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Cognitive Profile of Children with Neurofibromatosis and Reading Disabilities

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Abstract

A large percentage of children with Neurofibromatosis Type 1(NF-1) have learning disabilities, often in the realm of reading. Previous studies have indicated that children with NF-1 show a neuropsychological profile similar to idiopathic reading disabilities (IRD); however, studies typically have not subdivided children with NF-1 into those who do and not have RD (NF+RD and NFnoRD, respectively). The current study examined the cognitive profile of children with NF-1 with and without RD and compared them to children with IRD as well as to typically developing readers (Controls). Findings showed that children with NF+RD performed similarly to children with IRD on phonological, rapid naming, and reading comprehension measures; however, children with NF +RD displayed pronounced visual spatial deficits as compared to IRD and Control groups. In addition, when comparing the NF-1 groups to each other as well as to the CNT and IRD groups, the current study reported that there were no oral language differences; lack of findings in the realm of oral language was attributed to the fact that groups were equated on IQ. Overall, findings suggest that a more refined classification of children with NF-1 may be helpful for tailoring academic interventions.

Keywords

Neurofibromatosis; Reading Disabilities; Learning Disabilities; Cognitive; Neuropsychology

Neurofibromatosis Type 1 (NF-1) is a genetic disorder that has an incidence of 1:3,500 and is equally pervasive across ethnicities and gender. Currently, about 30% to 50% of the cases are due to spontaneous mutation, whereas the remainder of are due to familial mutation. A clinical diagnosis of NF-1 must include two or more of the following: six or more cafe au lait macules; two or more neurofibromas, or one plexiform neurofibroma; freckling in the axilla or inguinal region; an optic glioma; two or more Lisch Nodules; a distinct osseous lesion; and a first degree relative with NF-1.

Learning Disabilities in NF-1

Although a specific cognitive profile associated with NF-1 has remained elusive, one consistent finding is that Learning Disabilities (LDs) and other cognitive and behavioral difficulties are much more prevalent in the NF-1 population than in the general population, with approximately 70 percent showing LDs and/or behavioral difficulties such as Attention Deficit Disorder and other neuropsychological deficits (Koth, Cutting, & Denckla, 2000; Mautner, Kluwe, Thakker, & Leark, 2002; Moore, 2009; Noll et al. 2007; Rosser & Packer, 2003).

Initially, the cognitive profile of children with NF1 was characterized as “nonverbal” because most individuals with NF-1 show impairment in visual perceptual (specifically visuospatial) functioning. Although it is true that most children with NF-1 show visuospatial impairment, a variety of other (and more academically relevant) deficits have been noted, including those in the reading, language, and memory domains (Hyman, Shores, & North, 2006; Krab et al. 2008; Levine, Materek, Abel, O’Donnell, & Cutting, 2006; Watt, Shores, & North, 2008). Because of the tremendous importance of reading for life achievement, particularly regarding their children’s school and employment future, weaknesses in reading are often of utmost concern for parents and teachers (Krab et al.; Stine and Adams, 1989), and almost all studies that have examined reading abilities in NF-1 have reported deficits in this area (e.g., Brewer, Moore, & Hiscock, 1997; Cutting, Koth, & Denckla, 2000; Dilts et al., 1996; Hofman, Marris, Bryan, & Denckla, 1994; Mazzocco et al., 1995; Mautner, Kluwe, Thakker, & Leark, 2002; North et al., 1994; North, 2000; Watts et al., 2008). Reading and reading-related deficits reported in NF-1 include phonological processing, decoding, word recognition, and reading comprehension (e.g., Brewer et al.; Cutting et al., 2000; Dilts et al.; Hofman et al.; Mazzocco et al.; North et al.; Watts et al., 2008), which is a similar pattern of deficits that children with reading disabilities (RD) in the general population show. In fact, a study (Cutting et al., 2000) that used a general population of RD as a comparison group for children with NF-1 found that the NF-1 and RD groups were comparable in most areas, with the exception that the NF-1 group showed substantially more visuospatial perceptual deficits as compared to the RD group, as well as lower language abilities.

One limitation to the studies examining the reading abilities of children with NF-1 is that they have not typically specifically classified their NF-1 sample according to whether they do or do not meet RD criteria (e.g., Brewer et al., 1997; Cutting et al., 2000; Mazzocco et al., 1995; Moore, Ater, Needle, Slopis, & Copeland, 1994). While many studies have documented the number of children with NF-1 who meet RD criteria (e.g., Watts et al., 2008; Hyman et al., 2006), most studies have not specifically compared NF-1 groups subcategorized by RD status (or to children in the general population with RD). It may be important to classify children with NF-1 in this manner because children with NF-1 with RD (NF+RD) may represent a different phenotype of NF-1 than children with NF-1 who do not have RD. Because not all children with NF-1 have LDs, certain “protective” or compensatory factors may be associated with not having a LD in NF-1. For example, it may be that children with NF-1 who do not have a RD have stronger language skills (syntax, vocabulary); however, few studies have examined different aspects of oral language skills in depth in children with NF-1 in relation to reading.

Characteristics of RD in the General Population

In the past few decades, researchers have greatly refined the origins of reading failure in the general population of young children, finding that it is largely determined by the ability to read single words, or decode (Adams, 1990; Lyon, 1995, Torgesen, 2000). It has been established that children in the general population who have difficulty learning to decode (Idiopathic Reading Disabilities; IRD) have deficits in phonological processing, or the ability to manipulate the sound structure of the language (Fletcher et al., 1998; Lyon), which leads to difficulties comprehending information from text (Adams; Lyon; Shankweiler, 1999; Torgesen). Furthermore, studies have shown that both IQ achievement discrepancy and low-achieving definitions of IRD are valid, as both show core phonological processing weaknesses (e.g., Foorman, Francis, Fletcher, & Lynn, 1996; Francis, Shaywitz, Stuebing, Shaywitz, & Fletcher, 1996; Stanovich & Siegel, 1994).

It should be mentioned that while it is widely accepted that phonological processing is a core deficit in IRD, some studies have reported that many individuals with IRD have broader oral language deficits (Catts, Fey, Zhang, & Tomblin,1999), and others have reported subtle deficits in visuospatial perception (e.g., Eden, VanMeter, Rumsey, & Zeffiro, 1996; Eden, Stein, Wood, & Wood, 1995). These deficits have been speculated to be associated with abnormalities in the magnocellular pathway (Eden & Zeffiro, 1998). What remains poorly understood is whether there is a relationship (and if so what is the nature of that relationship) between visuospatial perceptual deficits and reading ability or responsiveness of reading disability to different types of reading instruction (Eden, Stein, Wood, & Wood, 1996). How visuospatial deficits relate to RD (if they do at all) may be particularly applicable to children with NF-1 who have poor reading ability, as existence of visuospatial perceptual deficits is a consistent finding across all studies of NF-1.

Current Study

A general aim of the current study was to further understand, within a neuropsychological framework, the characteristics and differences between children with NF-1 as compared to NF+RD, as well as how children with NF+RD compare to children with IRD. To this end, we compared children with NF-1 classified as either having a RD or not to children with IRD and those who were typically developing (Controls). Additionally, in the current study, it should be noted that we were careful to minimize differences in IQ across groups, as some have criticized previous studies as being difficult to interpret because of different IQ levels across groups (Fuchs, 2006). Our specific questions were:

1. Do children with NF+RD show the same patterns of reading and reading-related weaknesses as children with IRD do?
2. Do children with NF-1 in general show weaknesses in oral language, or are the oral language weakness in NF-1 confined to children with NF-1 who also have RD? If so, are these oral language deficits in NF+RD distinct from those often seen in IRD and are any areas of oral language that are particularly problematic?
3. Do NF+RD show any distinct weaknesses in visuospatial skills as compared to either NF-1 without RD (NFnoRD) or IRD? (Based on previous findings we hypothesized that in general children with NF-1 (regardless of RD status) would show weaker visuospatial skills than both the Control and IRD groups, but our specific interest was the degree to which these weaknesses are linked to presence of RD in NF-1.)

Methods

All the participants were selected from a study completed at Kennedy Krieger Institute in Baltimore, Maryland. Children were recruited through flyers distributed in the community, advertisements in local parent and advocacy groups' magazines, as well as through chapters of NF-1 support groups. Potential participants were screened via telephone screening prior to participation and were excluded if they met any of the following criteria: 1) first language other than English; 2) a history of a major psychological illness, previous diagnosis of intellectual disability, or Pervasive Developmental Disorder; 3) a Full Scale IQ score less than 80; 4) an uncorrectable hearing and/or visual impairment; or 5) history of known neurological disorder (e.g., epilepsy, cerebral palsy, or brain tumors). Children with NF-1 were excluded if they had optic gliomas or brain tumors; however, those with T2-Weighted Hyperintensities (or Unidentified Bright Objects; UBOs) were not excluded.

Socioeconomic status was measured by the Hollingshead questionnaire (1975) and the Wechsler Intelligence Scale for Children, Third Edition (WISC-III; Wechsler, 1991) was administered to measure overall intellectual functioning.

Because NF-1 is often associated with ADHD, we designated ADHD research criteria, which were determined by scores from the parent questionnaires. Criteria had to be met on two out of the three assessments for a participant to be categorized as ADHD. The scores from the Attention Problems subscale from the Child Behavior Checklist (CBCL; Achenbach, 1991) and one of the three DSM-IV ADHD scales (Inattentive, Hyperactive-Impulsive, Total) from the Conner's Parent Rating Scale – Long Form (CPRS; Conners, 1997) had to be 1.5 standard deviations above the mean ($t \geq 65$). To meet criteria on the DuPaul ADHD parent questionnaire (Dupaul, Power, Anastopoulos, & Reid, 1998), the raw score had to be equal to or greater than the 94th percentile or the child had to be rated with a two or greater (from three from the likert scale) on six out of the nine symptoms for either the inattentive scale or hyperactivity scale.

The children completed two days of evaluation. Informed consent was obtained from the parents and an assent was completed from the child prior to testing. Additionally, procedures were implemented in accordance with the Johns Hopkins Medical Institutional Review Board. Eligibility for each participant was determined on day one of assessment via cognitive and achievement assessments. On day two, additional neuropsychological and achievement measures were administered. Assessments were administered by staff supervised by doctorallevel faculty.

Participants

Control—The control (CNT) group (N = 36) consisted of participants that did not have any reading difficulties or a diagnosis of NF-1; however, 6 participants in this group met our research diagnosis ADHD criteria[1]. The participants' ages ranged from 7 to 15 years old (mean and standard deviation, 9.59 and 2.30) and consisted of 14 females and 22 males. A single word reading (SWR) composite was calculated by the average of the Basic Reading subtest from the Wechsler Individual Achievement Test – 1st edition (WIAT; Wechsler, 1992), and the Word Attack subtest from the Woodcock – Johnson Tests of Achievement – Revised (WJ-R; Woodcock, McGrew, & Mather, 1989). These two measures were used to assess word recognition and decoding, respectively. To insure that children in the CNT group were typically developing readers, they had to have a SWR score of greater than or equal to the 40th percentile and no discrepancy between IQ and SWR score greater than 22 points; this way of classifying children as typically developing readers is commonly accepted and used in studies of IRD (e.g., Foorman et al., 1996; Shaywitz et al., 2004).

Reading Disability—The IRD group (N = 33) consisted of children with basic reading difficulties; of these, 18 met our research ADHD criteria. The participants' ages ranged from 7 to 12 years old (mean and standard deviation, 9.33 and 1.18) and consisted of 10 females and 23 males. We operationalized IRD in a manner that is consistent with the IRD literature; this literature has demonstrated that discrepancy-based and low-achieving based criteria show common deficits in phonological processing, and thus both are valid ways to define IRD (Foorman et al., 1996; Stanovich & Siegel, 1994). To be classified as IRD, children had to meet low-achieving (i.e., have a SWR score of less than or equal to the 25th percentile; N= 14) or discrepancy-based criteria (i.e., had to have a discrepancy of 1.5 standard deviations or 22 points between the IQ score and SWR, N=19; of these, 15 also met low achieving criteria).

Neurofibromatosis Type 1—Children with Neurofibromatosis Type 1 (NF-1) were included in the study if they had documentation of a previous diagnosis of NF-1. The NFnoRD group (N = 12) consisted of children that did not have any reading difficulties (SWR $\geq$ 40th percentile and no discrepancy greater than 22 points between IQ and SWR); of these, three met our research ADHD criteria. The participants' ages range from 6 to 13 years old (mean

[1]Note that one Control participant had missing data so ADHD status could not be determined.

and standard deviation, 9.56 and 2.13) and consisted of seven females and five males. Of the 12 children with NFnoRD, six had UBOs in various regions, five did not, and one did not have a radiology report available (see Table 1). The NF+RD group (N=13) consisted of children with NF-1 who met criteria for reading difficulties; of these, six met our research ADHD criteria. Similar to the IRD group, all the children had a SWR score of less than or equal to the 25th percentile (N= 8) or had a discrepancy of one-and-a-half standard deviations or 22 points between the IQ score and SWR (N=5; of these two also met low achieving criteria). The participants' ages ranged from 7 to 14 years old (mean and standard deviation, 10.31 and 2.17) and consisted of 4 females and 9 males. Of the 13 children with NF+RD, nine had UBOs in various regions, two did not, and two did not have radiology reports available (see Table 1).

Measures

Reading-Related Measures—The Comprehensive Test of Phonological Processing (CTOPP; Wagner, Torgesen, & Rashotte, 1999) was used to measure children's phonological awareness, phonological memory, and rapid naming skills. The Phonological Awareness index consists of the Elision and Blending Words subtests and evaluates the child's awareness of the sound structure of oral language. The Phonological Memory index assesses the ability to hold phonological information in short term memory and consists of the Nonword Repetition and Digits subtests. Rapid Naming assesses a child's ability to rapidly retrieve and say aloud well learned stimuli; the Rapid Naming index on the CTOPP consists of a composite measure of the Letter and Number subtests.

Reading Comprehension—Reading comprehension was assessed using the Weschler Individual Achievement Test – First Edition reading comprehension subtest (WIAT-RC; Weschler, 1992), the Gray Oral Reading Test – Third Edition (GORT-3; Wiederholt & Bryant, 1992) Comprehension subtest, and the Gates-McGinitie Reading Test – Fourth Edition (GM-4; MacGinitie, MacGinitie, Maria, & Dreyer, 2000) Comprehension subtest. WIAT-RC requires the participant to read a passage silently and then verbally respond to a question asked by the examiner. On the GORT-3 Comprehension subtest, children answer multiple choice questions to passages they have read aloud. The examiner orally presents the questions as well as the written format is presented to the child. The GM-4 Comprehension subtest consists of the child silently reading passages and answering multiple choice questions.

Oral Language Measures—Measures of language included the Peabody Picture Vocabulary Test - Third Edition (PPVT-III; Dunn & Dunn, 1997), the Clinical Evaluation of Language Fundamentals – Third Edition (CELF-III; Semel, Wiig, & second, 1995), and the Test of Language Competence-Expanded (TLC-E; Wiig & Secord, 1989). The PPVT-III assesses receptive vocabulary by asking participants to select the picture that best represents the meaning of the stimulus word presented orally by the examiner. The CELF-III is a comprehensive language battery that measures both receptive and expressive language skills through a variety of subtests and provides overall expressive and receptive indices. The subtests from the TLC- E examine alternative interpretations of sentences (Ambiguous Sentences), listening to a scenario and deducing what may have happened (Making Inferences), and interpreting the meaning of figurative language phrases (Figurative Language).

Visual Spatial—Visual Spatial abilities were measured by Benton's Judgment of Line Orientation (JLO; Benton, Hamsher, Varney, & Spreen, 1983), Developmental Test of Visual Perception (DTVP; Hammill, Pearson, & Voress, 1993) visual closure (VC) and position in space (PS) subtests, and the Hooper Visual Organization Test (HVOT; Hooper, 1983). The JLO consists of a fan of eleven lines separated by 18 degrees. Each item consists of a display of two half lines from either the proximal, middle, or distal of the fan of lines. For each item, the participant selects the two lines from the fan that match the stimuli. In the VC subtest, children have to determine the missing parts of the figures. For each item the participant has to select which drawing, from a series of incompletely drawn figures, would match a target figure. The PS subtest involves the discrimination of reversals and rotations of figures. For each item, the participant selects, from a series of similar but differently oriented figures than the stimulus, which figure matches the target figure. The HVOT consists of 30 line drawings of common objects, which are cut into two or more parts and illogically arranged on the page. For each item, the participant is required to correctly name the drawing orally.

Procedures

Analyses consisted of multivariate analyses of variance (MANOVAs). After conducting initial analyses to determine differences on basic characteristics (ADHD and sex distributions, age, SES, IQ, and SWR) amongst the groups, we conducted a series of analyses to address our questions. To this end, we conducted three MANOVAs with group as the independent variable with: (1) the reading-related and reading comprehension measures (CTOPP, WIAT-RC, GORT-3, and GM), (2) the oral language measures (PPVT-III, CELF-III, and TLC-E) and (3) visuospatial measures (JLO, HVOT, PS, and VC). Since IQ measurements may be largely determined by factors related to cognition in NF-1 (e.g., Performance IQ test scores may be lowered by NF-1-associated visuospatial deficits) and our groups did not significantly differ on IQ measurements, we did not covary for IQ. Note that because only raw scores were obtained for the JLO and HVOT, for the visuospatial MANOVA we covaried for age and used raw scores for PS and VC. In addition, because ADHD symptomology has been questioned as being linked to the poor performance in NF-1, particularly on visuospatial measures (Schrimsher, Billingsley, Slopis & Moore, 2003), we re-ran all analyses covarying for ADHD symptomology. For all analyses, a significance level of $p < 0.05$ was selected. To control for Type I error, univariate analyses and post-hoc tests (Fisher's LSD) were used to examine group differences only when the MANOVA/MANCOVAs were significant, as indicated by Wilks' Lambda.

Results

Initial Analyses

We initially conducted ANOVAs and Chi-square analyses to determine if there were any differences in age or SES as well as distribution of ADHD and number of males and females across groups. There were no significant differences between the groups on age or SES ($p > .48$). Chi-square analyses indicated that the distribution of males and females was similar across all groups ($\chi^2 = 3.24$, $p = .36$) and no apparent linkage between presence/absence of UBOs and reading status in the NF-1 groups ($\chi^2 = 2.18$, $p = .34$); however, ADHD was over-represented in both RD groups (NF+RD and IRD; $\chi^2 = 13.12$, $p = .04$). Next, we conducted a MANOVA to examine the groups' performance on IQ and SWR measures; results were significant $F(12, 230) = 11.27$, $p < .001$ but revealed univariate statistically significant differences for only the SWR composite ($p < .001$). Post-hoc pairwise tests also indicated, as expected, that the CNT and NFnoRD groups scored significantly higher on SWR when compared to the NF+RD and IRD groups ($p < .003$). Means and significant pairwise comparisons are displayed in Table 2.

Reading-Related Measures and Reading Comprehension

The MANOVA conducted on the reading-related and reading comprehension measures (Phonological Memory, Phonological Awareness, Rapid Naming, GORT-3 Comprehension, WIAT-RC, and GM-4 Comprehension) revealed a significant group difference, $F(18, 241) = 2.72$, $p < .001$. Univariate follow-up analyses revealed significance for all of the individual tests (all $p < .03$). Post-hoc pairwise tests indicated that CNT scored significantly better than NF+RD and IRD on Phonological Awareness, Phonological Memory, and Rapid Naming (*p*

< .05); in addition, the NFnoRD group scored higher than the NF+RD group on Phonological Awareness and Phonological Memory, and higher than the IRD group on Rapid Naming ($p < .04$). Post-hoc pairwise tests also revealed that, consistent with our classification, the CNT group scored significantly higher than the NF+RD and IRD groups on the WIAT-RC and GORT-3 Comprehension ($p < .05$); however, the CNT group only scored significantly higher than the IRD group on the GM-4 Comprehension measure ($p = .003$). Additionally, the NFnoRD group scored significantly higher than the IRD and NF+RD groups on WIAT-RC and significantly higher than the IRD group on the GORT-3 Comprehension (p< .004). Means and significant pairwise comparisons for the reading measures are displayed in Table 3.

Oral Language

The MANOVA conducted on the reading measures (PPVT-III, CELF-3 Expressive Language and Receptive Language composites, as well as the TLC-E Making Inferences, Ambiguous Sentences, and Figurative Language subtests) revealed no significant group differences , F (18, 241) = 1.48, $p = .10$. Means for the language measures are displayed in table 4.

Visual Spatial

The MANCOVA conducted on the reading measures (JLO, PS, VC, and HVOT) revealed a significant group difference, F (12, 228) = 2.34, $p = .008$. Univariate follow-up analyses revealed significance for the JLO, PS, and VC (all $p < .02$) but not for the HVOT ($p = .93$). Post-hoc pairwise tests revealed that the NF+RD group scored significantly lower than the CNT and IRD groups on the JLO, PS, and VC (all $p < .02$). Means and significant pairwise comparisons for the visual spatial measures are displayed in Table 5.

Additional Analyses: Impact of Attention Deficit Hyperactivity Symptomology

Because some have questioned whether ADHD characteristics are related to the deficits in visuospatial realm in NF-1 (Schrimsher et al., 2003), we re-ran analyses on the visuospatial measures, as well as the other measures, covarying for ADHD symptomology. The results showed the same patterns for the reading, oral language, and visuospatial measures, suggesting, as Schrimsher et al. (2003) also reported, that these deficits are independent of ADHD status.

Exploratory Analyses: Visuo-spatial Abilities

Because of our findings suggesting that NF+RD in particular were vulnerable to lower visuospatial skills, we conducted several preliminary/exploratory analyses. First, although the groups all scored within the average range on IQ and there were not significant differences between groups on IQ measures, the medium-to-large effect sizes (see Table 2) suggested that this was due in part to issues of small sample sizes. Therefore, because the NF+RD group showed the lowest IQ scores, particularly Performance IQ, we were interested in whether this was related to a general lowering of “non-verbal” skills. To this end, we re-ran visuo-spatial analyses first covarying for Performance IQ; we also covaried for Verbal IQ in another analysis. In both cases, the patterns of significance remained the same. In a second set of analyses, we examined the partial correlations (controlling for age) between SWR and the JLO, PS, and VC; the correlations in the CNT group were all non-significant ($r = -.011$, .023, and .072, respectively). For the NFnoRD group the correlations were also all non-significant ($r = .249$, .137, and -.224, respectively). For the IRD group, the correlations between SWR and the JLO and PS were non-significant ($r = .014$ and .201, respectively), but VC did show a significant correlation with SWR ($r = .382$, $p < .031$). For the NF+RD group, the correlations between SWR and the JLO, PS, and VC were all consistent and significant ($p < .047$, $r = .632$, .602, and .585, respectively). We then re-ran these correlation analyses controlling for both age and ADHD symptomology; patterns remained the same. Noteworthy, however, was that the correlations between SWR and the JLO, PS, and VC became even higher (r = .766, .709, .756 all p < .016).

Discussion

In the current study, we focused on further understanding the NF-1 cognitive profile by examining the reading, language, and visuospatial skills of groups of children with NF-1 who were subdivided by whether they did or did not meet criteria for RD. Furthermore, to understand how children with NF-1 specifically classified as RD were similar or different to reading disabilities in the general population, we also compared these NF-1 groups to children with IRD. Overall, our findings indicated that children with NF+RD perform very similarly to children with IRD on all reading and reading-related measures and no statistically significant differences were found amongst any of the groups on oral language measures; however, there were some notable differences observed on the visuospatial measures. Below we address our findings with regard to our specific research questions.

Do children with NF+RD show the same patterns of reading and reading-related weaknesses as children with IRD do?

In general, findings suggested that children with NF+RD show a pattern of performance on phonological, rapid naming, and reading comprehension that is quite similar to those with IRD. Both RD groups tended to score lower, as expected by our classification scheme, on reading-related and reading comprehension measures; while not all comparisons were statistically significant in the expected directions, effect sizes were consistent with the expected pattern (e.g., although the NFnoRD group did not score statistically significantly higher than the NF+RD group on the GM-Comp, the effect size for this comparison was .77). Therefore, while not necessarily revealing any entirely unexpected findings (and are similar with ours and others' previous findings, Cutting et al., 2000; Watts et al., 2008), our results when subdividing NF-1 into those with and without RD do confirm our previous suggestion that children with NF+RD show a similar pattern of to those with RD, and therefore should receive interventions similar to those proven to work with IRD.

Do children with NF-1 in general show weaknesses in oral language, or are the oral language weakness in NF-1 confined to children with NF-1 who also have RD? If so, are these oral language deficits in NF+RD distinct from those often seen in IRD?

No statistically significant differences were seen across groups on oral language performance. This finding is different than what has been observed in some previous studies (Billingsley, Slopis, Swank, Jackson, & Morris 2003; Dilts et al. 1996; Cutting et al., 2000; Mazzocco et al. 1995), in which children with NF-1 were compared to either controls or siblings. However, unlike many previous studies, including ours (Cutting et al., 2000), we minimized differences in IQ amongst the groups, with mean Performance and Verbal IQs scores in the average range for all the groups. Therefore, the current findings suggest that oral language skills in NF-1 may not necessarily be distinct from those abilities seen in IRD and CNT groups. Nevertheless, our lack of statistically significant findings with regard to oral language should be interpreted with some caution: although there were no statistically significant differences between our groups on oral language measures, many of the effect sizes were in the medium range, and some were in the large range (see Table 4). Most notably, the effect sizes comparing the CNT to the NF+RD group were medium-to-large for almost all language measures. Other group effect size comparisons suggested other potential selective weaknesses in the NFnoRD group and the IRD group (e.g., receptive language and inferential language for the NFnoRD group). It would be fruitful for future studies comparing NFnoRD, NF+RD, IRD, and CNT groups to use larger sample sizes, as well as even more closely match groups on IQ (as some effect sizes between groups were notable, even though no statistically significant findings were observed). This approach would help to determine exact patterns of oral language weaknesses in NF+RD and NFnoRD as compared to IRD and CNT.

Do NF+RD show any distinct weaknesses in visuospatial skills as compared to either NF-1 without RD (NFnoRD) or IRD?

We had hypothesized, based on previous findings, that children with NF-1 would show significant weaknesses in visuospatial skills regardless of reading classification. Surprisingly, we found that of the two NF-1 groups, only the NF+RD group showed quite distinct weaknesses on visuospatial skills as compared to the IRD and CNT groups. Furthermore, we found that these visuospatial weaknesses were not related to IQ performance or, consistent with Schrimsher et al.'s (2003) findings, ADHD. Exploratory analyses also revealed that visuospatial skills correlated with basic reading skills, but this relationship was confined essentially to the NF+RD group. While weaknesses in particular visuospatial skills in the NFnoRD and the IRD groups as compared to the CNT group were somewhat suggested by modest effect sizes (in the .30-.40 range), these comparisons did not reach statistical significance and on the whole were substantially more modest than the effect sizes observed in the NF+RD comparisons. Thus, our findings together indicate that children with NF+RD are characterized by weak visuospatial skills, while in comparison children with NFnoRD and IRD show relatively solid visuospatial abilities. This suggests that while the overall profile of NF+RD is similar to IRD (in terms of phonological, rapid naming, and reading comprehension performance), they show additional difficulties in the visuospatial realm. It should be noted that although some studies have reported visuospatial weaknesses in IRD, the origin and significance of these weaknesses, which are typically attributed to magnocellular abnormalities, are uncertain (see Eden & Zeffiro, 1998) and may be more circumscribed than those of NF+RD. Further investigation using tasks that specifically designed to tap the magnocellular system may reveal whether these are present in both NF+RD and IRD groups.

In terms of intervention for the reading weaknesses in NF+RD, whether their visuospatial weaknesses relate somehow to actual reading ability and response to reading intervention is an open question. To this end, reading intervention trials with children with NF+RD may reveal if visuospatial abilities play any role in responsiveness to reading intervention. Although it is likely that children with NF+RD will require reading interventions that follow the basic principles that have been shown to work with the IRD population (i.e., teaching sound-symbol relationships in a systematic manner), a specific approach to reading intervention (e.g., a more phonological versus visual emphasis) may be needed for this population. For example, interventions that systematically teach linkages between phonemes and graphemes using controlled text may be helpful for addressing decoding difficulties in NF+RD; on the other hand, interventions that focus on teaching sound-symbol relationships with more of an emphasis on building orthographic knowledge and fluency (e.g., repeated reading) may address other aspects of their reading weaknesses that possibly are linked to their visuospatial deficits.

Our study contributes to the NF-1 literature in that it is the first to compare children with NF-1 subcategorized by whether they meet RD criteria to children with IRD. Findings suggest a more refined classification of NF-1 by RD status may be helpful in determining the NF-1 phenotype. Future studies will need to examine this issue with regard to other types of learning disabilities (e.g., math disability) in NF-1, as well as continue to confirm that ADHD status does not appear to be linked to visuospatial deficits. Additionally, although our analyses are suggestive of distinct differences amongst children with NF+RD in visuospatial skill and some sort of relationship with reading, the sample sizes in the current study are small. Thus, future studies will need to further investigate these potential linkages with larger samples; to this end, brain-behavior relationships as to the origin of the visuospatial deficit with regard to the magnocellular pathway would be of interest. Finally, future research studies should examine if children with NF+RD need distinct types of intervention programs that are specifically tailored to their cognitive profile.

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References

Achenbach, T. Manual for the Child Behavior Checklist.(Parent Form). University Associates in Psychiatry; Burlington, VT: 1991.

Adams, MJ. Beginning to read: Thinking and learning about print. MIT Press; Cambridge, MA: 1990.

Benton, AL.; Hamsher, KD.; Varney, NR.; Spreen, O. Contributions to Neuropsychological Asessment. Oxford University Press; New York: 1983. Judgement of Line Orientation.

Billingsley RL, Slopis JM, Swank PR, Jackson EF, Morris BD. Cortical morphology associated with language function in neurofibromatosis type 1. Brain and Language 2003;85(1):125–39. [PubMed: 12681352]

Brewer VR, Moore BD, Hiscock M. Learning disability subtypes in children with neurofibromatosis. Journal of Learning Disabilities 1997;30:521–533. [PubMed: 9293234]

Catts HW, Fey ME, Zhang X, Tomblin JB. Language basis of reading and reading disabilities: Evidence from a longitudinal investigation. Scientific Studies of Reading 1999;3:331–361.

Conners, CK. Conners' rating scales-revised. Multihealth Systems, Inc.; North Tonawanda, NY: 1997.

Cutting LE, Koth CW, David D, Denckla MB. Comparison of neuropsychological profiles of children with NF-1 and RD. Journal of the International Neuropsychological Society 2003;9:203.

Cutting LE, Koth CW, Denckla MB. How children with neurofibromatosis type 1 differ from "typical" learning disabled clinic attenders: Non-verbal learning disabilities revisited. Developmental Neuropsychology 2000;17:29–48. [PubMed: 10916573]

Dunn, LM.; Dunn, LM. Peabody Picture Vocabulary Test – Third edition. American Guidance Service; Circle Pines, MN: 1997.

Dilts CV, Carey JC, Kircher JC, Hoffman RO, Creel D, Ward K, et al. Children and adolescent with neurofibromatosis 1: A behavioral phenotype. Developmental and Behavioral Pediatrics 1996;17:229–239.

DuPaul, GJ.; Power, TJ.; Anastopoulos, AD.; Reid, R. ADHD Rating Scale-IV. Guilford Press; New York: 1998.

Eden GF, Stein JF, Wood HM, Wood FB. Verbal and visual problems in reading disabled and normal children. Journal of Learning Disabilities 1995;28(5):272–290. [PubMed: 7775847]

Eden GF, Stein JF, Wood HM, Wood FB. Differences in visuospatial judgement in reading-disabled and normal children. Perceptual & Motor Skills 1996;82(1):155–177. [PubMed: 8668471]

Eden GF, VanMeter JW, Rumsey JM, Zeffiro TA. The visual deficit theory of developmental dyslexia. Neuroimage 1996;4:S108–S117. [PubMed: 9345535]

Eden GF, Zeffiro TA. Neural Systems Affected in Developmental Dyslexia Revealed by Functional Neuroimaging. Neuron 1998;21:279–282. [PubMed: 9728909]

Fletcher JM, Francis DJ, Shaywitz SE, Lyon GR, Foorman BR, Stuebing KK, Shaywitz BA. Intelligent testing and the discrepancy model for children with learning disabilities. Learning Disabilities Research and Practice 1998;12:186–203.

Fuchs, D. Cognitive Profiling of Children with Genetic Disorders and the Search for a Scientific Basis of Differentiated Education. In: Alexander, P.; Winne, P., editors. Handbook of educational psychology. Erlbaum; Mahwah NJ: 2006.

Hammill, DD.; Pearson, NA.; Voress, JK. Developmental Test of Visual Perception – Second Edition. PRO-ED Inc.; Austin, TX: 1993.

Hollingshead, A. Four factor index of social status. 1975. Unpublished manuscript

Hofman KJ, Harris EL, Bryan RN, Denckla MB. The Journal of Pediatrics 1994;124(4):S1–8. [PubMed: 8151460]

Hooper. Visual Organization Test Manual (VOT). Western Psychological Services; Los Angeles: 1983.

Hyman SL, Shores A, North KN. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. Neurology 2006;65(7):1037–44. [PubMed: 16217056]

Koth CW, Cutting LE, Denckla MB. The association of neurofibromatosis type 1 and attention deficit hyperactivity disorder. Child Neuropsychology 2000;6(3):185–194. [PubMed: 11402396]

Krab LC, Aarsen FK, de Goede-Bolder A, Catsman-Berrevoets CE, Arts WF, Moll HA, et al. Impact of neurofibromatosis type 1 on school performance. Journal of Child Neurology 2008;23(9):1002–10. [PubMed: 18827266]

Levine TM, Materek A, Abel JR, O'Donnell M, Cutting LE. Cognitive profile of neurofibromatosis type 1. Seminars in Pediatric Neurology 2006;13(1):8–20. [PubMed: 16818171]

Lyon GR. Toward a definition of dyslexia. Annals of Dyslexia 1995;45:3–27.

Mautner VF, Kluwe L, Thakker SD, Leark RA. Treatment of ADHD in neurofibromatosis type 1. Developmental Medicine and Child Neurology 2002;44:164–170. [PubMed: 12005317]

Mazzocco MM, Turner JE, Denckla MB, Hofman KJ, Scanlon D, Vellutino F. Language and reading deficits associated with Neurofibromatosis Type 1: Evidence for a not-so-nonverbal learning disability. Developmental Neuropsychology 1995;11:503–522.

MacGinitie, WH.; MacGinitie, RK.; Maria, K.; Dreyer, LG. Gates–MacGinitie Reading Tests – Fourth Edition. Riverside; Itasca, IL: 2000.

Moore BD. Potential influences on mathematical difficulties in children and adolescents with neurofibromatosis, type 1. Developmental Disabilities research reviews 2009;15(1):45–51. [PubMed: 19213018]

Moore BD, Ater JL, Needle MN, Slopis JS, Copeland DR. Neuropsychological profile of children with neurofibromatosis, brain tumor, or both. Journal of Child Neurology 1994;9(4):368–377. [PubMed: 7822726]

Noll RB, Reiter-Purtill J, Moore BD, Schorry EK, Lovell AM, Vannatta K, et al. Social, emotional, and behavioral functioning of children with NF1. American Journal of Medical Genetics. Part A 2008;143A(19):2261–73. [PubMed: 17726688]

North KN. Neurofibromatosis type 1. American Journal of Medical Genetics 2000;97:119–127. [PubMed: 11180219]

North KN, Joy P, Yuille D, Cocks N, Mobbs E, Hutchins P, et al. Specific learning disability in children with neurofibromatosis type 1: Significance of MRI abnormalities. Neurology 1994;44:878–883. [PubMed: 8190291]

Rosser TL, Packer RJ. Neurocognitive dysfunction in children with neurofibromatosis type 1. Current Neurology and Neuroscience Reports 2003;3(2):129–36. [PubMed: 12583841]

Semel, E.; Wiig, EH.; Secord, WA. Clinical Evaluation of Language Fundamentals – Third Edition. The Psychological Corporation; San Antonio, TX: 1995.

Schrimsher GW, Billingsley RL, Slopis JM, Moore BD. Visual-spatial performance deficits in children with neurofibromatosis type 1. American Journal of Medical Genetics. Part A 2003;130A(3):326–30. [PubMed: 12838550]

Shankweiler D. Words to meanings. Scientific Studies of Reading 1999;3:113–127.

Stine SB, Adams WV. Learning problems in Neurofibromatosis patients. Clinical Orthopology 1989;245:43–48.

Torgesen JK. Individual differences in response to early interventions in reading: The lingering problem of treatment resisters. Learning Disabilities Research and Practice 2000;15:55–64.

Wagner, RK.; Torgesen, JK.; Rashotte, CA. Comprehensive Test of Phonological Processing. Pro-Ed; Austin, TX: 1999.

Watt SE, Shores A, North KN. An examination of lexical and sublexical reading skills in children with neurofibromatosis type 1. Child Neuropsychology 2008;14(5):401–18. [PubMed: 17963094]

Wechsler, D. Wechsler Individual Achievement Test – First Edition. The Psychological Corporation; San Antonio, TX: 1992.

Wechsler, D. Wechsler Intelligence Scale for Children- Third Edition. The Psychological Corporation; San Antonio, TX: 1991.

Wiederholt, L.; Bryant, B. Examiner's manual: Gray Oral Reading Test- Third Edition. Pro-Ed; Austin, TX: 1992.

Wiig, E.; Secord, W. Test of Language Competence-Expanded. The Psychological Corporation; San Antonio, TX: 1989.

Woodcock, RW.; McGrew, KS.; Mather, N. Woodcock Johnson Psychoeducational Battery –Revised Complete Battery. MNP American Guidance Service; Circle Pines: 1989.

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Table 1

UBO Information for Participants with NF-1

Participant	UBO(s) Present	UBO Location(s)	Thalamus	Basal Ganglia	Sex	NF Category
1	No				F	NF+RD
2	No				F	NF+RD
3	No				F	NFnoRD
4	No				F	NFnoRD
5	No				F	NFnoRD
6	No				F	NFnoRD
7	No				M	NFnoRD
8	Report N/A				M	NF+RD
9	Report N/A				M	NF+RD
10	Report N/A				M	NFnoRD
11	Yes	Periventricular White Matter-R (top of lateral ventricle)			M	NF+RD
12	Yes	Cerebellum-L			M	NF+RD
13	Yes	Thalamus-B; Middle Cerebral Peduncles-B	X		M	NF+RD
14	Yes	BG-B; Cerebellum-B		X	F	NF+RD
15	Yes	BG-L		X	F	NF+RD
16	Yes	Cerebellum-B; BG-L		X	M	NF+RD
17	Yes	BG-B; Medulla-R		X	M	NF+RD
18	Yes	BG-B; Thalamus-R; Cerebellum-B; Pons-R	X	X	M	NF+RD
19	Yes	BG-R; Thalamus-L; Pons-B; Cerebellum-B	X	X	M	NF+RD
20	Yes	Internal Capsule-B			F	NFnoRD
21	Yes	Thalamus-R; Cerebral Peduncle-R; Cerebellum-B	X		F	NFnoRD
22	Yes	BG-R		X	M	NFnoRD
23	Yes	BG-L; Hippocampus-B; Thalamus-B; Deep white/gray matter of posterior fossa-B	X	X	F	NFnoRD
24	Yes	BG-Bilateral; Thalamus-L; Cerebellum-B	X	X	M	NFnoRD
25	Yes	BG-B; Internal Capsule-B; Thalamus-B; Midbrain-B; Pons-B; Cerebellum-B	X	X	M	NFnoRD

Note: BG = Basal Ganglia; B = Bilateral; L = Left; R = Right; N/A = Not Available

Table 2

Scores from SWR and IQ Measures

	CNT		IRD		NFnoRD		NF+RD			ES	ES	ES	ES	ES	ES
Measures	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**		**CNT v. IRD**	**CNT v. NFnoRD**	**CNT v. NF+RD**	**IRD v. NFnoRD**	**IRD v. NF+RD**	**NFnoRD vs. NF+RD**
VIQ	105.17	9.54	101.30	16.49	101.58	12.03	94.08	16.95		0.29	0.33	0.81	−0.02	0.43	0.51
PIQ	101.50	11.77	101.79	13.06	98.67	11.96	92.77	18.55		−0.02	0.24	0.56	0.25	0.56	0.38
FSIQ	103.60	9.72	101.30	13.31	100.25	11.27	93.69	18.07		0.20	0.32	0.68	0.09	0.48	0.44
SWR	108.18	8.14	86.48	7.35	99.67	6.53	85.58	9.16	a, b, c, d, e	2.80	1.15	2.61	−1.90	0.11	1.77

Note. The Wechsler Intelligence Scale for Children – Third Edition Verbal Intelligence Quotient (VIQ), Performance Intelligence Quotient (PIQ), and Full Scale Intelligence Quotient (FSIQ) are from Wechsler (1991); the SWR is a combination of the Basic Reading subtest from the WIAT-1 (Wechsler, 1992) and the Word Attack subtest from the WJ-R (Woodcock et al., 1989). All values represent standardized scores. a-CNT and NFnoRD > NF+RD and IRD, $p < .001$, b-CNT > IRD, $p < .001$, c-NFnoRD > NF+RD, $p < .001$, d- NFnoRD > IRD, $p < .001$, e-CNT > NFnoRD, $p = .002$.

Table 3

Scores from Reading-Related Measures and Reading Comprehension

	CNT		IRD		NFnoRD		NF+RD			ES	ES	ES	ES	ES	ES
Measures	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**		**CNT v. IRD**	**CNT v. NFnoRD**	**CNT v. NF+RD**	**IRD v. NFnoRD**	**IRD v. NF+RD**	**NFnoRD vs. NF+RD**
G-Comp	9.92	2.58	6.91	3.14	10.17	1.53	8.00	4.06	a, b, d	1.05	−0.12	0.56	−1.32	−0.30	0.71
PAC	99.17	9.09	90.00	12.63	96.17	6.41	85.99	16.81	a, b, c	0.83	0.38	0.98	−0.62	0.27	1.32
PMC	96.03	10.30	90.64	12.66	95.08	9.51	85.69	11.17	a, b, c	0.45	0.10	0.96	−0.40	0.42	0.91
RNC	102.83	10.59	90.52	13.10	100.58	12.20	92.15	12.40	a, b, d	1.03	0.20	0.93	−0.80	−0.13	0.69
GM-Comp	−0.18	0.99	−0.86	0.87	0.09	0.63	−0.58	1.0558	b, d	0.73	−0.32	0.39	−1.25	−0.29	0.77
WIAT-RC	103.17	9.12	90.12	15.99	102.67	8.29	87.38	11.84	a, b, c, d	1.00	0.06	1.49	−0.99	0.02	1.50

Note. The Gray Oral Reading Test – Third Edition Comprehension subtest (G-Comp) is from Widerholt & Bryant (1992); the Comprehensive Test of Phonological Processing Phonological Awareness Composite (PAC), Phonological Memory Composite (PMC), and Rapid Naming Composite (RNC) are from Wagner et al. (1999); the Gates-MacGinitie Reading Tests – Fourth Edition Comprehension subtest (GM-Comp) is from MacGinitie et al. (2000); The Wechsler Individual Achievement Test – First Edition Reading Comprehension subtest (WIAT-RC) is from Wechsler (1992). a-CNT > NF+RD, $p < .05$, b-CNT > IRD, $p < .05$, c-NFnoRD > NF+RD, $p < .04$, d- NFnoRD > IRD, $p < .004$.

Table 4

Scores from Oral Language Measures

	CNT		IRD		NFnoRD		NF+RD		ES	ES	ES	ES	ES	ES
Measures	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**CNT v. IRD**	**CNT v. NFnoRD**	**CNT v. NF+RD**	**IRD v. NFnoRD**	**IRD v. NF+RD**	**NFnoRD vs. NF+RD**
CELF-RL	101.94	11.32	97.16	14.92	95.67	11.18	93.69	14.74	0.36	0.56	0.63	0.11	0.23	0.15
CELF-EL	98.50	10.76	90.33	16.27	98.50	7.78	90.54	12.56	0.59	0.00	0.69	−0.64	−0.01	0.78
TLC-AS	9.17	3.27	7.27	2.91	7.58	3.12	7.69	2.72	0.61	0.5	0.49	−0.10	−0.15	0.04
TLC-M I	11.33	2.69	10.39	3.07	10.58	2.02	9.62	3.10	0.33	0.32	0.59	−0.07	0.25	0.37
TLC-FL	9.25	3.15	8.58	3.67	8.92	2.61	8.00	3.16	0.20	0.11	0.40	−0.07	0.17	0.32
PPVT-III	106.89	12.11	104.76	14.41	102.17	13.97	98.31	7.51	0.16	0.36	0.85	0.18	0.56	0.34

Note. The Clinical Evaluation of Language Fundamentals – Third Edition Receptive Language Composite (CELF-RL), and Expressive Language Composite (CELF-EL) are from Semel et al. (1995); the Test of Language Competence – Expanded Ambiguous Sentences subtest (TLC-AS), Making Inferences subtest (TLC-MI), and Figurative Language subtest (TLC-FL) are from Wiig & Secord (1989); the Peabody Picture Vocabulary Test – Third Edition (PPVT-III) is from Dunn & Dunn (1997).

Table 5

Scores from Visual Spatial Measures

	CNT		IRD		NFnoRD		NF+RD			ES	ES	ES	ES	ES	ES
Measures	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**		**CNT v. IRD**	**CNT v. NFnoRD**	**CNT v. NF+RD**	**IRD v. NFnoRD**	**IRD v. NF+RD**	**NFnoRD vs. NF+RD**
JLO	17.33	6.06	16.09	6.58	14.92	9.23	13.38	7.50	a, b	0.20	0.31	0.58	0.15	0.38	0.18
HVOT	23.15	3.50	22.91	2.62	22.67	4.08	23.15	3.29		0.08	0.13	0.00	0.07	−0.08	−0.13
DTVP-PS	21.28	3.49	19.82	4.01	19.67	4.77	17.92	3.93	a, b	0.39	0.39	0.90	0.03	0.48	0.40
DTVP-VC	12.86	5.30	12.15	5.04	10.83	6.28	9.08	5.52	a, b	0.14	0.35	0.70	0.23	0.58	0.30

Note. Judgment of Line Orientation (JLO) is from Benton et al. (1983); Visual Organization Test Manual is from Hooper (1983); Developmental Test of Visual Perception – Second Edition Position in Space subtest (DTVP-PS), and Visual Closure subtest (DTVP-VC) are from Hammil et al. (1993). a-CNT>NF+RD, $p<.003$, b-IRD>NF+RD, $p<.02$.