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Cognitive and Psychosocial Phenotype of Young Children with Neurofibromatosis-1

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Abstract

Children with neurofibromatosis-1 (NF1), a neurodevelopmental disorder resulting from a mutation of the NF1 gene (17q11.2), often have difficulties with learning and attention, but there is little research in the early childhood years. In this study, the cognitive and psychosocial functioning of 40 young children with NF1 (ages 3 through 6) was examined and compared both to normative data and to a contrast group comprised of unaffected siblings and community members matched for age and socio-economic status (n = 37). Children with NF1 showed significantly weaker cognitive abilities across all domains and for the vast majority of subtests. Consistent with research in older children, a variety of patterns of intra-individual strength and weakness were present for young children with NF1. Few significant group differences in psychosocial functioning were observed, but the children with NF1 showed significantly greater functional communication problems than did the unaffected group. Overall, the results indicate that in participant groups matched for age and socioeconomic status, cognitive vulnerabilities are evident for close to half of young children with NF1, with some relations to psychosocial functioning, particularly functional communication, attention problems and social skills.

Keywords

Behavior; Attention; Cognition; Communication disorders; Child-preschool; Genetic diseases; Inborn

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INTRODUCTION

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Neurofibromatosis-1 (NF1) is a neurocutaneous disorder resulting from a single gene mutation with a prevalence of 1 in 3000. The NF1 gene codes for neurofibromin, which is involved in a neurodevelopmental cascade regulating neuronal cell growth. NF1 is associated with a range of medical features including cutaneous and plexiform neurofibromas and skeletal abnormalities, and with cognitive, learning, and attention problems. Most current research about cognitive and psychosocial functioning has been conducted with older children and adolescents with NF1. There are relatively few studies of the cognitive and psychosocial functioning of preschool children with NF1 (Lorenzo, Barton, Acosta, & North, 2011; Sangster, Shores, Watt, & North, 2011; Soucy, Gao, Gutmann, & Dunn, 2012). This study provides further in-depth examination of cognitive and psychosocial functioning in the preschool years in comparison to a well matched group of unaffected children, as a foundation to understanding the developmental trajectory of cognitive functioning and learning in NF1.

Cognitive Functioning

A general lowering of IQ in individuals with NF1 relative to both the general population and to unaffected siblings has been observed (Cutting, Clements, Lightman, Yerby-Hammack, & Denckla, 2004; Ferner, Hughes, & Weinman, 1996). Up to 60% of people with NF1 ultimately show learning problems. In a review of recent studies, Levine, Materek, Abel, O'Donnell, and Cutting (2006) found evidence for impairment in all academic areas including word reading, reading comprehension, mathematics, and spelling relative to siblings and other unaffected children. However, unlike some genetic disorders with consistent and distinctive psychological phenotypes (e.g., Williams or Fragile-X syndromes), there is no consensus on a distinctive cognitive or behavioral profile with clear sensitivity or specificity in NF1.

Difficulties with language, visuospatial skills, nonverbal reasoning, and motor development have all been observed. Earlier investigations of cognitive skills were suggestive of stronger verbal abilities and weaker nonverbal abilities (Legius et al., 1995; Wadsby, Lindehammar, & Eeg-Olofsson, 1989). Ozonoff (1999) has suggested that visuospatial deficits are the most common area of difficulty seen in NF1, with decrements in performance on the Judgment of Line Orientation task as the most consistent finding (e.g., Cutting, Koth, & Denckla, 2000; Moore, Slopis, Schomer, Jackson & Levy, 2000). Deficits on other visuospatial tasks are sometimes (Dilts et al., 1996; Eliason, 1986), but not always, observed (Eldridge et al., 1989; North et al., 1994). Verbal deficits are also commonly present (Cutting et al., 2004; Mazzocco et al., 1995; Moore et al., 1996; North et al., 1994). While a universal pattern is not shown, the majority of individuals with NF1 have at least one domain of cognitive deficit (Hyman, Shores, & North, 2005, 2006).

Psychosocial Functioning

On broad measures of psychosocial functioning, higher levels of problem behaviors are typically reported for children with NF1 than for unaffected siblings or in comparison to

normative populations and elevated rates of difficulties are observed (e.g., Descheemaecker, Ghesquière, Symons, Fryns, & Legius, 2005; Johnson, Saal, Lovell, & Schorry, 1999; Martin et al., 2012; Moore & Denckla, 2000). Findings regarding internalizing symptoms are inconsistent. Social difficulties are described for children with NF1 using a variety of methods, including parent and teacher report and peer ratings (Barton & North, 2004; Dilts et al., 1996; Huijbregts & Sonneville, 2011; Noll et al., 2007). Attention problems are the most consistently occurring difficulty (e.g., Payne, Hyman, Shores, & North, 2011; North, Hyman, & Barton, 2002). One-third to half of older children with NF1 meet diagnostic criteria for Attention Deficit/Hyperactivity Disorder (ADHD; Kayl, Moore, Slopis, Jackson, & Leeds, 2000; Koth, Cutting, & Denckla, 2000). Notably, children with comorbid ADHD and NF1 have shown significantly poorer parent-reported social skills (Barton & North, 2004) and weaker intellectual functioning (Mautner, Kluwe, Thakker, & Leark, 2002; Koth et al., 2000) than children with NF1 without ADHD.

Research in Young Children

There has been sparse research about the cognitive or psychosocial functioning of young children with NF1. Using an infant and toddler measure, Lorenzo and colleagues (2011) found that cognitive difficulties can be observed as early as two or three years of age. A very recent study using a parent report measure found that difficulties are more often reported in older children than in younger children (Soucy et al., 2012; Wessel, Gao, Guttman, & Dunn, 2012). In a small sample of 4- and 5-year-old children, Sangster and colleagues (2011) found overall decrements in intellectual functioning and spatial abilities. Attention problems assessed by a lab-based measure, but not parent ratings, were significantly related to intellectual functioning, and group differences in parent ratings for attention were not present once maternal education was statistically controlled. No significant group difference in psychosocial functioning was found, with the exception of the Somatization scale. However, the sample size was small (17–24 children with NF1 depending on the analysis), the unaffected group was on average 6 months younger than the NF1 group, of higher socio-economic status, and higher than average intellectual functioning (M IQ = 111.1; *SD* = 12.5). While the authors conducted analyses controlling statistically for these group differences, an a priori study design accounting for these factors is an important next step.

Rationale and Hypotheses

Given that up to 60% of people with NF1 show attention or learning problems in adulthood, further well-designed studies on cognitive and psychosocial functioning in children with NF1 are warranted. In the current study, we use measures designed to assess specific patterns of cognitive ability and psychosocial functioning in the preschool years and include a well-matched unaffected contrast group. In addition to knowing the mean performance levels in a representative sample of preschool children with NF1, an examination of the percentage of these children who have difficulties in particular aspects of cognitive and psychosocial functioning is important to provide the clinician or parent with a sense of the *likelihood* of impaired performance within particular areas for an individual child; examination of mean ratings alone may obscure the distribution of difficulties given that close to half of children with NF1 appear not to have difficulties. Hypotheses are as follows: (1) Overall intellectual functioning as well as verbal, nonverbal reasoning, and especially

spatial abilities will be weaker for children with NF1 than for unaffected contrast group. (2) Children with NF1 will show more areas of cognitive difficulty than children in the unaffected group, with most children with NF1 showing at least one area of impairment; (3) A characteristic or distinctive pattern of relative strengths and weaknesses is not expected; (4) Children with NF1 will show greater psychosocial difficulty than children in the contrast group, especially related to attention problems; (5) stronger cognitive functioning is expected to be related to stronger social skills and fewer attention problems. The current study adds to the existing literature by including a contrast group matched for socioeconomic status, thereby experimentally rather than statistically controlling for this variable which has been related to cognitive skills in NF1 in prior research. It also includes a different measure of cognitive abilities than used previously, providing a measure of the robustness of prior findings. Finally, in addition to providing a description of psychosocial functioning in preschool children, the relations of psychosocial and cognitive functioning in young children with NF1 are also examined.

METHOD

Participants

Demographic information about the participants is presented in Table 1. Participants were 40 children diagnosed with NF1, between the ages of 3 to 6 years and an unaffected contrast group of 37 children without NF1, ages 3 to 6 years. The contrast group was made up of 16 siblings of the children in the NF1 group and 21 children recruited from the community[1]. Siblings were included regardless of overall intellectual functioning. Participants recruited from the community were only included if intellectual functioning fell within the range seen in the NF1 group, to ensure that children with high intellectual functioning were not overrepresented. The participant groups did not differ in age ($t(75) = .63$; $p = .53$) or gender distribution ($\chi^2(1,77) = .02$; $p = .88$). Distribution across age of the NF1 and contrast group was similar, with somewhat greater representation of 3- and 4-year-olds than 5- and 6-year-olds in both groups. While the representation of particular minority groups differed slightly across the participant groups, the percentage of minority representation did not differ significantly ($\chi^2(1,77) = 1.15$; $p = .28$). The majority of the participants' mothers, in both groups, had some post high-school education (87.5% of the NF1 sample, 95% of the contrast sample), and the groups were matched for maternal education ($\chi^2(1,77) = 1.17$; $p = .28$) and socioeconomic status (based on the Hollingshead Index; $t(73) = 1.00$; $p = .32$). Only one participant with NF1 was prescribed medication for attention problems. For 16 participants with NF1 the mutation was familial (i.e., inherited from the parent), and sporadic (i.e., a spontaneous mutation not present in either parent) for 24.

[1]Comparison to siblings is ideal because it controls for a host of familial and environmental variables. The number of children with NF1 in this sample with siblings in this age range was small; therefore, we supplemented this sample with children from the community. Inclusion of the siblings in this sample only works against the hypothesis of expected group differences, as siblings would be expected to be more similar to the children with NF1 given shared familial and other environmental influences (Huijbregts & de Sonneville, 2012). No group differences were found between the siblings and community members in age, SES, or overall cognitive functioning, supporting combining these groups.

Measures

The Differential Ability Scales – Second Edition Early Years Form (DAS-II; Elliot, 2007) was administered to assess cognitive functioning. This is a comprehensive, individually administered battery of cognitive abilities for individuals 2½ through 17 years; the Early Years Form is appropriate for ages 3 through 8 with strong demonstrated reliability, validity, standardization, and excellent floor and ceiling levels. It yields an overall composite score (General Cognitive Abilities; GCA) akin to the Full Scale IQ, as well as Verbal Ability, Nonverbal Reasoning Ability, and Spatial cluster scores.[2] Supplementary diagnostic subtests include measures of Digit Span Forward (DF) and Early Number Concepts (ENC). Ipsative analysis of patterns of intra-individual performance are provided; significant relative strengths and weakness at both the cluster and subset level are identified, taking into account reliability and intercorrelations among subtests. The DAS-II was chosen because of its strong validation and usefulness for capturing strengths and weaknesses and its heavy usage in behavioral phenotyping research (e.g., Baron, Erickson, Ahronovich, Baker, & Litman, 2011; Bishop, Guthrie, Coffing, & Lord, 2011).

The Behavior Assessment Scale for Children – Second Edition (BASC-2; (Reynolds & Kamphaus, 2005) was administered to parents to assess psychosocial functioning, including Externalizing Problems (Hyperactivity and Aggression scales), Internalizing Problems (Anxiety, Depression, and Somatization scales), and Adaptive Skills (Adaptability, Activities of Daily Living (ADL), Social Skills, Leadership, and Functional Communication (FC) scales). The Behavior Symptoms Index consists of the Atypicality, Attention Problems, and Withdrawal scales, as well as the Hyperactivity, Aggression, and Depression scales. This measure has strong reliability and validity data. The form appropriate to the child's age was administered.

Procedure

Participants with NF1 and their siblings were recruited at medical NF clinic visits (rather than at a learning disabilities clinic) through consecutive referrals at yearly medical check-ins. Procedures of the study were briefly explained by the clinical geneticist. Once the family indicated an interest in participating, a member of the study staff explained further and, either in person or by phone, briefly reviewed the informed consent, and arranged the appointment time and location. Non-sibling contrast group participants were recruited *via* fliers in areas frequented by families such as libraries, coffee shops, and YMCA's. Questionnaire measures were mailed to participants in advance of the assessment appointment, including the consent form. Informed consent was reviewed at the assessment appointment. Questionnaire measures were collected and immediately reviewed for missing data. Each appointment lasted approximately 3 hours with breaks and included parent interview measures, cognitive assessment with the child (always administered first), and a variety of experimental measures administered to the child in a quiet room. This work was conducted in compliance with all IRB requirements.

[2]For children under 3½, only Verbal and Nonverbal Cluster scores.

RESULTS

Given the number of comparisons made, the False Discovery Rate approach (Benjamini & Hochberg, 1995; Pike, 2011) was used to determine a q-value adjusted for the number of comparisons within each set of analyses with multiple comparisons, and these q-values were compared with alpha = .05 to determine statistical significance. Tests for equal variances were examined (at alpha level of .01) and pooled variances were used when appropriate. Effect sizes are also reported. For continuous data, *D* was used for effect size, interpreted as follows: 0 to .14 negligible, .15 to .39 small, .40 to .74 medium, .75 and above large (Cohen, 1988). For categorical data analysis, *Phi* was used to determine effect size, interpreted as follows: 0–.10 weak, .11 to .15 moderate, and .16 to .25 strong, and > .25 very strong. For examination of intra-individual strengths and weaknesses, an alpha level of .05 was used.

Cognitive Functioning

Group-based analysis—Repeated measures analyses of variance were conducted to examine group differences in cognitive ability and patterns of cognitive strength and weakness at the cluster and subtest levels separately. Significant main effects of group were seen at the cluster [$F(1,56) = 16.41$; $p < .001$] and subtest [$F(1,46) = 12.35$; $p < .001$] levels, with significantly weaker cognitive functioning seen for the children with NF1 (see Table 2 for descriptive statistics at the cluster and subtest level). Effect sizes were large. No group × cluster interaction [$F(2,112) = 1.29$; $p = .280$] or group × subtest interactions [$F(7,40) = 1.12$; $p = .365$] were observed, indicating that the groups do not systematically differ in patterns of strengths and weaknesses.

Case-based analysis—There was no difference between the groups in the frequency of particular patterns of cluster strengths or weakness, although a trend for more children with NF1 to show weaker Spatial than Nonverbal abilities was observed (see Table 4). Group differences in the proportion of children showing performance one standard deviation (*SD*) below the mean on the clusters and subtests were examined (see Table 3). At the cluster level, significant group differences, with children with NF1 more often showing difficulty, were observed for GCA, Verbal, Nonverbal, and Spatial functioning. Forty-five percent of the children with NF1 (but only one child in the contrast group) showed at least one cluster score more than 1 *SD* below the mean. At the subtest level, significant group differences in the frequency of difficulties were observed for both spatial tasks (Pattern Construction and Copying) and for Naming Vocabulary (NV) but not Verbal Comprehension (VC) within the verbal cluster, and for ENC but not DF within the diagnostic subtests. No significant group differences in the frequency of difficulty were reported for the nonverbal reasoning subtests.

The number of children in each group showing performance one *SD* or more below the mean on one, two, or three subtests was compared. More children with NF1 (55%; $n = 22$) performed one *SD* below the mean on at least one subtest than in the contrast group (21.6%; $n = 8$; $\chi^2(1,77) = 9.01$; $p = .003$; *Phi* = .34). More children with NF1 (27.5%; $n = 11$) performed one *SD* below the mean on at least two subtests than contrast children (2.7%; $n = 1$; $\chi^2(1,77) = 8.98$; $p = .003$, *Phi* = .34). Finally, more children with NF1 (17.5%; $n = 7$)

performed one *SD* below the mean on at least three subtests than children in the contrast group ($n = 0$; $\chi^2(1,77) = 7.12$; $p = .008$; *Phi* = .30).

Relations to age, gender, and familial status—There were no significant bivariate correlations between cluster standard scores or subtest *t*-scores with age for either group. No significant gender differences were observed. Within the NF1 group, the effect of familiality was explored. There were no statistically significant effects at the cluster or subtest levels.

Psychosocial Functioning

Group comparisons—Two multivariate analyses of variance were conducted to examine group differences in psychosocial functioning, one at the broad index level and the other at the scale level. Descriptive statistics are in Table 5. No significant effect of group was observed at the broad scale level ($F(4,70) = 1.86$; $p = .127$). At the scale level, a main effect of group was observed ($F(12,62) = 2.04$; $p < .05$). As indicated in Table 5, the children with NF1 showed significantly weaker FC skills than did the contrast group. While there was no significant group difference in attention problems, a medium effect size was observed. No other significant group differences were observed.

Case-based analysis—In addition to examining mean performance, to gain a sense of the proportion of children with NF1 who show psychosocial difficulties, the number of children in each group showing parent ratings one *SD* or more above the standardization mean (for problem behavior scales) or below the mean (for adaptive scales) was examined (see Table 6). There were no significant group differences in the frequency of problem behavior or adaptive difficulties.

Relations to age, familial status, and cognitive abilities—Bivariate correlations between Index and Scale *t*-scores and age were examined, yielding no significant correlations. No significant effects of familial status on parent ratings were observed. Bivariate correlations between cognitive ability clusters and psychosocial functioning *t*-scores were examined. For the group as a whole, significant correlations between Adaptive skills and both GCA ($r(75) = .331$; $q = .032$) and Verbal skills ($r(75) = .392$; $q = .008$) were seen. At the scale level, significant correlations between FC and both GCA ($r(76) = .368$; $q = .018$) and Verbal Ability ($r(76) = .434$; $q = .001$) were found.

Given that FC emerged as an area of relative challenge for the children with NF1, DAS predictors of FC were examined separately using a regression approach, with group by cognitive ability interactions also examined. At the cluster level, Verbal cluster score was a significant predictor of FC ($\beta = .334$; $t = 3.44$; $p = .002$) with no significant group by predictor interaction. At the subtest level, there were trends toward effects of DF ($\beta = .314$; $t = 1.96$; $p = .056$) and NV ($\beta = .277$; $t = 1.74$; $p = .089$), with no significant group by subtest interactions.

Given the a priori expectation of a relation between intellectual functioning and both attention problems and social skills for children with NF1, regressions were conducted to examine effects of cognitive abilities on Attention Problems and Social Skills separately, including examinations of group by cognitive ability interactions. Verbal cluster score was a

significant predictor of both Attention Problems (β = −.338; t = 2.15; p = .036) and Social Skills (β = −.411; t = 2.69; p = .010) with no significant group by cognitive ability interactions.

DISCUSSION

The purpose of the current study was to examine the presence of cognitive vulnerabilities that lay the foundation for the developmental cascade toward learning and psychosocial difficulties in children with NF1. As emphasized by Karmiloff-Smith (2008) “genetic mutations are more likely to affect low-level cognitive processes that will have differing, cascading effects on different domains as development proceeds over time” (Karmiloff-Smith, 2008, p. 697). As hypothesized, evidence for a mild downward shift in global intellectual functioning was found, and difficulties in at least one broad area (e.g., verbal, nonverbal, or spatial skills) were present for close to half (45%) of the sample. As expected based on prior research with older children, no specific and distinctive pattern of cognitive difficulties emerged. Rather, it appears that the NF gene mutation confers a general vulnerability for cognitive difficulties that is observable even in the preschool years. One novel finding is that functional communication was identified as a difficulty, with suggestive evidence of relations to expressive language and memory. Even though psychosocial problems were generally low, as expected, stronger social skills and fewer attention problems were observed in children with stronger intellectual functioning.

For some genetically based neurodevelopmental disorders, a distinctive pattern of cognitive functioning emerges that is consistent across affected children. NF1 appears to confer a general vulnerability to cognitive difficulties that is manifest differently across children. Age differences were not generally apparent, but this sample included participants in a narrow age range. Longitudinal research is important to examine whether the sometimes subtle difficulties seen by children with NF1 become more pronounced over time, particularly with increased demands as the children enter elementary school. The variable cognitive phenotype highlights the potential predictive utility of identifying individual patterns of strength and weakness at an early age using a measure that captures functioning across many domains, so that early interventions can be individualized. The lack of group by predictor interactions suggests that cognitive contributions to psychosocial functioning also do not follow a distinctive pattern for children with NF1. It remains likely, therefore, that interventions tailored specifically to children with NF1 may not be needed, but rather that interventions useful for other children with similar difficulties are likely to be beneficial. Practitioners working with children with NF1 will need to elucidate mechanisms underlying each child’s difficulty on such tasks (i.e., spatial, verbal, motor, executive, attention, or likely a combination) to recommend the most suitable interventions. No brain-based markers of risk within the NF1 population have been definitively identified. Likely related to the significant phenotypic variability in NF1, investigations of brain-behavior relationships have yielded conflicting findings. Brain abnormalities associated with NF1 include brain tumors, macrocephaly, and so-called “unidentified bright objects (UBO),” (Cutting et al., 2004; Kayl & Moore, 2000). While some studies suggest a connection between UBOs (particularly in the thalamus) and cognitive impairment, Moore and colleagues (1996) caution that individuals with NF1 without UBOs can and do show learning difficulties. Combining

careful phenotyping with brain-imaging techniques may ultimately prove fruitful to gain a more nuanced sense of the neurocognitive profile of individual children with NF1. Recent studies have highlighted the potential diagnostic utility of MRI for young children with NF1 (Sabol et al., 2011), with high prevalence of UBOs in young children with NF1, however brain-based markers of cognitive risk within the NF1 population have not been definitively identified. There is good reason to expect neurocognitive difficulties in children with NF1, as there is an identified role for neurofibromin in regulating GABA release, which is critical to prefrontal-striatal communication and long-term potentiation in the hippocampus (Shilyansky et al., 2010), in turn affecting learning, attention, working memory, and processing speed, and general recruitment of brain areas for cognitive tasks (Costa & Silva, 2002; Cui et al., 2008; Genova, Hillary, Wylie, Rypma, & Deluca, 2009; Schneider et al., 2010).

A novel finding is that difficulties with functional communication were the most evident psychosocial challenge, suggesting that the language difficulties of children with NF1 translate into real-word difficulties with verbal communication. These communication challenges have the potential to set the stage for continued social and learning difficulties. Additional clarification of the language functioning of children with NF1 using more comprehensive language measures is also needed given the high rates of reading difficulties in the NF1 population and the role of language impairments as a risk factor for reading challenges. Other contributors to functional communication included rote verbal memory, which is often included in studies of attention in older children with NF1 (e.g., Philip & Turk, 1996) and has more broadly been tied to attention problems (Hellwig-Brida, Daseking, Keller, Petermann, & Goldbeck, 2011). This is the first study with young children with NF1 to use a digit span task, with evidence that this task may be useful to identify difficulties even in young children with NF1.

Group differences in parental reports of attention problems were not observed. The lack of clear attention difficulties reported by parents in these young children may be partly due to the high variability in attention functioning in the preschool years, and/or to the lower demands for sustained attention placed on preschool-aged children. It may also be a function of a somewhat small sample size, given that a moderate effect size was indeed observed. Regardless, the lack of clear difference suggests that attention problems as measured by parent report are not striking in these early childhood years. Further work examining attention in young children with NF1 is warranted to determine whether there are subtle behavior patterns present that may be predictive of later attention difficulties, and longitudinal work to track the point at which attention difficulties become evident would be useful. It has been suggested that inattentive rather than hyperactive symptoms characterize the attention difficulties of children with NF1 (Ferner et al., 1996; North et al., 1995; Hofman et al., 1994), and the developmental literature regarding inattention suggests that such symptoms are indeed more rarely observed in young children than in the schoolage years (Lahey et al., 1994; Smidts & Oosterlaan, 2007). The rote memory difficulties seen here, as well as the functional communication challenges, may be indications of attention problems. While in older children digit span is considered a measure of verbal memory span, in younger children this measure may approximate working memory function, which

is closely tied to inattention conceptually (e.g., Alloway, Gathercole, Kirkwood, & Elliott, 2009).

Difficulties with foundational number concept knowledge were also observed, placing children with NF1 at risk for later mathematics-related learning problems. There is ample evidence that the number knowledge of preschoolers is related to later mathematics abilities (Mazzocco & Thompson, 2005; Aunola, Leskinen, Lerkkanen, & Nurmi, 2004; Jordan, Kaplan, Ramineni, & Locuniak, 2009), with evidence that development of number specific skills depends on development of domain general abilities as well (e.g., Ansari et al., 2003; Halberda & Feigenson, 2008). Using a longitudinal design, LeFevre and colleagues (2010) found that linguistic abilities, spatial attention, and quantitative skills independently contribute to concurrent early number knowledge, which in turn predicts later math achievement. Hyman and colleagues (2006) found that some school-aged children with NF1 have specific deficits in academic and neuropsychological skills despite average intellectual functioning, while others have more general difficulties across areas. The Early Number Concepts measure included here likely taps both domaingeneral and domain-specific skills, both of which likely contribute to later mathematics knowledge. Inclusion of more purely domain-specific assessment as predictors of number knowledge in future research (e.g., subitizing ability, large number acuity; Mazzocco, Feigenson, & Halberda, 2011) would more effectively allow for examination of both domain-specific and domain-general pathways toward later learning difficulties for children with NF1.

CONCLUSION

In sum, close to half of the children with NF1 in this sample displayed some cognitive vulnerability at the broad cognitive cluster level, with considerable variability in the specific areas of difficulty. This replicates prior research with a larger sample and a different measure adding to the robustness of the findings. By controlling more carefully for age and SES in the research design rather than relying on statistical approaches, moreover, this study used a design that effectively rules out some critical alternative explanations of prior research findings. In contrast to some prior work (Sangster et al., 2011), difficulties with spatial functioning were indeed observed here, and do not appear to be accounted for by maternal education or socioeconomic status. Finally, while rates of psychosocial difficulties were generally low, cognitive and psychosocial functioning appear to be interrelated even in young children with NF1, pointing to the potential utility of cognitive assessment at identifying children at risk for psychosocial difficulty. Although functioning remains in the average range for the vast majority of children with NF1, the presence of even subtle cognitive difficulty appears to confer risk for everyday challenges affecting the quality of life of children with NF1 and their families.

While this is one of the larger studies of young children with NF1 involving direct child assessment, an even larger sample size would nevertheless be useful, especially given expected variability in cognitive and psychosocial functioning in the preschool years and the sometimes subtle nature of the cognitive and attention difficulties seen in children with NF1. Research examining even earlier precursors of the cognitive difficulties observed is also needed. Bernstein (2010) explains, “that the neuropathologies of childhood occur in the

context of dynamic change over the course of development and thus the pathology becomes part of the developmental course. Genetic and structural disorders set up conditions for alternative developmental trajectories" (p. 21). As the brain matures, the low-level global changes that are observed may very well affect local processing at some point down the line. While this study adds to research indicating that difficulties can be seen in early childhood that set the stage for potential future difficulties, further examination of cognitive functioning in infants is warranted to observe even earlier potential precursors of cognitive vulnerability (e.g., visual-spatial perception, attention). Further longitudinal study of cognitive functioning including the preschool years remains an important backdrop for brain-based studies. Future research should clarify the developmental trajectory of cognitive and psychosocial functioning, and also of brainbehavior relations in children with NF1 with attention to both domain-general and domain-specific factors. Longitudinal research examining the timing, placement, and natural history of neurological abnormalities, and most importantly, relations between these brain findings and neurocognitive functioning, is warranted.

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Table 1

Demographic data

	NF1 (*n* = 40)	Unaffected (*n* = 37)
Gender:		
Male	26	25
Female	14	12
Age (mean, *SD*)	4 years, 6 months (*SD* = 14.46)	4 years, 8 months (*SD* = 13.87)
Ethnicity		
Caucasian	27	29
Other	13	8
African-American	6	2
Latino	4	1
Asian	1	2
Mixed Ethnicity	2	3
Maternal level of education		
High school	5	2
Higher education	35	35
Hollingshead SES Index	34.71 (*SD* = 16.52)	38.36 (*SD* = 15.02)

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Table 2

Descriptive statistics for NF1 and unaffected groups on the DAS-II, differences from normative mean, and effect sizes

	NF1			Unaffected group			
Cluster/subtest	***N***	**Mean**	***(SD)***	***N***	**Mean**	***(SD)***	***D***
GCA	40	92.55	(12.30)**	37	104.16	(8.84)*	1.08
Verbal	40	95.23	(14.16)*	37	104.97	(10.04)*	0.79
Nonverbal Reasoning	40	92.75	(12.38)***	37	100.78	(10.37)	0.70
Spatial	31	93.16	(12.38)**	27	104.15	(9.73)	0.98
Verbal Comprehension	40	45.27	(9.44)**	37	50.05	(7.08)	0.57
Naming Vocabulary	40	48.78	(9.36)	37	55.49	(7.59)**	0.78
Picture Similarities	40	46.35	(6.68)**	37	50.51	(7.63)	0.58
Matrices	31	46.13	(7.48)*	27	49.37	(8.94)	0.40
Pattern Construction	40	48.03	(10.34)	37	53.97	(6.65)**	0.68
Copying	31	43.10	(8.31)***	27	50.56	(7.13)	0.96
Digits Forward	40	45.00	(11.42)*	36	51.61	(9.54)	0.62
Early Number Concepts	39	45.00	(7.69)**	23	52.48	(6.63)	0.89

Symbol near mean reflects difference from normative mean;

* $p < .05$;

** $p < .01$;

*** $p < .001$

Table 3

Frequency of Performance 1 standard deviation or more below the mean on DAS-II Clusters and Subtests

Cluster/subtest	NF1	Unaffected	df	χ^2	*p*	*Phi*	*q*-value	
GCA	10/40	0/37	1,77	10.63	.001	.372	.002	**
Verbal	9/40	0/37	1,77	9.43	.002	.350	.003	**
Nonverbal	12/40	1/36	1,77	10.21	.001	.364	.002	**
Spatial	7/31	0/27	1,58	6.93	.008	.346	.008	**
Verbal Comprehension	9/40	3/37	1,77	3.03	.082	.198	.105	
Naming Vocabulary	4/40	0/37	1,77	4.95	.026	.253	.046	*
Picture Similarities	7/40	3/37	1,77	2.22	.136	.170	.153	
Matrices	6/31	2/27	1,58	1.73	.188	.173	.188	
Pattern Construction	10/40	0/37	1,77	10.63	.001	.372	.004	**
Copying	9/31	1/27	1,58	6.49	.011	.334	.025	*
Digits Forward	10/40	3/35	1,75	3.52	.061	.217	.092	
Early Number Concepts	11/39	0/23	1,62	7.89	.005	.357	.015	*

Note.

* $p < .05$;

** $p < .01$; significant difference determined based on *q*-value (FDR derived significance threshold).

Table 4

Percent of participants demonstrating significant differences on DAS-II Cluster Scores

	% with Difference (*n*)					
Comparison	**NF1**	**Unaffected**	**χ^2**	***p*-value**	***Phi***	***q*-value**
Verbal > Nonverbal	17.5 (7)	24.3 (9)	.544	.461	.084	.922
Nonverbal > Verbal	7.5 (3)	8.1 (3)	.010	.921	.011	.949
Nonverbal > Spatial	16.7 (5)	0.0 (0)	4.933	.026	.294	.156
Spatial > Nonverbal	10.0 (3)	25.9 (7)	2.492	.114	.209	.342
Verbal > Spatial	26.7 (8)	25.9 (7)	.004	.949	.008	.949
Spatial > Verbal	13.3 (4)	11.1 (3)	.065	.799	.034	.949

Table 5

Descriptive statistics and group differences on the BASC-II T-scores

	NF1			Unaffected group					
Index/scale	***N***	**Mean**	***(SD)***	***N***	**Mean**	***(SD)***	***t***	***q*-value**	***D***
Externalizing Problems	40	50.50	(10.88)	36	49.72	(10.16)	.32	.749	.07
Internalizing Problems	40	51.40	(9.55)	36	48.06	(8.25)	1.62	.218	.37
Behavioral Symptoms	40	51.63	(10.64)	36	48.92	8.79	1.20	.311	.28
Adaptive Skills	40	47.38	(10.46)	35	50.91	7.14	−1.69	.218	.39
Hyperactivity	40	53.45	(11.73)	36	50.03	9.91	1.37	.370	.31
Aggression	40	47.83	(9.62)	36	49.39	10.05	.69	.620	.16
Anxiety	40	48.60	(9.29)	36	47.97	6.95	.33	.786	.08
Depression	40	51.38	(10.66)	36	49.69	8.75	.75	.620	.17
Somatization	40	53.10	(11.89)	36	47.92	10.31	2.02	.162	.46
Atypicality	40	51.50	(13.59)	36	46.81	8.18	1.80	.162	.41
Withdrawal	40	48.83	(9.11)	36	49.72	9.17	−.43	.786	.10
Attention	40	54.33	(10.22)	36	49.22	9.66	2.23	.114	.51
Adaptability	40	50.88	(9.83)	36	52.50	9.87	−.72	.463	.17
Social Skills	40	48.90	(11.36)	36	50.75	8.96	−.79	.620	.18
Activities of Daily Living	40	46.40	(10.08)	35	48.80	7.77	−1.14	.786	.26
Functional Communication	40	44.38	(10.05)*	36	50.69	7.69	−3.05	.048	.70

Note. Significantly different from normative data in one-sample *t*-test

* $p < .05$;

** $p < .01$,

*** $p < .001$. Data from one participant in the unaffected group was missing entirely, and data from a second was missing for Activities of Daily Living, which is included in the Adaptive Skills index.

Table 6

Frequency of ratings 1 standard deviation or more away from the mean on BASC-II indices and scales (higher for Problem Scales, lower for Adaptive Scales)

Cluster/scale	NF1	Unaffected	df	χ^2	*p*-value	*q*-value	*Phi*
Externalizing Problems	10/40	5/36	1,76	1.47	.224	.298	−.139
Internalizing Problems	8/40	3/36	1,76	2.03	.149	.298	.149
Behavioral Symptoms	7/40	7/36	1,76	.05	.827	.827	.025
Adaptive Skills	9/40	2/35	1,75	4.20	.040	.160	.298
Hyperactivity	11/40	6/36	1,76	1.28	.258	.554	−.130
Aggression	8/40	5/36	1,76	.50	.480	.576	−.081
Anxiety	3/40	3/36	1,76	.02	.893	.893	.015
Depression	8/40	5/36	1,76	.50	.480	.576	−.081
Somatization	9/40	4/36	1,76	1.73	.188	.554	−.151
Atypicality	6/40	3/36	1,76	.81	.369	.554	−.103
Withdrawal	6/40	3/36	1,76	.81	.369	.554	−.103
Attention	12/40	6/36	1,76	1.86	.172	.554	−.151
Adaptability	6/40	4/36	1,76	.25	.617	.673	−.057
Social Skills	8/40	3/36	1,76	2.08	.149	.554	−.166
Activities of Daily Living	9/40	5/36	1,75	.830	.362	.554	−.105
Functional Communication	10/40	3/36	1,76	3.71	.054	.554	−.221