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Written language achievement in children and adolescents with neurofibromatosis type 1 and Plexiform Neurofibromas

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ABSTRACT

Neurofibromatosis type 1 (NF1) is associated with below average writing achievement. However, little is known about specific aspects of written language impacted by NF1, changes in writing over time, and associations between cognitive aspects of the NF1 phenotype and writing. At three timepoints over six years, children with NF1 and plexiform neurofibromas (PNs) completed Woodcock-Johnson tests of writing mechanics (Spelling, Punctuation & Capitalization, handwriting), written expression of ideas (Writing Samples), writing speed (Writing Fluency), and tests of general cognitive ability, executive function, memory, and attention. Children ($N = 76$, mean age = 12.8 ± 3.4 years) completed at least one baseline writing subtest. Overall writing scores were in the Average range ($M = 93.4$, $SD = 17.4$), but lower than population norms ($p = 0.002$). Scores were highest on Writing Samples ($M = 95.2$, $SD = 17.3$), and lowest for Punctuation & Capitalization ($M = 87.9$, $SD = 18.8$, $p = 0.034$). Writing scores were mostly stable over time. Nonverbal reasoning was related to some tests of writing mechanics and written expression of ideas. Short-term memory and inattention explained additional variance in Writing Samples and Spelling. Poor handwriting was associated with writing content beyond the impact of cognitive factors. Children with NF1 and PNs may benefit from early screening and writing support. Interventions should address the contribution of both cognitive and handwriting difficulties in written language.

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Academic achievement; executive function; neurofibromatosis type 1; plexiform neurofibroma; written language disability

Neurofibromatosis type 1 (NF1) is a rare genetic condition caused by pathogenic variants in the gene which codes for the protein neurofibromin (Legius et al., 2021). NF1 occurs in approximately 1:3000 births (Gutmann et al., 2017), and can be inherited from a parent or arise due to a spontaneous *de novo* variant (Gutmann et al., 2017). Neurofibromin is involved in the RAS/MAPK pathway which regulates cell growth. Alterations in neurofibromin lead to dysregulated cell growth and increases risk of benign and malignant tumors (Legius et al., 2021). NF1 can be diagnosed based on the presence of at least 2 out of 6 cardinal symptoms in the revised NIH consensus criteria or based on having one symptom and a confirmed genetic variant or parent with NF1 (Legius et al., 2021). The development and severity

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of disease manifestations vary across individuals (Gutmann et al., 2017). For example, about 25–50% of individuals with NF1 develop plexiform neurofibromas (PNs) (Prada et al., 2012), which are complex tumors that develop along the nerves of the body. While they are not malignant, they are associated with significant morbidity, including chronic pain, compression of important nearby organs, and cosmetic effects (Darrigo et al., 2007; Gutmann et al., 2017).

While not included in the diagnostic criteria, cognitive and behavioral difficulties are a critical aspect of the NF1 phenotype and have been described as one of the most impactful complications of NF1 in childhood (Gutmann et al., 2017). The mechanisms by which NF1 leads to cognitive difficulties are not fully understood and are likely multifaceted. However, current research suggests that the changes to neurofibromin associated with NF1 can directly impact cognition by changing the typical development of synaptic signaling in the brain (e.g., Miller & Halloran, 2022). Additionally, several manifestations of NF1 can have downstream cognitive effects. For example, NF1 is associated with an increased risk of brain tumors (e.g., Taddei et al., 2019), which can affect cognition directly, as can brain tumor treatment. Additionally, many children with NF1 and PNs have chronic pain (Wolters et al., 2015) which can affect attention and executive function (Beckmann & Jastrowski Mano, 2021).

Academic achievement also can be affected in NF1. Up to 50% of children with NF1, both with (Hou et al., 2020) and without PNs (Hyman et al., 2005) are diagnosed with specific learning disabilities or meaningful difficulties with academic achievement. Academic challenges have a strong impact on quality of life in individuals with NF1 and are a research priority for youth with NF1 and their parents (Del Castillo et al., 2022). In terms of writing skills, Gilboa et al. (2010) demonstrated that children with NF1 had poorer handwriting legibility compared to same-aged peers and achieved lower ratings on a measure of quality of written expression. Other studies have found that children with NF1 have poorer spelling compared to sibling controls (Hyman et al.,2003, 2005; Lehtonen et al., 2015). Struggles with written language can interfere with children's ability to demonstrate knowledge. As students progress in school, writing demands increase and they are expected to write to express their knowledge across a variety of subjects. However, despite their importance, the basic components of writing skills that are affected in NF1 are not well understood.

Writing is a complex skill involving several steps. Even writing brief amounts of information requires coordination of multiple skills. For example, to write your name, you need to 1) decide to write your name, 2) call to memory how your name is spelled, 3) remember how to form each letter or where the letter is found on the keyboard, 4) use fine motor skills and motor coordination skills to write or type, 5) remember grammatical conventions like capitalizing the first letter of your name, 6) review your finished product, and 7) identify and correct any errors (Hayes, 2006). These tasks become automatic for experienced writers. However, new writers and struggling writers may make mistakes at any one of these steps. The DSM-5-TR indicates that a child may be diagnosed with a writing disability (specific learning disorder with impairment in written expression) if they experience significant difficulty in at least one writing skill such as spelling, grammar, or clarity/organization of written expression and have not responded adequately to intervention (APA, 2022). However, children who struggle with writing tend to have impairments across multiple elements, especially as children get older and writing tasks become more complex and dependent on multiple skills (Chung et al., 2020).

Multiple aspects of the NF1 phenotype can lead to writing difficulties. For example, children with NF1 often have visual-perception difficulties (Lehtonen et al., 2015) and fine motor difficulties (Pardej et al., 2022) which can make handwriting more challenging, and may also affect other aspects of writing. Of note, Gilboa et al. (2014) found that while children with NF1 had poorer motor coordination and visual perception compared to controls, only cognitive variables were associated with written language outcomes, indicating that cognitive factors may have a stronger relationship with written language compared to motor or visual-perception skills in this population.

Children with NF1 have cognitive risk factors that may increase their likelihood of developing writing difficulties. About 30–40% of children with NF1 meet criteria for Attention Deficit Hyperactivity Disorder (ADHD) (Hyman et al., 2005; Koth et al., 2000; Pride et al., 2012). Children with ADHD show impairments across several writing skills. One population-based registry study indicates that more than half of children with ADHD also will be diagnosed with a written language disability at some point over their school career, a rate dramatically higher than controls (Yoshimasu et al., 2011). In particular, spelling impairments in ADHD are well documented (Re et al., 2007; Silva et al., 2020), and additional studies suggest that children with ADHD also have more trouble with handwriting (Berninger et al., 2017) grammar (Re et al., 2007), organization, and length of written work (Molitor et al., 2016; Re et al., 2007).

The association between ADHD and writing difficulties is hypothesized to be largely due to difficulties with attention and executive function (EF) (Re et al., 2014). Executive functioning (Miyake et al., 2000), including difficulties with working memory (Bourke et al., 2014; Vanderberg & Lee Swanson, 2007), response inhibition (Altemeier et al., 2006; Arán Filippetti & Krumm, 2020) and cognitive flexibility (Berninger et al., 2017; Lubin et al., 2016), has been linked with difficulties with various aspects of written language, including handwriting, spelling, writing fluency and organization of written language. Children with NF1 have high rates of difficulties with EF, even when they do not meet criteria for a diagnosis of ADHD (Hyman et al., 2005; Templer et al., 2013). Consequently, it is not surprising that many children with NF1 struggle with both writing mechanics (such as handwriting, grammar, spelling) and content (Gilboa et al.,2010, 2014). This finding is noteworthy, because although children with NF1 tend to have somewhat lower IQ scores compared to the general population, their verbal skills, and particularly their oral language skills (Cutting & Levine, 2010), are a relative strength (Hou et al., 2020). Cognitive factors, such as higher rates of executive dysfunction and attention problems, may pose barriers to written expression despite relatively strong verbal skills. Few studies have investigated the relationships between neurocognitive processes and writing achievement in this population (Gilboa et al.,2010, 2014). These studies found associations between general cognitive ability and both handwriting and writing content, above the effects of visual-motor skills, but did not focus on processes such as EF, memory, and inattention. The current study extends previous research by examining the profile of written expression in children with NF1 more comprehensively, including examining changes in writing over time and relationships between various cognitive functions and written language. Based on the literature discussed above, the specific aims and hypotheses of the study are as follows:

Aim 1

To describe the profile of written language achievement in NF1 and PNs in greater detail, including handwriting, grammar and mechanics, writing fluency, and ability to express ideas through written language. This aim includes describing how writing mechanics skills, such as handwriting, spelling, and grammar, are associated with writing content at baseline.

Hypothesis 1. Children with NF1 and PNs will display more problems with grammar and writing mechanics compared to the general population.

Hypothesis 2. Poorer handwriting and poorer writing mechanics will be associated with poorer written content.

Aim 2

To examine how writing skills change over time as children grow older.

Hypothesis 3. Children's written expression scores will decrease as they get older, as expectations for written language achievement increase and become more complex and more dependent on fundamental writing mechanics skills.

Aim 3

To explore associations between cognitive functioning and their relationship to written expression in this population at baseline.

Hypothesis 4. EF skills will be associated with writing mechanics and written content, over and above associations between general cognitive functioning and writing.

Materials & methods

Participants

Participants were enrolled in a longitudinal study of the natural history of NF1 (clinicaltrials.gov: NCT00924196) at the National Cancer Institute. The aims of this multidisciplinary clinical research protocol were to explore and better describe a variety of medical, functional, cognitive, and academic areas affected by NF1. Individuals were eligible for the natural history study if they were diagnosed with NF1 based on either the National Institutes of Health Consensus Conference criteria (Stumpf, 1988) and/or a confirmed pathogenic variant in the NF1 gene. For the current sub-study, data were included for children and adolescents (ages 6–18 years) with NF1 and at least one PN who were administered a baseline neuropsychological evaluation and had completed at least one subtest of written language ($N = 76$).

Procedures

Participants completed comprehensive neuropsychological testing as part of their baseline evaluation as well as approximately three and six years after baseline. The study is closed to new enrollment, although current participants continue to complete follow-up testing. Children were tested between January 15th 2008 and a cutoff date of June 1st 2022.

After the study began, investigators added additional tests to further assess written language, including the Punctuation & Capitalization subtest of the WJ-III (March 2009) and the Test of Written Language-4th edition (TOWL-4) (March 2011). For most children ($n = 34$), the TOWL-4 was given at the 3-year assessment, while 10 participants completed the TOWL-4 at their baseline assessment when time permitted. The TOWL-4 scores of these participants were combined together for this cross-sectional analysis. Some children did not complete the TOWL-4 due to scheduling and time constraints.

Measures

Demographic & medical information

Parents completed a form about their child's demographic information. They also rated the perceived severity of their child's NF1 symptoms as mild, moderate, or severe on a modified version of the NF1 Symptom Severity Scale (Ablon, 1996; Wolters et al., 2015).

Written language measures

Participants completed the Woodcock-Johnson Tests of Achievement, Third Edition (WJ-III) (Woodcock et al., 2001) consisting of the following written language subtests: 1) Writing Samples measures the ability to construct sentences to convey ideas, irrespective of grammar or spelling errors; 2) Writing Fluency measures the ability to quickly construct sentences under time pressure; and 3) Spelling measures a child's ability to correctly spell words that they hear orally. As described above, a subset of children completed the Punctuation & Capitalization subtest, which measures the child's knowledge of punctuation and capitalization rules.

Authors 1, 2 and 7 rated children's handwriting on the Writing Samples subtest using the Handwriting Legibility Scale (two raters for each child's handwriting samples). Interrater reliability was excellent (Intraclass correlation coefficient = 0.92). This scale provides a qualitative assessment of handwriting based on criteria in the WJ-III manual, including consistency in letter formation, size, spacing, slant, and line thickness. Ratings range from 0 to 100 with the following anchors: 0-illegible, 10-poor, 30-fair, 50-satisfactory, 70-very good, 90-excellent, 100-artistic.

Test of Written Language-4th edition (TOWL-4)

Subtests from the TOWL-4 (Hammill & Larsen, 2009) were administered to a subset of children ages 9–18 years to obtain an in-depth assessment of spontaneous writing.

Children completed subtests comprising the Spontaneous Writing Index, where they are provided a picture and asked to write a story about it. This test approximates real-world writing assignments a child may be asked to complete in school. For Contextual Conventions, points are obtained for correct spelling, punctuation, and adherence to grammar rules (such as noun-verb agreement). For Story Composition, points are obtained for quality of written expression, including the complexity of vocabulary, degree of character development, and clear organization and sequencing of events in the story. Points are assigned based on detailed manual instructions and compared to age norms to create a scaled score with a mean (*M*) of 10 and standard deviation (*SD*) of 3.

Spelling, Punctuation & Capitalization, Contextual Conventions, and handwriting ratings were considered measures of writing mechanics. Writing Samples and Story Composition were considered measures of written expression, while Writing Fluency was used as a measure of writing speed.

Cognitive functioning

Participants completed the Wechsler Abbreviated Scales of Intelligence (WASI), comprised of four subtests. The Block Design and Matrix Reasoning subtests yield a Performance IQ score (PIQ) and assess nonverbal reasoning. The Vocabulary and Similarities subtests yield a Verbal IQ score (VIQ) and assess word knowledge and verbal reasoning (Wechsler, 1999). This abbreviated battery was selected as opposed to completing the full Wechsler IQ tests to reduce participant burden.

Executive functioning

Participants completed the Delis Kaplan Executive Function System (DKEFS) Verbal Fluency and Trailmaking subtests. Scaled scores ($M = 10$, $SD = 3$) from the Category Switching (Verbal Fluency) and Number Letter Switching (Trailmaking) tasks were used as measures of cognitive flexibility (Delis et al., 2001). From the Conners' Continuous Performance Test Second Edition (CPT-II) (Conners, 2000), errors of commission, presented as T-scores ($M = 50$; $SD = 10$), were considered a measure of response inhibition (Commissions). Parents completed the Behavior Rating Inventory of Executive Function (BRIEF), an observer report of an individual's EF behavior in real-world situations (Gioia et al., 2000), which generates T-scores in several domains as well as an overall Global Executive Composite (GEC). Higher GEC T-scores suggest greater overall EF behavioral difficulties and the GEC was used as a measure of parent-reported EF.

Attention

Scores from the Conners CPT, errors of omission (Omissions) and hit response time (CPT Hit RT) were considered to be measures of inattention (Conners, 2000).

Memory

Scaled scores from the Digit Span (DS) subtest from the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) (Wechsler, 2003) or the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) (Wechsler, 1997) measured short term auditory memory.

Psychomotor speed

Participants completed Symbol Search and Coding subtests from the WISC-IV (Wechsler, 2003) or WAIS-III (Wechsler, 1997). These paper-and-pencil tests ask individuals to mark matching shapes or create simple shapes under time pressure. The scaled scores are combined to produce a Processing Speed Index (PSI; $M = 100$, $SD = 15$), which was analyzed for this study.

Analyses

Descriptive statistics were used to describe performance across written language subtests in the sample. One sample t-tests were used to compare written language subtest scores to the normative mean ($M = 100$, $SD = 15$). Bivariate correlations, independent sample t-tests and ANOVAs were used to examine the relationships between demographic characteristics and writing, as appropriate. Due to the ordinal nature of handwriting ratings, Spearman's correlations and Mann Whitney U tests were used to assess between-group differences in handwriting. Repeated measures ANOVA was used to compare within-subject performance across written language subtests as well as to compare differences in WJ-III performance over time. Bonferroni corrections were used when appropriate for multiple comparisons.

Multiple regression was used to evaluate relationships between cognitive factors and written language. To allow for testing of each theoretically relevant predictor, first, simple regression was used to evaluate the relationship between each cognitive predictor and each writing outcome. A combined multiple regression model was then created for each writing outcome. First, significant demographic covariates were added to the model in one block. Then, each significant cognitive predictor identified via simple regression was included simultaneously in the next block. When handwriting was associated with the writing outcome, an additional block was added to the model assessing how handwriting was associated with writing after accounting for cognitive factors.

Results

Participant characteristics

Seventy-six children (mean age = 12.75 years, $SD = 3.36$, 59.2% male) were included in this sub-study. The majority of the sample (75%, $n = 57$) were White. Parents had an average of approximately 14 years of education. About one third (35.5%) of children ($n = 27$) had a parent-reported learning disability, including 22.4% ($n = 17$) with a writing disability. About a third of participants (32.9%; $n = 25$) had a parent-reported diagnosis of ADHD. Comprehensive demographic characteristics are reported in Table 1. Baseline cognitive scores are reported in Table 2.

Aim 1: Baseline written language achievement

Mean scores on baseline WJ-III subtests of written language are reported in Table 3. Scores on Writing Samples, Fluency, and Spelling were within the Average range, while the mean Punctuation & Capitalization score was in the Low Average range. Mean scores on overall writing performance and on each subtest were significantly below the

Table 1. Participant characteristics at baseline.

Mean Age (SD)	12.75 (3.36)
Mean Years of Maternal Education (SD)	14.4 (2.7)
Sex	Percent (n)
Male	59.2% (45)
Female	40.8% (31)
Race/Ethnicity	
White	75% (57)
Black	7.9% (6)
Hispanic	3.9% (3)
Asian American	2.6% (2)
Multiracial/Other	10.5% (8)
NF1 Severity	
Mild	35.5% (27)
Moderate	53.9% (41)
Severe	10.5% (8)
NF1 type	
Familial	43.4% (33)
Non-Familial	47.4% (36)
Unknown	9.2% (7)
Written Language Disability	22.4% (17)
ADHD diagnosis	32.9% (25)

Table 2. Baseline cognitive function.

	N	Mean (SD)	% Below Average
Performance IQ	76	94.68 (15.36)	36.8%
Verbal IQ	76	98.71 (16.12)	18.4%
Processing Speed Index (PSI)	74	90.41 (16.84)	39.2%
DKEFS Letter-Number Switch	66	7.98 (3.82)	37.9%
DKEFS Category Switch	67	9.84 (3.03)	23.9%
Digit Span	75	8.31 (2.67)	38.7%
CPT Commissions	72	53.85 (10.50)	31.9%
CPT Omissions	72	55.02 (13.66)	23.6%
CPT Hit Response Time	72	48.11 (12.54)	15.3%
BRIEF GEC	73	57.71 (11.27)	31.9%

*Scores 1 standard deviation below the mean were considered below average, this is below 85 for standard scores, 7 or below for scaled scores, 60 or higher for T scores.

Table 3. Baseline written language.

	N	Mean (SD)	% Below Average*	*p* value (One Sample t-test)
Broad Written Language Composite	74	93.38 (17.39)	25.7%	0.002
Writing Samples	76	95.21 (17.32)	25.0%	0.018
Writing Fluency	71	93.69 (17.95)	35.2%	0.004
Spelling	76	92.51 (17.23)	34.2%	<0.001
Punctuation & Capitalization	40	87.85 (18.79)	42.5%	<0.001
Handwriting Ratings	74	32.07 (21.19)	33.8%	N/A

*Scores <85 are considered below average.
*Using Bonferroni correction for related multiple comparisons, the significance level for each one sample t-test was set to .01.

population mean (Table 3). Using Bonferroni correction to account for multiple comparisons, each subtest remained significantly below the population mean, with the exception of Writing Samples. Within-subject differences across subtests were significant (F [3,36] = 3.499, $p = 0.025$). Post-hoc pairwise comparisons indicated that Writing Samples scores were higher than the Punctuation & Capitalization scores ($p = 0.034$). Children with a parent-reported writing disability ($n = 17$) had lower scores on all WJ-III written language subtests compared to those with no reported writing disability. Children who had not previously been identified as having a writing disability ($n = 59$) had written language scores that did not differ from the population mean, with the exception of Punctuation & Capitalization scores, which remained below the population mean (M = 90.97, SD = 17.46, t[33]=-3.016, $p = 0.005$).

Handwriting

The median handwriting rating was in the "Fair" range (35.2/100). About one-third of children (33.8%, $n = 25$) were rated as having illegible to poor handwriting (10 or lower).

Associations between written language scores and demographic characteristics

There were few associations between demographic variables and writing. There were no differences in scores on the WJ-III written language subtests by sex, age, or race/ethnicity. Children with a parent with NF1 had lower Punctuation & Capitalization scores ($n = 18$, $M = 80.78$, $SD = 16.0$) compared to those without a biological parent with NF1 ($n = 15$, $M = 96.87$, $SD = 11.38$, $p = 0.003$). Maternal education was associated with writing fluency scores ($n = 69$, $r = 0.30$, $p = 0.014$). Children with parent-reported ADHD had descriptively lower scores on all written language subscales, but these differences were not statistically significant.

There were several demographic factors associated with handwriting. Female participants (M rank = 44.85) were rated as having better handwriting compared to male participants (M rank = 32.20, U [$N_{female} = 31$ $N_{male} = 43$] = 438.5, z=-2.508, $p = 0.012$). Older children had higher handwriting ratings ($n = 74$, Spearman's rho = 0.43, $p <$ 0.001) as expected. Median handwriting varied with age, such that early elementary school age children (6–8 years, $n = 10$) had median handwriting ratings in the illegible range (7.5/100), later elementary school age children (9–11 years, $n = 20$) had median ratings in the poor range (22.5/100), middle school age children (12–13 years, $n = 17$) had ratings in the fair-to-satisfactory range (42.5/100), and high school age children (14–18 years, $n = 27$) had ratings in the fair range (35/100). However, even among children of high school age (≥14), over one-third (37%, $n = 10$) had lower than "fair" handwriting. Children with parent-reported ADHD had lower handwriting ratings (M rank = 30.15) compared to those without ADHD (M rank = 40.81, U [$N_{ADHD} = 23$ $N_{no\ ADHD} = 51$] = 417.5, z=-1.982, $p = 0.048$). NF1 severity, parental NF1 status, maternal education, and parent-reported writing disability diagnosis were not associated with handwriting.

Associations between writing mechanics and written expression

Among subtests, Spelling ($r = 0.68$, $p < 0.001$) and Punctuation & Capitalization ($r = 0.57$, $p < 0.001$) were moderately associated with Writing Samples scores. Higher handwriting ratings were associated with higher Writing Samples (rho = 0.25, $p = 0.03$), Spelling (rho = 0.41, $p < 0.001$), and Punctuation & Capitalization scores (rho = 0.33, $p = 0.046$) (Table 4). All associations between written language subtests remained significant after Bonferroni correction. In terms of handwriting ratings, only the relationship between Spelling and handwriting remained significant after Bonferroni correction.

Table 4. Correlations between cognitive function and writing scores.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. PIQ														
2. VIQ	0.58**													
3. PSI	0.50**	0.39**												
4. NLS	0.62**	0.48**	0.70**											
5. CS	0.43**	0.49**	0.51**	0.36**										
6. DS	0.51**	0.53**	0.31*	0.50**	0.45*									
7. CPT Comm	0.02	−0.21	0.03	0.00	0.0	−0.06								
8. CPT Omm	−0.20	−0.13	−0.21	−0.24	−0.12	−0.35**	−0.18							
9. CPT HitRT	−0.18	−0.01	−0.32**	−0.34**	−0.16	−0.24	−0.60**	0.60**						
10. BRIEF	−0.29*	−.31**	−0.38**	−0.23	−0.30*	−0.22	0.17	0.12	−0.03					
11. WJ Samples	0.55**	0.53**	0.40**	0.44**	0.39**	0.62**	0.11	−0.38**	−0.32**	−0.13				
12. WJ Fluency	0.60**	0.59**	0.57**	0.61**	0.45**	0.62**	0.12	−0.38**	−0.39**	−0.28*	0.65**			
13. WJ Spelling	0.46**	0.43**	0.37**	0.43**	0.38**	0.65**	0.16	−0.24*	−0.33**	−0.12	0.68**	0.63**		
14. WJ P & C	0.70**	0.66**	0.43**	0.42**	0.57**	0.67**	−0.02	−0.41*	−0.20	−0.28	0.57**	0.60**	0.68**	
15. Handwriting	0.16	0.06	0.27*	0.07	0.31*	0.21	0.22	−0.14	−0.32**	−0.28*	0.28*	0.17	0.41**	0.30

PIQ = Performance IQ, VIQ = Verbal IQ, PSI = Processing Speed Index, NLS = DKEFS Number-Letter Switching, CS = DKEFS Category Switching, DS = Digit Span, CPT Comm = CPT commissions, CPT Omm = CPT omissions, CPT HitRT = CPT Hit response rate, BRIEF = BRIEF Global Executive Composite, WJ Samples = Woodcock-Johnson Writing Samples, WJ Fluency = WJ Writing Fluency, WJ Spelling = WJ Spelling, WJ P&C = WJ Punctuation&Capitalization *p<.05, **p<.01. All correlations in this table are pearson correlations. Spearman Rho values for associations between handwriting and written language outcomes are reported in the text. Spearman rho values for associations between handwriting and cognitive scores are available upon request.

Table 5. Correlations between WJ-III writing tests and TOWL scores.

	Contextual Conventions	Story Composition
Spelling	0.64***	0.35*
Writing Fluency	0.57***	0.40**
Writing Sample	0.54***	0.39*
Punctuation & Capitals	0.46***	0.31*
Handwriting	0.35*	0.30

^Each academic skill was measured contemporaneously with the TOWL score. For those who completed the TOWL-4 at baseline, baseline academic skills were used, for those who completed the TOWL-4 at 3 years, academic skills at 3 year follow-up were used.
*$p < 0.05$.
**p <0 .01.
***p <0. 005 (significance level for Bonferroni correction).

Detailed written language testing

Forty-four children completed more detailed tests of written language using the TOWL-4 (M age = 14.04 years, SD = 2.68, range = 9.3–20.6 years). Both Contextual Conventions (M = 9.07, SD = 2.73) and Story Composition scores (M = 10.07, SD = 4.07) were within the Average range. Scores did not differ based on age, race, sex, parental NF status, NF1 symptom severity or mother's years of education. The Story Composition mean score did not differ from the population mean ($p > 0.05$), while Contextual Conventions mean score was lower compared to the population mean (t[43]=-2.263, $p = 0.029$), although this difference was not significant after correcting for multiple comparisons. Children with a history of ADHD ($n = 17$, $M = 7.76$, SD = 2.658) had lower Contextual Conventions scores compared to those without ADHD ($n = 27$, $M = 9.89$, SD = 2.486; t (42) = 2.687, $p = 0.012$), but these groups did not differ on Story Composition. Children with a Written Language Disability ($n = 11$) scored lower on both Contextual Conventions ($M = 7.55$, SD = 2.018) and Story Composition ($M = 7.45$, SD = 4.655) compared to those without a Written Language Disability ($n = 33$; Contextual Conventions: $M = 9.58$, SD = 2.773, t(42) = 2.232, $p = 0.031$; Story Composition: M = 10.94, SD = 3.508, t(42) = 2.625, $p = 0.012$). In terms of specific areas of difficulty within criteria for Contextual Conventions, 63.6% ($n = 28$) of children with NF1 misspelled at least six words in their story. Similarly, 63.6% ($n = 28$) had at least one run-on or rambling sentence. Over half of the sample, 56.8% ($n = 25$), failed to capitalize the first word of at least some sentences. Even older children (≥14 years, $n = 22$) struggled with aspects of Contextual Conventions. Fifty percent ($n = 11$) of older children had six or more misspelled words, 45.5% ($n = 10$) used at least one run-on or rambling sentence, and 50% ($n = 11$) had at least one capitalization error. Scores on each WJ-III writing subtest were significantly associated with Contextual Conventions and Story Composition scores. Handwriting was associated with Contextual Conventions scores, but not Story Composition scores (Table 5).

Aim 2: Written language achievement over time

Seventy-five percent of the sample ($n = 57$) completed at least one written language subtest on the WJ-III at the 3-year follow-up evaluation (mean time to follow up = 3.15 years, SD = 0.48; mean age at follow-up = 15.37, SD = 3.42) and 40.8% of the sample ($n = 31$) completed at least one written language subtest on the WJ-III at 6-year follow-up (mean time to follow up = 6.25 years, SD = 0.67; mean age at follow-up = 16.97, SD =

2.70). Reasons for missing follow-up testing included: attrition from the natural history study, participant declined or was unable to schedule further cognitive evaluations, participant completed cognitive testing but was missing written language testing, follow-up testing date missed due to the COVID-19 pandemic, or the participant had not yet reached time for follow-up testing. Unfortunately, six participants passed away in between baseline and follow up testing. Participants lost to follow up did not differ from those who completed follow-up in terms of baseline cognitive factors, written language scores, or demographic factors, except that those lost to follow up at three years were older at baseline ($M = 14.33$, $SD = 2.65$) compared to those who returned for follow-up ($M = 12.22$, $SD = 3.42$, $t[74] = 2.450$, $p = 0.008$). Participants lost to follow up at 6 years also were older at baseline ($M = 14.15$, $SD = 3.03$) compared to those who returned ($M = 10.72$, $SD = 2.75$, $t[74] = 5.014$, $p < 0.001$). Participants who were lost to follow up at each time point had higher handwriting ratings at baseline, likely due to the positive association of handwriting ratings and age.

Mean scores across written language subtests were compared for the paired samples who had both baseline and 3-year scores (Figure 1). Paired sample t-tests indicated a significant decrease in spelling scores from baseline ($M = 92.87$, $SD = 17.40$) to the 3-year follow-up ($M = 89.65$, $SD = 17.91$, $t[54] = 2.868$, $n = 55$, $p = 0.006$). This decrease remained significant after correcting for multiple comparisons. No other changes were significant. Repeated measures ANOVA was used to compare scores for the group of patients who had baseline, 3-, and 6-year assessments (Figure 2). There were no significant changes in scores between the three timepoints. There were three outliers (>2.5 SDs from the mean) in Writing Samples at three-year follow-up, making the variable kurtotic. Removing outliers reduced the kurtosis to acceptable levels. However, there were still no significant changes in Writing Samples scores when removing these outliers. Mann Whitney U tests for related samples

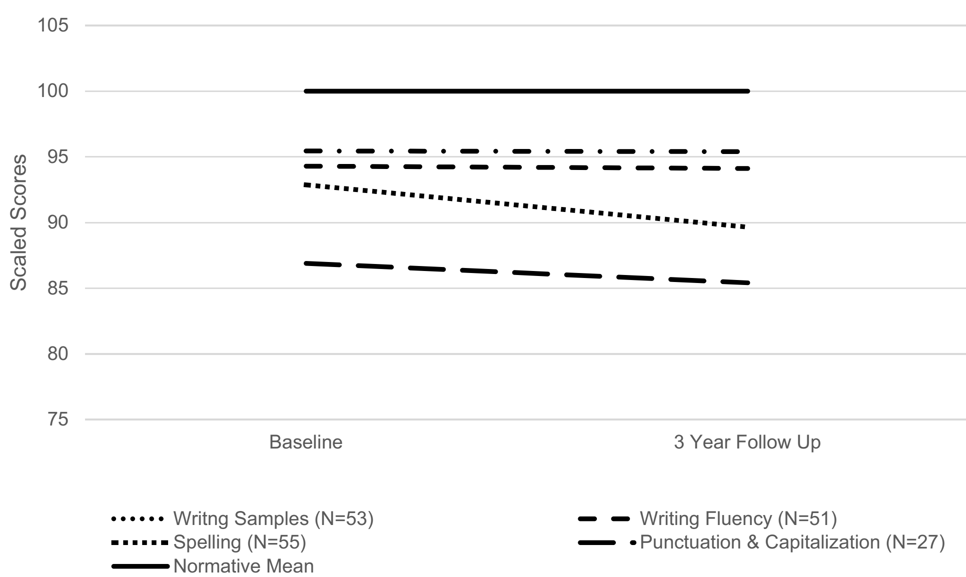

Figure 1. Mean written language scores over three years.

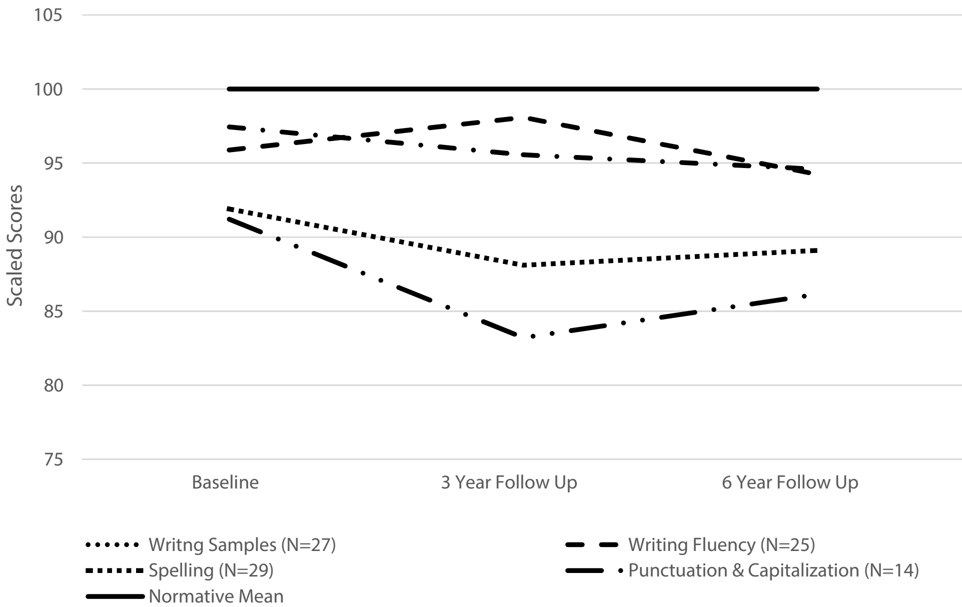

Figure 2. Mean written language scores over six years.

indicated that children had higher handwriting ratings at 3-year follow-up (Mean rank = 36.74) compared to baseline (Mean rank = 32.07, U [$N_{followup}$ = 43 $N_{baseline}$ = 74] = 630.5, z = 4.216, $p < 0.001$).

Aim 3: Associations between cognitive functioning and written language domains

Zero order correlations between written language subtests and cognitive function are reported in Table 4. Results of the combined multiple regression models looking at the impact of specific cognitive functions on each written language domain are described below.

For Writing Samples ($n = 61$), measures of nonverbal reasoning (PIQ), verbal reasoning (VIQ), short-term memory (DS), psychomotor speed (PSI), cognitive flexibility (DKEFS trails and DKEFS verbal fluency), and inattention (CPT Hit RT, CPT Omissions) were included in the combined model, and explained 58.7% of variance, (F [8,52] = 9.255, $p < 0.001$). Two cognitive scores contributed individual variance: PIQ (β = 0.310, $t = 2.435$, $p = 0.018$), and DS (β = 0.330, $t = 2.725$, $p = 0.009$). After accounting for cognitive factors, when adding handwriting to a second block, handwriting was associated with 4.4% increase in variance ($n = 60$, ΔF [1, 50] = 5.707, $p = 0.021$).

For Writing Fluency ($n = 56$), maternal education was entered first, and cognitive variables, including verbal and nonverbal reasoning (VIQ, PIQ), short-term memory (DS), psychomotor speed (PSI), cognitive flexibility (DKEFS trails and DKEFS verbal fluency), inattention (CPT Hit RT, CPT Omissions) and parent reported executive function (BRIEF GEC) were entered into a second block. The overall model explained 69.2% of variance (F [10,45] = 10.122, $p < 0.001$). VIQ (β = 0.342, $t = 2.777$, $p = 0.008$), DS (β = 0.238, $t = 2.080$, $p = 0.043$), and CPT Hit response time (β=-0.277, t=-2.392, p = 0.021) each explained unique variance in scores.

For Spelling ($n = 61$), verbal and nonverbal reasoning (VIQ, PIQ), short-term memory (DS), psychomotor speed (PSI), inattention (CPT Omissions, CPT HitRT) and cognitive flexibility (DKEFS trails and DKEFS verbal fluency) were added into the model. The overall model explained 44.8% of variance ($F[8,52] = 5.267$, $p < 0.001$). DS ($\beta = 0.390$, $t = 2.783$, $p = 0.007$) and CPT HitRT (β=-0.342, t=-2.483, $p = 0.016$) each explained unique variance. After accounting for cognitive factors, when adding handwriting into a second block, handwriting was associated with 14.7% increase in variance ($n = 60$, ΔF [1, 50] = 16.936, $p < 0.001$).

For Punctuation & Capitalization ($n = 28$), having a parent with NF1 was entered first, and verbal and nonverbal reasoning (VIQ, PIQ), short-term memory (DS), psychomotor speed (PSI), inattention (CPT Omissions) and cognitive flexibility (DKEFS trails and DKEFS verbal fluency) were added into a second block. The overall model explained 67.6% of variance ($F[8,19] = 4.952$, $p = 0.002$). After accounting for the effects of having a parent with NF1 ($\beta = 0.362$, $t = 2.148$, $p = 0.045$), no cognitive variables contributed unique variance. Adding handwriting into a third block did not add additional variance.

For Contextual Conventions ($n = 40$), verbal and nonverbal reasoning (VIQ, PIQ), psychomotor speed (PSI), inattention (CPT Omissions, CPT HitRT) and cognitive flexibility (DKEFS trails) and parent reported executive function (BRIEF) were added into the model. The overall model explained 51.7% of variance ($F[7,32] = 4.899$, $p = 0.001$). PIQ ($\beta = 0.389$, $t = 2.290$, $p = 0.029$) and CPT HitRT (β=-0.334, t=-2.107, $p = 0.043$) each explained unique variance in the model.

For Story Composition ($n = 43$), nonverbal reasoning (PIQ), psychomotor speed (PSI), inattention (CPT Omissions, CPT HitRT) were added into the model. The overall model explained 22.8% of variance ($F[4,38] = 2.806$, $p = 0.039$), but no individual predictor accounted for unique variance.

Discussion

This study comprehensively examined the handwriting and written language skills of children with NF1 and PNs. In examining the profile of writing skills in this population (aim 1), we found that children with NF1 and PNs tended to have stronger skills in written expression of ideas compared to their skills in writing mechanics. Children's strongest performance on the WJ-III writing tests was on the subtest assessing written expression of ideas (Writing Samples). Children's performance on the longer, more detailed TOWL-4 test of writing content (Story Composition) was similarly strong, with average performance comparable to population norms. In line with hypothesis 1, children in our sample struggled more with writing mechanics compared with expectations for their age. Specifically, children performed below expectations for their age on tests of spelling and punctuation and capitalization. Children in the sample had particular difficulty with punctuation and capitalization skills, with slightly under half scoring over a standard deviation below the population mean on this subtest.

As also described in aim 1, we investigated associations between different writing skills. We found that spelling, punctuation and capitalization, and writing fluency each were associated with written expression of ideas on both a subtest from the same test (WJ-III Writing Samples) and from a different test (TOWL-4 Story Composition). Handwriting was associated with spelling and with one of the two tests of writing content

(Writing Samples) over and above the effects of cognitive factors. Subsequently, the second hypothesis about writing mechanics being associated with written expression of ideas was partially supported. Prior research has found that poor handwriting and poor spelling can exacerbate each other (Pontart et al., 2013; Sumner et al., 2014), as spelling and handwriting difficulties may each increase memory load and slow down transcription. Similarly, poor handwriting may impact quality of written expression of ideas by increasing the load on the writer's short-term memory while they are writing. In addition to direct effects, it is likely that difficulties with writing mechanics can affect school performance indirectly. Children with poorer writing mechanics skills may get more frustrated while writing, reducing their motivation to complete writing assignments. Poor handwriting also can affect performance indirectly by negatively influencing teachers' perceptions of children's writing skills (Klein & Taub, 2005). Children with NF1 who are struggling with writing may benefit from interventions and accommodations focused on improving writing mechanics; the resulting improvements may allow the child's skills in written expression to be more apparent. Accommodations that are helpful for children without NF1 who have writing disabilities are likely to be useful in this population as well. For example, children with very poor handwriting and/or writing fluency may benefit from assistive devices and programs, such as typing and voice-to-text software. Children who struggle with spelling may benefit from spellcheck programs (Cado et al., 2019). Structured instruction and tutoring in writing mechanics may also be beneficial (Chung et al., 2020). Occupational therapy may be helpful in addressing handwriting problems, especially in light of the high rates of sensorimotor problems among children with NF1 (Pardej et al., 2022;).

As technology becomes more integrated into school curricula, children are less likely to practice handwriting as frequently and are using word processing programs to write more often. These programs minimize the need to handwrite and provide aids to check grammar and spelling, which may be beneficial to children with NF1. However, it is noteworthy that typing may not be so straightforward for children with NF1. Similar to handwriting, typing requires sensorimotor, planning, and short-term memory skills. Prior research has found that students who have poor typing abilities (Oullette & Tims, 2014) and younger writers who are less familiar with typing (Wollscheid et al., 2016) have poorer writing content when they type compared to when they handwrite. There are some suggestions that when students are taught to improve their typing skills, their typed written language content improves as well (van Weerdenburg et al., 2019). Future research should examine how typing and using computers affect writing and assess whether typing is an effective intervention for children with NF1.

In investigating aim 2, we found that standardized writing scores were relatively stable as children got older, although children tended to have more significant difficulties with spelling over time, partially supporting the third hypothesis. As expected for a non-standardized rating, older children had higher average handwriting ratings and these ratings improved over time. However, a significant portion of older high school age children with NF1 were rated as having poor handwriting. While it is unclear how these results compare to the general population, these results are similar to findings that children with NF1 tend to have fine and gross motor difficulties starting from a very young age, and while their motor skills improve over time, the rate of gain is slower than peers without NF1 (Pardej et al., 2022). As children with NF1 get older, their continued difficulties with skills like spelling, punctuation, and capitalization may stand out more compared to their peers. Given that children's written language skills do not appear to improve on their own, early and continued intervention may be especially important to prevent these difficulties from snowballing and impacting performance in other academic areas. As described in aim 1, most children with written language difficulties in this sample had previously been identified as having a specific learning disability in written language. Early screening for learning disabilities in written language among children with NF1 is likely to be effective in identifying the children with NF1 with the greatest need for intervention.

Our investigation of aim 3 indicated that several cognitive skills were important to written language achievement. After accounting for demographic factors, general intellectual functioning was related to both measures of written content (Writing Samples) and writing mechanics (Writing Fluency, Contextual Conventions). In particular, nonverbal reasoning was associated with Writing Samples and Contextual Conventions. It is important for parents and teachers to understand that children with NF1 who have strong oral verbal skills still may struggle with written language due to difficulties with nonverbal reasoning and analysis. Regarding our fourth hypothesis, specific cognitive functions, but not specifically EF, also were associated with writing, over and above the effects of general intellectual functioning. In particular, short-term memory explained meaningful variance in measures of writing content (Writing Samples), mechanics (Spelling), and speed of writing (Writing Fluency). This result is similar to previous findings that working memory impacts various aspects of written language performance, including spelling, fluency and content of written expression in children, and accounts for at least some of the impact ADHD has on written expression (Soto et al., 2021). Measures of inattention also were associated with writing mechanics (Spelling, Writing Fluency, Contextual Conventions). These findings underscore the need for interventions integrating support for cognitive skills along with writing instruction (Mason et al., 2011). In particular, the association of short-term memory across writing tasks suggests that children would benefit from supports to minimize the demands on a child's memory while they are writing. To this end, educators can help children by reducing the number of steps they need to complete while writing, including providing aids such as SpellCheck, or teaching children to use graphic organizers and other reminders of steps needed for writing as they work.

While our sample had a significant number of children with prior parent-reported diagnoses of ADHD and/or Written Language Disability, it appears unlikely that these comorbidities explain all the difficulties with written language in NF1. Written language scores were lower among children with ADHD, but these differences did not reach statistical significance. Children with ADHD are more likely to have difficulties with attention and short-term memory that can affect their writing skills. However, children with NF1 often experience such cognitive difficulties without meeting full criteria for ADHD (Templer et al., 2012; Hyman et al., 2005), possibly minimizing differences between the groups. As expected, children in our sample with diagnosed Written Language Disability had lower writing scores. However, children without a known Written Language Disability still struggled with punctuation and capitalization, suggesting that these aspects of writing mechanics may be a more pervasive area of weakness for children with NF1. A response to intervention framework where children can receive support before receiving a diagnosis or special education classification (Fletcher & Vaughn, 2009) may be especially useful in this population as children with NF1 may struggle with writing even in the absence of a specific learning disability.

Limitations

Despite the many strengths of this study, there are some limitations to consider. First, there are limits to the generalizability of these findings because the participants were all children with NF1 and PNs, who may have more severe clinical presentations compared to the general NF1 population. Additionally, our sample was mostly non-Hispanic White, but NF1 is equally prevalent across racial and ethnic groups. Recruiting more diverse samples, such as by engaging community stakeholders and creating recruitment plans specific to the target community (Ejiogu et al., 2011; Valerio et al., 2016), should be a priority for future research on NF1. While this study focused on cognitive functions that affect written language, future research would benefit from also examining the role of physical factors, such as visual acuity and fine motor skills, and their relationship with cognitive factors in the development of written language skills in children with NF1.

It is also important to note that clinically used measures of intelligence, attention, memory, and executive function were selected to evaluate specific cognitive constructs for this natural history study and to provide clinical results and recommendation to participants, although these tests may not be the most rigorous measures for assessing these constructs. Future research may benefit from using more experimental and robust measures of working memory and related constructs to further examine these domains. Another limitation is that handwriting was assessed using a subjective measure, although the reliability between raters was very high. Moreover, it was not possible to determine how handwriting ratings in our sample compare to the general population. Other methods, such as computer ratings of handwriting, may be important to explore in future research.

An additional limitation is that our sample size was relatively small, especially at follow-up timepoints and for the multiple regression analyses. There may have been cognitive variables important to written language at later evaluations that were therefore undetected in our study. However, given that NF1 is a rare disease, our longitudinal sample size could be considered respectable. Additionally, the current study did not have a control group, and instead compared results from our sample to the general population and focused on relationships among measures withtin the sample. However, future research using control groups may provide more rigorous tests of diffencences between children with NF1 and the general population. Finally, recommendations for standard measures of academic achievement are currently being developed by the Response Evaluation in Neurofibromatosis and Schwannamatosis (REiNS) collaboration (P.L. Wolters, personal communication, December 19 2022). Using a standard set of measures may be helpful to allow data to be merged across studies, increasing power for studies of NF1, and other rare conditions.

Conclusions and future directions

Prior research has indicated that children with NF1 have lower academic achievement, including difficulties with writing. The current study reinforces this finding among children with NF1 and PNs, and extends prior research by highlighting the importance of focusing on sub-skills needed for writing, including disaggregating writing mechanics from writing content, and the impact of cognitive processes, such as memory and inattention. Additional research is needed to evaluate early screening assessments and treatment programs that may be most helpful to identify and support children with NF1 who begin to exhibit writing difficulties as well as to assess the effects of other aspects of the NF1 phenotype, like sensorimotor problems and pain, on writing. Given the difficulties in written language skills and impact on academic functioning, there is sufficient research to indicate that early and continued interventions across a variety of disciplines is clearly needed for children with NF1.

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