical literature relating to each illness, with the literature being much smaller for bipolar disorder. The available literature on cognitive impairment in bipolar disorder leads to the conclusion that it is a core feature. However, cognitive impairments in bipolar disorder are milder in magnitude and affect only some domains as compared with the more general impairment seen in schizophrenia. Cognitive impairment may characterize only a subgroup of bipolar patients, but it characterizes the vast majority of schizophrenia patients. The fact that cognitive deficits appear to be related to functional outcomes in both disorders probably reflects their role as prerequisites for daily functioning, regardless of diagnosis. Evidence from the literature has resulted in cognition being considered a treatment target in schizophrenia, and based on the literature so far, it is reasonable to wonder whether cognition should also become a treatment target in bipolar disorder.

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.

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