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Teaching reading to children with neurofibromatosis type 1: a clinical trial with random assignment to different approaches

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Abstract

AIM—Neurofibromatosis type 1 (NF1) is a genetic disorder with a cognitive profile that includes visual–spatial perception deficits and a high incidence of reading disability. There is a paucity of information about how this cognitively complex population responds to mainstream reading interventions. The clinical trial goals were to determine whether children and adolescents with NF1 and reading deficits (NF+RD) benefit from mainstream remedial reading programs and whether responsiveness varies with differences in program-related visual–spatial demands.

METHOD—Forty-nine participants (18 males, 21 females; aged 8–14y) with either NF+RD ($n=17$, 11 males, 6 females) or idiopathic reading deficit (IRD) ($n=32$, 17 males, 15 females) were randomly assigned to intensive remedial teaching using one of two multisensory reading programs: one with greater kinesthetic demands and the other with greater visual–spatial demands. Two control groups – wait-list IRD ($n=14$, 11 males, 3 females) and typically developing readers ($n=26$, 13 males, 13 females) – received no treatment. Repeated measures and multivariate ANOVA analyses compared each group's growth in reading achievement from pre- to post-testing.

RESULTS—Treated groups showed significant growth whereas untreated groups did not. Comparing treated groups, the IRD group responded equally well to both interventions, whereas the NF+RD group showed a better response to the more kinesthetic approach.

INTERPRETATION—Results suggest that multisensory remedial reading teaching that emphasizes kinesthetic demands more than visual–spatial demands is suitable for students with NF+RD.

Neurofibromatosis type 1 (NF1) is a disorder with a population frequency of 1 in 3500 individuals worldwide.¹ It is caused by a single gene defect on chromosome 17 that

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Appendix S1: Detailed descriptions of Treatment A and Treatment B

produces aberrant neurofibromin, a protein involved in regulating cell functioning in multiple organ systems including the brain. Among the brain-related concerns raised by parents of children with NF1, the most common relate to negative impacts on cognition, learning, and behavior that are associated with academic underachievement.^{2,3} New treatment options for these children are on the horizon. Using genetically modified mice, researchers have mapped the connection between aberrant neurofibromin and altered cell signaling associated with defective learning and memory formation. Importantly, they found that impaired learning in these genetically defective mice could be improved via treatment with statin medications (e.g. lovastatin).⁴ Clinical trials to translate these animal studies to humans with NF1 are underway;⁵⁻⁹ however, routine drug treatment of children with NF1 is probably not in the immediate future. In the interim, many students with NF1 are currently experiencing academic underachievement, and yet there is limited information about their responsiveness to more immediately available treatments that would include non-pharmacological remedial teaching approaches. Thus, one goal of this study is to determine whether mainstream remedial teaching programs, which are widely available to the general public, will also be beneficial for this special population. However, there is also evidence that a combined treatment approach is beneficial. Specifically, promising studies in animal spatial learning and human motor learning have demonstrated improvement in genetically based learning deficits when medication is paired with direct training.⁴ Thus, a second goal of the study is to lay the groundwork for future treatment opportunities that mimic these recent trials. The current study is designed to assess efficacy of remedial teaching approaches to inform future combined treatment options that pair remedial teaching with pharmacological intervention. The ultimate objective is to treat the common problem of academic underachievement in children with NF1.

Cognitively, the majority of children with NF1 exhibit a mild downward shift in general ability (IQ) to about ten points lower than both the general population and their own unaffected siblings.¹⁰⁻¹² A more specific 'hallmark' feature of the cognitive profile of individuals with NF1 is impaired visual-spatial perception.³ Importantly, academic underachievement is the most common cognitive concern voiced by parents of children with NF1.^{2,3} Related to academic achievement, attention-deficit-hyperactivity disorder (ADHD) is a common comorbid diagnosis occurring in about 60% of children with NF1, and an estimated 30% to 75% have poor academic achievement in specific subjects like spelling, math, and reading.^{11,13-18} This is much higher than the estimated 5% incidence of ADHD and 5% to 17% incidence of specific learning disabilities in the general population.^{19,20} Indeed, compared to those *without* NF1, children *with* NF1 are four times more likely to qualify for special education services and six times more likely to receive remedial teaching.¹⁸ Despite these substantial educational needs there has been little research on how children with NF1 respond to instructional interventions.

Of specific interest for this study, reading deficits are the most common form of specific learning disability in the general population, and this is also true among children with NF1.¹⁶ However, thus far only a handful of studies have investigated children with NF1 and reading deficits (NF+RD) in any great depth.²⁰⁻²² Studies have shown that children with NF+RD have reading-related deficits similar to the general population with idiopathic reading

disabilities (IRD), including impairments in single-word reading, reading comprehension, picture naming, and phonological processing.^{19–21} Another similarity is that children with IRD also have an increased risk (odds ratio 3.8) of comorbid ADHD with incidence estimates ranging from 9% to 60%.²³ However, a distinctive feature of the cognitive profile of children with NF1 is the presence of comorbid visual–spatial deficits not commonly seen in children with IRD.²¹ Thus, while evidence-based reading interventions that are successful in the general population (IRD) are a good place to begin when proposing to treat children with NF+RD, it is also important to consider that there may be additional complexities. This study addresses the gap in the literature regarding whether academic treatments known to be beneficial in IRD are also beneficial for children and adolescents with NF1.

For children and adolescents with IRD, instructional reading interventions that explicitly target basic word-level reading skills have been associated with improved word-level reading ability as compared to typically developing control children.^{24–27} Although interventions targeting other aspects of reading - particularly spelling, reading comprehension, and frequency of reading practice - have also been shown to be beneficial,^{28,29} these higher-level skills can continue to be limited by deficient word-level reading even into adulthood.³⁰ This study therefore addressed basic word-reading skills in children with NF1. An additional beneficial feature of reading instruction in IRD is the use of a multisensory approach;^{31,32} yet different multisensory instructional programs differ in the relative demands placed on one sensory modality compared to another. A study in individuals with IRD showed no difference in responsiveness to multisensory word-level instructional programs that varied on relative sensory demands (i.e. kinesthetic vs visual–spatial emphases).³³ However, this finding may not extend to a population like NF+RD characterized by a high frequency of visual–spatial perception deficits.

Thus for this study, children and adolescents with either NF+RD or IRD were randomly assigned to one of two multisensory reading programs for short-term, intensive, individualized remedial instruction in sound-symbol correspondences and word-level reading skills. One program emphasized tactile–kinesthetic demands and the other emphasized visual–spatial strategies. Our goal was to address the following questions: (1) Do children and adolescents with NF+RD respond similarly to evidence-based remedial reading instruction when compared to students with IRD? (2) Is there differential responsiveness of children and adolescents with NF+RD associated with differential emphasis on sensory modality (tactile-kinesthetic versus visual-spatial)?

METHOD

The data were collected between 2007 and 2013 at two universities, Johns Hopkins University in Baltimore, Maryland and Vanderbilt University in Nashville, Tennessee. Prospective research ethics review and approval was obtained through the institutional review boards at each study location. The recommendations from both committees have been adhered to, including obtaining written informed assent from the participating minor and written informed consent from the minor's parent agreeing to participate and allow publication of the results.

Children *with* NF1 were recruited locally and nationally through educational clinics, neuropsychology clinics, neurofibromatosis advocacy and support organizations, and the clinicaltrials.gov website (trial identifier NCT00624234). The diagnosis of NF1 was confirmed through medical records provided by the participant's physician before entry in the study.

Control children *without* NF1, including typically developing readers and those with IRD, were recruited locally using flyers distributed to libraries, doctors' offices and other public locations in the community, e-mail notifications to select communities like the International Dyslexia Association, and via the StudyFinder website that notifies registered volunteers about opportunities to participate in clinical research studies.

All individuals were eligible for the study regardless of ethnic group, sex, and socio-economic status. All individuals expressing interest were contacted via telephone to ascertain whether any of the following exclusion criteria applied: (1) previous diagnosis of intellectual disability; (2) known, uncorrectable visual impairment; (3) documented hearing impairment greater than or equal to 25dB loss in either ear; (4) history of known neurological disorders including epilepsy, spina bifida, cerebral palsy, traumatic brain injury; (5) current or past diagnosis of an autism spectrum disorder; (6) treatment with any psychotropic medication, with the exception of stimulant medications for ADHD; or (7) parental report of significant symptoms of a severe psychiatric diagnosis including major depression, bipolar disorders, or conduct disorder – of note, individuals meeting criteria for ADHD, oppositional defiant disorder, adjustment disorder, and mild depression were not necessarily excluded from participation.

Participants

All participants had initial screening of general cognitive ability using the Wechsler Intelligence Scale for Children – Fourth Edition.³⁴ Two participants were excluded from further analyses because they had standard scores of <70 on all three index scores.

Thirty 8- to 14-year-old children and adolescents *with* NF1 and 72 *without* NF1 completed all pre- and post-test reading assessments. Thirteen of those with NF1 either had incomplete data or did not demonstrate impaired reading on the pretest battery; these 13 participants are not included in the analyses. An additional 55 participants without NF1 also completed pretesting but were not included in the analyses due to missing data or test scores that fell in the range between our typically developing readers and those with IRD. See flowcharts in Figure 1 for patterns of assignment to reading groups, treatment status, and program of treatment.

Measures

Eligible participants completed the following measures of reading achievement and visual-spatial skill, while parents completed questionnaires regarding ADHD symptoms. Research assistants, trained to high fidelity, administered all measures and were blinded to the participant's treatment group.

Woodcock-Johnson Tests of Achievement—Woodcock-Johnson Tests of Achievement, Third Edition Normative Update (WJ-III)³⁵ is a battery of standardized, norm-referenced academic achievement measures; this study used two subtests from this battery. Letter–word identification consists of a list of identifiable words that are read aloud and the score is based on the number correct. Word attack is similar but consists of a list of pronounceable pseudowords forcing the reader to rely on phonemic decoding rather than word recognition. Scores from these two subtests combine to compute the basic reading composite reported here as a W score – a scale with equal-interval units allowing for more accurate measurement of change within an individual over time.³⁶ Form A was used at pretesting and Form B at post-testing.

Wechsler Individual Achievement Test—Wechsler Individual Achievement Test, Second Edition (WIAT-II)³⁷ is a battery of standardized, norm-referenced academic achievement measures. The word-reading subtest consists of a list of identifiable words that are read aloud and scored by number correct. This subtest was administered only at pretest to facilitate assigning reading group status.

Judgment of Line Orientation—This test³⁸ assesses spatial discrimination by having the participant correctly match lines at different orientations on a page to a reference. The reference is a fan-shaped display of lines each numbered and each oriented in a direction 18-degrees different from those adjacent; thus the reference is essentially a protractor that the participant uses to indicate which reference line matches the orientation of a line presented as a test stimulus.

Developmental Test of Visual Perception—Two subtests were given from the Developmental Test of Visual Perception³⁹ battery: visual closure and position in space. Visual closure measures ‘form constancy’ by presenting a stimulus shape and asking the participant to choose which dotted line form of the shape correctly completes the drawing. Position in space requires the participant to select shapes that exactly match in orientation.

Conners’ Parent Rating Scale—Since ADHD commonly co-occurs in individuals with IRD and those with NF1,²¹ parents rated their child’s ADHD symptoms using the Conners’ Parent Rating Scale – Revised, Long Form⁴⁰ at pretesting only. The Conners’ total score was used to compare ADHD comorbidity across reading groups and entered as a covariate in the regression analyses.

Reading group assignment

Consistent with previous studies designed to compare poor readers to typically developing readers, a low achievement definition was applied to classify participants as reading deficit.^{41,42}

Inclusion in the reading deficit categories (NF+RD, IRD, and wait-list IRD [IRDWL]) required a standard score at or below 90 (25th centile) on at least one of the following reading achievement measures: (1) WJ-III letter–word identification; (2) WJ-III word attack; or (3) WIAT-II word reading, with the composite score of these three measures being no higher than a standard score of 92 (30th centile).

Inclusion in the typically developing group required a standard score of least 91 (27th centile) on all three of the following measures: (1) WJ-III word identification; (2) WJ-III word attack; and (3) WIAT-II word reading, with a composite of these three measures equaling a standard score of at least 95 (37th centile). All typically developing participants met these criteria.

Randomization

All study participants completed 5 hours of pretesting and 2.5 hours of post-testing 5 to 15 days later. All participants in the treatment condition also completed 15 hours of reading instruction, using one of the two treatment programs, during the 5- to 15-day interval between pre- and post-testing.

All NF+RD participants were assigned to receive treatment and all typically developing participants were assigned to receive no treatment. The study coordinator offered IRD participants the opportunity to participate in treatment; 32 were assigned to a treatment condition and 14 served as wait-list controls, i.e. IRD-WL group. After completing post-testing, the IRD-WL group also had the opportunity to complete treatment. Inclusion of the untreated typically developing and IRD-WL participants provided control conditions to compare treatment versus no treatment.⁴³

To randomize participants to a treatment program, the study coordinator (who was neither a tester nor tutor) assigned blocks of four participants (2 NF+RD and 2 IRD) by predetermined sequential order to one of the two treatment programs. Figure 1 shows the recruitment and randomization process. No participants withdrew after randomization. Regardless of program assigned, the participant received 15 hours of direct individual instruction in that program over a 5-day period; a typical schedule was 5 hours per day over 3 days.

Treatment

Both programs featured a multisensory instructional approaches that have been shown to be beneficial for children with IRD. The treatments differed in the degree of emphasis placed on particular sensory modalities. Treatment A emphasized kinesthetic demands and treatment B emphasized visual-spatial discrimination of frequent patterns in parts of words. It is important to note that there were no differences between the two treatment programs with regard to the number of breaks from instruction with the opportunities to physically get up and move around. The tactile and kinesthetic methods associated with treatment A were limited to the use of tutoring materials that lent themselves to tactile manipulation (like tiles or chips) and a focus on the oral motor movements associated with producing different phonemes. Eight NF+RD participants and 14 IRD participants completed treatment A. Nine NF+RD participants and 18 IRD participants completed treatment B. Each program was presented in a standardized sequence; however, tutors were trained to individualize the instruction by modifying the pace of instruction in response to the participant's needs. More detailed descriptions of treatment A and treatment B are included in Appendix S1 (online supporting information).

Fidelity

After training to high levels of fidelity, graduate students in education, psychology, and related fields administered testing and tutoring. The same individual did not do testing and tutoring for a given participant and testers remained blinded to tutoring assignment. All testing was double-scored and double-entered into the database. All tutoring sessions were audio-recorded and random samples were monitored for fidelity by the author of that program. Any discrepancies in behavioral testing or tutoring were corrected until fidelity was satisfactory.

Analyses

All data were analyzed using SPSS for Windows v.21.0 (IBM Corporation, Armonk, NY, USA). All statistical tests were required to meet the standard threshold of $p < 0.05$ to be considered significant. χ^2 tests assessed for sex frequencies across reading groups. Because of the presence of outliers and non-normal distributions for some *pretest* measures (age, IQ, reading, and visual-spatial skills) across the four reading groups (NF+RD, IRD, IRD-WL, and typically developing), nonparametric methods were used. Kruskal-Wallis analysis followed by Dunn-Bonferroni method for pairwise comparisons was used for comparing age and baseline cognitive profile across the groups.

In contrast, assumptions for parametric analyses were satisfied for pre- and post-test basic reading W scores. Therefore, since parametric statistics offer the advantage of being able to enter covariates into the model, parametric statistics were used to compare growth in reading across groups. Growth in reading was assessed with repeated measures ANOVA (rmANOVA) with a within-subjects factor of time (pretest vs post-test) and a between-subjects factor of group (NF+RD, IRD, IRD-WL, and typically developing); age and Conners' Parent Rating Scale total score were included as covariates.

Differential growth associated with treatment A versus treatment B was also assessed with rmANOVA with a within-subjects factor of time (pre- vs post-test) and between-subjects factors of group (NF+RD, IRD) and tutoring program (treatment A and treatment B); age and Conners' Parent Rating total score were again included as covariates. Cohen's d ⁴⁴ effect sizes were calculated to quantify pre- to post-test changes in basic reading W scores.

A supplementary univariate ANOVA using a difference score (post- minus pretest basic reading W scores) included a between-subjects factor of group (NF+RD, IRD) with age and Conners' Parent Rating score included in the model as covariates. Effect sizes using Cohen's d were computed as described above.

RESULTS

Table I summarizes group demographics and standardized scores for ADHD ratings, general cognitive ability, reading, and visual-spatial skill along with group comparisons using nonparametric analyses. χ^2 analysis demonstrated comparable sex frequency across categories. However, within the subset of treated participants, random assignment resulted in unequal sex distribution by treatment program for NF+RD (treatment A: 5 females/3 males and treatment B: 1 female/8 males; $p = 0.04$) although not for IRD (treatment A: 6

females/8 males; treatment B: 9 females/9 males; $p=0.48$). Nevertheless, there were no significant differences for the interaction of sex by treatment within the NF+RD group in the primary analyses of reading growth reported below. All groups were comparable on age and ADHD ratings. Consistent with previous research, typically developing children had the highest scores on measures of general cognitive ability, and the NF+RD group showed relative weakness on measures of visual-spatial perception compared to the typically developing children and IRD groups. Pretest reading scores, as expected, were highest in the typically developing group and not significantly different between the three reading deficit groups (Table II).

With basic reading W scores as the dependent variable, within-subjects *rmANOVA* with age and Conners' Parent Rating score as covariates revealed a main effect of time (pretest, post-test; $F[1,83]=8.050$, $p=0.006$) and an interaction for Conners' score by time ($p=0.022$). There were significant effects of age ($p<0.001$) and category ($p<0.001$). A significant interaction for time by group ($F[3,83]=2.726$, $p=0.049$) persisted even after controlling for IQ.

Post-hoc pairwise comparisons using Fisher's Least Significant Difference (LSD) revealed significant changes in reading scores from pre- to post-test for treated groups, NF+RD ($p=0.005$) and IRD ($p=0.007$) and no significant change for untreated groups, typically developing ($p=0.685$) and IRD-WL ($p=0.740$). Pairwise comparisons of each treated group versus each untreated group showed medium effect sizes (around 0.5; see Table III). Pairwise comparisons between untreated groups (typically developing vs IRD-WL) and between treated groups (NF+RD versus IRD) showed small effect sizes (see Table III). Overall, treatment was associated with greater reading growth than no treatment.

Restricting the analysis to comparison between the treated groups (NF+RD, IRD), the within-subjects *rmANOVA* with age and Conners' Parent Rating score as covariates revealed a main effect of time ($F[1,43]=4.315$, $p=0.044$) and significant interactions for time by treatment program (treatment A, treatment B: $F[1,43]=7.6$, $p=0.009$) and time by group by treatment program (treatment A, treatment B; $F[1,43]=6.07$, $p=0.018$). These interactions remained significant even when controlling for IQ. Examination of the Time by treatment program interaction with post-hoc pairwise comparisons using LSD revealed a significant difference between pre- and post-test reading scores for treatment A ($F[1,43]=19.72$, $p<0.001$) but not for treatment B ($F[1,43]=0.463$, $p=0.5$). Finally, pairwise comparisons examined the time by group by treatment program interaction with NF+RD showing a significant change in reading scores with treatment A ($F[1,43]=17.163$, $p<0.001$) but not with treatment B ($F[1,43]=0.109$, $p=0.743$). IRD showed overall reading growth but not when each treatment program was considered individually (treatment A: $F[1,43]=3.266$, $p=0.078$; treatment B: $F[1,43]=2.775$, $p=0.103$).

Univariate ANOVA with age and Conners' Parent Rating score as covariates using post-minus pretest difference scores allowed for direct comparison of treatment A versus treatment B within each group. Consistent with the *rmANOVA*, there were no significant main effects of group ($F[1,43]=0.703$, $p=0.41$); however, there was a significant effect of tutoring program ($F[1,43]=7.6$, $p=0.009$) and a significant interaction of group by treatment

program ($F[1,43]=6.1, p=0.018$). Post hoc analysis for NF+RD using LSD revealed significantly greater reading growth with treatment A than treatment B (A: mean = +14.5, SD = 13.6; B: mean = -1.1, SD = 6.9; $p=0.002$). IRD showed no difference between treatment programs (treatment A: mean = +5.9, SD = 9.3; treatment B: mean = +3.1, SD = 9.9; $p=0.792$). NF+RD showed more reading growth than IRD with treatment A at a moderately large effect size (i.e. nearer 0.8 than 0.5). IRD showed more reading growth with treatment B than NF+RD, but only at a medium effect size (see Table III).

DISCUSSION

The first purpose of this study was to address a gap in the literature regarding whether children and adolescents with NF1 and reading deficits would respond to mainstream remedial reading instruction as well as children with IRD. Unlike untreated controls who showed no reading growth in this study, the NF+RD and IRD groups both showed significant reading growth in response to a short-term but intensive period of remedial reading instruction. This supports our hypothesis that mainstream evidence-based methods of reading instruction are appropriate for treating reading-related academic underachievement in children and adolescents with NF1.

The second goal was to determine, in the context of comparing two multisensory treatment programs, whether a relative emphasis on one sensory modality versus another would impact responsiveness. More specifically, given the visual-spatial perception deficits commonly associated with NF1, the study assessed whether a program emphasizing visual-spatial perception would be as beneficial as one emphasizing a different modality. The NF+RD group did have the expected relative weakness in visual-spatial skills compared to the equally reading-impaired IRD group.²¹ Furthermore, our NF+RD group responded better to the more kinesthetic reading program than the one requiring greater visual-spatial demands. In contrast but consistent with previous research, our IRD group responded similarly to both programs.³³ The findings support the hypothesis that students with NF+RD may respond better to multisensory approaches that do not emphasize the visual-spatial skills that are frequently an area of identified weakness. The practical implication is that, for children and adolescents with NF1, special attention should be paid to the format of reading instruction, and perhaps also instruction in other subjects such as mathematics and spelling.

An important consideration in assessing growth in reading skills in response to intervention is the role of ADHD in the response. A particular strength of this study was the direct comparison of the children with NF+RD to children with IRD, as both groups have a similarly increased risk of comorbid ADHD. In our sample, this is supported by the presence of similar numbers of children with prior diagnoses of ADHD among the NF+RD (six participants total with four on ADHD medication), IRD (four participants with two on ADHD medication), and IRD-WL (five participants with four on medication) groups. There were also two children with prior diagnoses of ADHD (one on medication) in the typically developing group. Furthermore, since the study included a direct measure to assess parental report of ADHD symptoms, it allowed us to demonstrate a lack of significant difference of symptoms across reading groups and a similar distribution of reading scores regardless of whether the Conners' Parent Rating scores indicated low (T score <50), medium (T score=

50–65) and high risk (T score >65) of ADHD. These observations support the assertion that our reading measures capture reading skill distinct from ADHD symptomatology. A related consideration is whether differences in response to different reading programs could be accounted for by ADHD symptoms. First, it is important to note that there were no differences between the two treatment programs with regard to the number of breaks from instruction with the opportunities to physically get up and move around. The tactile and kinesthetic methods associated with treatment A were limited to the use of tutoring materials that lent themselves to tactile manipulation (like tiles or chips) and a focus on the oral motor movements associated with producing different phonemes. In addition, the differential response to treatment A versus treatment B within the NF+RD group is better explained by something other than ADHD given that the IRD group, that also included similar numbers of individuals with ADHD, responded equally well to both treatment programs.

Limitations of the study include the relatively small size of the entire sample and the different group sizes. In addition, the process of random assignment to treatment program in combination with the small sample size resulted in some asymmetry of pretest reading scores, namely the NF+RD group receiving treatment B started at a mean reading score that was significantly higher than that those receiving treatment A. Overall, this may limit generalizability of the results because it is impossible to rule out concern that this higher initial reading achievement affected responsiveness more than the assigned tutoring program. However, both IRD groups started with lower reading achievement similar to the lower achieving treatment A NF+RD group; thus, the fact that there was no significant differential growth between treatment A or treatment B in IRD, suggests that lack of responsiveness to treatment B was not solely caused by higher baseline reading achievement in the NF+RD group.

In the future, studies to assess reading intervention in NF+RD would benefit from larger sample sizes and more experimental design control over the distribution of IRD participants to treatment versus non-treatment – perhaps by adding a sham tutoring condition. Nevertheless, the current study does suggest a practical starting point for addressing urgent concerns about reading and academic achievement raised by parents of children with NF1. Furthermore, while students did show improvement, they did not achieve ‘average’ reading compared to unaffected peers. Thus, a beneficial instructional treatment may benefit from being paired with one of the pharmaceutical interventions currently being considered for use in children with NF1 to improve cognitive functioning, for example lovastatin.^{4,8} For children and adolescents with NF1, pairing medication with direct instruction in the target areas of weakness, for example reading deficits in NF+RD, could afford a unique opportunity to catch-up academically to unaffected peers. Such an approach would closely parallel the mouse model pharmaceutical trials where mice with poor visual–spatial functioning before medication showed improved responsiveness to visual–spatial training after medication.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

IRD	Idiopathic reading deficit
IRD-WL	Wait-list IRD
NF1	Neurofibromatosis type 1
NF+RD	NF1 and reading deficits
WIAT-II	Wechsler Individual Achievement Test, Second Edition
WJ-III	Woodcock-Johnson Tests of Achievement, Third Edition Normative Update

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What this paper adds

- Children with NF+RD benefit from mainstream approaches to remedial reading instruction.
- They may benefit more from multisensory instruction that does not emphasize visual–spatial discrimination.
- A relevant short-term learning task for testing efficacy of drug treatments for cognitive deficits in NF1.

Figure 1.

The flow of numbers of participants from initial assessment through random assignment to treatment category. The lowest row indicates the six final study groups: untreated control groups are TD and IRD-WL. Treated Groups are IRD assigned to treatment A, IRD assigned to treatment B, NF+RD assigned to treatment A, NF+RD assigned to treatment B. TD, typically developing; IRD, idiopathic reading deficits; IRD-WL, wait-listed IRD; NF+RD, individuals with NF1 and reading deficits; NF1, individuals with NF1 without clear evidence of reading deficits.

Table I

Pretest profiles by group

	NF+RD	IRD	IRD-WL	TD	Between group differences <i>p</i> -values
Total participants (Female)	17 (6)	32 (15)	14 (3)	26 (13)	NS
Mean age in years (SD)	10.4 (1.5)	10.2 (1.9)	10.7 (2.3)	9.7 (1.5)	NS
WISC-IV FSIQ mean standard score (SD)	84.9 (12.5)	89.6 (10.1)	85.6 (12.9)	101.8 (10.5)	TD > NF+RD $p<0.001$ TD > IRD-WL, IRD $p<0.01$
WISC-IV PRI mean standard score (SD)	87.6 (17.0)	95.3 (13.4)	89.1 (16.0)	102.6 (10.7)	TD > NF+RD $p<0.01$ TD > IRD-WL $p<0.05$
WISC-IV VCI mean standard score (SD)	92.6 (12.4)	95.3 (11.5)	90.6 (11.5)	104.9 (11.5)	TD > NF+RD, IRD-WL $p<0.01$ TD > IRD $p<0.05$
Conner's Parent Rating total mean T score (SD)	61.3 (13.4)	59.5 (14.5)	61.4 (12.8)	58.2 (12.8)	NS
WJ-III letter word identification mean standard score (SD)	84.8 (8.9)	77.4 (14.2)	78.1 (12.6)	105.0 (7.7)	TD > all others $p<0.001$
WJ-III word attack mean standard score (SD)	82.2 (8.8)	83.6 (9.2)	84.9 (7.7)	102.1 (7.3)	TD > all others $p<0.001$
WIAT word reading mean standard score (SD)	85.1 (10.1)	76.4 (11.9)	77.1 (9.8)	105.6 (10.1)	TD > all others $p<0.001$
JLO mean z-score (SD)	-2.16 (1.48)	-1.08 (1.44)	-1.83 (2.17)	-0.42 (1.2)	TD > NF+RD $p<0.01$ TD > NF+RD ^a $p<0.001$ IRD > NF+RD ^a $p<0.05$
DTVP position in space mean scaled score (SD)	6.0 (4.1)	8.7 (2.5)	7.4 (3.7)	9.6 (2.8)	TD > NF+RD $p<0.01$ TD > NF+RD ^b $p<0.01$ IRD > NF+RD ^b $p<0.05$
DTVP visual closure mean scaled score (SD)	5.2 (4.2)	7.6 (5.0)	7.1 (4.5)	9.0 (3.9)	NS TD > NF+RD ^b $p<0.05$

Reported *p*-values are based on nonparametric Kruskal–Wallis analyses.

NF+RD, neurofibromatosis 1 and reading deficits; IRD, idiopathic reading deficits; IRD-WL, participants with idiopathic reading deficits on the wait list for intervention; NS, not statistically significant; SD, standard deviation; WISC-IV, Wechsler Intelligence Scale for Children 4th edition; FSIQ, full-scale IQ; TD, typically developing; PRI, perceptual reasoning index; VCI, verbal comprehension index; WJ-III, Woodcock-Johnson Tests of Achievement (third edition normative update); WIAT, Wechsler Individual Achievement Test (second edition); JLO, Judgment of Line Orientation; DTVP, Developmental Test of Visual Perception.

^a ANOVA results presented because JLO z-scores had no violations to assumptions for parametric analysis.

^b Kruskal-Wallis analysis results with the potentially biased and highly variable IRD-WL group removed to reveal the statistically significant differences between NF+RD and IRD.

Table II

Pre- and post-test WJ-III basic reading standard scores and W scores by group

Score format	Test time	Control groups		Treated groups	
		TD	IRD-WL	IRD	NF+RD
Basic reading W scores (SD)	Pre	501.2 (16.0)	467.1 (20.9)	460.7 (23.9)	470.4 (26.7)
	Post	501.1 (13.8)	467.2 (18.5)	464.9 (22.6)	476.2 (21.5)
Basic reading standard scores (SD)	Pre	103.8 (7.4)	79.6 (9.7)	78.8 (11.3)	82.2 (8.8)
	Post	103.3 (7.7)	79.5 (8.5)	81.1 (9.9)	85.0 (8.6)

TD> all groups $p<0.001$ No other significant group differences.

TD, typically developing; IRD-WL, participants with idiopathic reading deficits on the wait list for intervention; IRD, idiopathic reading deficits; NF+RD, neurofibromatosis 1 and reading deficits; SD, standard deviation.

Table III

Effect sizes for pairwise group comparisons of change in basic reading W score from pre- to post-test

	Pairwise comparisons						
	Treated versus untreated			Treated versus treated	Untreated versus untreated	Treated versus treated	
	IRD versus TD	IRD versus IRD-WL	NF+RD versus IRD-WL	NF+RD versus IRD	IRD-WL versus TD	Treatment A NF+RD versus IRD	Treatment B NF+RD versus IRD
ES Cohen's <i>d</i>	0.57	0.47	0.61	0.53	0.04	0.66	-0.49

Rule of thumb for interpreting Cohen's *d* effect sizes (small: 0.2; medium: 0.5; large: 0.8).
IRD, idiopathic reading deficits; TD, typically developing; IRD-WL, participants with idiopathic reading deficits on the wait list for intervention; NF+RD, neurofibromatosis 1 and reading deficits.