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Growth curve analyses of neuropsychological profiles in children with neurofibromatosis Type 1: Specific cognitive tests remain "Spared" and "Impaired" over time

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Abstract

Cognitive deficits in neurofibromatosis Type 1 (NF-1) have been documented in both the verbal and visuospatial domains. Previous investigations from our laboratory have determined a specific pattern of "spared" (Picture Arrangement, Picture Completion, and Rapid Automatized Naming) and "impaired" (Judgment of Line Orientation, Vocabulary, and Block Design) performance on cognitive measures in this population when compared to sibling-matched controls in pairwise designs. Growth curve analyses were conducted on these repeated measures in 19 patients with NF-1 and their siblings to investigate the longitudinal course and growth pattern of these spared and impaired measures. Results indicated that over time children with NF-1 do not catch up to their siblings on impaired measures, and they continue to perform similarly to their siblings on the spared measures. With respect to growth rates, on average across the 6 cognitive measures there was no significant difference between the groups. However, the variation *among* families for level of performance was estimated to be larger than variation among siblings within a family for 2 out of 6 cognitive measures (i.e., providing for these 2, Vocabulary and Rapid Automatized Naming, evidence of substantial familial correlation), suggesting that there is need to consider NF-1 associated deficits within a familial context. (*JINS*, 2002, *8*, 838–846.)

Keywords: Genetics, Cognition, Longitudinal analyses

INTRODUCTION

Neurofibromatosis Type 1 (NF–1) is a common autosomal dominant genetic disorder with an incidence of 1:4000 in the population (Huson, 1989, 1994; Stumpf et al., 1988). About half of the NF-1 cases are sporadic, *versus* familial, in nature. National Institutes of Health Consenses Conference diagnostic criteria, two or more of which must be present for diagnosis of NF-1, include *café au lait* macules, nerve tumors within or below the skin, Lisch nodules, optic glioma, a bony lesion, freckling in armpit or groin area, and/or a first degree relative with NF-1. Other neurological signs/symptoms of NF-1 that are not currently within the diagnostic criteria are megalencephaly, T2 weighted hyperintensities (unidentified bright signals seen on magnetic resonance imaging scans; UBS), and elevated *N*-acetylaspartate/choline ratio in the thalamus (Cutting et al., 2000a; Denckla et al., 1996; North et al., 1997; Wang et al., 2000). In addition to these neurological abnormalities, the NF-1 gene appears to have an impact on cognition; specifically, there is a much higher prevalence rate of learning disabilities in the NF-1 population than in the general population (30–65% *vs.* 5–17.5%; North et al., 1997; Riccardi, 1981; Shaywitz & Shaywitz, 1999).

While it was originally thought that the type of learning disability associated with NF-1 was nonverbal, or visuospatial, in nature (Eliason, 1986), recent investigations have established that children and adolescents with NF-1 have

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reading and language deficits. These language and reading deficits are much more dramatic than their visuospatial/nonverbal deficits (e.g., Brewer et al., 1997; Mazzocco et al., 1995) and are similar to those children in the general population who have reading disabilities (Cutting et al., 2000b). However, children with NF-1 are differentiated from children in the general population who have reading disabilities by the presence of additional deficits in broad language as well as visuospatial areas (Cutting et al., 2000b).

Another distinctive feature that has been observed in our laboratory in the domain of cognition in NF-1 is the presence of a pattern of "sparing" and "impairing" on certain neuropsychological tests that represent specific cognitive functions in the verbal and nonverbal domain (see Table 2). Previous studies from our laboratory (Hofman et al., 1994; Mazzocco et al., 1995), which have used a sibling matched pair design (see below for discussion of sibling pair matched designs *vs.* randomly selected control group designs), have established that despite the reading, language, and visuospatial deficits in NF-1, there appears to be a consistent pattern of impaired and spared tests across the verbal and nonverbal domains. Within the verbal domain, Rapid Automatized Naming (Denckla & Rudel, 1976) is spared, while Vocabulary (Wechsler, 1974, 1991) is impaired. Within the nonverbal domain, Picture Completion and Picture Arrangement are spared, while Block Design and Judgment of Line Orientation (JLO; Benton et al., 1983) are impaired. Picture Completion and Picture Arrangement are labeled as nonverbal tests because they don't require a verbal response; however, it should be noted that these tasks do imply covert language components (such as, unless the person chooses to point, word retrieval for Picture Completion, and demands for inner language as story narrative for guiding the card sequencing in Picture Arrangement). On the other hand, Block Design and the JLO, which are also considered to be within the nonverbal domain, have fewer implicit word retrieval and inner language demands; thus, they are more likely to be representative of visuospatial ability. It should be noted that exactly *why* children with NF-1 exhibit this distinctive pattern of performance is not clear at this time, as the pattern was derived *empirically* and did not originate from theoretically driven hypotheses. Thus, the explanation behind this distinctive pattern on these measures in children with NF-1, as well as replication of the pattern across laboratories, awaits further study.

Even though this pattern of spared and impaired performance on neuropsychological tests is known to be present in children with NF-1, there have been no investigations of the growth patterns of these cognitive tests within a familial, or sibling pair-wise, design. Thus, it is not known whether performance on these tests remain, respectively, impaired or spared over time. Growth curve analysis provides a way to take into account both continued *absolute lowering* (i.e., impairment) over time as well as possibility of abnormal *patterns of growth* in children with NF-1. Previous investigations (Hofman et al., 1994; Mazzocco et al., 1995) conducted in our Center have utilized a sibling matched pair design. A sibling matched pair design, unlike that which involves a control group from the general population, takes into account familial and environmental factors (Mackintosh, 1998), thus allowing for a clearer determination of the impact of the NF-1 gene on cognition. In this present investigation, we used the sibling design because of our desire to specifically investigate the impact of the NF-1 gene on cognition over time, as well as because of some associated specific areas/questions of interest, which were as follows:

- What is the relative size of variation among siblings within a family as compared to variation among families? This question is important because it addresses the fundamental issue of whether the sibling-matched pair design *is* really essential when studying the impact of a genetic disorder on cognition.
- Do the absolute differences between NF-1 and their siblings on impaired tests remain significant over time? Do the absolute differences between NF-1 and their siblings on spared tests remain nonsignificant over time?
- What are the growth patterns, or developmental trajectories, for these cognitive tests in children/adolescents? Are they different in children with NF-1 *versus* their siblings?

MATERIALS AND METHODS

Research Participants

Children/adolescents in the NF-1 group were originally included in the study if they were between 6 and 16 years old, had received a diagnosis of NF-1, and had an unaffected sibling (or siblings) also between the ages of 6 and 16 years old. Both the child/adolescent with NF-1 and his/her sibling could have no other known neurological disorder that could contribute to having a learning disability. Specific exclusionary criteria for children with NF-1 were presence of optic gliomas and/or other brain tumors. Subjects were recruited from a variety of sources, such as NF-1 clinics, newsletters, and national organizations. (Please see Hofman et al., 1994; Mazzocco et al., 1995 for full descriptions of recruitment procedures and inclusionary/exclusionary criteria.) Since the beginning of the study in 1989, approximately 35 NF-1/sibling pairs have participated in the LDRC project. Participation in the LDRC project includes 1 day of comprehensive psychoeducational (IQ and achievement) and neuropsychological (visuospatial, visual–motor, language, working memory, reading, and reading-related) tests in addition to another day of neuroimaging (a structural magnetic resonance imaging scan) and other neurological tests (e.g., oculomotor testing). The study was approved by the local IRB committee and informed consent (and assent) was obtained for all subjects participating in the study.

The 35 NF-1/sibling pairs who originally participated in the LDRC project were invited to participate in the longitudinal component of the study. To date, approximately 19 families have expressed interest in participating in the lon-

Table 1. Descriptive statistics for NF-1 and sibling groups

Variable	NF-1	Siblings
Mean age and age ranges[1]	9.16 (2.32; range 6–13)	9.14 (2.59; range 6–14)
Mean IQ and IQ ranges[1]	98.74 (12.20; range 80–127)	110.71 (12.13; range 89–136)
Gender	16 males, 3 females	13 males, 8 females

[1]*Note.* Age ranges and mean IQ and IQ ranges are from the initial visit.

gitudinal component of the study; of these 19 NF-1 sibling pairs (note that two "pairs" actually were triplets and had 2 nonaffected siblings and 1 child with NF-1), 7 have been seen only once, 2 have been seen twice, and 10 have been seen between three and five times (see Analyses section for the rationale as to why we included subjects seen less than three times). Subjects initially completed the comprehensive 2 days of cognitive and neurological testing described above; thereafter, every alternate year the comprehensive cognitive battery was re-administered, with between-year visits consisting of an abbreviated battery of tests (which included the impaired and spared tests). Socioeconomic status (SES) was estimated by the Hollingshead (1975); the mean Hollingshead score for 18 of the 19 families (1 family did not complete the Hollingshead questionnaire) was 49.56 (SD = 10.58), with 8 of the families in the highest SES category (Level I), 7 scoring at Level II, 2 at Level III, and 1 at Level IV. The racial distribution of the group was predominately White (17 of the 19 pairs), with only 2 non-White families, 1 African American and the other biracial, in the group. Mean age and age ranges and mean IQ (and IQ ranges) at the initial visit, as well as gender distribution, for children with NF-1 and their siblings are listed in Table 1.

Neuropsychological Measures

Neuropsychological measures were selected based upon previous findings (Mazzocco et al., 1995) that NF-1 is associated with a certain pattern of sparing and impairing on specific tests; a brief description of each measure and its spared or impaired status is provided in Table 2. All analyses were conducted using raw scores (age was accounted for in the statistical model; see Analyses section below). For the four subtests (Vocabulary, Picture Arrangement, Picture Completion, and Block Design) that were administered from the Wechsler Intelligence Scales (Wechsler, 1974, 1981, 1991), one of three tests/versions were administered, depending on the age of the child/adolescent and/or when the subject participated in the study (i.e., the first phase of the LDRC, 1989 to 1994 or the second phase of the LDRC, 1995 to 2000). The versions of the Wechsler Intelligence Scales utilized were (1) the Wechsler Intelligence Scales for Children–Revised (WISC–R; Wechsler, 1974; for children younger than 17 years who were seen any time from 1989 to 1994); (2) Wechsler Intelligence Scales for Children–Third Edition (WISC–III; Wechsler, 1991; for children younger than 17 years who were seen after 1994); or (3) Wechsler Adult Intelligence Scales–Revised (WAIS–R; Wechsler, 1981; for adolescents 17 and older and adults). The four subtests are very similar from all three Wechsler Intelligence Scales; however, any possible effects of using different versions were accounted for statistically (see Analysis section).

Analyses

Growth curve analyses were conducted on the cognitive tests in patients with NF-1 and their siblings in order to investigate the longitudinal nature and the growth pattern of these spared and impaired tests. All 19 NF-1/sibling pairs were used in analyses; subjects who had missing data points (i.e., were unable to complete certain cognitive tests/

Table 2. Description of "impaired" and "spared" neuropsychological tests

Tests	Description
"Spared" tests	
Rapid Automatized Naming	The ability to name quickly within a well learned restricted category of visual stimuli (e.g., letters and numbers)
Picture Completion	Attention to and recognition of missing visual details in pictures
Picture Arrangement	A visual sequencing and language related task involving the sequencing of pictures to tell a story
"Impaired" Tests	
Block Design	Timed task of assembling blocks to replicate a two-dimensional geometric model
Vocabulary	Word knowledge and oral expression; requires formulating definitions of words
JLO	Requires one to determine the orientation of two lines from 11 different possible orientations

Note. JLO = Judgment of Line Orientation.

subtests because of testing was discontinued due to fatigue or extreme difficulty with the test) were excluded for the particular analysis with that cognitive test. Two siblings and 1 child with NF-1 did not receive Picture Completion on their third visits; 1 sibling did not receive Rapid Automatized Naming on his/her second visit; 2 children with NF-1 did not receive the JLO on their first visit; and 1 child did not receive the JLO on his/her second visit. We used random effects regression models to describe the relationship of each cognitive score with age, NF-1 status (either affected or unaffected), test type (WISC–R, WISC–III, WAIS–R), and gender. A random effects model was used, rather than traditional linear regression, for several reasons. Linear regression ignores the association among measurements from the same child and the association among measurements from the same family (correlation of observations of cognitive tests from the same child arises because of the heterogeneity among children and families in their true growth curves) and would therefore yield inefficient parameter estimates and incorrect inferences (Liang & Zeger, 1993). In addition, children also entered the study at different baseline cognitive scores and therefore would be likely to have different growth rates. A random effects model is therefore a reasonable description of the data if collection of baseline cognitive scores and growth rates can be thought of as sampling from a distribution across families and children.

The random effects model[1], fitted separately for each of the cognitive tests, was as follows: $Y_{ijk} = (B_0 + b_{0ij}) + [(B_1 + b_{1i})(\text{age}_{ijk} - 14)] + B_2(\text{age}_{ijk} - 14)^2 + B_3\text{NF-1}_{ijk} + B_4\text{Test1}_{ijk} + B_5\text{Test2}_{ijk} + B_6\text{gender}_{ijk} + B_7[(\text{age}_{ijk} - 14) \times \text{NF-1}_{ijk}] + \epsilon_{ijk}$

- age_{ijk} = the age of ith family's jth child at kth visit (Note: age was centered at 14 years to avoid collinearality)
- $\text{NF-1}_{ijk} = 1$ if the child had NF-1 and 0 if the child did not have NF-1
- $\text{Test1}_{ijk} = 1$ if the test was the WISC–R or 0 if not
- $\text{Test2}_{ijk} = 1$ if the test was the WISC–III or 0 if not
- $\text{Gender}_{ijk} = 1$ if the child was a boy and 0 if the child was a girl

In the model, Y_{ijk} represents the cognitive scores for the ith family, the jth child, and the kth measurement. $B_0, B_1 \ldots B_7$ are fixed effects, which are constant; b_{0ij} and b_{1i} are random effects, which follow a bivariate normal distribution. The above random effects model has two important features. First, based on the exploratory data analysis (not shown), we assumed that the growth rates between a child/adolescent with NF-1 and his/her unaffected sibling were the same across families. Second, we used all 19 sibling pairs in the analysis, even when only 10 of them had three or more visits. The rationale for this is that children/adolescents with less than three visits still inform us about the differences in the cognitive scores at the earlier visits. They also provide useful information about the variability across people and over time in the cognitive scores.

[1]Note that test type predictors were not included in the model for Rapid Automatized Naming and JLO cognitive tests.

RESULTS

From the results in Table 3 the following can be seen:

1. There were no significant differences between males and females on any cognitive measure.
2. Subjects scored higher on WISC–R subtests than WAIS–R subtests for Vocabulary, Block Design, Picture Arrangement, and Picture Completion; subjects scored higher on WISC–III subtests than WAIS–R subtests for Block Design, Picture Arrangement, and Picture Completion; subjects scored higher on the WISC–R Vocabulary and Block Design subtests than on WISC–III Vocabulary and Block Design subtests. (Note that this suggests that there were significant differences between the different versions of the tests; however, having these terms in the

Table 3. *P*-values for terms in the model each cognitive test

Effect	Estimate	Standard error	*P*-value
Test			
Vocabulary			
(age − 14)	1.9198	.3268	.0001
$(\text{age}_{ijk} - 14)^2$	−.1842	.0476	.0026
NF-1 status	−6.6336	1.4130	.0001
$(\text{age}_{ijk} - 14) \times$ NF-1 Status	−.1084	.2895	.7101
Block Design			
(age − 14)	3.0668	.4638	.0001
$(\text{age}_{ijk} - 14)^2$	−.1237	.0644	.0810
NF-1 status	−12.5644	3.6898	.0015
$(\text{age}_{ijk} - 14) \times$ NF-1 Status	−.7302	.4661	.1251
JLO			
(age − 14)	.5524	.2020	.0194
$(\text{age}_{ijk} - 14)^2$	−.1194	.0303	.0023
NF-1 status	−4.7290	1.3368	.0010
$(\text{age}_{ijk} - 14) \times$ NF-1 Status	.3602	.2459	.1505
Picture Arrangement			
(age − 14)	2.0746	.4904	.0014
$(\text{age}_{ijk} - 14)^2$	−.2142	.0758	.0165
NF-1 status	−1.6420	2.7929	.5599
$(\text{age}_{ijk} - 14) \times$ NF-1 Status	.1262	.5033	.8032
Picture Completion			
(age − 14)	1.0643	.2185	.0005
$(\text{age}_{ijk} - 14)^2$	−.1030	.0342	.0118
NF-1 status	−1.0060	.8786	.2596
$(\text{age}_{ijk} - 14) \times$ NF-1 Status	−.2050	.1951	.3002
Rapid Automatized Naming			
(age − 14)	−1.5702	.3843	.0018
$(\text{age}_{ijk} - 14)^2$	.3002	.0475	.0001
NF-1 status	.6032	1.7255	.7284
$(\text{age}_{ijk} - 14) \times$ NF-1 Status	.2014	.3301	.5452

Note. JLO = Judgment of Line Orientation.

model essentially covaries, or controls, the influence of the different tests on the rest of results.)

3. The linear age term in the model, $(B_1 + b_{1i})(\text{age}_{ijk} - 14)$ was significant for all cognitive tests, suggesting, not surprisingly, that over time there is growth in these cognitive tests.
4. The quadratic age term, $B_2(\text{age}_{ijk} - 14)^2$, was significant for all cognitive tests *except* Block Design, suggesting (also not surprisingly) that over time there is a tendency for these tests to begin to level out in their growth. Note that there was a trend toward significance for the quadratic term for Block Design ($p = .0810$).
5. The coefficient for $(\text{age}_{ijk} - 14) \times \text{NF-1}_{ijk}$ was not significant for all six cognitive tests; therefore, on average, NF-1 children and their siblings show the same growth rates across these six tests.
6. Children/adolescents with NF-1 scored significantly lower on Vocabulary, Block Design, and JLO ($p = .0001$, $p = .0015$ $p = .0010$, respectively) than their unaffected siblings (see Figure 1).
7. Children/adolescents with NF-1 did not score significantly lower than their siblings on Picture Arrangement, Picture Completion, and Rapid Automatized Naming ($p = .5599$, $.2596$, $.7284$, respectively; see Figure 2).

Other results, concerning families' level of performance and growth rates, were obtained by examining results of b_{1i} in the random effects model (shown above). Ideally, we seek to estimate the variation in the level (intercept) and trend (slope) in cognitive functioning measures among children within and across families. For the level of functioning, there would be two variance components, the first describing differences among siblings within a family, σ_1^2,and the second quantifying differences among families, σ_2^2. The correlation of siblings is then given by $\sigma_1^2/(\sigma_1^2 + \sigma_2^2)$.

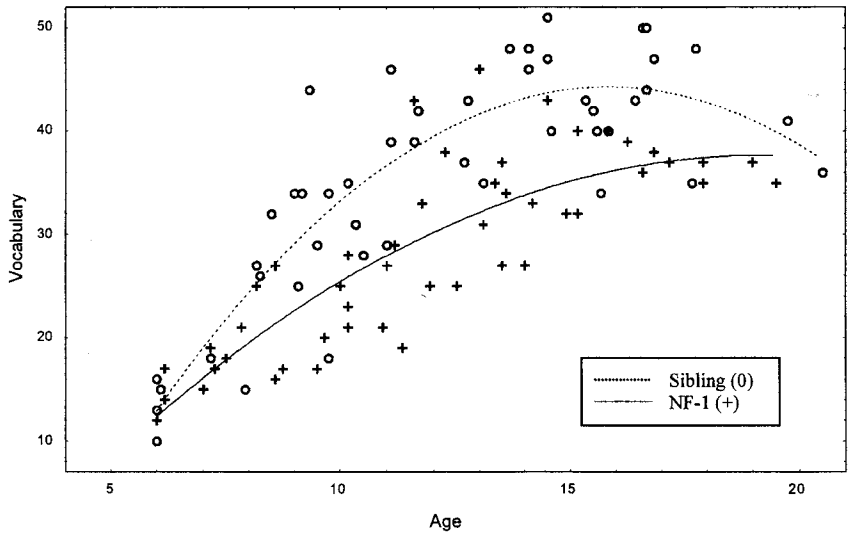
We attempted to estimate a model that allows for variation across children in both the level and trend in functioning. However, there was insufficient evidence in the data set. Hence, we have estimated the two variance components for only the level of functioning. Table 3 shows the results for each of the six measures.

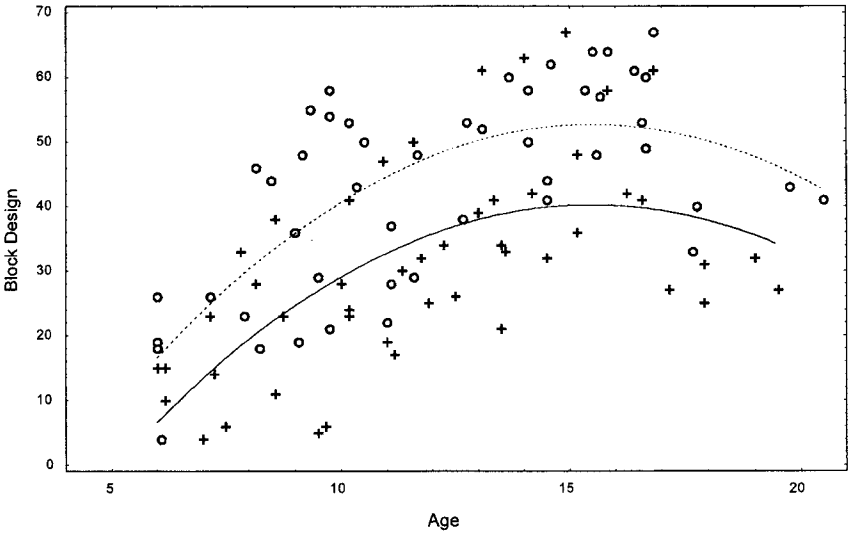
For Picture Completion, Picture Arrangement, Block Design, and Judgment of Line Orientation, we estimate that the variation between siblings from a given family is substantially larger than the differences among families. For these variables, the correlation among siblings in the level of functioning will be small. That is, siblings do not appear to be more similar in level of performance to each other than unrelated children. However, for Vocabulary and Rapid Automatized Naming, the estimated variation among families is relatively larger, providing evidence of greater familial correlation. Caution in interpreting these patterns is warranted as the data set is small and the variance components are not well determined because of large confidence intervals.

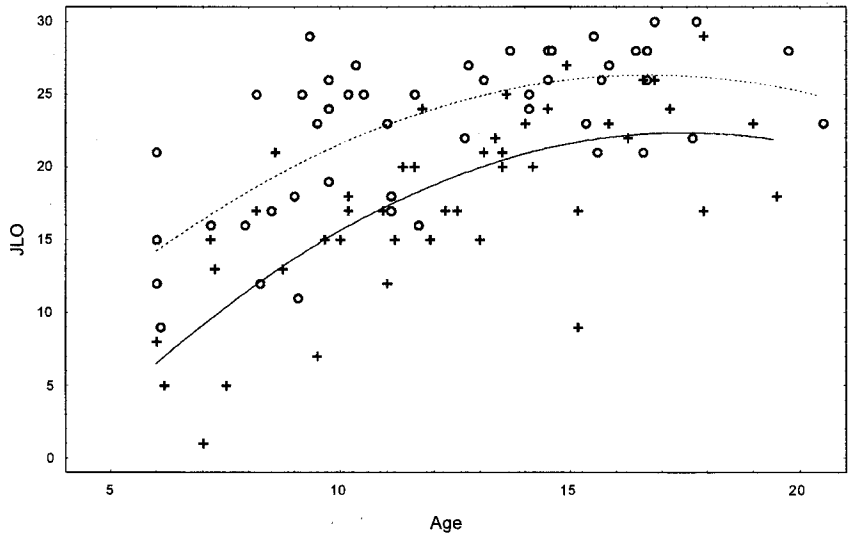
DISCUSSION

This study was conducted to examine the patterns of growth on certain cognitive measures over time in children with NF-1, as compared to their unaffected siblings. In terms of overall growth in all children (both NF-1 and siblings), not surprisingly, there were increases in performance on all the cognitive measures over time; in addition, for all the cognitive measures except Block Design (which showed a trend towards significance), there was a gradual leveling off of growth, thus suggesting that children have a tendency to gain more at an earlier age and that growth is not as rapid as children/adolescents get older. In terms of differences between children/adolescents with NF-1 and their siblings, results indicated that those cognitive tests that were spared remained so over time, as did those tests that were impaired, thus suggesting that the profile of spared and impaired tests is stable, with a specific pattern of cognitive strengths and deficits characterizing NF-1 over the long term. However, it was not only of interest to determine whether these cognitive tests remained stable in their spared/impaired status, but also whether children with NF-1 had different patterns, or trajectories, of growth in these tests as compared to their siblings. Results indicated that over time, children with NF-1 do *not* appear to have patterns of growth different from their siblings on these cognitive tests. Thus, while children/adolescents with NF-1 continue to have lower scores as they get older, their pattern of growth is similar to that of their siblings. (In other words, if thought of mathematically, the graph of cognitive scores for children with NF-1 and their siblings are parallel in slope, but the lines for the scores for children/adolescents with NF-1 are lower in their y-intercept value than those of their siblings.) Finally, it was found that there is evidence for greater familial correlation than for unrelated children for the level of performance on two out of the six cognitive tests.

Because children/adolescents with NF-1 continue to have this certain spared/impaired cognitive pattern without a deviant pattern of growth, there are potential clinical implications from the findings of this study. It may be useful to monitor and/or provide early intervention within certain areas of cognitive development in children/adolescents with NF-1; therefore, providing opportunities for vocabulary enrichment as well as guided experience and practice with visuospatial material early may be worthy of consideration to decrease the chances of academic difficulties and/or frustrations arising. Likewise, early identification of areas of strength is an important consideration so that these areas can be capitalized on and used to compensate for weaknesses throughout cognitive development. Of course, it should be kept in mind that even though a score represents a weakness within a child's cognitive profile and within a genetic/familial context, it may *not* be below average when compared with national norms; however, the presence of a *relative* deficit could instigate issues of frustration and low self-esteem with regard to academics.

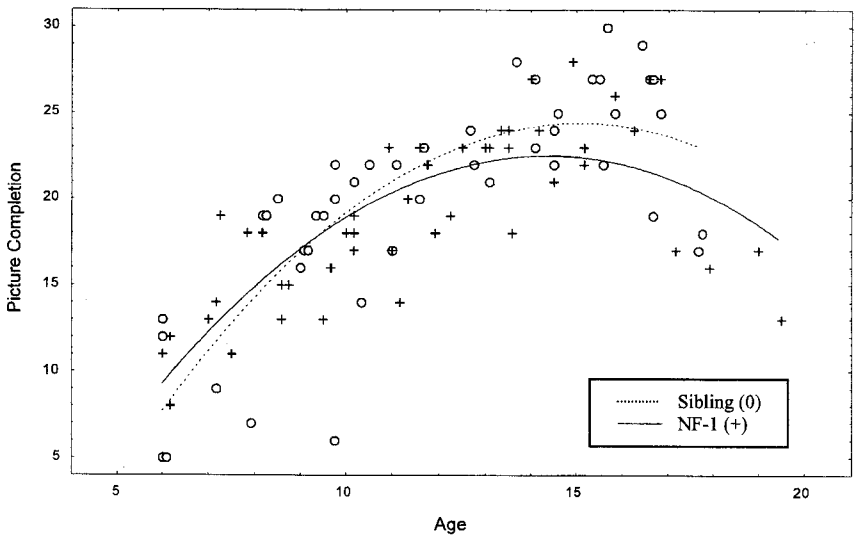


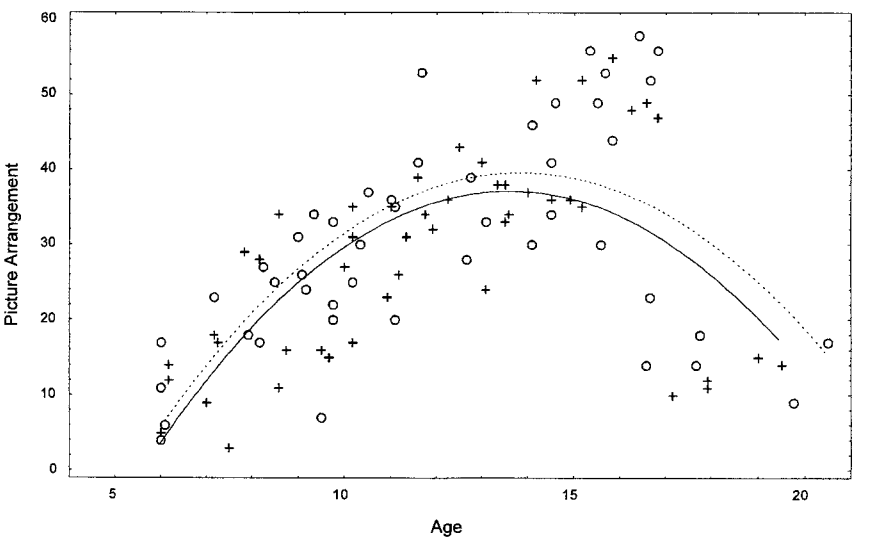




Note: JLO = Judgment of Line Orientation

Fig. 1. Growth curves for "impaired" functions





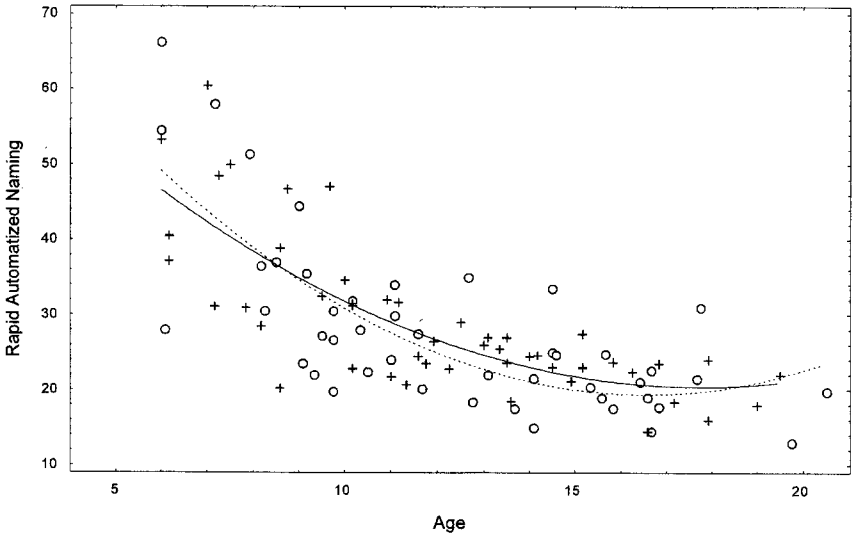


Fig. 2. Growth curves for "spared" functions

An important implication of this study for future studies of cognitive deficits in genetic disorders is the finding that for *certain* cognitive tests, there is evidence for greater familial correlation than for unrelated children for the level of performance. Exactly why we found evidence for greater familial correlation for Vocabulary and Rapid Automatized Naming, and not for Picture Completion, Picture Arrangement, Block Design, and Judgment of Line Orientation is not entirely clear. While those cognitive measures that showed family-specific growth rates were those tests that were verbal in nature, on which performance is often associated with SES (see Sattler, 1992), *post-hoc* analyses indicated that Vocabulary and Rapid Automatized Naming performance was *not* associated with SES. One of the reasons for this finding may have been that our sample was relatively similar in SES. Nonetheless, these findings suggest that the familial association for these certain tests may be intrinsic in nature for this sample; to this end, it has been suggested that verbal abilities are genetically influenced (see Sattler, 1992). Regardless of the reason for this inconsistency between different tests, the fact that we cannot predict which cognitive performances are strongly familial suggests the need to study the specific phenotypic impact of the NF-1 gene on cognition in a familial context. Furthermore, these findings suggest the need to use the same methodology when studying cognitive phenotypes in other genetic disorders.

Despite some of the important implications from this study, there are limitations to the present study. Because of the small sample size, there was possibility insufficient power to detect differences in growth rates between NF-1 and siblings. In addition, while it would have been ideal to estimate variation not only in the level of performance but also the growth of cognitive functioning measures across families, there was insufficient evidence in the data set to estimate growth, so that only level of performance could be estimated. It also should be noted that some of the subjects followed longitudinally were members of the sample upon which earlier reports of the pattern of sparing and impairing of certain cognitive functions in children with NF-1 was based.

Future studies may benefit from examining the longitudinal course of more specific language functions, such as syntax, semantics, and phonology, since reading and language deficits have been shown to be prominent in NF-1 (Cutting et al., 2000b; Mazzocco et al., 1995; North et al., 1997). A more detailed examination of the development of language functions with multiple tests representing one cognitive function (i.e., several tests of vocabulary) could determine if measures examined in this study are actually representative of spared and impaired cognitive *functions* in the NF-1 population (i.e., not just performance on specific *tests*). Thus, future longitudinal studies would not only allow for further clarification of exact deficits (and strengths) in cognitive functions, especially in the language domain, but also greatly aiding in planning early intervention (as discussed above). Another issue for future research is the influence over time of attention deficit hyperactivity disorder (which has recently been confirmed to be much more prevalent in NF-1 than in the general population; Koth et al., 2000) on cognitive functioning in NF-1. In addition, longitudinal cognitive data should be considered in conjunction with neuroimaging data; it may be that different compartments and/or areas of the brain (such as white matter volumes, increased in children/adolescents with NF-1 according to Cutting et al. (2000c) and Said et al. (1996) are differentially associated with performance on spared and impaired tests/functions.

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