
A 39-Year Followup of the Genain Quadruplets

Abstract The Genains, a unique group of monozygotic female quadruplets, all developed a schizophrenic disorder by age 24. They have been studied since the 1950s, because of the rarity of this occurrence (estimated to be one in 1.5 billion) and because their illnesses varied in severity. The identical inheritance would tend to rule out genetic differences as the cause of the neuropsychological differences; however, we cannot disentangle the effects of early brain injury and harsh punitive treatment as factors accounting for the differences in the severity of their disorders. We conducted neuropsychological examinations of the Genains at age 66, compared their test profiles, and contrasted certain test scores at 66 with those at ages 27 and 51. Test results indicate generally stable (or even improved) performance over time and support the notion that cognitive decline is not a degenerative process in schizophrenia. The Genains remind us of the exquisite interaction among variables that must be understood before additional, satisfactory progress can be made in preventing the development and predicting the course of schizophrenia. **Keywords:** Schizophrenia, neuropsychology, multiple births, aging. *Schizophrenia Bulletin*, 26(3): 699–708, 2000.

by Allan F. Mirsky, Linas A. Bieliauskas, Louis M. French, Daniel P. Van Kammen, Erik Jönsson, and Göran Sedvall

In one of the classic studies in psychopathology, Rosenthal (1963) published an account of an intensive investigation of a remarkable family, the Genains. What made the family remarkable was the fact that the four female children (date of birth, April 14, 1930) were identical quadruplets and had all been hospitalized for a schizophrenic disorder by the time they were in their early 20s. The nicknames given to them by Rosenthal—Nora, Iris, Myra, and Hester (N-I-M-H)—indicate their order of birth. The probability of identical quadruplets all developing a schizophrenic disorder was estimated by Rosenthal to be roughly one in 1.5 billion births. The rarity of this event was sufficient to ensure great interest in the Genain quadruplets on the part of schizophrenia researchers and to justify intensive study of them at the National Institute of Mental Health (NIMH) for an extended period of time during the late 1950s through the early 1960s. They were re-admitted to NIMH during the

early 1980s for further study with the newer biochemical and imaging techniques that had been developed in the interim (Buchsbaum et al. 1984; DeLisi et al. 1984; Mirsky et al. 1984).

The Genains are of special interest from the point of view of theories of the nature-nurture interaction in the etiology of schizophrenia. The father of the Genains was irritable, abusive, and intrusive. Psychological testing conducted at age 66 reported a “real lack of interest in others, in cooperating with others, and by some suspiciousness” (Rosenthal 1963, p. 306). He showed electroencephalogram abnormalities and was reported to suffer seizures. His mother was described as probably suffering from paranoid schizophrenia (Rosenthal 1963). Nevertheless, despite apparently identical genetic endowment, the quadruplets varied markedly with respect to time of onset and severity of illness. Thus, Hester, the last born, may have been showing early prodromal signs of a schizophrenic

disorder at age 11; moreover, she was the only sister who was unable to complete high school, having dropped out for nervousness, irritability, and various physical complaints in her junior year (Rosenthal 1963). She has never been able to function independently outside of a home or institution. In marked contrast, Myra, the third born, has been able to work as a secretary for most of her life, was married, and had two sons (Mirsky and Quinn 1988; Mirsky et al. 1992).

The other Genain sisters, Nora and Iris, have had life outcomes somewhat worse than Myra’s but better than Hester’s: both worked outside the familial home or the hospital for some period of time, but neither married or had a substantial career.

Scientific interest in the Genain quadruplets remains high (their photograph may have adorned as many introductory and abnormal psychology textbooks as that of Sigmund Freud), and they continue to provide opportunities to test new

hypotheses concerning the etiology of schizophrenia. In keeping with this tradition, the present investigation was stimulated, in part, by the possibility that a genetic anomaly (an extra band in chromosome 15p), recently found in a group of Swedish triplets with schizophrenia, might also be found in the Genains (Jönsson et al. 1997a).

The question also arose as to how the Genain sisters, all of whom now reside in or near the city of their birth, were faring as they entered the latter half of their seventh decade of life. To answer these questions, we arranged to visit the Genains in their hometown (dubbed "Envira" by Rosenthal 1963). We visited the Genains in the Midwestern town of Envira during March and May of 1996, when they were approaching their 66th birthday. We took blood samples from them to obtain DNA and perform the necessary karyotyping to see whether the abnormality seen in the Swedish triplets would also be present in their genetic makeup. In addition, we took the opportunity to interview them and to administer a brief battery of neuropsychological tests, some of which they had taken nearly 40 years earlier (Mirsky, in Rosenthal 1963). We obtained a blood sample from Myra's only surviving son, who was married, as well. Myra's elder son had died of AIDS several years earlier.

The chromosomal abnormality seen in the Swedish triplets was not seen in the Genains, and the results of the cytogenetic analysis were published in 1997 (Jönsson et al. 1997b).

We report here the results of the brief neuropsychological assessment of the Genain sisters conducted in March and May of 1996. A question of particular interest in this assessment concerned the pairing of the four sisters. Traditionally, Nora and Myra were considered to be one "pair," and Iris and Hester the other pair. This dichotomy was based on the fact that Nora and Myra were thought to be brighter and taller, were treated better by their parents, and were more successful in life than the other two (Rosenthal 1963). However, the proposition had been advanced that, based on a consideration of a variety of data, an equally compelling dichotomy would have Myra

and Iris constituting one pair (more intact neurologically) and Nora and Hester as the other pair (more damaged neurologically). We speculated that this was due, at least in part, to a greater degree of subtle pathological brain insult acquired at birth for Nora and Hester than for Myra and Iris (Mirsky et al. 1992). This speculation was based on the fact that Nora was the first of the quadruplets to pass through the birth canal; Hester was the last born and the smallest, and she was placed in an incubator for a number of days after birth. She was also found to have a double hernia (Rosenthal 1963). In addition, other neuropsychiatric data supported the view of greater injury in Nora and Hester than in Myra and Iris, including the number of neurological soft signs (greater in Nora and Hester than in Myra and Iris), differential response to withdrawal from neuroleptic medication (more devastating for Nora and Hester than for Myra and Iris), and dissimilarity in smooth pursuit eye movements (more abnormal in Nora and Hester than in Myra and Iris; Mirsky and Quinn 1988; Mirsky et al. 1992). However, computed tomography scans of the head conducted in the 1981 study did not reveal significant differences (Buschbaum et al. 1984). We wished to see, therefore, whether any data bearing on the issue of pairing could be derived from this evaluation.

This assessment also provided an opportunity to evaluate, over a 39-year period, the effects of aging and prolonged illness and treatment on the Continuous Performance Test of sustained attention (CPT; Rosvold et al. 1956); a version of this test was administered to the Genains first in 1957, then in 1981, and as part of the latest assessment in 1996. The ages of the Genains at these three times were 27, 51, and 66, respectively.

Attentional impairments have been noted in individuals with schizophrenia at least as early as 1919 (Kraepelin 1919/1972). Later work by Shakow (1979) and Zubin (1975), among others, advanced the idea that this impairment in attention was a core symptom of the disorder and that it could be subdivided into various elements, among them deficits in the capacity to *shift* and *sustain* attention. The CPT is the paradigmatic method of as-

sessing this latter aspect of attention. Additionally, previous work has shown the value of the CPT in assessing individuals at high risk for developing schizophrenia (Cornblatt and Erlenmeyer-Kimling 1985; Nuechterlein 1985; Rutschman et al. 1986; Mirsky et al. 1995b). Goldberg et al. (1990) found no significant differences on the CPT between a sample of unaffected members of monozygotic twin pairs discordant for schizophrenia and a sample of normal monozygotic twins. However, they acknowledged that the absence of a difference may have been related to the relatively simpler (nondegraded stimuli) version of the CPT task used; thus, it would be premature to conclude that the unaffected twins showed no deficit.

Method

Interview and Neuropsychological Testing. The Genain sisters were tested individually in a nursing facility in their hometown. The manager of the facility made rooms available for the drawing of the blood samples and for the interviews and neuropsychological testing. Nora, Hester, and Myra were interviewed briefly to determine their recent health history. Iris' dementia was sufficiently profound that she was unable to answer simple questions or to follow simple commands, beyond "please stand up" or "sit down." Although some attempts were made to test her, they proved fruitless; she was unable to answer questions, to use a pencil, or to press the response button of the CPT apparatus. The data on her health history were obtained from her medical chart and from her sisters. The following tests were administered to Nora, Hester, and Myra:

- Three subtests from the Wechsler Adult Intelligence Scale-Revised: Digit Span, Arithmetic, and Digit Symbol
- The Talland Letter Cancellation Test
- The Trail Making Test, Parts A and B
- The Wisconsin Card Sorting Test
- The Visual X, Visual AX, and Auditory Tones Tasks from the CPT

The measures derived from the tests were as follows: scaled scores for Digit

Span, Arithmetic, and Digit Symbol; mean number of correct cancellations for the Talland Letter Cancellation Test; time to completion scores for the Trail Making Test, Parts A and B; number of categories achieved for the Wisconsin Card Sorting Test; and number of correct responses and mean response times for each of the three tasks of the Continuous Performance Test.

A complete description of these tests appears in Mirsky et al. 1991 and Mirsky et al. 1995a.

Results and Discussion

Present Status, General Health, and Medical History. The Genain sisters continue to reside in Envira, where they still have the status of minor local celebrities, dating back to their celebrated birth on April 14, 1930.

The examination was conducted at a nursing home where one of the sisters (Iris) has been a resident since March 1995 with the diagnosis of dementia with agitation and schizophrenia, chronic (Axis I, 298.9 and 295.90). The overall health of the remaining sisters varied from good (Myra) to fair (Nora) to poor (Hester). All had evidence of some cardiovascular disease and were taking medications for either angina, hypertension, or hypercholesterolemia. Hester had suffered cardiovascular complaints for several years and in March 1996 had a heart pacemaker implanted; the diagnosis was unstable angina and ischemia, atypical. In January 1998, Hester had three-artery angioplasty and as of this writing was feeling well. Myra had angioplastic surgery in the winter of 1995, and Nora was taking medications for hypertension and angina pectoris. All were taking a neuroleptic medication: Nora, trifluoperazine, 5 mg twice daily plus benztropine, 1 mg daily; Iris, haloperidol 4 mg twice daily plus benztropine, 1 mg daily; Myra, risperidone, 5 mg twice daily; and Hester, trifluoperazine, 5 mg twice daily plus benztropine, 0.5 mg daily.

The etiology of Iris' dementia is unclear. She is noted to suffer from chronic obstructive pulmonary disease. It has been speculated that her schizophrenic illness is in some ways unique (Mirsky et

al. 1984), as evidenced by aberrant levels of norepinephrine and homovanillic acid in her cerebrospinal fluid and an increased antinuclear antibody titer (related to her history of rheumatic heart disease). Although the overall severity of her schizophrenia is less than that of Hester, Iris has spent more time in the hospital. Of all the sisters, Iris showed the greatest drop in IQ scores between ages 16 and 51 (Mirsky et al. 1984). It may be that she had the least "cognitive reserve" and that she was especially sensitive to the cognitive effects of normal manifestations of aging in the brain (e.g., neurofibrillary tangles; Dwork et al. 1998).

Nora and Hester reside together in an apartment, as they have done for several years. Nora manages the household, pays the bills, and keeps the checking account. Neither is employed, although they participate in some community activities. Myra lives in her own home in Envira, where she rents out a room for additional income. She is employed part-time as a secretary in a residence for elderly persons, and she visits Nora and Hester often.

Myra's elder son contracted the AIDS virus from a blood transfusion. He had been working with a carnival and had had a finger crushed as he helped pack the equipment for a move to the next town. The finger was amputated in the hospital, where he received the transfusion. He died, unmarried, in 1996.

Myra's younger son lives in a nearby city and helps to manage her financial affairs. He is very much involved in his mother's day-to-day life, including decisions about whether she should rent out rooms in her home to tenants; he is rarely, if ever, in contact with Nora, Iris, or Hester. He is married, has a young son, and is employed as a maintenance worker for a real estate management company. He was a reluctant participant in the blood drawing study, and he did not permit a blood sample to be taken from his son. He finally agreed to have his own blood drawn contingent (in part) on having a screen of his blood for exposure to the AIDS virus. (He was negative.) He also refused neuropsychological testing and was generally suspicious and mistrustful of the investigators. He stated

his belief that no good would come to either his mother or his aunts from their participation in the study.

Several years prior to our visit, the local television station did a special report on the sisters. Myra was the chief spokesperson. There have also been articles about them in local newspapers and magazines as "Envira's Four Goddaughters"; one article appeared in an insurance company publication in February 1998. In all of these media celebrations of the quadruplets, there was considerable discussion of their history in the town; however, in none of the articles was there any mention of the sisters' illness or of their many years of treatment. Their visits to the National Institutes of Health were discussed, but only in relation to the fact of their multiple birth. At present they receive support from local community and social service agencies and occasional income from the sale of their photograph to publishers of psychology, genetics, and psychiatry textbooks. Nora manages this enterprise.

Comparisons of the Genains With Aged Healthy Controls. Z scores were computed in the following manner: the score of each sister on each test was compared with the mean of a group of 27 healthy adults, in the age range from 65–74 (Mirsky et al. 1995a). In addition, the normative scores from the CPT Auditory Tones Task, from the same healthy aged adults, were obtained from Tatman (1992).

The majority of the z scores (24 of 39) fell more than one standard deviation below the mean of the controls; only 4 of the 39 scores from the three sisters, combined, reached the control (zero) levels. The interpretation of this result is to some extent ambiguous, however, in that the average duration of education of the controls was 16.3 ± 3.2 years (Mirsky et al. 1995a), whereas Nora and Iris completed high school only, Myra had 2 years of business college, and Hester's education did not extend beyond the eleventh grade (DeLisi et al. 1984). Because of the relatively high educational level of the control subjects, additional analyses were performed. Each test score was compared with the mean score of a group of ten healthy adults, in the age

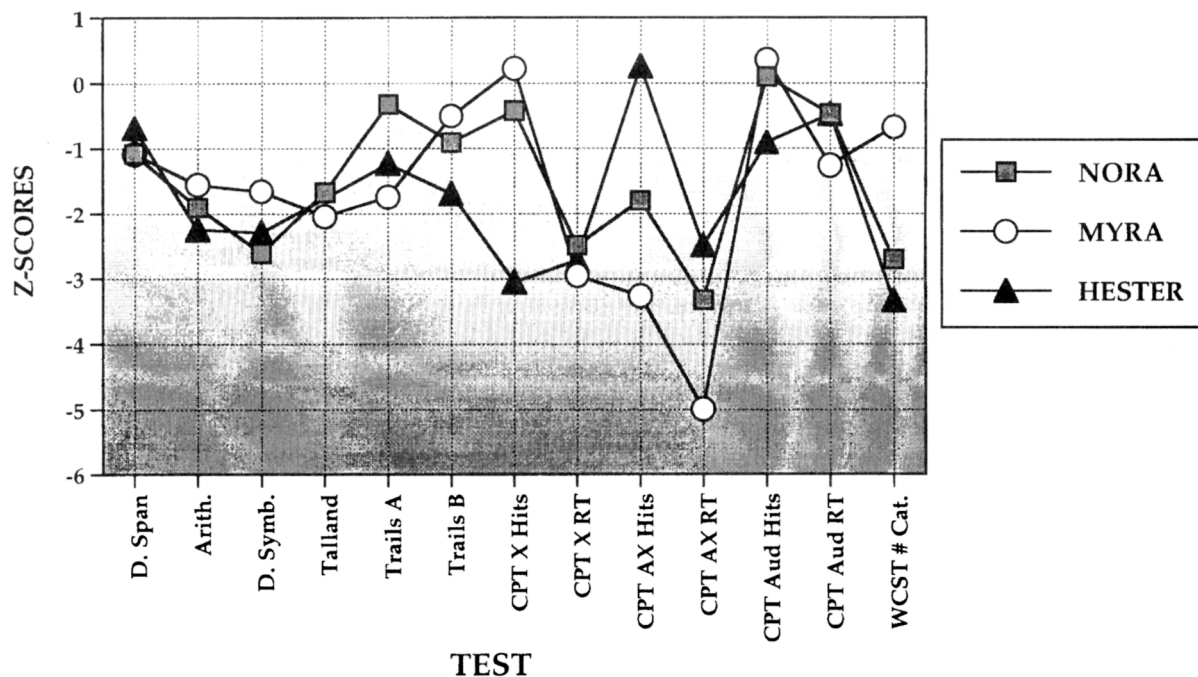


Figure 1. Z score profiles of Nora, Myra, and Hester¹

Note.--Aud Hits = number of high-pitched tones responded to within the allowable time of 700 msec. in the three-tone Auditory Tones Task; Aud RT = mean reaction time, all responses, Auditory Tones Task; AX Hits = number of "X" after A targets responded to within the allowable time of 700 msec. in the Visual AX Task; AX RT = mean reaction time, all responses, Visual AX Task; CPT = Continuous Performance Test; D. Span = Digit Span; D. Symb. = Digit Symbol Substitution; Talland = Talland Letter Cancellation; Trails A = Trail Making, Part A; Trails B = Trail Making, Part B; WCST # Cat. = Wisconsin Card Sorting Test, number of categories; X Hits = number of "X" targets responded to within the allowable time of 700 msec. in the Visual X Task; X RT = mean reaction time, all responses, Visual X Task.

¹ A complete description of these tests appears in Mirsky et al. 1991 and Mirsky et al. 1995a. The raw scores are available, upon request, from the senior author.

range from 40–70 (mean age 59.1 ± 7.8 ; educational level 12.3 ± 2.3 ; Tatman 1992). The differences from the mean of these less educated healthy controls, divided by their standard deviation (i.e., the z scores), are plotted in figure 1. The zero line represents the mean score for the controls.

It would be difficult, if not impossible, to parcel out the contributions to this generally depressed psychological test profile made by level of education, the 45+ years of a schizophrenic illness, and the modest intellectual endowment of the Genains. The Henmon-Nelson IQ measured in 1946 and the IQ estimated in 1981 from the Luria-Nebraska, respectively, were as follows: Myra, 87, 89; Nora, 99, 97; Iris, 89, 82; and Hester, 77, 80 (Mirsky et al. 1984).

Differential Performance of the Sisters. It is possible to speculate about the relative contribution of the schizo-

phrenic illness to the profile in figure 1 by contrasting the test scores obtained by Myra with those of Nora and Hester. It has been agreed, generally, that Myra's illness was the least severe of all the sisters. Myra had the most education, was the only sister to be married, bore two children, had the shortest period of time spent in the hospital and the least amount of medication for long periods of time, and apparently did not show symptoms of disorder until a later age (24) than any of her sisters (DeLisi et al. 1984; Mirsky and Quinn 1988).

With this in mind, we examined the z scores of Myra and noted that she had the highest score of the three sisters on 6 of the 13 measures in figure 1: Arithmetic; Digit Symbol Substitution; Trail Making Test, Part B; CPT X Hits; CPT Auditory Tone hits (number of correct responses to targets); and the Wisconsin Card Sorting Test. Myra scored considerably

higher on the Wisconsin Card Sorting Test than either of her sisters, achieving a total of four categories, as compared with one category (Nora) and none (Hester). Patients with schizophrenia characteristically perform poorly on tests of sustained attention such as the CPT and on tests of shifting attention such as the Wisconsin Card Sorting Test (see, for example, the results in Mirsky et al. 1995b). Consequently, Myra's pattern of relative successes on these tests could be viewed as consistent with a relatively mild form of schizophrenic illness. Myra also obtained the lowest score on six of the measures depicted in the figure, but three of these are reaction time measures (for the CPT Visual X Task, Visual AX Task, and Auditory Tones Task). Two of the other measures are from times tests, as well—the Talland Letter Cancellation Test and the Trail Making Test, Part A.

What the pattern of lowest scores indicates is that Myra had a slow, deliber-

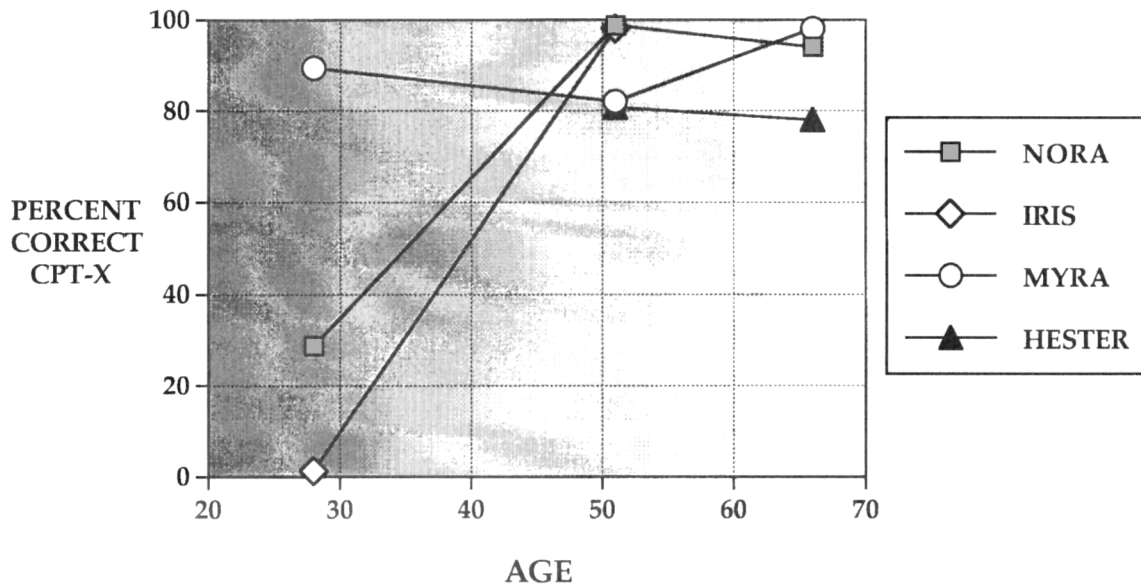


Figure 2. Percentage of "X" Targets responded to within the allowable time of 700 msec. in the Visual X Task¹

Note--CPT-X = Continuous Performance Test, Visual X Task.

¹Tests were conducted when the Genains were 27, 51, and 66 years of age, in 1957, 1981, and 1996. No score appears for Hester at age 27, as she was unable to execute the task at that time (pre-antipsychotic treatments). Iris' demented state at age 66 prevented her from performing the test. The mild reduction in Myra's score at age 51 may be related to her medication status at that time. She performed more poorly on both X and AX tasks on medication than she did off medication.

ate, careful strategy, which sometimes benefited and sometimes penalized her. The latter is suggested by her low score on CPT AX Hits. In the 1981 evaluation, Myra was the only one of the sisters to show evidence of tardive dyskinesia. Some of her motor slowing may be attributed to her long-term exposure to neuroleptic medication.

These considerations suggest that the milder form of schizophrenic illness suffered by Myra may be evidenced by, at least in part, her relatively stronger performance on these neuropsychological measures. It is also the case, however, the Myra most likely had less neuroleptic medication over the years than her sisters. While test performance is clearly improved in the short term with neuroleptic treatment (possibly because of decreased psychosis), the evidence for adverse cognitive effects of long-term neuroleptic administration is inconclusive (Jeste et al. 1998). Some studies (Chakos et al. 1994; Keshavan et al. 1994) have shown changes in brain caudate volume in humans with neuroleptic exposure. Other studies (see Jeste et al. 1998 for a review) have shown neuropathologic changes in animals with long-term neuroleptic exposure. Myra's dif-

ferential performance may be attributed to her milder form of schizophrenic illness, the performance-enhancing effects of risperidone contrasted with more traditional neuroleptic treatment (Stip and Lussier 1996), or other, more obscure, factors.

Schizophrenia Versus Brain Injury.

As seen in figure 1, Hester scored lowest on five of the neuropsychological test measures: Arithmetic; the Trail Making Test, Part B; CPT X Hits; CPT Auditory Tone Hits; and the Wisconsin Card Sorting Test, where she achieved no categories. This is not unexpected, in view of the fact that Hester is usually assumed to be the most impaired and the most severely ill of the Genains. As noted above, she was the last born, as well as the smallest and lightest at birth, and she needed more hospital care as a newborn than the other quadruplets.

Hester was the first of the Genains to show symptoms of psychiatric disorder (i.e., inability to complete high school due to "emotional problems"), and she never left home, except for extended periods of hospitalization (in excess of 15 years, by age 51). Hester's paradoxically high score on CPT AX Hits bears expla-

nation. She had the fastest reaction time on the Visual AX Task, as well, and was tied for fastest (with Nora) on the Auditory Tone Task. She also made a very large number of commission errors on the visual AX Task (three times as many as Nora, and six times as many as Myra). Her response style on the CPT, in contrast to the deliberate strategy of Myra, was to try to respond as rapidly as possible, often before adequate information was available.

Although a case may not be made unambiguously, it would seem that the scores of Nora are generally closer to those of Hester than to those of Myra. This is suggested by the scores for Digit Symbol Substitution, CPT AX Reaction Time, CPT Auditory Reaction Time, and especially the Wisconsin Card Sorting Test. This result provides some modest support for the proposition, advanced earlier, that the appropriate pairing of the Genains should be Nora and Hester, both of whom showed more signs indicative of early brain injury than the less injured pair of Myra and Iris (Mirsky et al. 1992). Unfortunately, due to the demented state of Iris, it was not possible to view her scores with respect to this proposed pairing. Conventional neuropsy-

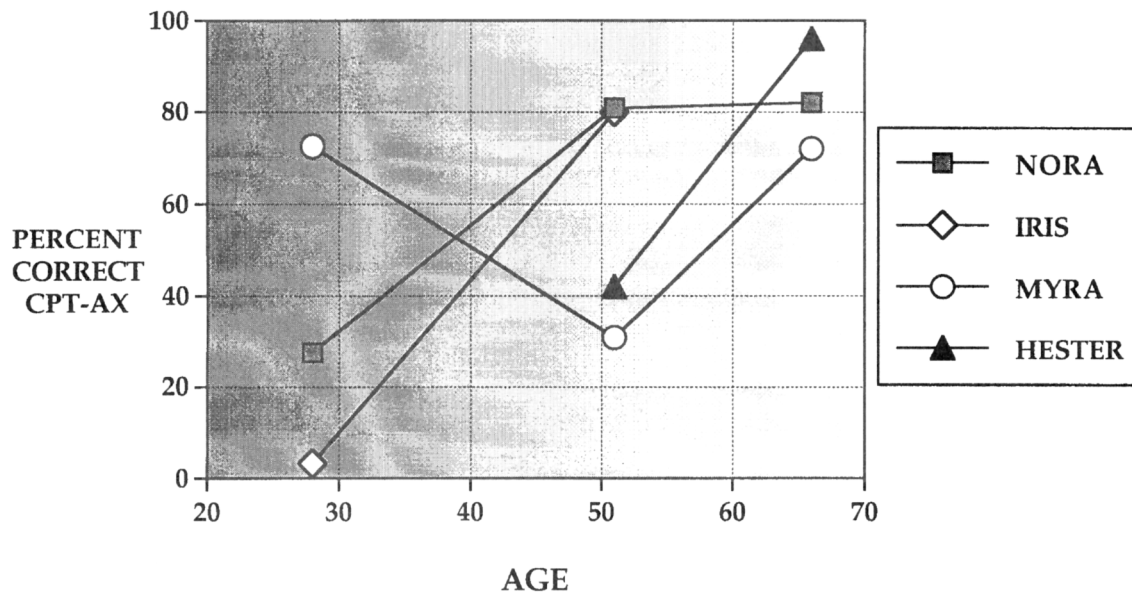


Figure 3. Percentage of "X" after "A" targets responded to within the allowable time of 700 msec. in the Visual AX Task1

Note.--CPT-AX = Continuous Performance Test, Visual AX Task.

¹Tests were conducted when the Genains were 27, 51, and 66 years of age, in 1957, 1981, and 1996. No score appears for Hester at age 27, as she was unable to execute the task at that time (pre-antipsychotic treatments). Iris' demented state at age 66 prevented her from performing the test. The reduction in Myra's score at age 51 may be related to her medication status at that time. She performed more poorly on both X and AX tasks on medication than she did off medication.

chological wisdom would assert that Hester and Nora have a greater degree of injury to the prefrontal cortex than Myra (e.g., Seidman et al. 1991). Further, Hester, because of her generally lower accuracy scores on the CPT (despite her paradoxically higher score on the AX task; see discussion above), would appear to have more injury to brainstem structures than either Nora or Myra (Mirsky and Duncan 1986).

CPT Scores From Age 27 to 66. A version of the CPT comprising both the X and AX tasks was administered to the Genain sisters in 1957, in 1981, and in 1996, when they were 27, 51, and 66 years of age, respectively (Mirsky and Quinn 1988). The CPT, as a measure of sustained attention, is generally considered to be one of the most sensitive measures for assessing the deficit in schizophrenia as well as the risk for the development of schizophrenia (Nuechterlein and Dawson 1984; Rutschmann et al. 1986; Mirsky et al. 1995b). It is therefore of interest to plot the trajectory of their performance over a 39-year interval, and their scores (percent correct responses, or "correct hits")

on the Visual X and Visual AX tasks are presented in figures 2 and 3.

The initial performance of the four women in 1957 (at age 27) is similar in figures 2 and 3. Myra had the best scores (within normal limits on the X task), followed as a not-so-close second by Nora. Iris could barely grasp the significance of the task and made only a few correct responses. Hester was unable to perform the task and refused even to touch the response key.

At the next testing, in 1981, when the Genains were 51 years old, antipsychotic drug treatment had long been introduced into the United States, and all the Genains were on some neuroleptic medication (DeLisi et al. 1984). As seen in figure 2, there was a dramatic improvement in the scores of Iris and Nora on the X task, whereas Myra's performance fell slightly. Hester was able to perform the task in 1981, when she was 51. On the AX task (figure 3), as well, Nora and Iris show substantial improvement at age 51. As was the case with the X task, Hester was able to perform the AX task, and she achieved 40 percent correct responses. There is a paradoxical decline in Myra's performance on the AX task, compared

with her score at age 27; it is possible that she was on too high a dose of medication when she was tested at age 51. This is consistent with the view that she has had a mild form of schizophrenia and has required relatively little medication. Some support for this conjecture is provided by the data obtained when the Genains were tested off all neuroleptic medication, for at least 6 weeks, in 1981 (Mirsky et al. 1984; DeLisi et al. 1984). The CPT scores (not reported here) of Nora and Hester fell dramatically—by as much as 73 percent—when they were off medication. In contrast, there was only a relatively modest drop, or a slight improvement, in the CPT scores of Myra and Iris off medication. This reinforces the view that Myra has a relatively mild disorder; in fact, there have been long intervals in her life when she was on no medication at all (Mirsky and Quinn 1988).

In 1996, three of the Genains were able to perform the CPT; Myra and Nora scored within normal limits on the X tasks, and Hester was at about the same level as she was in 1981. The high score of Hester on the AX task, attributable to

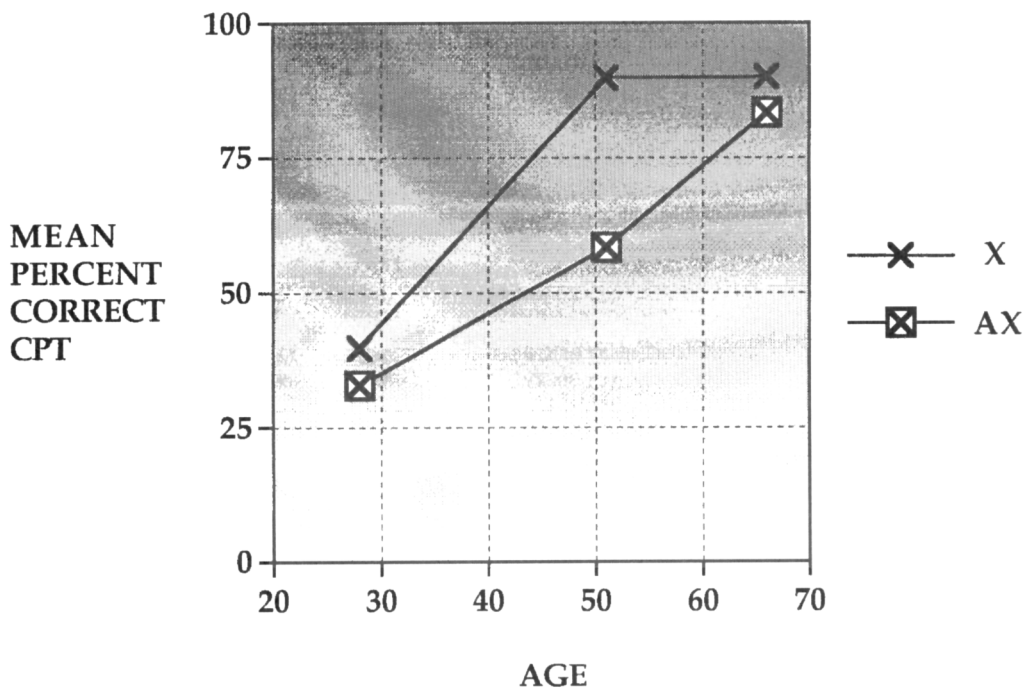


Figure 4. Mean performance of the sisters that were tested at each age point on the Visual X and AX tasks

Note.—AX Visual Task; CPT = Continuous Performance Test; X = Visual X Task.

her impulsive performance style, is discussed above.

The sense conveyed by the CPT data over the five decades is that the Genain quadruplets (with the unfortunate exception of Iris) are more than holding their own. Figure 4 shows the mean performance of the sisters at each time point, demonstrating their improvement over time as a group. This assessment of their attentive capacities indicates that at age 66 they are functioning considerably better than they did at age 27. Much of the benefit is due to antipsychotic medication and to the substantial, even loving, care provided them by the community in Envira. The concept of schizophrenia as a chronic, unremitting, deteriorating, and dementing disorder is not supported by these data, which are consistent with the findings of Harding and colleagues (e.g., Harding and Zahniser 1994) concerning the long-term recovery of many patients diagnosed early in life with schizophrenia. These findings are also consistent with those of Rund (1998), who reviewed 15 longitudinal studies of cognitive functions in patients with schizophrenia and concluded that while cognitive decline may be apparent in a subset of 10–

20 percent of the cases, it is not the natural course of the illness. Rather, stability or even improvement over time is found.

What Can the Differences Among Nora, Iris, Myra, and Hester Teach Us About Schizophrenia? The fact that Myra has a generally more intact neuropsychological profile than Nora and Hester do is conceivably a confounding of two factors: the milder form of the disorder Myra suffered as well as the putative smaller brain insult, if any, she sustained during the earliest moments of her life. Or are these two factors really one? Current theories of the etiology of schizophrenia have implicated a variety of cerebral structures, including the frontal lobes (e.g., Friston 1992), the temporal lobes (Shenton et al. 1992), portions of the limbic system (e.g., Benes et al. 1991), the brainstem reticular activating system (Mirsky and Duncan 1986; Karson et al. 1991), the cerebellum (Martin and Albers 1995), or a variety of structures, depending upon the specific deficits shown by the patient (Seidman et al. 1991). These findings have been interpreted as supporting the general proposition that schizophrenia is a disease of the

brain, although it is not clear that any (or all) of the injuries would account entirely for the symptoms of the disorder.

In trying to account for the relatively superior scores (and life course) of Myra, we may not exclude the possible effects of the more preferential treatment she received from her parents. She and Nora were clearly favored over Iris and Hester in many respects; more was given to them and expected from them. The less preferential treatment given to Iris and Hester was documented by Rosenthal (1963). They were treated harshly by their father, in particular. Hester was considered by both parents to be the “moron type” and a “sex maniac.” In order to cure her masturbatory behavior and that of Iris, both were subject to circumcision at the advice of the family physician.

Although the genetic endowment of the Genains is presumed to be identical, the phenotypic expression of the disorder is relatively unique in each of the sisters. The outcome and life course of the Genain quadruples remind us that any genetic model that would account for such diversity must include the participation of a number of environmental fac-

tors, such as those we have reviewed (i.e., differing amounts and loci of brain injury at birth, differential expectations of and treatment by parents, and, most likely, the operation of chance factors) in the expression of the disorder. Therefore, an appropriate genetic model would most likely be similar to that of other complex human disorders, such as heart disease, hypertension, diabetes, and cancer (Lander and Schork 1994). We owe to the Genains this reminder of the exquisite complexity that must be understood before additional satisfactory progress can be made in understanding, preventing, and predicting the course of schizophrenia. As long as we are able to do so, we should continue to study this remarkable group of women for any additional insights into the nature of the disorder they share with millions of other Americans, and many millions of other persons worldwide.

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The Authors

Allan F. Mirsky, Ph.D., is Chief, Section on Clinical and Experimental Neuropsychology, Laboratory of Brain

and Cognition, NIMH, Bethesda, MD; Linas A. Bieliauskas, Ph.D., is Associate Professor, Neuropsychology Program, Department of Psychiatry, University of Michigan Medical Hospitals, Ann Arbor, MI; Louis M. French, M. A., is Pre-Doctoral Fellow, Section on Clinical and Experimental Neuropsychology, Laboratory of Brain and Cognition, NIMH, Bethesda, MD; Daniel P. Van Kammen, M.D., Ph.D., is Director, Global Research and Development, The RWJ Pharmaceutical Research Institute, Raritan, NJ; Erik Jönsson, M. D., Ph.D., and Göran Sedvall, M.D., Ph.D., are Research Scientist and Professor, respectively, Department of Clinical Neuroscience, Psychiatry Section, Karolinska Hospital, Stockholm, Sweden.