0196-206X/88/0905-0257$02.00/0
DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS

Vol. 9, No. 5, October 1988
Printed in U.S.A.

Neurofibromatosis and Psychological Processes

CONNIE K. VARNHAGEN, PH.D.
Developmental Disabilities Centre, University of Alberta, Edmonton, Alberta, Canada

SUSAN LEWIN, M.B.B.C.H.
Shodair Children's Hospital, Helena, Montana

J.P. DAS, PH.D.
Developmental Disabilities Centre, University of Alberta, Edmonton, Alberta, Canada

PETER BOWEN, M.D.
KEN MA, M.D.
MARION KLIMEK, B.S.N.
Division of Medical Genetics, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada

ABSTRACT. A minimal degree of mental handicap is commonly seen in neurofibromatosis (NF). Despite the prevalence, little is known about the nature of the mental handicap. In this study, schoolchildren with NF and unaffected siblings were studied clinically and given a series of psychological tests. The psychological battery consisted of standardized tests of intelligence and cognitive processing, laboratory tests of cognitive processing, and personality and mood questionnaires. Clinical data included a medical and family history, results of physical, audiological, and ophthalmological examinations, EEG, tissue biopsy when necessary, and (in NF individuals) a CT scan. Results demonstrate slightly deficient cognitive processing in the NF individuals, particularly in terms of visual-spatial integration. These deficits are related to age-independent severity with more severely affected individuals exhibiting more severe deficits. The findings are discussed in terms of their diagnostic and prescriptive implications. *J Dev Behav Pediatr 9:257–265, 1988.* Index terms: *neurofibromatosis, psychological processes, cognition, learning disability.*

Neurofibromatosis (NF), also known as peripheral neurofibromatosis or von Recklinghausen's neurofibromatosis, is a relatively common genetic disorder, affecting approximately one in 3,000 people.[1,2] NF is an autosomal dominant trait, meaning that each child of an affected parent has a 50% chance of inheriting the disorder. New mutations are common, accounting for up to 50% of new diagnoses.[1] NF occurs with equal frequency in males and females and has been diagnosed everywhere in the world.[2]

Common as it is, very little is known about NF. Presently, no laboratory test is available to diagnose NF. Numerous manifestations are variable and difficult to diagnose in early, mild, and atypical forms. The clinical manifestations of NF were first described by von Recklinghausen in 1882 and have been expanded by others since then.[1-3] In addition, other forms of NF have recently been distinguished (e.g., central, peripheral, and other forms); the focus of this study remains the most common form of the disorder. The most common NF manifestations include café-au-lait spots and neurofibromas.[1,2] Café-au-lait spots are small pigmented areas of the skin. Although they have no clinical importance, six or more café-au-lait spots generally raise suspicions of NF.

Address for reprints: Connie K. Varnhagen, Development Disabilities Centre, 6-123d Education North, University of Alberta, Edmonton, Alberta, Canada, T6G 2G5.

Neurofibromas are benign tumors of nervous tissue and surrounding fibrous tissue; they may be discrete lesions or may be invasive. Usually, they are just under the skin surface, where the effect is mainly cosmetic in nature, or they occur internally, causing considerable difficulty. Common locations for internal neurofibromas are on the auditory and optic nerves. Other manifestations of NF include Lisch nodules, axillary freckling, macrocephaly, short stature, pseudarthrosis, kyphoscoliosis, seizures, and hypertension.

Although the clinical manifestations are well documented, psychological and intellectual aspects of NF have only recently become a concern of clinicians and researchers. NF individuals are frequently characterized as having some degree of mental handicap, ranging from hyperactivity and mild learning disability to frank mental retardation.[1-9] The incidence of mental handicap has been variably reported as ranging from 24%[5] to 45%.[8] However, in most of these studies, conclusions are based on rather crude measures, such as school records (examination results, number of years of schooling, class placement), personal history, or parental reports, rather than more objective measures, such as standardized intelligence test (IQ) scores or behavioral measures.

According to Riccardi's analysis of IQ measures, about 2–5% of individuals with NF are severely or profoundly mentally retarded and about 40% have at least a mild mental handicap.[3,7] The incidence of severe and profound mental retardation in Riccardi's patients is comparable to that in

the general population, but the incidence of mild handicap in his group is almost twice that of the general population. Although Riccardi concludes that various clinical manifestations "specifically and nonspecifically contribute to the severity and impact of the intellectual handicap" (p 219), he does not report any particular correlations between clinical severity of NF and intellectual ability.[7]

Rosman and Pearce[6] have attempted to relate mental handicap to structural alterations in the cerebral cortex. In autopsies of 10 NF patients, all five who were characterized as mentally retarded demonstrated various cortical abnormalities. In contrast, less severe abnormalities were found in the five nonretarded individuals. Rosman and Pearce argue that the abnormalities were likely due to some genetic disruption of normal cortical development in the embryo. This would result in mild mental retardation (a static disorder) rather than a degenerative disorder. Fienman and Yakovac[5] agree with Rosman and Pearce's findings, claiming that such a hypothesis explains the static or nonprogressive nature of the mental handicap observed in their patients.[5] Based on this hypothesis, then, it should be possible to discover a relationship between psychological processing and other clinical manifestations of NF.

However, Rosman and Pearce's hypothesis does not account for Riccardi's adult NF patients, who demonstrate higher average IQ scores than his child patients.[3,7] It is uncertain whether these findings are a function of a cohort effect, or due to some malleable relationship between NF and intellectual functioning. Given the relatively static nature of intelligence, the former is likely a more valid explanation for Riccardi's findings.

Regardless of their discrepant findings, these studies do not pinpoint the nature of the mental handicap experienced by individuals affected with NF. Recognizing how little is known about the psychological characteristics associated with NF, Eliason[4] examined intellectual and cognitive deficits in children with NF referred to a clinic for learning and behavioral problems. Using intelligence, language, and neuropsychological test measures, Eliason classified children according to visual-perceptual, language, or mixed language-perceptual learning disability subtypes. Eliason's findings demonstrated a different pattern of subtypes than is commonly found in the general population of children with learning disabilities: Whereas learning disabled children commonly display a language deficit, the NF-affected children predominantly were characterized as having a visual-perceptual deficit. This type of learning disability, resulting in problems in completing workbook assignments, blackboard comprehension, and organizing written work, is often associated with hyperactivity, a common finding in NF.

Although these findings do much to elucidate the type of mental impairment experienced by individuals affected with NF, the study has two important limitations. First, only children referred for learning and/or behavior problems were included. Thus, the results cannot be generalized to the general population of individuals affected with NF. Second, although there is extreme variability in the test results, little attempt was made to explain the variability, particularly in terms of severity of the clinical manifestations.

It is apparent that the relationship between NF and intellectual handicap requires further study. In particular, predictive factors need to be identified in order for clinicians and school psychologists to provide adequate counseling and, where necessary, educational or medical recommendations.

This study is an initial attempt to examine the relationship between NF and psychological processing. Schoolchildren affected with NF and, when possible, siblings close in age participated in the study. Siblings, as opposed to unrelated children, were used as a comparison group to allow for the possibility that the NF children did not represent a random sample, but were self-selected according to some characteristic(s) unknown to the researchers. Test results from the NF children were compared with results obtained with the comparison children in addition to normative values.

Psychological and clinical tests were performed on the participants. The psychological battery consisted of standardized tests of intelligence and cognitive processing, laboratory measures of cognitive processing, and personality and mood questionnaires. The clinical tests consisted of a complete physical, ophthalmological and auditory examinations, and EEG. A family history was obtained in every case. Computed tomographic (CT) scans were done only on the NF group, as were tissue biopsies of suspicious neurofibromas.

This study protocol is quite similar to the one advocated by Riccardi.[3,7] However, additional information was obtained with the cognitive processing tests and the personality and mood questionnaires. The cognitive processing measures represent a new approach to the assessment of intellectual functioning and learning abilities. They are also more useful than standardized intelligence tests reported in the literature for specifically identifying intellectual or learning handicaps in terms of particular deficient cognitive processes. The personality and mood questionnaires provide vital information about the psychological and motivational state of the individual. This information is not generally collected, but may be very important for a complete assessment. The sometimes severe psychosocial burden that NF places on the affected individual and his or her family may strongly affect intellectual and cognitive performance.[3]

METHODS

Subjects

Sixteen schoolchildren with neurofibromatosis (NF) (median age = 12.0 years, range = 4.3–18.7 years; nine males and seven females) and nine unaffected siblings (median age = 13.4 years, range = 4.7–20.9 years; two males and seven females) participated in the study. The sibling controls who were selected were as close in age as possible to the affected subject; it was not possible to obtain comparable proportions of males and females in the unaffected and NF groups. The subjects were recruited from local physicians or obtained as volunteers through the Neurofibromatosis Association of Alberta, and lived within a 100-km radius of Edmonton, Alberta, Canada. All subjects were initially screened by the Edmonton Genetics Clinic, University of Alberta Hospitals, prior to inclusion in the study. Subjects

with questionable NF diagnosis or with multiple diagnoses were excluded.

On the basis of the clinical examinations, the affected individuals were classified according to the severity of their clinical manifestations: A child with café-au-lait spots and cutaneous neurofibromas was classified as mildly affected (severity 1); a child with café-au-lait spots, cutaneous neurofibromas, and internal neurofibromas and/or other significant complications, such as scoliosis, seizures, etc., was classified as more severely affected (severity 2).

These two severity categories are grosser than Riccardi's; the mildly affected, severity 1 children who participated in this study correspond to Riccardi's severity classification Stage I, Minimal, and the most severely affected, severity 2 children correspond to Riccardi's severity classifications Stages II–IV, Mild–Severe.[3] Only two categories were distinguished because of the small numbers of subjects and the difficulties in distinguishing between Riccardi's stages that were encountered by the pediatricians attempting to classify the NF children. Eight individuals were classified as severity 1, and eight were classified as severity 2. The severity classification did not depend on age, as there was no significant difference in median age between the groups. Thus, any group differences cannot be interpreted as due solely to age effects, but may be related to severity of manifestations of NF.

Assessment Procedure

Psychological Tests. The psychological battery consisted of intelligence tests (WPPSI, WISC-R, WAIS-R), a standardized test of cognitive processing (K/ABC), unstandardized tests of cognitive processing (Das tests), and personality (EPQ-Junior, EPQ-Senior) and mood (POMS, PAMS) questionnaires. Master's or doctoral students, preparing for certification by the Alberta Psychological Association, administered the tests under the supervision of the first and third authors.

The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) was given to children who were 4–6.6 years old, the Wechsler Intelligence Scale for Children-Revised (WISC-R) to those who were 6.6–16 years old, and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) to individuals 16–18 years old.[11-13] Although the tests are composed of somewhat different subtests, three comparable scaled scores can be determined, namely, Verbal, Performance, and Full Scale. Because of the differences in the subtests, only performance on the three scales was analyzed. The Wechsler tests provided standardized IQ scores.

The K/ABC was administered to children who were less than 14 years old.[14] Although the subtests are also somewhat different for different age ranges, many are consistent across ages, and four comparable scaled scores can be determined, namely, Sequential Processing, Simultaneous Processing, Mental Processing Composite, and Achievement. Performance on the consistent subtests and on the four scales was analyzed. The Kaufman Assessment Battery for Children (K/ABC) provided a standardized test of cognitive processing.

Das tests of cognitive processing also were administered.[15,16] Trail Making is a modification of a neurological screening test for brain damage adopted by Armitage.[17] The task requires planning of cognitive and motoric behavior and consisted of connecting numbers (Trail Making A subtest), followed by connecting alternating numbers and letters (Trail Making B subtest) for older children. Time taken to complete each of the tasks was recorded. Auditory Serial Recall, requiring the ability to recall words in sequential order, consisted of recall for lists of 4 to 7 words. The longest list of words recalled in correct serial order was recorded for this task. Finally, Memory for Designs, a modification of the Graham-Kendall test for brain damage, requires memory for and correct reproduction of geometric figures.[18] The number of items correctly reproduced from memory was recorded as the Memory for Designs measure.

The Eysenck Personality Questionnaire (EPQ) comprised the personality measure.[19] The EPQ-Junior was administered to children under age 16 years; the EPQ-Senior was given to individuals who were 16 years old or older. Both versions of the questionnaire are comparable and yield scores on scales of Psychoticism, Extroversion, and Neuroticism.

The mood questionnaire consisted of the Profile of Mood States (POMS), administered to individuals age 14 years or older, and the Pre-Adolescent Mood Scale (PAMS), administered to children under age 14 years.[20,21] Each questionnaire yields different mood scales: The POMS is analyzed into scales of Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment; the PAMS is analyzed into scales of Surgency, Sadness, Aggression, and Mastery-Self Esteem.

Clinical Tests. Clinical tests consisted of history, physical examination, and specialized laboratory and clinical tests. The second, fourth, and fifth authors completed the histories and physicals. Appropriate specialists completed and provided reports for the special assessments and follow-up examinations.

A detailed history was obtained from each participant or from the parents, including age at which common manifestations of NF were first noted, complicating symptoms such as seizures, headaches, deafness, visual problems, and cardiovascular problems, and reports of developmental delay, learning disability, special education, and speech problems. Family histories and genealogies also were obtained.

A complete physical examination was done on each child to identify clinical traits of NF and to assess severity. Special attention was paid to the child's skin, eyes, ears, spine, nervous system, and blood pressure. Any problems detected during the physical were followed up, such as performing tissue biopsies of suspect neurofibromas.

Special assessments included ophthalmological examination for Lisch nodules and evidence of optic gliomas. A comprehensive audiological examination was performed. EEGs were also obtained. Finally, CT scans of the head, including temporal and orbital areas, were done on the affected children.

Testing Sequence. Whenever possible, as much of the protocol as possible was accomplished over two consecutive days. As a result of scheduling conflicts and delays, equipment malfunctions and other unavoidable incidents, complete data were not obtained on all subjects. In addition, due to age limits on several psychological tests, not all tests

TABLE 1. Medians (and Interquartile Ranges) for the Different Psychological Measures

Measure	Subject Group: Unaffected Siblings	NF[a] Severity 1	NF Severity 2
	Wechsler Intelligence Scales		
	n = 9	n = 7	n = 7
Verbal	111 (5.0)	92 (20.5)	96 (15.5)
Performance	105 (12.0)	102 (21.5)	87 (7.0)
Full Scale	110 (7.0)	96 (24.5)	91 (9.0)
	Kaufman Assessment Battery for Children Scales		
	n = 5	n = 7	n = 5
Sequential	104 (15.0)	93 (13.0)	83 (9.0)
Simultaneous	106 (6.0)	96 (22.0)	83 (10.0)
Mental Processing Composite	110 (7.0)	95 (19.5)	84 (3.0)
Achievement	110 (7.0)	102 (32.0)	97 (6.0)
	Das Tasks		
	n = 9	n = 8	n = 8
Trail Making A	44 (27.0)	46 (62.5)	67 (127.5)
Trail Making B[b]	81 (28.5)	145 (59.0)	145 (195.0)
Auditory Serial Recall	5.5 (2.0)	4.0 (0)	4.0 (2.0)
Memory for Designs	58.0(11.0)	36.5(39.5)	45.0 (14.5)
	Eysenck Personality Questionnaire		
	n = 8	n = 4	n = 7
Psychoticism	2.5 (3.5)	2.0 (2.5)	4.0 (3.0)
Extraversion	18.5 (5.0)	15.0 (4.0)	19.0 (7.5)
Neuroticism	11.0 (7.0)	10.5 (7.0)	15.0 (9.5)
	Profile of Adolescent Mood States Questionnaire		
	n = 5	n = 7	n = 4
Surgency	13.0 (2.0)	14.0 (1.5)	6.0 (10.5)
Sadness	0 (1.0)	3.0 (3.5)	2.0 (7.0)
Aggression	0 (1.0)	5.0 (3.5)	4.5 (6.5)
Self Esteem	12.0 (1.0)	14.0 (7.0)	11.5 (6.0)
	Profile of Mood States Questionnaire		
	n = 4	n = 5	
Tension-Anxiety	4.5 (5)	7.0 (5)	
Depression-Dejection	4.0 (0)	3.0 (14)	
Anger-Hostility	11.0 (4)	11.0 (15)	
Vigor-Activity	20.5 (3)	20.0 (5)	
Fatigue-Inertia	9.5 (11)	9.0 (10)	
Confusion-Bewilderment	2.5 (1)	6.0 (2)	

[a] NF, neurofibromatosis.
[b] n = 7, 3, and 7 for the three groups, respectively.

were administered to all subjects. Because of the resulting small sample sizes, nonparametric statistics were used to analyze the results and should be interpreted with caution.

RESULTS AND DISCUSSION

Psychological Tests

Performance on the psychological tests was compared across the three groups, namely, unaffected siblings, neurofibromatosis (NF) severity 1 (mild), and NF severity 2 (more severe); with available norms; and across subtests within each of the three groups. Medians and interquartile ranges for the various measures are found in Table 1. Because there were few NF subjects who were administered the POMS, results for the questionnaire are collapsed across the two NF groups. Wald-Wolfowitz runs tests were performed in order to rule out any confounding sex differences in psychological functioning. All results were nonsignificant, indicating no sex effect.

Wechsler Intelligence Scales. Kruskal-Wallis one-way analyses of variance showed statistically significant differences between the groups for all three scales, $\chi^2 = 8.58$, 6.75, and 8.31, $df = 2, p < 0.05$, for Verbal, Performance, and Full Scale IQ, respectively. In general, there is a decline in IQ across groups, from unaffected to severity 2. However, with the exception of Performance IQ for the severity 2 children, median IQs fall within the average range of intelligence; Performance IQ for the severity 2 children falls in the low average range.

Box plots of performance on the three subscales are shown in Figure 1. This type of representation provides a good index of the degree of overlap and/or difference in performance by the groups of children. The brackets cut off 95% confidence intervals around each median. Nonoverlapping brackets therefore represent group differences that are significant at the 5% level.[22] The confidence intervals in Figure 1 demonstrate that Verbal IQ is comparable in the two groups of NF children and significantly higher for the group

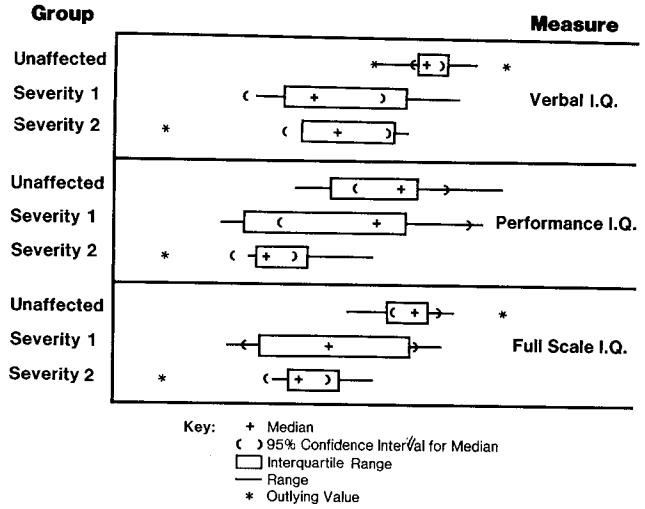

FIGURE 1. Box plots for performance by the three groups on Verbal, Performance, and Full Scale IQ.

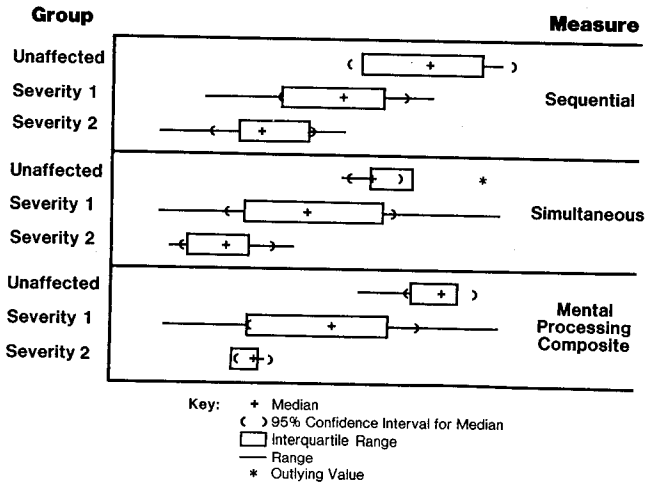

FIGURE 2. Box plots for performance by the three groups on the Sequential, Simultaneous, and Mental Processing Composite scales.

of unaffected children. The plots for Performance IQ are somewhat different; Performance IQ for the severity 2 children is less than for either the unaffected or severity 1 children. Finally, Full Scale IQ for the severity 2 children is less than it is for the unaffected children, with the severity 1 children falling in between.

However, more important is the comparison across Verbal and Performance IQ for each group of children. For both the unaffected and severity 1 children, Verbal and Performance IQ was at a comparable level. However, for the more severely affected severity 2 children, Performance IQ was significantly lower than Verbal IQ. Individual differences between Verbal and Performance IQ corroborate the group differences; greater discrepancies between Verbal and Performance IQ are found with children in the severity 2 group than with the children in either of the other two groups. This Verbal-Performance disparity has been documented by Eliason.[4] The present results are interesting, in that the more severely affected individuals demonstrate this distinction, whereas the mildly affected individuals do not demonstrate such a discrepancy between Verbal and Performance IQ.

K/ABC Scales. Kruskal-Wallis analyses revealed statistically significant differences between the three groups on the Sequential, $\chi^2 = 8.03$, $df = 2, p < 0.05$, Simultaneous, $\chi^2 = 6.93$, $df = 2, p < 0.05$ and Mental Processing Composite, $\chi^2 = 7.97$, $df = 2$, $p < 0.05$, scales, but not on the Achievement scale. Examination of the 95% confidence intervals for the box plots in Figure 2 reveals that performance on all three scales by the severity 2 children is significantly lower than the unaffected children, with performance by the severity 1 children falling somewhere in between.

Comparing across scales, sequential and simultaneous performance is comparable within each group of children, indicating no particular strength or weakness in either of the general forms of cognitive processing. There are also no differences between the Mental Processing Composite scale and Achievement in the unaffected and severity 1 children; for these children, academic achievement matches predicted achievement given their level of cognitive processing. However, the severity 2 children demonstrate a large discrepancy between the Achievement and Mental Processing Composite scales, indicating that the more severely affected children demonstrate academic achievement that is much greater than would be predicted from their level of cognitive processing. This discrepancy is also supported by the individual results, with three of the five severity 2 children who were administered the K/ABC having much higher Achievement scores than Mental Processing Composite scores. According to Kaufman and Kaufman,[23] this type of discrepancy is commonly encountered with children who demonstrate a strong Verbal-Performance discrepancy on the WISC-R. Thus, the K/ABC results support the Wechsler results in terms of identifying higher verbal ability relative to other intellectual and cognitive abilities in the more severely affected NF children.

K/ABC Subtests. Kruskal-Wallis analysis of variance documented statistically significant differences between the three groups on the Word Order subtest of the Sequential scale, $\chi^2 = 6.62$, $df = 2$, $p < 0.05$, and on the Triangles and Spatial Memory subtest of the Simultaneous scale, $\chi^2 = 7.44$ and 9.17, $df = 2$, $p < 0.05$, respectively. The box plots in Figure 3 show that for the Word Order and Triangles subtests, both the severity 1 and 2 children perform at a lower level than the unaffected children. The Spatial Memory subtest distinguishes all three groups of children. This test depends heavily on visual-spatial integration; differential performance on this subtest supports Eliason's finding that her learning disabled NF children have a particular visual-perceptual disability.[4]

Median scores for each group on these subtests were also examined in order to determine profiles of performance for the three groups of children. As expected, uniformly high scores were obtained with the unaffected siblings, and no particularly strong or weak areas were identified.

The severity 1 children demonstrated slightly better performance on the Hand Movements subtest of the Sequential scale and on the Gestalt Closure subtest of the Simultaneous

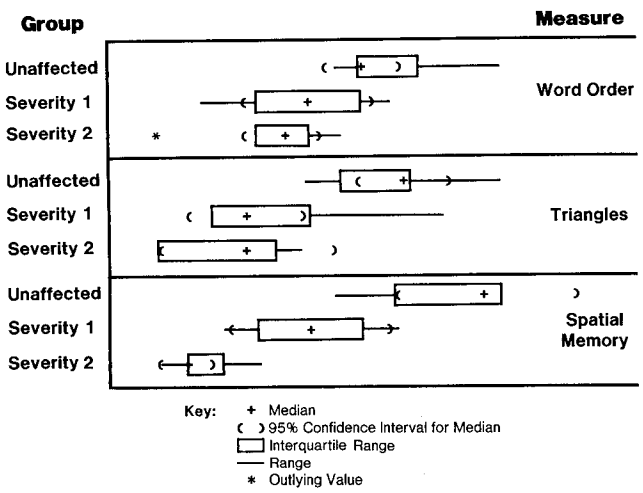

FIGURE 3. Box plots for performance by the three groups on the Word Order, Triangles, and Spatial Memory subtests.

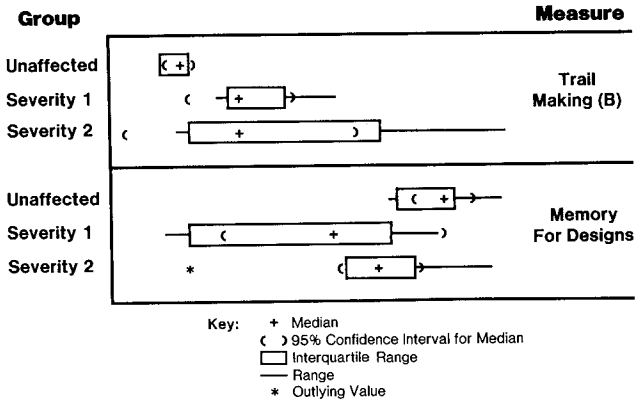

FIGURE 4. Box plots for performance by the three groups on the Trail Making B and Memory for Designs tasks.

scale. The Hand Movements subtest requires repetition of a sequence of three different hand positions, e.g., make a fist, put open palm down, turn hand sideways, put open palm down. Although it is classified as a visual-perceptual task, Hand Movements can be easily accomplished using verbal mediation, i.e., saying the required movements. Similarly, Gestalt Closure can be completed using verbal mediation by labeling different parts of the stimulus picture. This subtest requires identifying an incomplete picture of some object, and is supposed to be a visual-perceptual task. However, it too can be easily performed using verbal mediation rather than by integrating spatial information. Performance on the other visual-perceptual subtests of the K/ABC is relatively poor. If the Hand Movements and Gestalt Closure subtests are being accomplished without using the intended forms of cognitive processing, then this lends further support to Eliason's findings that NF individuals experience particular difficulties in visual-perceptual processing.[4]

This difficulty becomes even more obvious in the more severely affected children. Their higher verbal skills seem to give rise to a relative strength in Gestalt Closure; conversely, their visual-spatial integration difficulties are apparent in the other subtests relying on such processing, particularly in Spatial Memory, which can only be performed using visual-spatial integration.

These group profiles are maintained in the individual profiles and demonstrate a good deal of homogeneity among the severity classification groups. Thus, this examination of the K/ABC subtests replicates Eliason's findings of visual-perceptual difficulties and extends them to pinpoint a difficulty in integrating and abstracting spatial information that is presented visually.[4]

Das Tests. Performance on the three Das tests of cognitive processing corroborate the K/ABC results. Kruskal-Wallis analysis of variance for each of the tests revealed a marginally significant difference between the children on the more complicated Trail Making B test, $\chi^2 = 5.38$, $df = 2$, $p < 0.06$, and a significant difference on Memory for Designs, $\chi^2 = 6.08$, $df = 2$, $p < 0.05$. Trail Making requires planning and a certain degree of perceptual organization and Memory for Designs relies upon visual-spatial integration and memory. The box plots in Figure 4 show that, for both tests, performance by the NF children is poorer than that by the unaffected children. Thus, the laboratory tests of cognitive processing provide further support for a visual-spatial processing defict in individuals with NF which may or may not be related to severity of the clinical manifestations of the disorder.

Eysenck Personality Questionnaire (EPQ). There are no statistically significant differences between the three groups on any of the personality measures. The severity 2 children are, however, slightly higher than the norm-referenced general population on the Neuroticism scale.[19] Individuals who score relatively higher on Neuroticism are phenotypically considered to be anxious and preoccupied with potential disasters. This profile is entirely reasonable, given the uncertain nature and course of NF, and is consistent with Riccardi's concern about the psychosocial burden that NF places on the affected individual and his or her family.[3,7]

Mood States Questionnaires. Because of the small group sizes, responses to the Profile of Mood States (POMS) were collapsed across the two NF groups. Responses to the mood questionnaires were consistent across the three groups of children, with the exception of the Aggression scale for the Pre-Adolescent Mood Scale (PAMS), Kruskal-Wallis $\chi^2 = 7.74$, $p < 0.05$. Responses made by the unaffected children demonstrate no aggressiveness, whereas responses made by both groups of NF children demonstrate minimal aggressiveness; this difference may not be extreme enough to allow for a reliable clinical interpretation. However, this minimal amount of aggression is indicative of hyperactivity, a common characteristic of NF children.

All responses made by all individuals to either questionnaire are within normal limits, demonstrating no emotional disturbance among the unaffected and affected individuals. These questionnaires were also included to provide a measure of whether the subjects found the extensive battery of tests disturbing. Generally administered at the end of the first day of testing, the questionnaires required responses based on how the individual felt "right now." Although

TABLE 2. Distribution of Reports of Educational Problems for the Severity 1 and Severity 2 Children[a]

Educational Problem	Subject Group	
	NF[b] Severity 1	NF Severity 2
Speech problem	2	4
Developmental delay	3	2
Learning disability	5	4
Special education	4	4
Total	14	14

[a] Values represent number of occurrences of each finding. Multiple findings were observed for some children.
[b] NF, neurofibromatosis.

TABLE 3. Distribution of Positive Clinical Findings for the Severity 1 and Severity 2 Children[a]

Clinical Finding	Subject Group	
	NF[b] Severity 1	NF Severity 2
Lisch nodules	5	7
Other eye problems	0	3
EEG	2	0
CT scan	0	2
Tissue biopsy	0	1
Total	7	13

[a] Values represent number of occurrences of each finding. Multiple findings were observed for some children.
[b] NF, neurofibromatosis.

feelings of hostility, anxiety, fatigue, etc., were expected, the responses indicated that the subjects were quite unperturbed. This finding adds to the overall reliability of the test results.

Clinical Tests

A complete analysis of the histories, physicals, and specialized clinical examinations is beyond the scope of this paper. Two elements of the clinical battery examined are educational problems reported during the history and/or physical and the results of the specialized clinical evaluations.

Reported Educational Problems. Educational difficulties reported during the history/physical included whether the child experienced a significant developmental delay, such as extremely late development in muscle tone or in walking, or had speech problems or diagnosed learning disability, and whether the individual had ever been enrolled in any special or remedial education program. None of the nine unaffected individuals had experienced any of these educational problems; six of the eight severity 1 and five of the eight severity 2 individuals had experienced at least one of them.

Incidence of educational problems was spread quite evenly across the two groups and across the four categories of problems, as shown in Table 2. Twice as many severity 2 children as severity 1 children were reported to have speech problems (commonly delayed speech, or lisp); however, one-half of the children in either group were reported to be receiving special education, generally in the form of resource room assistance.

Clinical Examinations. Findings from the ophthalmological examination for Lisch nodules and other eye problems (e.g., focusing problems), audiological examinations, EEG, CT scan (for the NF group), and tissue biopsy (as indicated) were recorded. Five of the nine unaffected individuals had at least one finding on the clinical examinations; there were two children with other eye problems and four children with abnormal EEG recordings (all of which were reported as mildly and diffusely slow for chronological age).

Six of the eight severity 1 and seven of the eight severity 2 individuals had at least one clinical finding; the number and nature of these findings are shown in Table 3. Almost twice as many positive results were obtained in the severity 2 children than in the severity 1 children. In general, more positive ophthalmological findings were obtained with the more severely affected individuals, in terms of Lisch nodules and in terms of other eye problems. More significantly, two abnormal CT scans were obtained in the more severely affected children, one being a temporal cyst, the other bilateral optic gliomas.

It may be argued that the more severe manifestations of NF could be the cause of poorer psychological functioning by the children, particularly the two children with diagnosed brain abnormalities. However, the psychological profiles of these two children are comparable to the other severity 2 children (i.e., the child with the optic glioma was not particularly poor in visual-spatial processing). Thus, although the more severe clinical manifestations observed in these children are certainly related to poorer psychological functioning, without additional subjects, we would not like to make a direct, causal interpretation of these findings.

Correlational Analyses

Analyses of Spearman rank order correlations between the different subject groups and the dependent measures are completely consistent with the group differences. For correlations, we compared the unaffected versus combined groups of NF children and the severity 1 versus severity 2 children. Statistically significant correlations ($p < 0.05$) are found in Table 4. All but two of the correlations for the psychological measures are negative, for the first set of correlations, indicating poorer performance by the NF children. The Trail Making B correlation is positive because the NF children required more time to complete the task. In addition, the PAMS Aggression correlation is higher because the NF children demonstrated more aggressiveness than their unaffected siblings. The two significant K/ABC correlations in the second set are also negative, and indicate poorer performance by the severity 2 children. The correlations for the clinical measures are positive for both sets, indicating that the affected individuals, for the first set of correlations, or the severity 2 children, for the second set, are more likely to have a positive finding for the particular measure.

Considering the rank correlations for the unaffected versus NF children, two meaningful variables stand out as most predictive of NF, namely, the Spatial Memory subtest of the K/ABC Simultaneous scale, and the Aggression scale of the PAMS. To evaluate the importance of these predictors, we calculated multiple correlations for the ranked data.

TABLE 4. Statistically Significant[a] Spearman Rank Order Correlations

Measure	Unaffected/NF[b]	Severity 1/ Severity 2
Wechsler Intelligence Scales		
Verbal	−0.62	
Performance	−0.48	
Full Scale	−0.59	
Kaufman Assessment Battery for Children Scales		
Sequential	−0.62	
Number Recall	−0.55	
Word Order	−0.60	
Simultaneous	−0.55	
Triangles	−0.65	
Spatial Memory	−0.74	−0.74
Photo Series	−0.69	
Mental Processing Composite	−0.61	−0.47
Achievement	−0.46	
Reading-Decoding	−0.56	
Das Tasks		
Trail Making B	0.57	
Auditory Serial Recall	−0.43	
Memory for Designs	−0.46	
Profile of Adolescent Mood States Questionnaire		
Aggression	0.71	
History		
Speech difficulty	0.41	
Learning disability	0.55	
Special education	0.50	
Clinical Examination		
Lisch nodules	0.76	
Other eye problems		0.47

[a] $p < 0.05$.
[b] NF, neurofibromatosis.

Combined, these two variables account for 72% of the variance in predicting whether an individual is or is not affected with NF, S.E.E. = 0.29. Presence of Lisch nodules is also highly correlated with NF. As this characteristic is diagnostic of NF, the relationship is not clinically meaningful.

As stated previously, the Spatial Memory subtest is representative of visual-spatial integration, and the Aggression measure can be indicative of hyperactivity. Thus, the most characteristic psychological aspects of NF seem to be a difficulty in visual-spatial integration and mild hyperactivity/aggressiveness. More important, this visual-spatial integration deficit can be used to distinguish between mildly and more severely affected individuals, accounting for 55% of the variance in predicting severity, S.E.E. = 0.38.

GENERAL DISCUSSION

In this exploratory study, subjects with neurofibromatosis (NF) were easily distinguished from their unaffected siblings in terms of intelligence, sequential and simultaneous cognitive processing, planning, aggressiveness, educational difficulties, and specific clinical findings. What is more important, the two groups of NF subjects were further differentiated in terms of Performance IQ, sequential and simultaneous processing, and positive clinical findings. These results suggest that the cognitive deficit of NF children increases as a function of severity of the clinical manifestations. In addition, even though the children probably are less severely affected, this study supports Rosman and Pearce's hypothesis about the static nature of the intellectual handicap associated with NF.[6]

A profile of cognitive and psychological functioning can be developed for both mildly and more severely affected children: compared with their average-achieving, unaffected siblings, mildly affected children demonstrate slightly lower IQs, although still well within the average intelligence range, and perform slightly lower on tests of cognitive processing. These children are also slightly more aggressive and/or hyperactive than their unaffected siblings. In short, these children display a slight, generalized decrement in psychological functioning.

In contrast, the more severely affected children have even lower IQs, still within the low average range, however, with slightly higher verbal skills and lower performance on tests of cognitive processing, particularly those tests that require visual-spatial integration. These more severely affected children seem more likely to be classified as learning disabled, as described by Eliason.[4]

Given their slightly lower performance on the various intellectual and cognitive tasks, and the number of educational problems reported, mildly affected children are certainly at risk for learning disabilities. Even mild hyperactivity and/or aggressiveness can impair learning, especially when a child has mild, generalized deficits in cognitive processing. These mildly affected NF children need to be monitored carefully for the development of attention deficit disorder and/or behavioral problems. In addition, they may require remedial instruction to ensure that they do not slip too far in academic achievement.

The more severely affected children demonstrating poor visual-spatial integration are at a much greater risk for learning disability. This sort of deficit would lead such a child to be classified as having a visual-perceptual disability. This type of learning disability can affect all forms of school activity, from difficulty in learning, remembering, reading, and writing words and letters to difficulty in understanding and reproducing numbers and arithmetic procedures. These children often need specialized learning assistance, either in the form of a resource room or a segregated class for learning disabled children. The more severely affected children in the present study have a visual-perceptual disability that is comparable to that demonstrated by the children in Eliason's study; all of her subjects had been referred to a Learning Disorders Clinic for learning and/or behavioral problems.[4]

One critique of this study concerns the unequal proportions of males and females in the NF and unaffected groups. Although any replication should include a control for sex, it is most unlikely that there are any intervening effects of sex in this study. All measures obtained for the control children (two males, seven females) are within normal limits and, therefore, the control children represent a remarkably average comparison group. Compared with the controls, there are relatively more males in the affected group (nine males, seven females). However, no differences as a function of sex were obtained for the combined NF group. Thus,

the unbalanced numbers of males and females does not likely reflect any bias toward learning disabilities affecting a greater proportion of males.

Although only an initial exploration with very few subjects, this study has begun to enhance our understanding of the nature of the mental handicap associated with NF. If further research supports these exploratory findings, the determination of a relationship between degree of cognitive deficit and severity of clinical manifestations can provide important diagnostic and prognostic information for pediatricians and psychologists. The nature and extent of clinical involvement and visual-spatial integration problems should be evaluated carefully to determine appropriate educational placement and/or remediation. In this way, any learning disability or intellectual deficit associated with NF can be minimized.

Acknowledgment. This research was supported by a grant to Connie K. Varnhagen and Susan Lewin from the Central Research Fund, University of Alberta. Travel and housing for out-of-town participants was provided by the Neurofibromatosis Association of Alberta. The contributions of the Edmonton Genetics Clinic, University of Alberta Hospitals, and the Developmental Disabilities Centre are greatly recognized. Appreciation is also due to the numerous clinicians and psychologists who completed the testing. Most grateful appreciation is extended to the participants and their families. Finally, the authors wish to thank John Opitz for his thorough reading of an early draft and three anonymous reviewers for their helpful comments.

REFERENCES

1. Crowe FW, Schull WJ, Neel JV: A Clinical, Pathological, and Genetic Study of Multiple Neurofibromatosis. Springfield, IL, Charles C Thomas, 1956
2. Wander JV, Das Gupta TK: Neurofibromatosis. Curr Probl Surg 14:1–81, 1977
3. Riccardi VM: von Recklinghausen neurofibromatosis. N Engl J Med 305:1617–1627, 1981
4. Eliason MJ: Neurofibromatosis: Implications for learning and behavior. J Dev Behav Pediatr 7:175–179, 1986
5. Fienman NL, Yakovac WC: Neurofibromatosis in childhood. J Pediatr 76:339–346, 1970
6. Rosman NP, Pearce J: The brain in multiple neurofibromatosis (von Recklinghausen's disease): A suggested neuropathological basis for the associated mental defect. Brain 90:829–838, 1967
7. Riccardi, VM: Neurofibromatosis as a model for investigating hereditary vs. environmental factors in learning disabilities, in Arima M, Suzuki Y, Yabuuchi H (eds): The Developing Brain and Its Disorders. Tokyo, University of Tokyo Press, 1984, pp 211–221
8. Samuelsson B, Akesson HO: Neurofibromatosis: An epidemiological, clinical and genetic study in Gothenburg, Sweden, in Berg JM (ed): Perspectives and Progress in Mental Retardation, vol 2, Biomedical Aspects. Baltimore, MD, University Park Press, 1984, pp 63–72
9. Samuelsson B, Axelsson R: Neurofibromatosis. Acta Derm Venereol (Stockh) 95(Suppl):67–71, 1981
10. Vernon PE: Intelligence: Heredity and Environment. San Francisco, CA, WH Freeman & Co., 1979
11. Wechsler D: Wechsler Preschool and Primary Scale of Intelligence (WPPSI). New York, The Psychological Corporation, 1967
12. Wechsler D: Wechsler Intellgence Scale for Children — Revised (WISC-R). New York, The Psychological Corporation, 1974
13. Wechsler D: Wechsler Adult Intelligence Scale — Revised (WAIS-R). New York, The Psychological Corporation, 1981
14. Kaufman AS, Kaufman NL: Kaufman Assessment Battery for Children. Circle Pines, MN, American Guidance Service, 1983
15. Das JP, Kirby JR, Jarman RF: Simultaneous and Successive Cognitive Processes. New York, Academic Press, 1979
16. Das JP: Planning: Theoretical considerations and empirical evidence. Psychol Res 41:141–151, 1980
17. Armitage SG: An analysis of certain psychological tests used for the evaluation of brain damage. Psychol Monogr 60: No 277, 1946
18. Graham FK, Kendall BS: Memory-for-Designs Test: Revised general model. Percept Mot Skills 11:147–188, 1960
19. Eysenck HJ, Eysenck SBG: Eysenck Personality Questionnaire (Junior & Adult). San Diego, CA, Educational and Industrial Testing Service, 1975
20. McNair DM, Lorr M, Droppleman LF: Profile of Mood States. San Diego, CA, Education and Industrial Testing Service, 1971
21. Schokman-Gates K: The development and investigation of Pre-Adolescent Mood Scale. Presented at the Psychologists' Association of Alberta Annual Conference. Edmonton, Alberta, Canada, October, 1983
22. McGill R, Tukey JW, Larsen WA: Variations of box plots. Am Stat 32:12–16, 1978
23. Kaufman AS, Kaufman NL: Kaufman Assessment Battery for Children: Interpretive Manual. Circle Pines, MN, American Guidance Service, 1983