

Cognition in Schizophrenia

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Cognitive dysfunction has been described as a hallmark feature of schizophrenia since the first descriptions of the illness. Kraepelin [1] described a number of features of the disorder that he thought reflected impairments in cognition and attention. He also speculated that cognitive impairments were mediated by neurobiologic dysfunction, specifically impairments in the functions of the frontal lobe. Since Kraepelin's time, there have been many changes in the general conceptions of schizophrenia, including ideas regarding the status and importance of cognitive impairment in the illness. Due to increased sophistication of neuropsychologic assessment and neuroimaging techniques, cognitive impairment has again risen to the forefront of importance in terms of theories regarding the etiology and treatment of schizophrenia.

Introduction

In the past 5 years, the importance of cognition has been increasingly recognized. The research published in the past year reflects several different trends in the study of cognition in schizophrenia. These include the course of cognitive impairment, including characteristics of first episode patients, the course through middle life, and changes with aging. Functional deficits are common and severe in schizophrenia, and cognitive impairments are a primary predictor, with this concept being increasingly studied in the recent past as well. Treatment efforts for the reduction of cognitive impairment in schizophrenia are also on the rise, with several promising lines of evidence including treatment with newer antipsychotic medications, and treatments with pharmacologic compounds that enhance cognitive functioning, but without antipsychotic effects. These treatment efforts also include more sophisticated behavioral treatments as well. Substance abuse and its effect on cognitive deficits in schizophrenia are also being increasingly studied. For years, patients with schizophrenia who also abused substances were excluded from research studies, despite the fact that at least 50% of patients

with schizophrenia have evidence of substance abuse. Finally, the cognitive functioning correlates of the symptoms of schizophrenia, both positive and negative, are an increasing topic of study.

In this paper, the authors review the past years' research in these topic areas, beginning with studies on the course of schizophrenia.

Course of Schizophrenia

Cognitive deficits are very common in schizophrenia, with up to 70% of patients showing impairments on at least two neuropsychologic measures [2]. Impairments in cognitive skills are typically found before the onset of clinical symptoms, and persist throughout the course of the illness. However, controversy over the lifetime course of cognition functioning in schizophrenia continues. In the past decade, several studies [3,4] concluded from cross-sectional data or short-term follow-up methodology that the course is characterized by stable or static functioning. However, different findings emerged when older patients were studied over longer follow-up intervals. In a 30-month follow-up study of chronic patients over the age of 65, 30% of patients evidenced cognitive decline [5]. Studies using similar methodology also found support for an age-related decline in cognitive functioning in schizophrenic patients who were referred from long-stay psychiatric hospitals to nursing home care [6]. Studies on this topic were common in 2000 and early 2001, as well.

Premorbid deficits in cognitive functioning are well supported in the literature, and regarded as a vulnerability indicator. Amminger *et al.* [7] found that subjects who later developed schizophrenia had lower intelligence quotient (IQ) scores, specifically on the Performance IQ Scale, than control individuals and those with affective disorder. Similarly, Cannon *et al.* [8•] found that cognitive functioning in patients who were later diagnosed with schizophrenia, as well as their siblings, was stable from age 4 to 7 years, and more impaired than nonpsychiatric control individuals. Thus, cognitive functioning is a stable vulnerability indicator throughout the premorbid phase.

Similar to previous research across the lifespan, first-episode schizophrenia patients show a large generalized deficit, and relative deficits in memory and executive functioning, which are related to functional impairment [9,10]. Moreover, even first-episode patients with relatively higher cognitive functioning have memory deficits [9].

Recent evidence has also demonstrated that, even at first-episode, cognitive deficits in schizophrenia are more severe than they are in psychotic affective disorders [11]. With the characterization and specificity of cognitive functioning in the first-episode of schizophrenia established, it will be important for future research to examine correlates of impairments, and their relation to current functioning and long-term outcome.

A decline in certain aspects of cognitive functioning has been found in the early stages of the illness [12•] and after initial hospitalization [13]. Age-related declines in executive functioning [14] and processing resources [15] have also been found cross-sectionally. Together with earlier studies that have established a progressive decline in cognitive and functional status in poor-outcome patients [5], these studies suggest a dynamic course of cognitive functioning in at least some patients with schizophrenia. Given the heterogeneity of the illness, it is not surprising that some investigations have failed to replicate these findings. It appears that schizophrenia patients with relatively good outcome (*ie*, lifelong ambulatory, community-dwelling patients) have stable cognitive impairments across a wide age-range [16] and in longitudinal studies [17]. In these studies, however, small numbers of truly older patients limit the comparability of the findings to studies where declines have been found. Longitudinal studies with more rigorous methodology would better elucidate the course of cognitive impairments in better outcome patients with schizophrenia. Among the current open issues are 1) do older (age greater than 65) patients with a lifelong history of higher functioning decline more than would be expected according to their age over longitudinal follow-up studies? And 2) are there additional confounds (medication, environmental factors) that are associated with poor outcome patients in later life that are as yet unresolved?

Functional Importance

In the past several years, the importance of cognitive deficits in schizophrenia has been exemplified with their relation to functional impairment. Functional deficits are common in schizophrenia and span many domains, including independent living, social functioning, and vocational functioning. Green [18] highlighted the importance of the relationship by demonstrating that certain neurocognitive domains (*eg*, vigilance, verbal memory, and executive functions) were significantly related to functional outcome.

More recently, Green *et al.* [19] reviewed 37 studies to confirm original hypotheses [18] that secondary (delayed) verbal memory, immediate (working) verbal memory, executive functions, and vigilance were the most significant predictors of functional outcome. Specifically, secondary verbal memory and executive functions were related to all three outcome variables: community or daily activities, social problem solving or instrumental skills, and psycho-

social skill acquisition; although vigilance was related to the latter two, and immediate verbal memory was associated with psychosocial skill acquisition.

The relationship between cognitive functions and functional outcome has sparked much interest, but most studies have examined associations at one time-point, limiting the predictive power of the data. Addington and Addington [20] found that baseline performance on tasks measuring verbal ability, verbal memory, and vigilance were predictive of social problem solving after a 2.5-year interval. Velligan *et al.* [21•] found that after a follow-up period of 1 to 3.5 years, verbal memory predicted all measures of community outcome, and vigilance predicted social outcome and executive functioning predicted work and daily living activities. Thus, cognitive functioning appears to be not only related to, but also predictive of functional outcome in schizophrenia.

The overlap between negative symptoms and cognitive functioning complicates the study of relationships between cognitive and functional impairments. McGurk *et al.* [22] found that, despite both variables being predictive of adaptive functioning, cognition was more strongly related to functional skills assessments, and remained significant across very different levels of negative symptom severity in chronically institutionalized geriatric schizophrenic patients.

Collaboration with other disciplines allows schizophrenia researchers to assess more comprehensive dimensions of outcome. Cognition has been found to be a strong predictor of outcome as rated by methods from the field of occupational therapy [23]. Broadening the construct of functional outcome may make the importance of cognitive functioning even more germane to outcome in schizophrenia.

A developing interest in schizophrenia outcome, especially among higher functioning patients, is vocational functioning. With only approximately 10% of schizophrenia patients employed [24], resulting in annual lost wages of approximately \$15 billion [25,26], this is clearly an important area of study. Additionally, vocational functioning is a more ecologically valid measure of outcome than laboratory-based measures of social skills. Schizophrenia patients who are employed full-time perform better on tests of executive functioning, working memory, and vigilance than unemployed patients, and better than part-time employed patients on measures of vigilance and executive functioning [27]. Patients with higher cognitive functioning also appear more likely to benefit from vocational rehabilitation [28].

Additional rehabilitation efforts have focused on cognitive functioning as a target of intervention. In specific, some effort has been linked directly at reduction of cognitive deficits. Medalia *et al.* [29] used short-term problem solving training for patients who were acutely admitted to inpatient care. The patients who received active treatment, compared with placebo, improved in both symptom status and in problem solving training. Velligan *et al.* [30•] attempted to bypass cognitive impairments, using a novel procedure

referred to as “cognitive adaptation training.” This procedure attempts to increase the skill levels of patients in functional skills by teaching them in relatively small, manageable steps. Patients receiving this training had a significantly lower relapse rate at a 9-month follow-up than patients treated with standard treatments, as well as greater improvements in global functioning.

Recent findings have supported the association between cognitive functioning and functional outcome, as well as expanded on previous work by introducing exciting new areas of interest such as novel treatments. Future research should continue to search for more externally valid outcome measures. Additionally, more studies are needed to clarify the longitudinal relationship between cognitive and functional impairment as well as the influence of negative symptoms on specific outcome measures.

Treatment of Cognitive Deficits in Schizophrenia

As recently as 1994, evidence was presented to suggest that the overall functional outcome of schizophrenia had not markedly improved since the days of Kraepelin [1,31]. The most plausible reason for that finding is that conventional antipsychotic medications do not have a particularly beneficial effect on cognitive functioning, and that rehabilitation efforts are not successful against this backdrop. As reviewed, cognitive functioning is a major determinant of functional status. It has been widely suggested that enhancement of cognition in schizophrenia may have the potential to alter functional outcome and reduce the disability in the illness [32]. Yet, cognitive enhancement has proven an elusive goal, until some recent developments.

One of these interesting new developments in cognition in schizophrenia is the discovery that novel antipsychotic medications appear to improve cognitive functioning in schizophrenia. In a meta-analytic review of the studies published up until mid-1998, Keefe *et al.* [33] found that the effects of newer antipsychotic treatment on cognition were significantly better than the effects of conventional treatments. One of the limitations of many of these studies in this meta-analysis is that they are quite variable in their methodology. As of mid-year 2000, a review published by Harvey and Keefe [34•] noted that the entire published worldwide database from double blind trials studying cognitive enhancement in schizophrenia with novel antipsychotic medications was only 208 patients. This is actually an overestimate, because some of these trials were also marked by high dropout rates, and these sample sizes were entry-level figures. In fact, the typical methodology employed was an open-label switch study, where patients were examined at baseline on conventional medications, and then switched in an open design to treatment with the newer medications. Obviously, this design is quite vulnerable to bias effects as well as being unable to discriminate treatment effects from practice effects at retesting. Additional methodologic

factors in these early trials also included failure to control for or report adjunctive medication status, baseline pharmacologic status, and clinical symptom status.

Despite these methodologic limitations, this is an exciting new field. It is not reasonable to expect that all of the information on the cognitive effects of these newer medications would be collected within 5 years of their introduction. After all, haloperidol was introduced to the market in 1969, and studies of the cognitive effects of haloperidol were still being published in the 1990s.

The evidence to date suggests that some aspects of cognitive functioning may be more generally improved than other aspects by treatment with newer medications. For example, in an analysis of the weighted effect sizes of the previous studies, Harvey and Keefe [34•] found that declarative (*ie*, secondary) memory, vigilance, and verbal fluency were improved most consistently across medications and methodologies, although immediate memory and executive functioning were improved the least. Although this type of analysis is intrinsically limited by aggregation across somewhat disparate assessment devices, it is of some heuristic value for later research. The level of improvement for the aspects of cognitive functioning that are improved the most was moderate in size ($n=4$). These are all deficits that are typically found to be impaired at a level of at least 2.0 standard deviation (SD) below the mean, this would suggest that the average patient is improving by about one fifth of the difference toward normal performance. No studies to date have had large enough sample sizes to identify the specific predictors of individual patients who have cognitive change with treatment, however. If the patients who had the least impairment were to improve the most, then it might develop that there were some patients whose performance was improved by a substantial amount. Further, there is very little information from adequately powered studies that compare across different novel medications. This is an area where substantial additional research will be required. The only study that made an effort to directly compare between different novel medications [35•] was handicapped by a very small sample size and high levels of dropout.

One of the other issues that is critical to address in this domain is whether or not newer medications, through their cognitive enhancing effects, actually benefit patients' functional status or influence their ability to learn new skills. In a direct study of the rates of skill learning with newer medications, Harvey *et al.* [36] randomized outpatients with schizophrenia to treatment with either low doses of conventional antipsychotic medications or with risperidone. The patients were then given extensive practice on high and low demand attentional tests. Using a difficult version of the continuous performance test, patients who were treated with risperidone manifested significant improvement in both lower and higher demand conditions. In fact, these patients improved to the point where their performance was significantly better than the baseline performance of healthy control individuals. In

contrast, patients who remained on low-dose treatment with haloperidol or fluphenazine failed to manifest improvement, despite experiencing nearly 9000 exposures to the target stimuli. This finding is particularly important because a recently published study [37] found that patients who were treated with risperidone and tested only twice on the same continuous performance test—identical pairs (CPT-IP) failed to improve, when compared with a sample of patients treated with haloperidol. Thus, these findings indicate that one of the effects of newer medications may be to enhance the ability to acquire skills with practice and exposure, similar to the techniques often employed in cognitive remediation training. Apparently certain cognitive skills can be acquired with practice even if there would be no direct treatment effect without practice. Later studies will have to examine the association between training and medication status, in order to determine if the interaction of medication x training is more beneficial than the two influences alone.

Substance Abuse and Schizophrenia

Half of all patients with schizophrenia are substance abusers, but very often these individuals are excluded from research studies of cognitive functioning, because of concerns that their substance use would “confound” assessment. If at least half of all patients abuse substances, then they are the typical patients and should receive more attention. In a study of the effects of alcohol on cognition, Allen *et al.* [38•] reported that schizophrenic patients who abused alcohol had more abnormalities on a neurologic examination, especially in the domain of perceptual deficits. Cocaine-abusing schizophrenic patients were reported to manifest selective impairment in memory functioning in two separate studies [39,40]. In these two studies, recently abstinent cocaine abusers with concurrent schizophrenia had more rapid forgetting of verbal material than non-substance-abusing comparison subjects. Because memory deficits are well-known predictors of functional skill deficits, later research should certainly focus on the functional importance of substance abuse in patients with schizophrenia.

Correlates of Symptomatology

There is an intrinsic paradox in research on cognition in schizophrenia. Standardized neuropsychologic tests are potent predictors of functional deficits, but surprisingly unassociated with the severity of clinical symptoms such as hallucinations or delusions. Yet, delusions and hallucinations are striking features of schizophrenia, as are impairments of communication, and they have an intrinsically cognitive basis. Several studies in the past year attempted to identify the correlates of these symptoms, in order to proceed with the identification of the causes of these impairments.

For instance, Brebion *et al.* [41] reported that deficits in the ability to monitor the origin of information in short-term memory were correlated with the severity of delusions and hallucinations. Further, tendencies toward believing that information that was never presented was actually self-generated was related to symptom severity as well. Deficits in source monitoring were found for hallucinating patients in another study as well [42]. In a study addressing the cognitive correlates of clinical symptoms, O’Leary *et al.* [43•] found that communication impairments were related to lower verbal IQ scores and poor performance on tests of concept attainment. Thus, delusions, hallucinations, and communication disorders were found to have different patterns of cognitive correlates.

For years, it has been reported that negative symptom severity was also associated with the severity of performance deficits on various neuropsychologic tests. These findings were replicated by O’Leary *et al.* [43•], as well as by Brebion *et al.* [44] in a separate study of memory, negative symptoms, and depression. Research will still need to untangle the potential confounds among these different symptom dimensions, because negative symptoms could conceivably have a direct impact on the validity of measurement of cognitive deficits. Results from longitudinal studies such as those of McGurk *et al.* [22] that find different correlates of negative and cognitive symptoms address this concern to some extent.

Conclusions

Cognitive functioning is an increasing active area of research in schizophrenia, driven by new appreciation of the functional importance of these impairments. Treatment of these deficits is a clear research and clinical priority, as is continuing to develop understanding of the cognitive factors that underlie other symptoms. It is still too early to tell what the eventual outcome of this research will be, however, there is reason for optimism, because understanding the importance of cognitive functioning and its correlates is a critical first step in solving the concurrent problems of functional impairment and lifelong disability in schizophrenia.

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