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Research Article

Longitudinal association between executive function and academic achievement in children with neurofibromatosis type 1 and plexiform neurofibromas

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Abstract

Objective: To examine how executive functioning (EF) relates to academic achievement longitudinally in children with neurofibromatosis type 1 (NF1) and plexiform neurofibromas (PNs) and whether age at baseline moderates this relationship. **Method:** Participants included 88 children with NF1 and PNs (ages 6–18 years old, $M = 12.05$, $SD = 3.62$, 50 males) enrolled in a natural history study. Neuropsychological assessments were administered three times over 6 years. EF (working memory, inhibitory control, cognitive flexibility, and attention) was assessed by performance-based (PB) and parent-reported (PR) measures. Multilevel growth modeling was used to examine how EF at baseline related to initial levels and changes in broad math, reading, and writing across time, controlling for demographic variables. **Results:** The relationship between EF and academic achievement varied across EF and academic domains. Cognitive flexibility (PB) uniquely explained more variances in initial math, reading, and writing scores; working memory (PB) uniquely explained more variances in initial levels of reading and writing. The associations between EF and academic achievement tended to remain consistent across age groups with one exception: Lower initial levels of inhibitory control (PR) were related to a greater decline in reading scores. This pattern was more evident among younger (versus older) children. **Conclusions:** Findings emphasize the heterogeneous nature of academic development in NF1 and that EF skills could help explain the within-group variability in this population. Routine cognitive/academic monitoring via comprehensive assessments and early targeted treatments consisting of medication and/or systematic cognitive interventions are important to evaluate for improving academic performance in children with NF1 and PNs.

Keywords: working memory; attention; inhibitory control; cognition; math; reading; neuropsychological test; multilevel analysis

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Neurofibromatosis type 1 (NF1) is a genetic disorder affecting approximately 1:3500 individuals worldwide and characterized by a wide range of tumors (e.g., plexiform neurofibromas [PNs]) and non-tumor manifestations that can negatively impact quality of life (Gutmann et al., 2017; McClatchey, 2007). Cognitive impairments and academic difficulties are common non-tumor manifestations of NF1 (Lehtonen et al., 2015; Vogel et al., 2017). Many studies of the general population have demonstrated that cognitive functioning, particularly executive functioning (EF), is a significant predictor of academic achievement (Diamond, 2013; Spiegel et al., 2021). Some cross-sectional studies on the link between EF and academic achievement in the NF1 population showed inconsistent findings (Gilboa et al., 2014; Janke et al., 2014). The current study aims to provide a comprehensive understanding of how EF predicts academic achievement in children with NF1, addressing several gaps in the existing literature. Understanding the cognitive factors contributing to academic problems longitudinally will inform future interventions to help remediate learning difficulties and improve quality of life in youth with NF1.

EF and academic achievement in the general population

EF is a higher-order prefrontal cognitive capacity responsible for goal-directed behavior (Diamond, 2013; Spiegel et al., 2021). Despite definitional inconsistencies regarding the specific cognitive abilities that are involved in EF, prior studies tend to agree on three core components: (a) working memory, the ability to keep information in mind and mentally manipulate information; (b) inhibitory control, the ability to resist distractions and temptations to do what is needed; and (c) cognitive flexibility, the ability to flexibly adjust to new rules and change perspectives (Diamond, 2013; Spiegel et al., 2021). Some scholars conceptualize attention, the

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ability to focus on one thing and ignore distractions, as the fourth component of EF (Jacob & Parkinson, 2015).

EF plays an important role in various aspects of life, from school success to job success (Diamond, 2013). Recent studies focusing on the relation between EF and academic achievement have demonstrated that EF is widely associated with math, reading, writing, and oral language (Ahmed et al., 2019; Berninger et al., 2017; Jacob & Parkinson, 2015; Spiegel et al., 2021). These prior studies suggest that the link between EF and academic achievement may vary across EF domains, academic domains, age, and types of measure. A recent meta-analysis of 299 studies focusing on school-age children found that working memory, compared to inhibitory control and cognitive flexibility, was more strongly associated with academic achievement and the effect sizes were similar across math and reading. Moreover, working memory was associated more strongly with math and reading than oral language (Spiegel et al., 2021). In early (versus late) elementary school, inhibitory control was associated more strongly with reading and oral language, and cognitive flexibility was associated more strongly with math (Spiegel et al., 2021). Another meta-analysis study demonstrated that the four EF components (working memory, cognitive flexibility, inhibitory control, attention) were associated with math and reading similarly, and the association seemed to be stronger for performance-based (PB) (versus informant-reported) measures (Jacob & Parkinson, 2015). Additionally, a study found that PB (versus informant-reported) measures of EF accounted for more variances in reading, writing, and oral language skills during middle childhood to early adolescence (Berninger et al., 2017).

EF and academic achievement in the NF1 population

Most studies on EF and academic achievement in the NF1 population used a cross-sectional and between-group design to compare EF and academic achievement of individuals with NF1 with a control group. These studies found that children with NF1 have lower EF, academic achievement (e.g., math, reading, writing), and educational attainment than the normative control group (Arnold et al., 2021; Beaussart et al., 2018; Johansson et al., 2021). For example, a recent meta-analysis of 19 studies on EF in children with NF1 (ages 2–18) found a moderate effect for overall EF impairment compared to controls, and the extent of impairment varied across EF domains (Beaussart et al., 2018). Specifically, there were more significant impairments in working memory than inhibitory control and cognitive flexibility.

The relation between EF and academic achievement within the NF1 population remains under-explored. Only a few existing studies investigated how EF relates to academic outcomes of children with NF1. Similar to findings from the general population, these studies suggest that the link between EF and academic achievement may vary across EF domains, academic domains, and types of measures. However, the specific patterns of results are inconsistent even among studies on children with NF1. For example, a study of 26 adolescents with NF1 (ages 12–18 years old) found that PB inhibitory control and cognitive flexibility have a stronger association with reading comprehension than numerical operations, whereas parent-rated EF (e.g., inhibitory control, working memory, cognitive flexibility) was correlated with numerical operations but not reading comprehension (Janke et al., 2014). On the other hand, a study of 29 children (ages 2–21) with NF1 demonstrated that PB EF was correlated with math, whereas parent-reported (PR) EF problems were related to reading (Friedhoff et al., 2020). In addition, one study of 29 children with NF1 (ages 8–16) found that some parent-rated executive function subscales such as working memory (but not inhibitory control and cognitive flexibility) were related to teacher-rated academic skills, including reading/language arts, mathematics, and critical thinking (Gilboa et al., 2014). Another study of children aged 7–12 years with NF1 ($n = 60$) demonstrated that stronger PB working memory and fewer PR inattentive behaviors predicted better word reading skills (Arnold et al., 2021).

Although these studies provide preliminary insights into the relationship between EF and academic outcomes in children with NF1, multiple gaps exist. First, the inconsistent findings in these prior studies may be partly due to the instability of results with small sample sizes (in most cases, $n < 30$). Small sample sizes are problematic in terms of low replicability and low power to detect potential significant predictors of academic achievement. Second, all these studies are cross-sectional. No known published studies have examined how EF relates to academic development longitudinally in the NF1 population. Third, findings in the general population suggest that the association between EF and academic achievement may vary across age groups (Spiegel et al., 2021). Limited studies have tested this potential moderator in the NF1 population.

Another important consideration is that the NF1 population is heterogeneous. PNs are present in about half of children with NF1 (Jett & Friedman, 2010). Neurocognitive functioning (including EF and academic achievement) may differ in NF1 children with versus without PNs. PNs are associated with an overactive RAS-MAPK pathway, which has been associated with neurocognitive dysfunction (Shilyansky et al., 2010). Some scholars have used PNs as one of their inclusion/exclusion criteria in their studies targeting neurobehavioral functioning (Hou et al., 2020; Hyman et al., 2006). However, no studies have examined the link between EF and academic achievement, specifically among children with NF1 and PNs.

The current study

The current study aimed to examine how EF predicts academic development over time among children with NF1 and PNs. This study moved beyond prior studies in multiple ways. First, this study used a relatively large sample ($n = 88$) for a rare disease and focused specifically on children with NF1 and PNs. Second, moving beyond prior cross-sectional studies, this study used a longitudinal design. A previous study using the same longitudinal dataset found that children with NF1 and PNs experienced increasing academic difficulties across time (e.g., decreasing math and writing z-scores) and identified demographic predictors of academic development (e.g., parental education and parental NF1 status) (Hou et al., 2020). Extending this prior study, the current study examined how EF domains (i.e., working memory, inhibitory control, cognitive flexibility, and attention) relate to developmental patterns of academic achievement (i.e., math, reading, and writing). Both PB and PR measures of EF were included to see whether the link between EF and academic achievement varies across EF measures. Furthermore, the current study also explored whether the links between EF skills and academic achievement vary across age groups. Finally, the present study tested which EF component uniquely explains more variances in academic development after controlling for other EF components and demographic variables (i.e., parental education, parental NF1 status, child sex) that have been associated with academic achievement in prior studies (Hou et al., 2020; Janke et al., 2014).

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Method

Participants and inclusion criteria

Individuals diagnosed with NF1 using the NIH Consensus Conference criteria (Stumpf et al., 1988) or a confirmed NF1 germline mutation with analysis performed in a CLIA-certified laboratory were eligible for a natural history study (ClinicalTrials.gov Identifier: NCT00924196) at the National Cancer Institute (NCI). Participants under 35 years of age were eligible for the neurocognitive evaluations conducted on this study. The protocol specified that comprehensive neurocognitive evaluations should be administered three times with approximately 3-year intervals between assessments. Youths ages 6–18 years who had at least one PN and completed a minimum of one neurocognitive evaluation were eligible for this EF/Academic sub-study. The protocol was approved by the NCI Institutional Review Board and the research was completed in accordance with Helsinki Declaration. The data cutoff for this sub-study was May 20, 2019.

Measures

Academic achievement

Academic achievement was assessed by the Woodcock-Johnson Tests of Achievement-Third Edition (WJ-III) (Woodcock et al., 2001). Reading achievement was assessed by the broad reading cluster consisting of three subtests: Letter-Word Identification, Reading Fluency, and Passage Comprehension. Math achievement was assessed by the broad math cluster consisting of three subtests: Calculation, Math Fluency, and Applied Problems. Writing achievement was assessed by the broad written language cluster comprised of three subtests: Spelling, Writing Fluency, and Writing Samples. All scores were standardized using age norms. All tests demonstrate good reliability in children and young adults (Woodcock et al., 2001).

Executive function

One PB and one PR measure were used to assess each of the four EF components. For PB measures, working memory (PB) was assessed by the Digit Span – Backwards subtest of the Wechsler Intelligence Scale for Children – Fourth Edition (Wechsler, 2003). Inhibitory control (PB) was assessed by Commissions T-score from the Connors Continuous Performance Test (CPT-II, Conners, 2000). Cognitive flexibility (PB) was assessed by the Number-Letter Switching condition of the Trail-Making subtest from the Delis-Kaplan Executive Functioning System (Delis et al., 2001). Attention (PB) was assessed using the Omission T-score from the CPT-II. For PR measures, working memory, inhibitory control, and cognitive flexibility were assessed using the Working Memory, Inhibit, and Shift subscale, respectively, from the Behavior Rating Inventory of Executive Function (BRIEF, Gioia et al., 2000). All subscales of BRIEF have demonstrated good reliability in normative and clinical samples (Gioia et al., 2000). PR attention was assessed with the Attention Problems subscale of the Behavior Assessment System for Children (BASC II, Reynolds & Kamphaus, 2002, 2015).

Covariates

Parental education and NF1 status (whether at least one parent has NF1) and child sex were reported on a PR demographic background form.

Statistical analysis

We transformed all the standard scores of the cognitive and academic measures into *z*-scores and reversely coded negative measures so that higher scores represent better cognitive functioning for all measures. Multilevel growth modeling was conducted in four steps. Step 1 tested unconditional multilevel models with each academic outcome as the dependent variable without any predictors to calculate intraclass correlation coefficients (ICC). Step 2 tested unconditional multilevel growth models, in which assessment time was added as the predictor. At this step, multiple models were compared to identify the model that fits the data best. In Step 3, we added each EF predictor, age at baseline, and their interaction effect to the best fit model identified in Step 2 to explore the separate effect of each EF predictor. In Step 4, all significant predictors identified in Step 3 were simultaneously tested, and covariates were added, including demographic variables. This final combined model examined the unique effect of each EF predictor on academic outcomes controlling for other EF predictors and covariates.

When a significant interaction effect was detected, we conducted simple slope tests. We plotted the interaction effect using the predicted values of academic outcomes at each time point at different levels of the predictors: For EF predictors, we used 1 Standard Deviation (*SD*) below the normative mean (−1), at the normative mean (0), and 1 *SD* above the normative mean (1); for age at baseline, we used 8 years (1 *SD* below the mean), 12 years (the mean), and 16 years (1 *SD* above the mean).

We compared two approaches to handling missing data in R: (1) multiple imputation using the "mice" package (Van Buuren & Groothuis-Oudshoorn, 2011) and (2) using the "na.action= na.omit" function in the "nlme" package, which made use of all available data points in multilevel modeling (Pinheiro et al., 2018). In multiple imputation, the missing values at one timepoint were predicted by available values at other timepoints within individuals (Van Buuren, 2018). For example, the individual's missing value of working memory at 6-year assessment was predicted by the individual's working memory scores at baseline and 3-year assessment. Five completed datasets were imputed. Analyses were conducted with each dataset, and then final results were pooled across datasets to be reported. The results from the two approaches showed similar patterns in general. However, multiple imputation generally produced smaller standard errors for estimated coefficients, suggesting more precise estimates. Thus, as recommended by prior studies (Young & Johnson, 2015), we reported results using multiple imputation.

Results

Characteristics of participants

Among the 176 participants of the natural history study, 117 under 35 years old completed at least one neurocognitive evaluation. Of these, 95 were 6–18 years of age; however, seven did not have a PN, so they were excluded. The 88 participants of the current sub-study were predominately White, with 67 (76%) Caucasian, 6 (7%) African American, 4 (5%) Hispanic, 2 (2%) Asian, 9 (10%) others and male ($n = 50$, 57%), and just under half had at least one parent with NF1 ($n = 41$, 47%). The median parental education was 14 years of school (interquartile range = 4). Per parent report, 55 children (63%) received special education at some point, and 30 (34%) were diagnosed with a learning disability. Of the 88 patients assessed at Time 1, 65 (75%) also were assessed at Time 2, and 34 (39%) were assessed at Time 3. Independent samples *t* test indicated no significant differences between patients with and without missing data at later assessments except that patients with data at Time 3 ($n = 34$) are younger than patients without data at Time 3 ($n = 54$; $t = 3.10$, $p < .01$, Cohen's $d = .67$).

Descriptive statistics of cognitive and academic variables

Means and SDs for all cognitive and academic variables and Pearson correlations between all study variables at baseline are provided in Table 1. At baseline, significant cognitive correlates of math included working memory (PB and PR), inhibitory control (PR), cognitive flexibility (PB and PR), and attention (PB and PR). Significant cognitive correlates of reading included working memory (PB), cognitive flexibility (PB), and attention (PB). Significant cognitive correlates of writing included working memory (PB and PR), cognitive flexibility (PB), and attention (PB).

EF predictors of academic outcomes

ICC for math, reading, and writing were .73, .78, and .75, respectively, meaning that 73 ~ 78% of variances in academic outcomes were attributed to between-individual differences, whereas 22 ~ 27% of variances in academic outcomes were attributed to within-individual changes across time. Model comparisons showed that the models with random intercepts (initial levels of academic outcomes) and slopes (changes in academic outcomes across time) fit the data best. Variance components of intercepts and slopes in math, reading, and writing were significant, indicating that individual predictors could be added to the multilevel growth models with random intercepts and slopes to explain variance in academic outcomes. Table 2 presents results of the separate models tested in Step 3. Table 3 presents results of the final combined models tested in Step 4.

Math

In the separate models, working memory (PB and PR), inhibitory control (PR), cognitive flexibility (PB and PR), and attention (PB and PR) were positively associated with initial levels of math. Age at baseline was positively associated with the effect of cognitive flexibility (PB) on initial levels of math ($\beta = .07$, $SE = .03$, $p < .05$). However, in the combined model, only cognitive flexibility (PB) remained positively associated with initial levels of math, suggesting that children with higher levels of cognitive flexibility (PB) tended to have higher initial levels of math ($\beta = .35$, $SE = .08$, $p < .001$). The combined model explained 59% of variances in math.

Reading

In the separate models, working memory (PB), cognitive flexibility (PB), and attention (PB) were positively associated with initial levels of reading. Working memory (PB) was negatively associated with change of reading scores across time ($\beta = -.03$, $SE = .01$, $p < .05$), indicating children with higher levels of working memory (PB) at baseline were likely to experience a greater decline in reading scores across time (see Figure 1). Meanwhile, age at baseline had a significant moderation effect on the relation between inhibitory control (PR) and change of reading scores across time ($\beta = -.01$, $SE = .00$, $p < .05$). Simple slope analysis and interaction plot (see Figure 2) demonstrated that lower levels of inhibitory control (PR) at baseline were associated with a greater decline in reading scores across time. This pattern was more evident among younger (e.g., 8-year-old) than older (e.g., 12-year-old) children. In the combined model, these two interaction effects remained significant, and working memory (PB, $\beta = .30$, $SE = .12$, $p < .05$) and cognitive flexibility (PB, $\beta = .21$, $SE = .08$, $p < .01$) continued to be positively associated with initial levels of reading. The combined model explained 32% of variances in reading.

Writing

In the separate models, working memory (PB and PR), cognitive flexibility (PB), and attention (PB) were positively associated with initial levels of writing. Working memory (PB) was negatively associated with changes of writing scores across time ($\beta = -.04$, $SE = .02$, $p < .05$), suggesting that children with higher levels of working memory (PB) at baseline were likely to experience more dramatical decline in writing scores across time (see Figure 3). In the combined model, the interaction effect remained significant, and working memory (PB, $\beta = .35$, $SE = .13$, $p < .01$) and cognitive flexibility (PB, $\beta = .18$, $SE = .09$, $p < .05$) continued to be positively associated with initial levels of writing. The combined model explained 32% of variances in writing.

Discussion

This report describes the first longitudinal study to examine cognitive predictors of academic achievement among children with NF1 and PNs. We documented how baseline EF relates to initial levels of and changes in academic achievement across six years. The relationship between EF and academic achievement varies across specific EF and academic domains. Cognitive flexibility uniquely explained more variances in math, reading, and writing after controlling for other variables. The most robust EF predictor for math was cognitive flexibility and for reading and writing was working memory. Generally, the association between EF and academic achievement was similar across childhood and adolescence, except that age at baseline moderated the association between inhibitory control (PR) and changes in reading. These findings highlight domain-based differences in the academic development of children with NF1 and PNs, and the role of distinct cognitive skills in explaining such differences. Understanding the cognitive factors contributing to academic problems will inform more targeted interventions for specific learning difficulties in youth with NF1.

Previous studies have demonstrated that children with NF1 tend to experience cognitive deficiencies and academic difficulties (Lehtonen et al., 2015; Vogel et al., 2017). For example, a longitudinal study indicated that academic difficulties of children with NF1 and PNs persist or even worsen over time (Hou et al., 2020). These findings make it imperative to better understand the factors contributing to progressive deficits in academic achievement. Hou et al. (2020) indicated that demographic factors, such as parental education and parental NF1 status (but not age, sex, NF1 disease-related complications), can predict initial levels or changes of math, reading, or writing. The current study extends these prior findings by examining how EF relates to academic development and whether the association between EF and academic achievement vary across age, controlling for parental education, parental NF1 status, and child sex.

The results suggest that, in general, all EF components (i.e., working memory, cognitive flexibility, inhibitory control, and attention) tend to have separate effects on academic achievement (as shown in the separate models). However, the effect size decreased in the final model controlling for other EF components and demographic variables. In the final model, only cognitive

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Table 1. Descriptive statistics and bivariate correlation between cognitive and academic outcomes and covariates at baseline

	Mean	*SD*	*n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Math	−0.47	1.03	88	1															
2. Reading	−0.47	1.12	88	.61***	1														
3. Writing	−0.39	1.17	88	.68***	.90***	1													
4. Working memory (PR)	−0.93	1.25	88	.33***	.12	.24*	1												
5. Working memory (PB)	−0.49	1.03	88	.43***	.42***	.46***	.16	1											
6. Inhibitory control (PR)	−0.68	1.32	88	.24*	.12	.15	.58***	.13	1										
7. Inhibitory control (PB)	−0.44	1.09	88	.02	−.15	−.15	.15	.18	−.02	1									
8. Cognitive flexibility (PR)	−0.56	1.12	88	.28**	.03	.17	.50***	.15	.48***	−.03	1								
9. Cognitive flexibility (PB)	−0.73	1.24	88	.59***	.44***	.48***	.22*	.38***	.22*	0	.16	1							
10. Attention (PR)	−0.49	1.02	88	.27**	.14	.18	.68***	.18*	.69***	.14	.43***	.16	1						
11. Attention (PB)	−0.59	1.34	88	.27*	.27*	.35**	.08	.32***	.23*	−.08	.2	.22*	.17*	1					
12. Full IQ	−0.39	0.99	88	.70***	.56***	.58***	.29**	.50***	.24*	.15	.25*	.56***	.30**	.22	1				
13. Age	12.05	3.62	88	−.14	−.02	−.05	−.1	.02	.12	−.16	−.05	.1	.08	.26*	.11	1			
14. Parental education	14.34	2.41	88	.48***	.27*	.24*	.1	.2	.07	.08	.15	.28**	.13	.06	.48***	−.03	1		
15. Parental NF1 status[a]	–	–	88	−.20*	−.07	−.03	0	−.01	−.1	.12	−.05	−.1	−.08	−.03	−.17*	−.02	−.27***	1	
16. Child sex[b]	–	–	88	.12	−.14	−.07	.23*	0	.1	.25*	.1	−.02	.11	−.03	.06	−.04	.15	−.01	1

Note. PR = parent-reported; PB = performance-based.
[a]Dummy variable (0 = parent without NF1, 1 = parent with NF1).
[b]Dummy variable (0 = female, 1 = male).
**p* < .05; ***p* < .01; ****p* < .001.

Table 2. Fixed effects of multilevel growth models examining separate effects of each EF skill on academic outcomes with age at baseline as a moderator

	Math		Reading		Writing	
Parameters	*β*	*SE*	*β*	*SE*	*β*	*SE*
Intercept	−.21	.14	−.36*	.15	−.17	.16
Assessment time	−.10**	.03	−.04	.02	−.08**	.02
Age	−.01	.04	.04	.04	.01	.05
Working memory (PR)	**.26****	.09	.08	.1	**.24***	.11
Working memory (PR) × Time	.01	.02	0	.01	−.02	.02
Working memory (PR) × Age	.02	.02	.04	.03	.01	.03
Time × Age	0	.01	0	.01	0	.01
Working memory (PR) × Time × Age	0	0	0	0	0	0
Intercept	−.23	.12	−.23	.13	−.12	.14
Assessment time	−.10***	.02	−.05*	.02	−.08***	.02
Age	−.04	.04	−.01	.04	−.02	.04
Working memory (PB)	**.45****	.14	**.44*****	.12	**.53*****	.13
Working memory (PB) × Time	0	.01	**−.03***	.01	**−.04***	.02
Working memory (PB) × Age	.01	.03	−.02	.04	−.01	.04
Time × Age	0	0	0	.01	0	.01
Working memory (PB) × Time × Age	0	0	0	0	0	0
Intercept	−.32*	.13	−.41**	.14	−.30*	.15
Assessment time	−.09***	.02	−.03	.02	−.06**	.02
Age	−.03	.04	.03	.04	.01	.04
Inhibitory control (PR)	**.21***	.08	.1	.09	.15	.1
Inhibitory control (PR) × Time	.01	.01	.01	.01	0	.01
Inhibitory control (PR) × Age	.03	.02	.05	.03	.04	.03
Time × Age	0	0	0	.01	0	.01
Inhibitory control (PR) × Time × Age	0	0	**−.01***	0	0	0
Intercept	−.42**	.13	−.51***	.13	−.45**	.14
Assessment time	−.11***	.02	−.04	.02	−.05**	.02
Age	−.02	.04	0	.04	−.01	.04
Inhibitory control (PB)	.02	.11	−.16	.11	−.17	.13
Inhibitory control (PB) × Time	0	.02	.01	.02	.02	.02
Inhibitory control (PB) × Age	.04	.03	.01	.03	.02	.03
Time × Age	0	0	0	.01	0	.01
Inhibitory control (PB) × Time × Age	0	0	0	0	0	0
Intercept	−.30*	.13	−.43**	.14	−.28	.14
Assessment time	−.10***	.02	−.03	.02	−.06**	.02
Age	−.02	.03	.02	.04	.01	.04
Cognitive flexibility (PR)	**.26***	.1	.03	.11	.18	.13
Cognitive flexibility (PR)× Time	.01	.01	.01	.01	0	.02
Cognitive flexibility (PR)× Age	.04	.03	.04	.03	.05	.04
Time × Age	0	0	0	.01	0	.01
Cognitive flexibility (PR)× Time × Age	0	0	0	.01	−.01	.01
Intercept	−.10	.1	−.15	.13	−.05	.14
Assessment time	−.11***	.02	−.05*	.02	−.08**	.02
Age	−.01	.03	.01	.04	0	.04
Cognitive flexibility (PB)	**.53*****	.08	**.43*****	.09	**.49*****	.1
Cognitive flexibility (PB) × Time	−.01	.02	−.02	.01	−.04	.02
Cognitive flexibility (PB) × Age	**.07***	.03	.04	.03	.04	.03
Time × Age	0	0	0	.01	0	.01
Cognitive flexibility (PB) × Time × Age	0	0	0	0	−.01	0
Intercept	−.33**	.12	−.40**	.14	−.29	.15
Assessment time	−.09***	.02	−.03	.02	−.06**	.02
Age	−.03	.03	.02	.04	0	.04
Attention (PR)	**.27***	.12	.13	.14	.22	.14
Attention (PR) × Time	.02	.02	0	.02	−.01	.02
Attention (PR) × Age	.04	.03	.05	.03	.03	.03
Time × Age	0	0	0	0	0	.01
Attention (PR) × Time × Age	−.01	0	−.01	0	0	0
Intercept	−.31*	.12	−.28*	.13	−.17	.14
Assessment time	−.11***	.02	−.05**	.02	−.08***	.02
Age	−.06	.03	−.03	.03	−.05	.04
Attention (PB)	**.29****	.09	**.23***	.09	**.34*****	.1
Attention (PB) × Time	−.01	.01	−.02	.01	−.03	.02
Attention (PB) × Age	.03	.03	−.02	.03	−.01	.03
Time × Age	.01	0	.01	.01	.01	.01
Attention (PB) × Time × Age	0	0	0	0	0	0

Note. PR = parent-reported; PB = performance-based. *$p < .05$; **$p < .01$; ***$p < .001$.

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Table 3. Fixed effects of multilevel growth models examining unique effects of EF predictors on academic outcomes with covariates

	Math		Reading		Writing	
Parameters	*β*	*SE*	*β*	*SE*	*β*	*SE*
Intercept	.10	.16	.08	.18	.29	.19
Assessment time	−.10***	.02	−.04	.02	−.08***	.02
Age	−.03	.03	.02	.03	−.01	.03
Working memory (PR)	.04	.10	–	–	.11	.08
Working memory (PB)	.19	.09	**.30***	.12	**.35****	.13
Inhibitory control (PR)	.01	.10	−.01	.08	–	–
Cognitive flexibility (PR)	.06	.10	–	–	–	–
Cognitive flexibility (PB)	**.35*****	.08	**.21****	.08	**.18***	.09
Attention (PR)	.06	.14	–	–	–	–
Attention (PB)	.09	.06	.06	.07	.10	.07
Cognitive flexibility (PB) × Age	.05	.03	–	–	–	–
Working memory (PB) × Time	–	–	**−.03***	.01	**−.04***	.02
Inhibitory control (PR) × Time	–	–	.01	.01	–	–
Inhibitory control (PR) × Age	–	–	.05*	.02	–	–
Time × Age	–	–	.00	.01	–	–
Inhibitory control (PR) × Time × Age	–	–	**−.01***	.00	–	–
Parent education	.10**	.04	.07*	.04	.07	.04
Parental NF1 status	−.21	.18	−.06	.18	−.10	.16
Child sex	.08	.18	−.31	.17	−.29	.17

Note. PR = parent-reported; PB = performance-based. *$p < .05$; **$p < .01$; ***$p < .001$.

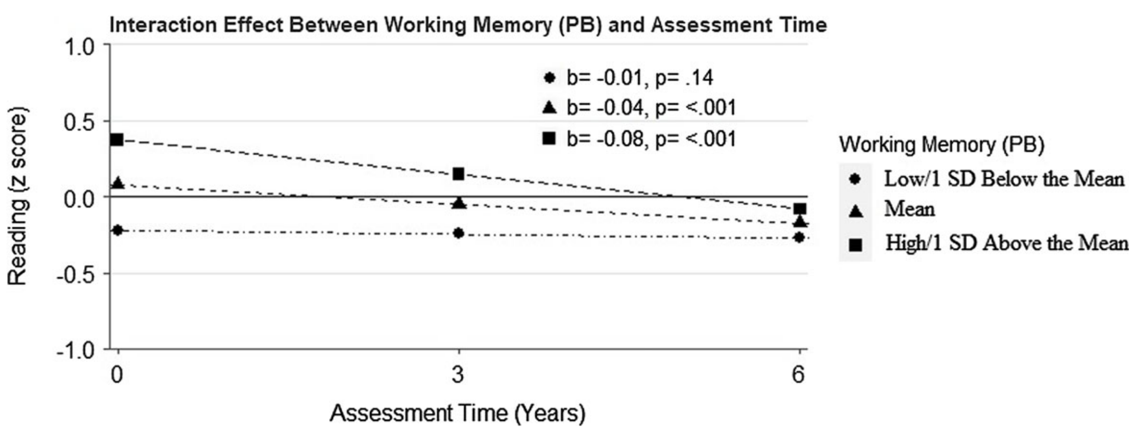

Figure 1. Plot for the interaction effect between working memory (performance-based) and assessment time on reading.
Note. PB = performance-based.

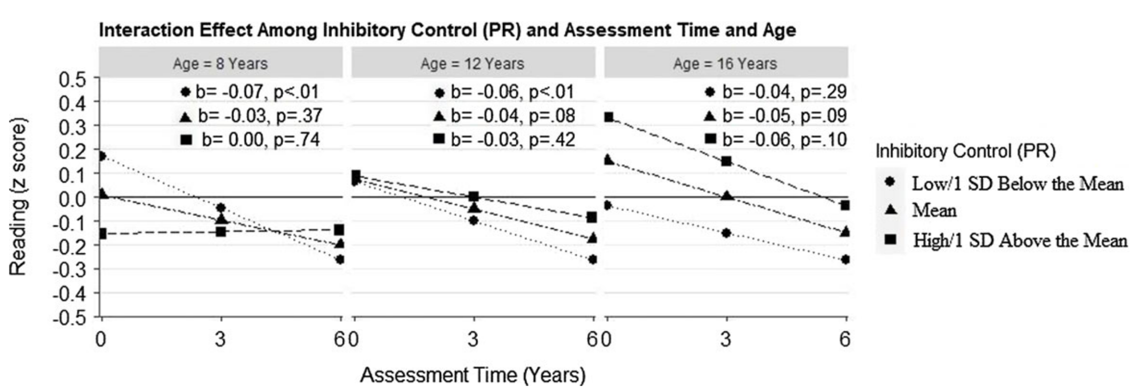

Figure 2. Plot for the interaction effect among inhibitory control (parent-reported), assessment time, and age at baseline on reading.
Note. PR = parent-reported.

flexibility (PB) uniquely explained more variances in initial levels of math; cognitive flexibility (PB) and working memory (PB) uniquely explained more variances in initial levels of reading and writing. These results contrast with prior studies in the general population, which demonstrated that all four EF components uniquely explain more variance in math and reading (Jacob & Parkinson, 2015; Spiegel et al., 2021). There are two potential explanations for this inconsistency. First, unique EF predictors for various academic domains may be different for the general population and the NF1 population, which might be due to

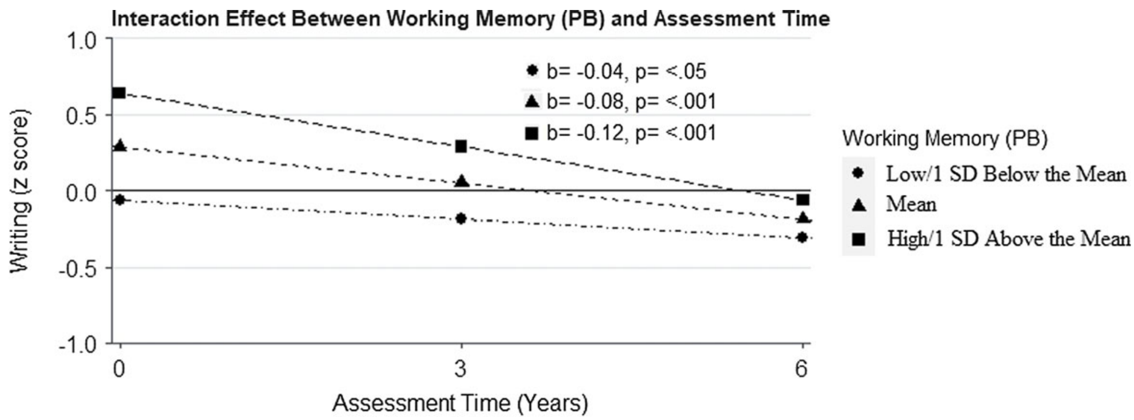

Figure 3. Plot for the interaction effect between working memory (performance-based) and assessment time on writing.
Note. PB = performance-based.

varying levels of cognitive impairment in children with NF1. Specifically, working memory was the strongest predictor for math in the general population (Spiegel et al., 2021), whereas cognitive flexibility was the strongest predictor for math in the current NF1 study. This result may be because working memory is impaired to a larger extent than cognitive flexibility in children with NF1 (Beaussart et al., 2018). Second, the lack of a unique effect of some EF components in the final model may be partly due to the relatively small sample size of NF1 children compared to prior studies with large samples from the general population. Thus, to make more reliable conclusions, it is important for future studies to test cognitive predictors of academic achievement in larger NF1 samples. The current study included a larger sample than most of the previous published research on cognitive and academic function of children with NF1 and provided more robust tests of EF predictors of academic achievement than limited extant studies (Gilboa et al., 2014; Janke et al., 2014).

Moreover, the present study extended prior cross-sectional studies to investigate how EF relates to changes in academic outcomes across time. We found that higher levels of working memory (PB) at baseline were related to greater declines in reading and writing scores across time, with decreasing standard scores being indicative of slower progress in learning new academic skills compared to same-aged peers. These findings are somewhat surprising given the positive associations between EF and initial levels of academic outcomes. The results may be partly due to regression to the mean (RTM). RTM is a common phenomenon in repeated measurements: participants with relatively high scores at the beginning are more likely to have lower scores near the participants' true mean in later assessments (Barnett et al., 2004). Children with high levels of working memory also had high reading and writing scores at baseline and thus showed a greater decline in scores later. To reduce the effect of RTM, future studies can include a larger sample, reduce missing data in follow-up assessments, and include a control group (see Barnett et al., 2004 for more discussion). Another possible explanation of these paradoxical findings is that the decline in academic scores may be associated with a decrease in working memory scores across time. A prior study using the same sample has shown that working memory scores declined over time, and children with higher working memory at baseline are more likely to experience such a decline (Hou et al., 2020). Future studies with larger longitudinal samples should examine how working memory and academic achievement co-develop over time.

The current study is among the first to explore potential age differences in the association between EF and academic achievement in the NF1 population. We found that EF was related to academic achievement similarly across age groups for math and writing, which is in line with findings from the general population (Spiegel et al., 2021). This finding is likely because the inherent complexity of tasks involved in math and writing is consistent across childhood and adolescence, according to the intrinsic cognitive load theory (Spiegel et al., 2021). There was a significant three-way interaction effect between inhibitory control (PR), time, and age on reading. Specifically, lower (versus higher) initial levels of inhibitory control were related to a greater decline in reading scores. This pattern was more evident among younger (versus older) children. It also was consistent with the finding of a meta-analytic study on the general population, which showed that inhibitory control was more strongly related to reading in early (versus late) elementary school (Spiegel et al., 2021). One possible explanation for this pattern is that younger children have a shorter attention span, and thus their initial inhibitory control skills (e.g., control impulses, resist distractions) are more predictive of reading development. Overall, the findings highlight the critical role of EF in academic achievement across developmental stages and the need to investigate further how specific EF components relate to specific academic outcomes at different developmental periods to provide a more nuanced picture of the co-development of EF and academic achievement across age groups.

Moreover, the current study found nonsignificant or small correlations between PB and PR measures of EF, which is consistent with prior studies (Ten Eycke & Dewey, 2016). This suggests that PB and PR measures of the same EF component actually assess distinct constructs. Different EF measures have shown distinct predictive validity for academic performance and other developmental outcomes, as shown in the current study and prior studies (Berninger et al., 2017; Jacob & Parkinson, 2015; Ten Eycke & Dewey, 2016). Future research needs to select the measures with better predictive validity for their focal study outcomes. For example, it seems that PB (versus PR) EF can better predict academic achievement.

Implications

The current study extends a large body of literature documenting cognitive and academic weaknesses in children with NF1, and more specifically, demonstrates how EF components relate to academic development over time. Academic difficulties demonstrated in previous studies have suggested the need to evaluate the effectiveness of medications and intervention programs for children with NF1. Several clinical trials have evaluated the effectiveness of certain medications (e.g., methylphenidate, simvastatin, lovastatin) in improving cognitive outcomes of individuals with NF1 (Acosta et al., 2011; Krab et al., 2008; Mautner et al., 2002). In addition, computerized working memory training was found to be feasible and potentially helpful in children with NF1 in a pilot intervention study (Hardy et al., 2021). Thus, there is some preliminary but inconsistent evidence regarding the effectiveness of various treatments, which emphasizes the need for future studies with more robust methodologies (Walsh et al., 2016).

Results of the current study point to the need to personalize EF interventions toward specific academic skills. For example, children with early math weakness may benefit from interventions aimed at strengthening cognitive flexibility. Similarly, supporting the development of inhibitory control may bolster reading skills, particularly among younger children. Writing skills may benefit from helping children practice the EF skills of working memory and cognitive flexibility. A few interventions have been shown to positively impact multiple aspects of executive functions in children, including cognitive flexibility and response inhibition, such as mindfulness (Lassander et al., 2020) and attention/memory practice (Tamm & Nakonezny, 2015). Future research and clinical efforts should be put toward adapting intervention programs developed for the general population and other patient populations to meet the needs of the NF1 population. Children with NF1 face a range of challenges besides EF deficits and academic difficulties, such as physical and socioemotional problems (Martin et al., 2012; Vogel et al., 2017). For example, physical activity programs that improve cognitive and motor skills in children with ADHD (Jiang et al., 2022; Sun et al., 2022) may not be as feasible or effective in children with NF1 who have physical difficulties, and the exercises may need to be modified and re-evaluated. Moreover, future studies that develop and evaluate systematic programs targeting multiple aspects of development, such as EF and academic achievement as well as socioemotional and physical development, may be more effective for children with NF1 than programs that target EF alone (Diamond & Lee, 2011).

Limitations

The current study has several notable limitations. First, no control group was included, which limited our ability to directly compare the focal study relationships between the NF1 group and a control group matched in demographic characteristics. That said, by comparing findings from the current study and prior results of published research in the general population, we found interesting patterns that may be unique to the NF1 population. Second, in addition to PB and PR EF measures, future studies also should include teacher-reported EF measures, which may be more predictive of academic achievement than PR EF measures. Third, although EF was proposed to be a predictor of academic achievement, our correlational study design cannot determine a causal relationship. EF and academic achievement may mutually influence each other (Ahmed et al., 2019; Peng & Kievit, 2020). It would be interesting to examine how cognitive function and academic achievement co-develop across time in future studies. With considerable attrition from baseline to Time 3, our longitudinal sample size is too small to test more complicated research questions like this. Future studies should include larger samples and obtain more frequent longitudinal assessments with less attrition. Data sharing and integrative data analysis are highly recommended, given the difficulty of examining a large sample for any individual investigator (Curran & Hussong, 2009). A larger and more diverse sample not only can address research aims that are hard to achieve with a small sample but also can produce more robust results that are more generalizable. As the current study focused on children with NF1 with PNs, the generalizability of our results to the whole NF1 population still needs to be tested in future studies with more diverse NF1 samples. Individuals with NF1 and PNs may have greater cognitive deficits than those without PNs due to an overactive RAS-MAPK pathway (Shilyansky et al., 2010).

Conclusion

Existing studies indicate that children with NF1 are at high risk for experiencing cognitive deficits and academic difficulties; however, the association between cognitive function and academic difficulties is understudied in this population. As the largest comprehensive longitudinal study of cognitive and academic achievement in children with NF1 and PNs, the current results identified EF components associated with the specific academic domains of math, reading, and writing. Findings emphasize the heterogeneous nature of academic development among children with NF1 and how EF skills could help explain the within-group variability in this population. Routine cognitive/academic monitoring via comprehensive assessments, early targeted treatments consisting of medication and/or cognitive interventions, and consistent school-based supports will be important to evaluate for improving academic performance of children with NF1.

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Conflicts of interest. None.

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