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Course of Schizophrenia: Neuropsychological Evidence for a Static Encephalopathy

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Abstract

The course of cognitive function in schizophrenia has often been debated. In one view, it is thought to be akin to that of a progressive dementia with relentless cognitive decline. In another view, the deficits are thought to remain relatively stable, analogous to those of a static encephalopathy. Review of longitudinal and cross-sectional studies strongly supports the latter interpretation. In particular, we present data from a recent cross-sectional study in which cohorts of patients in their third, fourth, fifth, sixth, and seventh decades of life were administered a battery of tests known to be sensitive to progressive dementing diseases. All patients were carefully screened to exclude those with neurologic, systemic, or psychiatric comorbid conditions, and cohorts were matched on estimated premorbid intellectual capacity. Although scores on most tests were impaired, no evidence of decline across groups was observed. These results are also consistent with neuroimaging and neuropathological studies in that no evidence for an active degenerative process has been discovered.

Debate about the natural course of cognitive deficits in schizophrenia is commonplace and perhaps not unexpected, given the often baffling nature of the disorder. In particular, there are two contrasting views. In the first, cognitive deficits are thought to follow a course analogous to and suggestive of a progressive dementia. After an insidious onset, the patient's symptoms become ever more disabling; memory functions, more impaired; intellect, more enfeebled; and social skills, coarser. In the second view, the cognitive deficits are viewed as relatively stable and thus more consistent with the notion of a static encephalopathy. With the onset of clinical symptoms, the patient's cognition declines and he or she becomes disabled. The patient then remains in this stable, but impaired, condition for many years.

In this report, we review the longitudinal, cross-sectional, and correlational studies that examine the association between cognitive impairment and duration of illness in schizophrenia. We chose to study cognitive impairment because it occupies a central place in research on the clinical phenomenology of the dementias, providing the chief laboratory corroboration of declines in social and occupational functioning: Measures of cognitive impairment are routinely used to monitor progression in Alzheimer's disease, Huntington's disease, and Parkinson's disease. In addition, cognitive impairment is increasingly being viewed as a central and enduring feature of schizophrenia (Goldberg et al. 1993). More selectively, we also review studies of the association of brain morphology and illness duration because the course of morphological variations can logically be seen as a useful reference for understanding the course of cognitive symptoms.

Premorbid Cognitive Function

The first issue to be considered is when cognitive deficits appear in

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the course of illness. Cognitive performance in schizophrenia before the onset of the disorder has been studied in several different research designs. One such approach has studied the children of parents who have suffered from schizophrenia. In general, findings have suggested that high-risk infants demonstrate subtle neuromotor abnormalities (Fish et al. 1992), whereas children and adolescents of schizophrenia parents often exhibit problems in visual attention and early visual processing, as indicated by results on the Continuous Performance Test (CPT; Rosvold et al. 1956) and on the span of apprehension tests (Cornblatt and Erlenmeyer-Kimling 1985; Nuechterlein 1985; Asarnow et al. 1991). IQ is thought to be relatively well preserved (Asarnow and Goldstein 1986). This approach, however, is problematic because it is unclear which, if any, of the children will go on to develop schizophrenia. In another more direct approach, Walker and Lewine (1990) examined the premorbid social and gross motor function of schizophrenia patients by studying home movies of the patients when they were children and comparing the index case patients with siblings. They found that the schizophrenia patients appeared to have neurologic abnormalities, especially "left hemisyndromes," even in infancy. These abnormalities apparently abated and were not obvious in later childhood. In primary and secondary school, the index case patients did not differ from their siblings in educational achievement (Walker, personal communication 1992).

Still another approach has been taken by Goldberg et al. (unpublished manuscript). They compared the unaffected members of monozygotic (MZ) twin pairs discordant for schizophrenia and normal MZ twins. No group can be at higher risk for schizophrenia than such "unaffected" subjects by virtue of identical genomes and family environments. Before the onset of the illness, the unaffected and affected twins appeared to have been cognitively similar. Wide Range Achievement Test (WRAT–R; Jastak and Wilkinson 1985) reading scores, a putative measure of premorbid IQ, did not differ significantly; and grades, standardized tests of academic proficiency, and rates of special education did not differ between the groups (E. Taylor, personal communication 1993). Thus, the functioning of the unaffected twin may accurately represent the premorbid performance of the affected twin. This suggests that the marked intellectual deficits found after onset of illness in these patients were not present before. However, other data suggest that some subtle deficits may have predated the emergence of the illness but were not specific to the illness itself. When the unaffected twins were compared with normal MZ twins, Goldberg et al. (unpublished manuscript) found subtle attenuations of performance on some aspects of visual and verbal memory, Wisconsin Card Sorting Test (WCST; Heaton 1981) performance, and tests of psychomotor speed and scanning and speed of access to the lexicon on tests of color naming and word reading. No deficits in vigilance were noted on a simple version of the CPT. The twin groups were closely matched with regard to age, education, and socioeconomic status. It is important to note, moreover, that though measures of social, vocational, and family functioning of the unaffected and normal twins differed significantly on the Global Assessment Scale (Endicott et al. 1976), both groups' ratings were well within the normal range. However, subtle differences between the unaffected and affected twin cannot be definitively ruled out because the groups were not directly compared prospectively.

Pogue-Geile et al. (1991) compared the siblings of schizophrenia patients with a well-matched control group and found differences on a number of memory tests, on the WCST, and on tests of psychomotor speed. Thus, the profile of results was similar to that observed by Goldberg et al. (unpublished manuscript). These data are relevant to the issue of course because the cognition of the siblings may be considered similar to that of the schizophrenia index case subjects in the premorbid period. In general, these results suggest that, before the onset of illness, schizophrenia patients may have very mild and relatively focal diminutions in cognitive ability that do not grossly interfere with their ability to move along well-defined developmental lines (e.g., attainments in school, friendships, vocation).

Emergence of Cognitive Impairment

What then happens to cognition once clinical manifestations of the illness become obvious? A number of recent neuropsychological studies have addressed this question. Goldberg et al. (1988) found that adolescents with diagnoses of schizophreniform disorder or schizophrenia demonstrated patterns in IQ similar to those of patients with chronic schizophrenia but dissimilar to those of psychiatric control subjects. Hoff et al. (1991) found that the neuropsychological profiles of first-episode schizophrenia patients were remarkably similar to those of patients with chronic schizophrenia.

The patients performed poorly on a wide range of tests, including those assessing memory, executive functions, and attentional abilities. Hoff et al. (1991) retested their patients 2 years later and noted significant improvements in executive function (WCST and Category Test; Reitan and Wolfson 1985) and attention (including the Symbol Digit Test; Lezak 1983), and continuing deficits in memory function (California Verbal Learning; Delis et al. 1987). Bilder et al. (1991), assessing language, motor, attention/executive, verbal and visual memory, and span abilities in a large group of first-break patients, found many neuropsychological deficits, although those deficits were not as severe as the deficits found in a group of chronic patients. The investigators concluded that these results suggest that deterioration of function may follow the onset of overt psychosis in some patients.

In a longitudinal study spanning premorbid and morbid periods, Schwartzman and Douglas (1962) found that schizophrenia patients assessed on an army intelligence examination displayed a significant decrement of 0.5 standard deviations (SDs) in performance after the onset of illness, while control subjects improved their score. The patients were similar to control subjects at induction (i.e., premorbidly). Over the 10-year followup period, patients lost about another 0.5 SDs in comparison with the control group. A study by Kingsley and Struening (1966) on an Armed Forces classification test came to similar conclusions. In the third such study using Armed Forces personnel, Lubin et al. (1962) demonstrated that when patients were retested 2 years after their induction test, they showed decrements of 0.16 to 0.33 SDs on all subtests of the army classification battery (reading and vocabulary, arithmetic reasoning, mechanical aptitude, and clerical speed), with the exception of a test of pattern analysis. These comparisons of premorbid with morbid intellectual function suggest, therefore, that cognitive abilities decline and do so at the onset of the illness.

Stability of Cognitive Impairment

It is unclear from the studies discussed above if decline continues during the more chronic phase of the illness. A number of longitudinal studies have attempted to address this issue. Smith (1964) examined 11 relatively younger chronic patients and 13 older patients (mean age of onset after age 40) on a number of cognitive measures over an 8-year interval. These measures included the Wechsler Bellevue intelligence test (Wechsler 1944), the Porteus Maze Test (Porteus 1959), the Homograph Test, and the Weigl Sorting Test, a precursor of the WCST. No signs of progressive deterioration were noted on the IQ test, the test of verbal set shifting, or the maze test; performance on the Weigl shifting task declined, but it is unclear if this was simply due to aging. Klonoff et al. (1970) studied a large group of chronic schizophrenia patients over a period of 8 years and noted no deterioration on the Wechsler Adult Intelligence Scale (WAIS; Wechsler 1955). In fact, the group improved its performance. However, performance on the Halstead-Reitan Neuropsychological Test Battery (Reitan and Wolfson 1985) (assessed at one time point only) was, unsurprisingly, grossly impaired. Foulds and Dixon (1962) retested 186 chronic patients on the Progressive Matrices Test (Raven 1968) of intelligence and the Mill Hill Vocabulary (Raven 1958) after a 2-year interval, and they noted no significant decline.

A recent study by Sweeney et al. (1991) of younger chronic patients (mean age = 29 years, mean duration of illness = 7 years) found some improvement in neuropsychological functioning over a 1-year test/retest interval. The WCST and tests of psychomotor speed and attention (Trail Making [Reitan and Wolfson 1985] and Digit Symbol from the Wechsler Adult Intelligence Scale–Revised [WAIS-R; Wechsler 1981]) as well as of recognition memory (but not recall) and Judgment of Line Orientation (Benton 1983) all improved, perhaps owing to improved motivation and/or reduced symptoms. However, a control group was not used to control for practice effects. No evidence for a decline in functioning was found.

Another approach to detecting deterioration in the more chronic phase of the illness involves examining the relationship between intrapair difference scores in MZ twins discordant for schizophrenia and duration of illness. This paradigm is potentially powerful because the magnitude of the difference between endowment, as reflected in the score of the unaffected twin, and disease-related level of functioning in the affected twin is known. If schizophrenia were a progressive disease, increasing intrapair differences would be expected to vary directly with duration of illness. When we examined 10 neuropsychological variables, including the CPT, IQ, WCST, Wechsler Memory Scale (Wechsler 1945), Trail Making, Stroop Color Word Test (Golden 1978), and Verbal Fluency (Lezak 1983), we found no significant relationships between duration of illness and cognitive intrapair differences (Goldberg et al., unpublished manuscript).

Goldstein and colleagues (1991)

have assessed large cohorts of schizophrenia patients on the Halstead-Reitan Battery to examine the effects of duration of hospitalization and age. They found that the association between increasing deficit on the neuropsychological battery and duration of hospitalization was no greater than would be anticipated simply on the basis of aging (Goldstein et al. 1991). Furthermore, when they examined younger and older schizophrenia patients without neurologic dysfunction, they found no differences on complex cognitive tasks that typically decline with age or are attenuated by brain damage (Goldstein and Zubin 1990).

We (Hyde et al., in press) used a cross-sectional approach in which successive cohorts of patients in their third, fourth, fifth, sixth, and seventh decades of life were assessed to examine the progression of cognitive deficits in chronic patients. While such a paradigm has obvious shortcomings—notably increased variability, as comparisons are made between groups rather than within subjects, and decreased power—the study design also has specific strengths. First, it allows comparison over an extremely wide range of duration of illness (patients ranged from 18 to 70 years of age). Second, efforts were made to match the groups on premorbid ability (through use of the WRAT-R reading scores, a measure that yields an estimate of premorbid intellect). Third, tests known to be sensitive to progressive dementia—namely, the Mini-Mental State Examination (MMSE; Folstein et al. 1975), the Dementia Rating Scale and semantic fluency test (Mattis 1976), list learning (Knopman and Ryberg 1989), and the Boston Naming Test (Kaplan et al. 1983)—were administered to all subjects. Fourth, patients could be carefully screened in relatively large numbers to exclude cases with confounding medical and neurologic conditions that become increasingly frequent with advancing age. We found no significant differences between age cohorts on the MMSE, the Dementia Rating Scale, verbal list learning, and semantic fluency. A cohort effect was found for the Boston Naming Test, but this appeared to be due to age rather than to duration of illness. Thus, over five decades of illness, there was no indication of progressive, relentless cognitive decline. We concluded that the course of cognitive function in schizophrenia appears to be consistent with a static encephalopathy rather than with a progressive dementing disorder. However, the use of a normal control group will be important in future studies to assess for the presence of subtle declines (Davidson et al. 1991).

When the results from the previously discussed studies are taken in to account, they are consistent with Kraepelin's observation (1919/1971) that most cases of schizophrenia resolve into a stable deficit state. Shakow (1946) also noted that, despite marked individual variations in course, "the most frequent type is that which resembles temporally the process of obliviescence, a considerable drop at first with the tapering off through a slowed period to a fairly stable level" (p. 72). After reviewing the literature in detail, Heaton and Drexler (1987) came to a similar conclusion. In short, the cognitive studies provide no convincing evidence for progressive deterioration in intellectual function.

It is unclear what happens to the cognitive performance of schizophrenia patients when they become elderly. It might be expected that, because they lose "cerebral reserve," they might show a more rapid or precipitous decline. This may be reflected in the high rates of severe cognitive impairment found on dementia screening tests in this population (Davidson et al. 1991). However, it is unclear to what extent other systemic illnesses or psychiatric and neurologic comorbidity might also reduce the cerebral efficiency of such patients. The susceptibility of schizophrenia patients to neurologic comorbidity is very high, given their propensity toward substance abuse, closed head trauma, and untreated or inadequately treated medical disorders. The high frequency of neurologic comorbidity in elderly schizophrenia patients makes it difficult to conclude whether severe neurocognitive disorders are directly related to the illness and its course, or are more related to the comorbid disorders. Furthermore, Harding et al. (1987) have suggested that a significant minority of patients actually demonstrate symptomatic and social improvement late in their lives.

Neuroimaging and Neuropathological Evidence for a Static Encephalopathy

Neuroimaging and neuropathological studies are generally consistent with the cognitive account. Thus, patients who have undergone serial magnetic resonance imaging (MRI) or computed tomography (CT) scanning for as long as 9 years do not exhibit progressive changes (Abi-Dargham et al. 1991; Degreef et al. 1991). However, marked variability in individuals may be present (DeLisi et al. 1991), probably to a large degree because of methodologic issues and other epiphenomena (e.g., weight changes). Longitudinal studies of chronic patients by CT scanning (Nasrallah et al. 1986; Il-

lowsky et al. 1988) have generally been negative, although Woods and Yurgelun-Todd (1991) have presented some MRI evidence to the contrary. Correlations of various brain parameters, especially ventricle-to-brain ratio, with duration of illness also have generally been nonsignificant (Zigun and Weinberger 1992). Moreover, in an elderly sample of schizophrenia patients, Weinberger et al. (1987) found that age did not influence size on CT scans in a qualitatively distinct manner. In postmortem studies, gliosis, a marker of an active degenerative process, has usually not been observed (Roberts et al. 1986). For instance, Bruton et al. (1990) did not find evidence of gliosis in those samples in which other neurologic diseases had been ruled out. Rather, the most common morphologic abnormalities have involved ventricular enlargement and reductions in the volume or cytoarchitectonic irregularities in the medial temporal lobe. These abnormalities are consistent with neurodevelopmental abnormalities and represent in the strictest anatomical sense a static encephalopathy.

Medication

Cognitive evidence for a static encephalopathy may, however, be confounded with the effects of medication. In short-term studies, neuroleptic medication appears to have little impact on higher level cognitive function, including intellect, memory, and abstraction, and it may, in fact, improve attention (Medalia et al. 1988; Cassens et al. 1990; King 1990). Although a recent review of the outcome literature (McGlashan 1988) indicated that treatment does not have a marked impact on long-term outcome, Wyatt (1991) argued that neuroleptics alter the long-term course and offer protection against "neurotoxic" factors associated with active schizophrenic symptoms. However, the observation that a significant minority of patients early in their course may sustain remission for long periods while drug free would appear to be problematic for this view (Fenton and McGlashan 1987).

Significance

Knowledge about the course of an illness has obvious implications for understanding its pathogenesis, devising treatments, and making a prognosis. Determining whether cognitive deficits in schizophrenia are static, plastic, or progressive would have major and very different implications for the patients, families, and health care professionals, not to say insurers. It is possible that deinstitutionalization may have fared better with a fuller knowledge of the extent and course of the cognitive deficits of schizophrenia patients. For instance, a number of neuropsychological measures have been found to be strongly associated with levels of social and vocational functioning (Breier et al. 1991; Goldberg et al. 1993). In a coarse way, such measures may assay those executive planning and mnemonic consolidation and retrieval abilities necessary for competent performance in jobs or social interactions. Insofar as scores on these tests do not appear to change over time, they may also prove to have prognostic significance. Also, knowledge about course derived from typical patients in whom schizophrenia begins in the third decade of life could be applied to patients who exhibit schizophrenic symptoms beginning late in life. Similarities or dissimilarities to the cognitive account offered here might aid in understanding whether these disturbances are "simply" schizophrenia with an unusually late onset or indicate a disorder with its own unique course and perhaps pathogenesis.

It is remarkable that after 100 years of research, the course of schizophrenia in its cognitive aspects is still at issue. To be certain, it is not easy to study patients over many years. Unfortunately, schizophrenia may lend itself only too well to this task. Our review of the literature and our own research lead us to believe that schizophrenia's course is that of a static encephalopathy.

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