The Longitudinal Course of Cognitive Impairment in Schizophrenia: An Examination of Data From Premorbid Through Posttreatment Phases of Illness

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Cognitive impairment is a core feature of schizophrenia that is present across the course of the illness. However, due to complexities of studying cognitive decline in patients prior to the onset of illness, the longitudinal course is not fully understood. The cognitive effects in patients with schizophrenia are robust, with a 1.5 to 2.5 standard deviation gap between patients and healthy controls on composite scores. People with schizophrenia manifest a prior history of cognitive impairment in the premorbid phases of the illness. Examination of school records suggests that children who will eventually develop schizophrenia begin school at a level of functioning that is a full grade behind their peers, with the gap increasing by the time they finish high school. Epidemiologic work suggests that there are both static cognitive impairments and developmental lags in these patients during childhood, well before the illness is fully manifest. Although there was initial promise of improved cognitive function with second-generation antipsychotic treatment, more recent studies have suggested no differences among antipsychotics, with the initial appearance of improvement very likely attributable to practice effects, inappropriate medication dosing, and poor study design. Two large, prominent studies evaluating first- and second-generation antipsychotics suggested that, although there was slight to modest improvement in cognitive function for all treatments, there were no differences among medications, regardless of the generation of the agents. In summary, patients who develop schizophrenia, on average, demonstrate cognitive impairment beginning as early as the first grade, with deterioration seen across school years. Further, these patients had substantial cognitive deficits after the initiation of psychosis. Finally, while antipsychotic treatment improves symptoms, antipsychotics have little impact on cognition, and there appear to be no differences in the degree of cognitive improvement between first- and second-generation agents. *(J Clin Psychiatry 2014;75[suppl 2]:8–13)*

Cognitive impairment is widely considered a core feature of schizophrenia. The central reason for this consensus stems from the presence of these deficits at various time points in the lifetime of patients with the illness. However, the longitudinal course of cognitive dysfunction in patients with schizophrenia is not clearly understood. The key questions that need to be answered include (1) When does cognitive dysfunction begin? (2) Does it predate the onset of psychosis? (3) Is there further decline in function after the onset of psychosis and what is the course of the decline? and (4) Do factors such as clinical symptoms affect cognitive performance?

Cognitive dysfunction regularly begins in adolescence in those that later develop schizophrenia.[1–7] The evidence examining the course of deficits after illness onset is less consistent. A pattern of decline in cognitive function from before to after the onset of psychotic symptoms is evident.[8–13] However, cognitive function improvement after the emergence of initial psychosis has also been demonstrated,[9,14–16] suggesting a potential enigma regarding the longitudinal course of cognitive impairment in schizophrenia. Further, there is no clear evidence of progressive decline across time in the cognitive function of prospectively analyzed first-episode patients, suggesting stability and possible mild improvement.[17–20]

Cross-sectional cognitive data suggest that virtually every aspect of cognition (eg, attention, memory, and language) is impaired in schizophrenia patients on average.[21–28] However, not all patients with schizophrenia show the same pattern or degree of impairment. While the majority of patients demonstrate some type of impairment, some patients fall within the normal range (± 1 standard deviation of the healthy population mean). However, even this small percentage of patients in the normal range may have significant decline from premorbid levels of cognitive function.[29]

A consistent relationship between cognitive deficits and negative symptoms, psychotic symptoms, and disorganized symptoms has been seen across a variety of studies. The negative symptom dimension appears to have the strongest relationship with cognitive performance. Negative symptoms are correlated with deficits in measures of generalized brain dysfunction,[30] visual and motor processing,[24,25,31,32] long-term memory,[33,34] and attentional processes.[34–38] Positive symptoms on the other hand have an inconsistent relationship with cognitive function. Although auditory processing deficits,[35] verbal memory impairments[24,25] and auditory distractibility[37] were correlated with positive symptoms in small samples, more recent data from a large sample suggest that these 2 domains are largely orthogonal to one another.[29]

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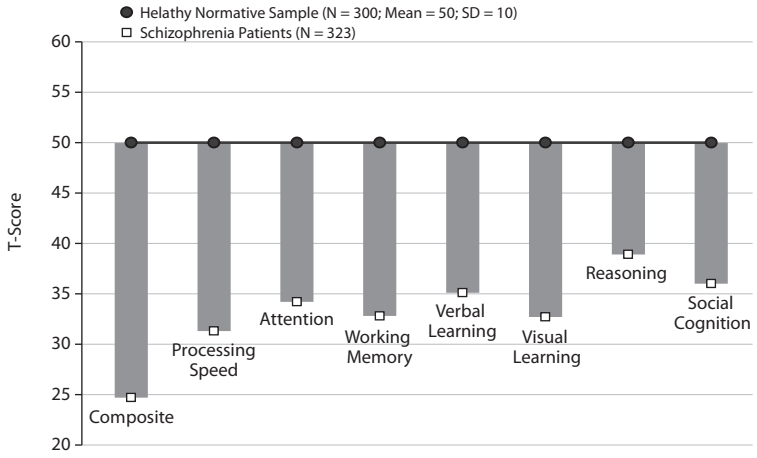
doi:10.4088/JCP.13065su1.02

Figure 1. Severity and Profile of Cognitive Impairment in Schizophrenia at Baseline of Clinical Trial[a]



[a]Based on Keefe et al.[40]

The aim of this review is to examine some of the more recent studies evaluating the course of cognitive impairment in order to determine our current understanding. Additionally, the gaps in the literature on the longitudinal course of schizophrenia will be discussed.

A SAMPLE OF CROSS-SECTIONAL COGNITIVE DEFICITS IN PATIENTS WITH SCHIZOPHRENIA

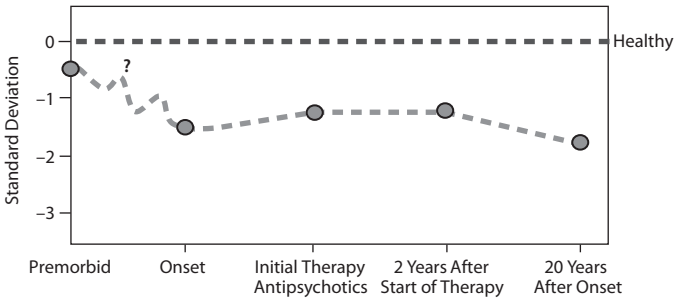
The first reviewed data are from the cognitive test battery derived from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project. The MATRICS Consensus Cognitive Battery (MCCB) was designed to evaluate the cognitive effects of treatment in schizophrenia patients and allowed an in-depth examination of the cross-sectional baseline differences between patients with schizophrenia and healthy adults.[39] Patients with schizophrenia were approximately 2.5 standard deviations below the healthy control mean on the composite score, with deficits seen across all individual scores (Figure 1).[40] To put the severity of this impairment into perspective, a difference of 2.5 standard deviations from the healthy control mean on measures of intellectual functioning such as IQ scores would be <70, consistent with a diagnosis of mental retardation. These results are consistent with other studies indicating a similar range of impairment.[41,42]

The severity and profile of cognitive impairment have also been evaluated at the initial onset of schizophrenia. In one such study by Bilder et al,[43] patients exhibited global cognitive deficits of 1.5 standard deviations relative to a healthy control group at the first psychotic episode. Memory was the most impaired specific domain, with additional deficits in motor and executive function. The data from this and other similar studies make clear that the level of cognitive impairment at the first episode is severe.

Although no single study has evaluated cognitive impairment from adolescence through mortality, an amalgamation of cross-sectional studies and short-term longitudinal studies allows us to attempt to infer the longitudinal pattern across time.[44] As reviewed below, a wealth of evidence suggests that, on average, individuals in the prodromal period prior to psychosis onset have relatively mild cognitive impairment, with the mean level of cognitive function about 0.5 standard deviation below the general population mean. However, what is the course of cognitive impairment from prodrome to psychosis onset? Very few studies have been able to examine this question, and it remains unclear whether these patients have severe cognitive impairment immediately prior to the onset of psychosis or whether this cognitive impairment emerges alongside the onset of psychosis. After initial treatment with antipsychotic medication in first-episode patients, it appears that there is a small cognitive improvement that is likely due to the reduction of positive symptoms such as hallucinations and delusions (Figure 2).[44] However, these data do not suggest much further improvement beyond the initial 1–2 years of treatment.

One of the important questions that arises in the consideration of cognitive impairment in schizophrenia is "Which patients are affected?" Since some patients will perform up to healthy control means on cognitive tests, there is some question as to whether they have cognitive impairment. It is difficult to determine whether these individuals' cognitive functioning has been unaffected by schizophrenia, or whether they would have been performing in the higher reaches of the general population if they had not developed the illness. However, one way of determining whether individuals have current cognitive functioning that is worse than expected is to compare them to the predictions made of their current cognition based on antecedent factors such as parental education. One such analysis suggested that there is a strong relationship between maternal education and current cognitive function, with about 50% of individuals performing above expectations and 50% performing below expectations. However, 98% of the

Figure 2. Course of Cognitive Impairment and Treatment in Schizophrenia[a]



[a]Adapted from Keefe and Eesley,[44] with permission.
Symbol: ? = the course of cognitive decline between the premorbid phase and onset of illness is not well known.

patients with schizophrenia in this study performed below the expectations set by their mothers' education.[45] These data suggest that almost all patients with schizophrenia have some worsening of cognitive functioning compared to cognitive performance that would be expected if they did not have the illness.

EXAMINATION OF PREMORBID AND LONGITUDINAL SYMPTOMS IN PATIENTS WHO LATER DEVELOP SCHIZOPHRENIA

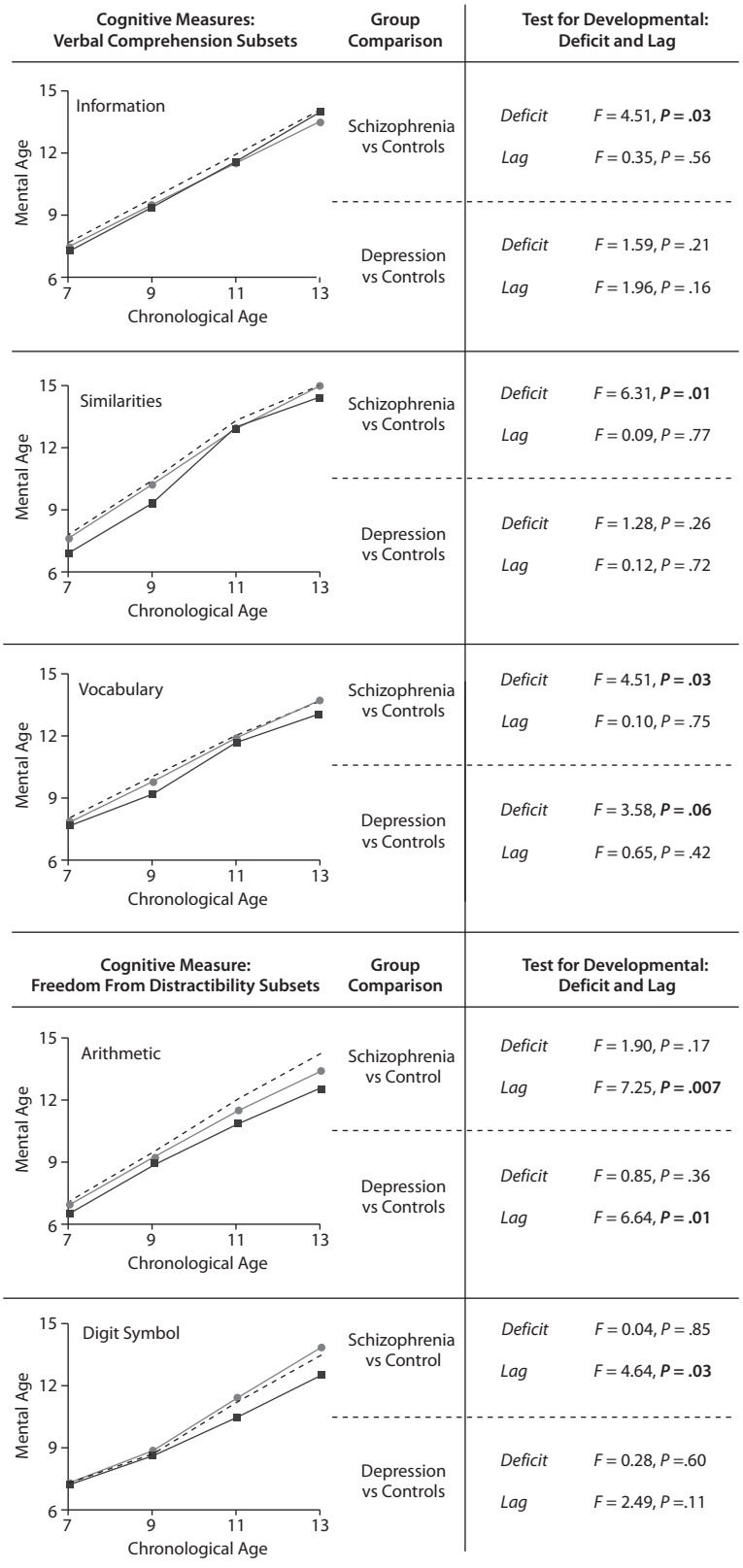
A number of studies have reported a prior history of cognitive impairment in those who eventually develop schizophrenia.[46] Draftees into the Israeli army who were later diagnosed with schizophrenia performed 0.5 standard deviation worse than the draftees who did not develop psychiatric illness,[47] and studies examining school records have suggested that children who will develop schizophrenia later in life on average start out 1 grade level behind their peers and, by the time they finish high school, are even further behind.[48] These data suggest that there are important cognitive deficits in at least a small percentage of children who will eventually develop schizophrenia; however, it is not practical to use this approach to identify those individuals because only a minority of patients can be successfully predicted, and the false positive and false negative rates are very high.

Premorbid academic performance was used in a retrospective longitudinal study of schizophrenia patients to determine if their performance differed from that of their healthy peers.[49] Standardized test scores were lower than average at grades 4 and 8, but not significantly different. However, a significant drop in scores occurred between grades 8 and 11, a timeframe corresponding to the onset of puberty. Further, these declines predicted those who subsequently developed schizophrenia. Although these deficits may be striking when looking at data from the average performance of the children who developed schizophrenia, it is likely that the day-to-day experience with individual adolescents is not noteworthy in the classroom. Teachers often monitor their children within each school year, and the main concerns that prompt attention and action are disciplinary issues, serious academic difficulty, and behavioral problems. Thus, the subtle cognitive decline identified between the 3-year interval from grades 8 and 11 may not be recognized in real world educational systems.

Differences in academic performance were demonstrated in a similar premorbid study, with a full grade level difference seen in first grade.[48] The early grade gap was expanded to 1.8 grades by the end of high school, indicating that those who later developed schizophrenia exhibited an immediate deficit at the onset of school, with impairment slowly increasing across time to nearly 2 full grades. Conclusions from these data were that schizophrenia is marked by substantial cognitive deficits upon entry into school. Additionally, subtle declines occurred across time, preceding the overt onset of psychotic symptoms, with further impairment at the initial episode of illness.

A community study from New Zealand assessed most of the approximately 1,000 residents (91%) from birth, with a series of assessments initiated at 3 years of age extending out 30 years.[13] Thirty-five adults went on to develop schizophrenia, allowing retrospective examination of premorbid symptoms. These data allowed evaluation of the 3 potential theories of the course of cognitive decline: (1) the developmental deterioration hypothesis that predicts steady decline; (2) the developmental deficit hypothesis that predicts consistent but stable cognitive impairment; and (3) the developmental lag hypothesis that predicts growth in cognitive abilities, but growth that lags behind that of healthy individuals. There were 2 interrelated developmental processes evident from childhood to early adolescence (ages 7–13 years). Static cognitive impairments were found on measures assessing verbal and visual knowledge acquisition, reasoning, and conceptualization in the children who developed schizophrenia as adults (Figure 3). Impairments emerged early and remained stable. In addition to the static deficits, these children exhibited developmental lags in processing speed, attention, visual-spatial problem solving ability, and working memory. Accordingly, these data provided evidence for both the cognitive developmental deficit and the developmental lag theories.[13]

Figure 3. Verbal "Deficit" and Processing Speed "Lag" in Young Subjects Who Later Develop Schizophrenia[a,b]



[a]Adapted from Reichenberg et al,[13] with permission.
[b]Dotted lines represent healthy comparison subjects; lines connected to squares represent children who later developed schizophrenia; lines connected to circles represent children who later developed depression.

THE COURSE OF COGNITIVE IMPAIRMENT POSTTREATMENT: WHAT IS THE EVIDENCE FROM RECENT LARGE TRIALS?

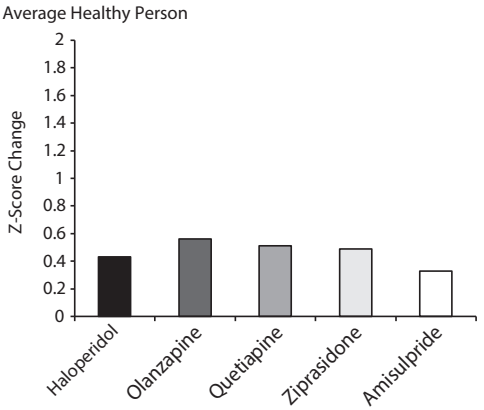
As documented previously, cognitive deficits are pervasive in schizophrenia and are an important target for treatment. Although early studies raised promise that second-generation antipsychotics may provide cognitive benefit beyond first-generation antipsychotics,[50,51] large multisite trials have suggested that there are no differences among antipsychotics and that the original apparent benefit is attributable to practice effects, inappropriate medication dosing, and poor study design.[53] The impact on cognitive function of haloperidol and several second-generation antipsychotics was assessed in patients with schizophrenia after the first episode of psychosis.[52] The study design provided more generalizability because of the broad eligibility criteria. Composite cognitive scores improved modestly across the 6-month period in the treatment groups (Figure 4),[52] and there were no significant treatment differences between antipsychotics. The authors concluded that there were minimal to no differences in cognitive improvement across the 5 antipsychotics.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study was designed to compare cognitive performance between perphenazine (first-generation antipsychotic), olanzapine, quetiapine, and risperidone (second-generation drugs).[54] Cognitive function was slightly improved in all groups after 2, 6, and 18 months of treatment; however, there were no significant differences in cognitive scores between the groups. The overall conclusion from CATIE was that the second-generation agents appeared to provide no cognitive advantage compared with perphenazine, and that the small cognitive benefit reported in all groups was consistent with a small practice effect.[55]

CONCLUSION

In summary, cognitive impairment is a core feature of schizophrenia. However, due to complexities of studying cognitive decline in patients prior to the onset of illness, the longitudinal course is not fully understood. Substantial cognitive deficits, ranging from 1.5 to 2.5 standard deviations below healthy controls, have been reported in numerous studies. Further, the functional ability of patients, even those with cognitive performance within the normal range, is affected. Premorbid academic performance in longitudinal studies suggests that, on average, cognitive deficits are present on entry into

Figure 4. Change in the Cognitive Composite Score From Baseline to 6 Months in First Episode Psychosis[a]



[a]Based on Davidson et al.[52]

school.[48,49] Additional deficits may accumulate or worsen across time prior to the onset of psychotic symptoms. Finally, while antipsychotic treatment improves symptoms, which may have some secondary effect of improving cognitive performance in the very early stages of psychosis, there are no differences in the degree of cognitive improvement between first- and second-generation agents.[53,54]

Drug names: haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).

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Potential conflicts of interest: **Dr Keefe** received a fee for service from Otsuka America Pharmaceutical, Inc., and Lundbeck for participation in the meeting and preparation of this manuscript. Currently or in the past 12 months, he has received investigator-initiated research funding support from the Department of Veterans Affairs, Feinstein Institute for Medical Research, National Institute of Mental Health, Research Foundation for Mental Hygiene, Inc, and the Singapore National Medical Research Council; has received honoraria, served as a consultant, or served as an advisory board member for Abbvie, Akebia, Amgen, Asubio, AviNeuro/ChemRar, BiolineRx, Biomarin, Boehringer-Ingelheim, EnVivo, GW Pharmaceuticals, Lundbeck, Merck, Mitsubishi, Novartis, Otsuka America Pharmaceutical, Inc., Roche, Shire, Takeda, and Targacept; receives royalties from the BACS testing battery, the MATRICS Battery (BACS Symbol Coding), and the Virtual Reality Functional Capacity Assessment Tool (VRFCAT), and is also a shareholder in NeuroCog Trials, Inc, and Sengenix.

Acknowledgments: This article is derived from a roundtable meeting titled "Understanding the lifetime course of schizophrenia: a longitudinal perspective on neurobiology to promote better outcomes and recovery," which was held October 15, 2013. Editorial assistance in developing the manuscript was provided by Healthcare Global Village.

Funding/support: The meeting, manuscript preparation, and dissemination of the supplement were sponsored by Otsuka America Pharmaceutical, Inc., and Lundbeck.

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April 2014 03US14EUP0061