ACADEMIC ABILITIES OF LATE SCHOOL AGE CHILDREN WITH NEUROFIBROMATOSIS TYPE 1: A REPLICATION STUDY AND EXAMINATION OF EARLY SCHOOL AGE COGNITIVE PREDICTORS

by

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A Dissertation Submitted in
Partial Fulfillment of the
Requirements for the Degree of

Doctor of Philosophy
in Psychology

at

The University of Wisconsin-Milwaukee
August 2022

ABSTRACT
ACADEMIC ABILITIES OF LATE SCHOOL AGE CHILDREN WITH NEUROFIBROMATOSIS TYPE 1: A REPLICATION STUDY AND EXAMINATION OF EARLY SCHOOL AGE COGNITIVE PREDICTORS

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The University of Wisconsin-Milwaukee, 2022
Under the Supervision of Professor Bonita P. Klein-Tasman

Learning problems are commonly reported for children with neurofibromatosis type 1 (NF1); however, there are no known studies examining early school age predictors of late school age academic functioning in children with NF1. Based on the review of the literature of predictors of academic functioning for typically developing children and pre-academic/academic functioning in children with NF1, pre-academic and neuropsychological predictors (intellectual functioning, attention, executive functioning, visual spatial, oral language) were examined in relation to late school age academic performance in children with NF1. Concurrent intellectual functioning, performance-based attention, performance-based working memory, oral language and visual spatial abilities were associated with late school age reading and/or math abilities. Phonological processing and foundational number knowledge at early school age were associated with late school age reading-related and math abilities, respectively. Intellectual functioning, performance-based attention, performance-based working memory, oral language abilities and visual spatial abilities at early school age were associated with reading-related and/or math abilities at late school age. Hierarchical multiple regressions were also assessed and suggested that domain specific abilities may be particularly important for reading while domain general abilities may be particularly important for math abilities in children with NF1. Canonical correlations also identified similar patterns for the relation between pre-academic/ neuropsychological variables as when relations were studied individually. Overall, the study findings suggest the importance of assessing pre-academic and neuropsychological variables in young children with NF1 to identify who may be at greater risk for later academic problems.

To

my parents,

and my friends.

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Academic Abilities of Late School Age Children with Neurofibromatosis Type 1: A Replication Study and Examination of Early School Age Cognitive Predictors

Individuals with neurofibromatosis type 1 (NF1) have a range of cognitive, psychosocial, and medical complications associated with their genetic condition including vulnerability to attention-deficit/hyperactivity disorder (ADHD; e.g., Pride et al., 2012), optic pathway gliomas (e.g., Gutmann et al., 2017), and difficulties with social functioning (e.g., Barton & North, 2004). Unlike other genetic conditions that have a distinct profile (e.g., Williams syndrome), the presentation of NF1 can vary greatly across individuals, even within members of the same family. Learning problems are often the most commonly reported concern for individuals with NF1 (e.g., McKeever et al., 2008) and can have long-term impacts on functioning (Granström et al., 2014). Despite the knowledge that half or more of individuals with NF1 report learning problems (e.g., Coutinho et al., 2016; Hyman et al., 2005), more research needs to be conducted to examine neuropsychological abilities which may impact academic performance. Additionally, there are no current studies that examine early school age predictors of later school age academic functioning in children with NF1. Knowledge about which early predictors can predict later academic difficulties in individuals with NF1 is vital given the high rates of learning difficulties. This information would allow for identification of the children with NF1 who will likely benefit from additional academic interventions and provide the necessary supports beginning from a young age.

This introduction will be organized as follows: To delineate potential predictors of later academic functioning in children with NF1, the literature on cognitive predictors of later academic functioning in typically developing children will be discussed. Next, the academic literature on children with NF1 will be reviewed. Based on these two sets of literature, a study rationale and aims/hypotheses will be provided.

Correlates and Predictors of Academic Functioning in Typically Developing Children

Neuropsychological Predictors of School Age Reading Abilities

Identification of pre-literacy skills associated with later reading is vital as difficulties in reading identified in 1st grade have been found to persist through the end of high school for children diagnosed with reading disabilities (RD; Ferrer et al., 2015). A meta-analysis that examined early predictors of later reading abilities found that phonological awareness, phonological memory, alphabet knowledge, rapid automatic naming (RAN), and oral language skills had moderate relationships with future decoding and/or reading comprehension abilities (National Early Literacy Panel, 2008). In this section, the association between preschool/early school age cognitive abilities (pre-literacy, intellectual functioning, attention, oral language, executive functioning, and visuospatial abilities) and later school age reading abilities will be examined.

Many studies have examined the relationships between pre-literacy factors in early childhood with academic functioning in early grade school (e.g., kindergarten through second grade). Roth and colleagues (2002) found that phonological awareness in kindergarten before children had started learning to read was a significant predictor of later word reading ability in both first and second grade. Similarly, Brunswick and colleagues (2012) examined the association between pre-literacy skills and reading for children before they started reading up through first grade. Phonological awareness and phonological memory were both found to be significant predictors of later reading. Cirino and colleagues (2018) found kindergarten phonological awareness and RAN variables to predict first grade reading performance. Lonigan and colleagues (2000) examined preliteracy abilities in preschool children and found that phonological processing skills and letter knowledge predicted later word reading in kindergarten or first grade. Phonological processing skills and letter knowledge together were able to account for 45% of the variance in word reading.

School age reading abilities have been linked to intellectual functioning (e.g., Deary et al., 2007; Zaboski et al., 2018); however, there is mixed evidence to support the association between preschool/early school age intelligence and later reading performance. Some studies have found evidence that suggests intellectual functioning is related with later reading abilities (e.g., Peng et al., 2019), while other studies have not found significant associations (e.g., Alloway & Alloway, 2010; Chu et al., 2016). Additionally, some studies suggest that intelligence may not contribute significantly to the prediction of later reading outcomes when other variables are also being considered. For example, Horbach and colleagues (2018) found that preschool nonverbal IQ significantly predicted word fluency and pseudoword fluency three years later. However, when examining linear regression models that included additional predictors (e.g., sound-symbol paradigm), nonverbal intelligence was no longer a significant predictor of reading outcomes. Relations between intelligence and reading ability may also vary based on the specific predictor/outcome examined. For example, Peng and colleagues (2019) found that nonverbal reasoning was significantly related to growth in reading comprehension, but not word reading. Similarly, Fuchs and colleagues (2016) found that first grade language comprehension had direct effects on third grade word reading, but the direct effect of first grade nonverbal reasoning on later word reading was not significant.

Oral language abilities are also examined frequently in addition to pre-literacy abilities to predict later word reading and reading comprehension abilities. Oral language may contribute to later reading abilities by way of being involved in the development of phonological awareness (Cooper et al., 2002). Vocabulary abilities in infancy were a significant predictor of word reading and reading comprehension in addition to phonological awareness when assessed five years later (Duff et al., 2015). Language measures assessed at age 4 had moderate correlations with word decoding abilities at age 7 and reading comprehension abilities at age 10 (Hayiou-Thomas et al., 2010). Further evidence suggests that early oral language abilities is important for reading comprehension. Oral language abilities at kindergarten added significantly to the prediction of reading comprehension in second grade over and above word reading abilities in the first grade (Catts et al., 2016). Associations with pre-literacy skills and receptive vocabulary have also been shown to have associations with both word reading and reading comprehension when children were in 5th grade (Ribner et al., 2017).

Attention problems may be related to poorer preliteracy skills in addition to later reading abilities (Dally, 2006; Walcott et al., 2010; Welsh et al., 2010). For example, greater symptoms of inattention by multiple rates (e.g., parents, teachers) were all associated with poorer early literacy skills (i.e., letter knowledge, vocabulary, and phonological awareness) in preschool children (Allan et al., 2018). Attention abilities have an impact on reading abilities that can be found in early school age as well as in high school. In the early school years, inattention difficulties have been associated with poorer word reading (Dittman, 2013). As children continue in school, we see that attention problems continue to predict word reading in late elementary school (Rabiner et al., 2016) and reading fluency in the beginning of high school (Becker et al., 2018). Attention abilities as rated by teachers at age 6 continue to predict reading achievement through high school (Breslau et al., 2009). This suggests that attention is an important predictor in reading ability that has long-term implications.

Executive functioning (EF), which has some construct overlap with attention, has also been studied in relation to later reading abilities. Relations between EF and pre-literacy skills have also been observed. For example, self-regulation has been found to be associated with preliteracy skills such as phonemic awareness and letter identification (Blair & Razza, 2007). EF of children at age 5 was shown to uniquely predict later basic reading and reading comprehension abilities in the fifth grade. Notably, EF was measured using a composite score of working memory, inhibition, and attention shifting so it is difficult to ascertain if any particular EF component contributed more than the others to later reading abilities (Ribner et al., 2017). Similarly, Best and colleagues (2011) used a composite score of EF and found that EF was related to reading achievement beginning in early grade school and was related all the way through adolescence. Some evidence has suggested that working memory, in particular, may be important for reading abilities. Welsh and colleagues (2010) found that working memory predicted growth of pre-literacy abilities in preschool and uniquely contributed to later reading abilities when children were in kindergarten. Nevo and Breznitz (2011) assessed working memory in kindergarten before children began reading and found it was related to decoding and reading comprehension abilities one year later.

Neuropsychological Predictors of School Age Mathematical Abilities

Early math abilities in kindergarten children have been shown to be the strongest predictor of later academic achievement (Duncan et al., 2007; Romano et al., 2010). Early detection of mathematical difficulties is vital as children who have poorer mathematics performance in kindergarten have lower math growth rates from first to fifth grade than children without mathematical difficulties (Morgan et al., 2009). Early numerical abilities investigated in young children are related to symbolic number skills and non-symbolic number abilities.

Symbolic number skills often assessed include Arabic number knowledge, understanding the numerical meaning of number words (e.g., “six”), counting abilities, and the cardinality principle (Raghubar & Barnes, 2017). Non-symbolic number skills include tasks that represent numbers without the use of symbols. This is generally accomplished through the use of objects/shapes, with which children are able to complete simple math problems and compare quantities (Raghubar & Barnes, 2017). The ability to compare quantities is often used as a means to test the approximate number system (ANS). ANS is thought to be an innate ability that animals have to signify and manipulate quantity information, which is then used to help humans learn formal mathematical skills (De Smedt et al., 2013).

There is stronger evidence to support the relationship between symbolic number skills and later math achievement (De Smedt et al., 2013; Merkley & Ansari, 2016; Schneider et al., 2017). Symbolic number knowledge (counting, number knowledge (e.g., number recognition) in preschool significantly predicted math fluency abilities in primary school (ages 5-7) (Moll et al., 2015). Advanced counting skills in preschool (e.g., counting forward starting at number 3) was found to be the strongest predictor of math achievement (e.g., multiplication, geometry) for children in the fifth grade (Nguyen et al., 2016). While non-symbolic skills have also been linked to later math achievement, the association is less consistent (De Smedt et al., 2013; Schneider et al., 2017). For example, Toll and colleagues (2016) assessed children at the end kindergarten on a task of non-symbolic and symbolic number sense in order to determine the ability to predict math fluency and math problem solving abilities at the end of first grade. While visual working memory, symbolic number sense and non-symbolic number sense were all predictors of math fluency, only the visual working memory and symbolic number sense were also significant predictors of math problem solving. One hypothesis for the less consistent relationship between

ANS and math abilities is that their relationship is mediated by symbolic abilities (Merkley & Ansari, 2016).

There is evidence to suggest the role of intellectual functioning in school age math abilities (e.g., Deary et al., 2007; Zaboski et al., 2018); however, the role of intellectual abilities in preschool/early school age children to predict later math outcomes is unclear. Some findings suggest that intelligence is a predictor of later math functioning (e.g., Alloway & Alloway, 2010; Geary, 2011; Ribner et al., 2017), while other studies do not find it to be a significant predictor (e.g., Chu et al., 2016). Notably, intelligence may be related to later math performance, but it may not necessarily predict the most variance in math outcomes. For example, Alloway and Alloway (2010) found that verbal working memory predicted the most variance (21%), but nonverbal IQ predicted an additional 6% of the variance in numeracy score (composite measure of math reasoning and calculations). Mixed findings could be related to a variety of differences across studies such as different measures of intelligence (e.g., overall cognitive ability versus nonverbal/verbal reasoning), different outcome variables, inclusion of varying additional cognitive variables in analyses, and differing lengths of time of the longitudinal follow-up.

EF has been found to be an important predictor of later mathematical abilities from early grade school throughout high school (Best et al., 2011). EF has also been found to be related to early mathematical abilities (Blair & Razza, 2007; Moll et al., 2015). Mazzocco and Kover (2007) found that EF scores at ages 6 and 7 were associated with later mathematical abilities. In particular, working memory has commonly been examined in relation to later mathematical performance. Working memory has been associated with early mathematical skills (Purpura & Ganley, 2014) as well as later mathematical abilities. As mentioned early in this section, Toll and colleagues (2016) found that verbal working memory was associated with both later math fluency and math problem solving. Toll and colleagues (2011) also found that working memory was a predictor of later mathematical abilities even when controlling for early mathematical abilities.

Attention is another area that has been examined in relation to later mathematical abilities. Studies have found long-term associations between mathematic abilities and attention. Attention problems as rated by teachers at age 6 have been shown to predict math performance at age 17 (Breslau et al., 2009). Additionally, symptoms of inattention in preschool have been linked to poorer math calculations, math fluency, and math problem solving at the end of ninth grade (Becker et al., 2018).

Relations between early school age visual spatial abilities and later academic functioning have been explored through a variety of tasks assessing visual spatial working memory (e.g., Toll et al., 2016), visual spatial short-term memory (e.g., Soto-Calvo et al., 2015) as well as spatial/nonverbal reasoning (e.g., Peng et al., 2016). Associations between early school age visual spatial abilities and later school age mathematical abilities have been found (e.g., Bull et al., 2008; Toll et al., 2016). For example, Bull and colleagues (2008) examined visual spatial short-term memory when children were in preschool and found that it was significantly related to later math abilities at age 7. However, findings are mixed, and some studies find that visual spatial abilities are not the best predictors of later math abilities when other domain specific or domain general variables are considered (e.g., Peng et al., 2016). As mentioned earlier in this section, nonverbal reasoning abilities may be related to later math abilities but may not necessarily predict the most variance (Alloway & Alloway, 2010).

Summary of Neuropsychological Predictors of School Age Academic Functioning in Typically Developing Children

One difficulty with examining the literature of predictors of later academic functioning in typically developing children is that measures and the number/types of predictors often vary across studies. Additionally, children were often followed for varying lengths of time and the relationships between predictors and outcome variables may vary based on the length of time between the visits. Based on the studies reviewed, however, there are many potential predictors for later academic functioning. For reading abilities, it will be important to examine pre-literacy abilities (i.e., phonological awareness, phonological memory, RAN), letter knowledge, oral language, attention, and EF. For math abilities, future work should examine the role of both domain general (i.e., symbolic and non-symbolic knowledge) and domain-specific (e.g., attention, EF, language, visual spatial) predictors.

Cognitive Phenotype of Neurofibromatosis Type 1

NF1 is an autosomal dominant disorder caused by a mutation or deletion of the *NF1* gene. The *NF1* gene is located on chromosome 17q11.2 and encodes for neurofibromin. Neurofibromin is a tumor suppressor protein, which is produced in many types of cells and inhibits cell growth. Neurofibromin regulates the signaling pathway of another protein, RAS, which controls cell growth (Miller et al., 2019). The functional loss of neurofibromin is thought to allow for hyperactivation of RAS leading to the increase of cell growth (Gutmann et al., 2017). Approximately half of cases are new mutations while the other half are inherited (e.g., McKeever et al., 2008). Estimated rates of the incidence and prevalence vary for individuals with NF1. Incidence is approximately 1 in 2000 to 1 in 3000 (e.g., Evans et al., 2010; Lammert et al., 2005; Uusitalo et al., 2015). Prevalence rates often range between approximately 1 in 3000 to 1 in 5500 (e.g., Evans et al., 2010; Kallionpää et al., 2018; Lammert et al., 2005; McKeever et al., 2008).

The NIH Consensus Conference in 1987 developed a set of clinical criteria for diagnosis of NF1. To meet diagnostic criteria, individuals must meet at least two of the seven criteria. The seven clinical criteria include six or more café-au-lait spots over 5mm in greatest diameter in prepubertal individuals and over 15mm in greatest diameter in postpubertal individuals, two or more neurofibromas of any type or plexiform neurofibroma, freckling in the axillary or inguinal regions, optic gliomas, two or more Lisch nodules, a distinctive osseous lesion such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudarthrosis, and a first degree relative with NF1 who meets for the above criteria (NIH, 1988). Individuals with NF1 are at risk for a range of medical complications that can range in severity, including neurofibromas, pigmentary lesions, skeletal deformities, cardiovascular abnormalities in addition to central and peripheral nervous system tumors (for reviews see Gutmann et al., 2017; Hirbe & Gutmann, 2014).

Cognitive Functioning in Children with NF1

Individuals with NF1 do not have a distinct cognitive phenotype; rather, patterns of cognitive functioning vary across children with NF1. Previous studies have suggested that children with NF1 may have cognitive difficulties in a variety of domains including problems with attention, executive functioning, motor skills, visuospatial functioning, oral language, memory, and a general mild lowering of intellectual functioning (for review see Lehtonen et al., 2013). Mean scores for intellectual functioning are often in the lower end of the average range (e.g., Hyman et al., 2005; Sangster et al., 2010). Cross-sectional studies suggest that this downward shift in intellectual functioning can be found in young children (e.g., Klein-Tasman et al., 2014; Sangster et al., 2010) and school age children with NF1 (e.g., Hyman et al., 2005; Clements-Stephens et al., 2008). Notably, Sangster and colleagues (2010) found that differences in intellectual functioning when young children with NF1 were compared to an unaffected peer group persisted even when maternal education (a demographic factor which may impact IQ) was taken into account.

Attention problems are common among youth with NF1 and approximately 30-50% of children with NF1 meet diagnostic criteria for ADHD (e.g., Hyman et al., 2005; Mautner et al., 2002; Pride et al., 2012). While there are mixed findings regarding the presence of attention problems in young children with NF1 (e.g., Casnar et al., 2014, Klein-Tasman et al., 2014; Sangster et al., 2010), attention difficulties are commonly found in school age children with NF1 (e.g., Hyman et al., 2005; Mautner et al., 2002; Payne et al., 2011). Attention problems are evident based both on parent report as well as performance on performance-based measures in school age children with NF1 (e.g., Galasso et al., 2014; Hyman et al., 2005; Payne et al., 2011). Some evidence suggests that the inattentive features of ADHD may be more common in children with NF1 (e.g., Pride et al., 2012). Pride and colleagues (2012) found that children with NF1 met criteria for the combined presentation of ADHD most frequently (52%), followed by the inattentive presentation (35%) and the hyperactive/impulsive presentation was found least frequently (13%).

EF problems are commonly found in youth with NF1. Evidence for poorer EF has been found in young children with NF1 (e.g., Lorenzo et al., 2013). In particular, working memory appears to be an area of difficulty in young children with NF1 (Casnar & Klein-Tasman, 2017; Sangster et al., 2010). Casnar and Klein-Tasman (2017) found the BRIEF working memory subscale was the only scale on which young children with NF1 had poorer functioning compared to unaffected peers when rated by parents. Additionally, young children with NF1 had poorer working memory functioning when compared to the normative mean based on both parent and teacher report. In school age children with NF1, EF difficulties include working memory, planning, inhibition, and cognitive flexibility (e.g., Hyman et al., 2005; Payne et al., 2011; Plasschaert et al., 2016; Roy et al., 2010; Roy et al., 2014). For example, Payne and colleagues (2011) found poorer EF on all scales and indices of the BRIEF when children with NF1 were compared to unaffected siblings. Poorer EF abilities are found based on both parent reported measures (e.g., Casnar & Klein-Tasman, 2017; Gilboa et al., 2014) as well as performance based assessments of EF (e.g., Payne et al., 2011; Roy et al., 2014). While it would be reasonable to assume that the difficulties with EF are a consequence of high rates of ADHD, past findings have suggested that EF difficulties can be found in youth with NF1 without ADHD (e.g., Pride et al., 2012; Roy et al., 2014).

Visuospatial and visuomotor abilities are another area in which youth with NF1 have difficulties. Children with NF1 have been shown to perform more poorly on visuospatial and visuomotor tasks when compared to unaffected siblings (e.g., Dilts et al., 1996; Hyman et al., 2005). However, prior studies have not consistently found visuospatial and visuomotor difficulties in children with NF1 (e.g., Billingsley et al., 2002; Clements-Stephens et al., 2008; Mazzocco et al., 2001). Van Eylen et al.'s (2017) findings suggest that poorer visuoperceptual abilities may be the result of EF problems in children with NF1. Thus, EF abilities should also be taken into consideration when assessing visuospatial abilities in children with NF1.

Language difficulties are a concern for children with NF1. Approximately 20 to 40% of young children with NF1 show delays in expressive and/or receptive language abilities (Brei et al., 2014; Soucy et al., 2012; Thompson et al., 2010). While young children with NF1 have been found to show poorer than the normative mean (Brei et al., 2014) and unaffected controls on language tasks (Lorenzo et al., 2011; Lorenzo et al., 2013), Sangster and colleagues (2010) found language differences were generally no longer significant once maternal education and IQ were accounted for. Language difficulties are also evident in the school age years as approximately 30% of school age children with NF1 had receptive and expressive language abilities one standard deviation below unaffected siblings (Hyman et al., 2005). However, mixed findings have been noted for language abilities in school age children with NF1 across various studies (e.g., Cutting et al., 2010; Dilts et al., 1996; Hyman et al., 2005; Krab et al., 2008; Mazzocco et al., 1995). Findings for language abilities in school age children with NF1 may vary based on type of language functioning being assessed, the assessment measure in use, and whether intellectual functioning is accounted for.

Motor difficulties are evident in children with NF1 beginning in early childhood (Lorenzo et al., 2011; Soucy et al., 2012) and support for both fine and gross motor difficulties is noted in school age children with NF1 (Champion et al., 2014; Coutinho et al., 2016; Rietman et al., 2017). Coutinho and colleagues (2016) found there were high rates of fine motor problems in school age children with NF1. Rietman and colleagues (2017) examined motor problems in a wide range of youth with NF1 (ages 4-16) using the Movement Assessment Battery for Children), which assesses both fine and gross motor abilities. Based on these findings, 61% of children with NF1 had total scores in the clinically significant range while only 22% were in the normal range. Champion and colleagues (2014) also found gross motor impairments on balance, running speed and agility, and upper limb coordination tasks in school age children with NF1.

Difficulties with memory have mixed findings in youth with NF1; however, past studies suggest this is an area that is more commonly spared (e.g., Dilts et al., 1996; Hyman et al., 2005; Pride et al., 2012). When difficulties with visual memory are reported, they are often found for the Rey Complex Figure Test (e.g., Coutinho et al., 2016; Descheemaeker et al., 2005; Krab et al., 2008). Difficulties with visual memory on this task may be related to poorer visuospatial and EF abilities often found in youth with NF1, which are abilities that are required to perform the Rey Complex Figure Test. Verbal memory tasks also have mixed findings as some studies suggest youth with NF1 have poorer verbal memory (Billingsley et al., 2003) while others find no differences (e.g., Hyman et al., 2005; Pride et al., 2012). Notably, Descheemaeker and colleagues (2005) found that approximately 30-40% of children had verbal memory scores one standard deviation or more below the mean. Mixed findings may be related to the different tasks used to assess verbal memory (e.g., California Verbal Learning Test for Children, Verbal Selective Reminding Test) and using a combined memory score for verbal and visual memory (Moore et al., 2000).

In sum, children with NF1 have a wide range of neuropsychological domains which may potentially be impacted; however, there is no clear cognitive profile for children with NF1 and areas of difficulty will vary. Thus, a wide range of neuropsychological domains which could potentially impact learning in children with NF1 should be assessed in order to have a better understanding of an individuals' strengths and weaknesses and how to better intervene to address academic weaknesses.

Academic Functioning in Children with NF1

While medical complications are often the focus of medical management for individuals with NF1, learning problems (e.g., grade repetitions, consideration of placement in special schooling) are often reported as the most common complication of NF1 (Coudé et al., 2006; McKeever et al., 2008). Learning difficulties are often reported for approximately half or more children with NF1 (e.g., Brewer et al., 1997; Coutinho et al., 2016; Descheemaeker et al., 2005; Hyman et al., 2005; Hyman et al., 2006; Krab et al., 2008). Learning disabilities in children with NF1 have also reported to be associated with quality of life (Wolkenstein et al., 2009). Notably, it is important to recognize that children with NF1 may show weaker performance compared to their same-aged peers on tasks of academic functioning even though they may not meet formal diagnostic criteria for a specific learning disability. The literature on academic functioning for children with NF1 will be discussed in order to assess the current knowledge of school age academic functioning, pre-academic functioning, longitudinal examinations of academic functioning, and neuropsychological correlates of academic functioning for children with NF1.

Academic Performance in School Age Children with NF1.

Reading Performance. Reading difficulties for children with NF1 have been found when compared to unaffected siblings and controls on basic reading and reading comprehension tasks (e.g., Clements-Stephens et al., 2008; Cutting et al., 2000; Hyman et al., 2005; Mazzocco et al., 1995). Mean scores for reading performance of children with NF1 is often in the low average to average range (e.g., Billingsley et al., 2004; Clements-Stephens et al., 2008; De Winter et al., 1999; Hofman et al., 1994; Hyman et al., 2005; Mazzocco et al., 1995); however, approximately 10-45% of children showing impairments on reading tasks (e.g., Chaix et al., 2018; Coutinho et al. 2016; Dilts et al., 1996; De Winter et al., 1999; Hyman et al., 2005; North et al., 1994; North et al., 1995). The wide range of impairments is likely due in part to the different study classifications of reading impairment. For example, Coutinho and colleagues (2016), classified impairments as reading scores that were 1.5 standard deviations at or below the mean z-score. However, Hyman and colleagues (2005) classified impairments as 1SD below the normative mean. Similarly, there is a wide range of percentages of RD diagnoses seen across studies ranging from approximately 5-60% (Clements-Stephens et al., 2008; Dilts et al., 1996; Hyman et al., 2006; Mazzocco et al., 1995; Orraca-Castillo et al., 2014; Watt et al., 2008). Notably, some studies with small sample sizes also indicated high rates of RD so these studies may not be representative of the larger NF1 population (e.g., Mazzocco et al., 1995). Also, many studies used an intelligence-achievement discrepancy model to classify RD which is no longer the recommended way of determining specific learning disabilities (e.g., Hyman et al., 2006; Mazzocco et al., 1995). However, prior studies have not found consistently found reading deficits in children with NF1 (e.g., Billingsley et al., 2004). There are potentially several reasons for these mixed findings included matched IQ between groups (Billingsley et al., 2004) and small sample size (Billingsley et al., 2002).

Several studies have examined whether basic reading difficulties may be attributed to problems employing whole word decoding strategies (i.e., surface dyslexia) or phonological decoding (i.e., phonological dyslexia) in children with NF1. The findings have been mixed, which may be attributed to different languages as well as differences in methods and measures used to determine RD diagnosis (Orraca-Castillo et al., 2014; Watt et al., 2008). The potential role of phonological processing abilities in reading abilities of school age children with NF1 has also been investigated in several studies. Phonological awareness skills were found to be lower for children with NF1 when compared to unaffected children (Cutting et al., 2000; Mazzocco et al., 1995) and unaffected children with RD (Cutting et al., 2000). Chaix and colleagues (2018) found that a group of children with NF1, some with reading difficulties and some without, had poorer phonological awareness than an unaffected group of children who were matched based on age, handedness, sex, and reading level. Difficulties with reading related abilities (e.g., RAN and phonological awareness) appear to be similar for school age children with NF1 and RD when compared to unaffected children who are diagnosed with RD (Cutting et al., 2010).

Mathematical Performance. Children with NF1 have been found to have significantly poorer math performance than unaffected siblings and controls (e.g., Billingsley et al., 2003; Dilts et al., 1996; Mazzocco et al., 1995). Performance on tasks of both math calculations (Cutting et al., 2000; Mazzocco et al., 1995), and math problem solving (e.g., Billingsley et al., 2004; Cutting et al., 2000; Mazzocco et al., 1995) has been poorer for children with NF1. Mean scores for math abilities are typically in the low average to average range (e.g., Billingsley et al., 2004; Cutting et al., 2000; De Winter et al., 1999; Dilts et al., 1996; Hofman et al., 1994; Hyman et al., 2005; Mazzocco et al., 1995; Janke et al., 2014; Pride et al., 2010), which suggests that children with NF1 are having mild deficits but are not always meeting criteria for a specific learning disability. Some studies do not find significant differences for math calculations compared to the normative mean or unaffected children (Billingsley et al., 2002; Billingsley et al., 2004; Janke et al., 2014). Approximately 20-40% of children with NF1 have reported math difficulties (De Winter et al., 1999; Dilts et al., 1996; Hyman et al., 2005; Janke et al., 2014; North et al., 1994; North et al., 1995) and math disabilities are reported for approximately 10-40% of children with NF1 (Billingsley et al., 2004; Descheemaeker et al., 2005; Dilts et al., 1996; Hyman et al., 2006; Mazzocco et al., 1995; Orraca-Castillo et al., 2014).

Studies examining math abilities in children with NF1 typically find deficits in math problem solving, with less frequent support for math calculations. This may be because math calculations may rely more on rote memory of math facts and memory is often spared in children with NF1. However, math problem solving likely involves a greater range of cognitive abilities such that multiple kinds of cognitive difficulties may lead to an endpoint of challenges on math problem-solving tasks. There is only one known study that has examined potential domain-specific abilities underlying math performance in school age children with NF1 (Orraca-Castillo et al., 2014). Even though children with NF1 who were classified as having developmental dyscalculia performed poorly on a task of basic arithmetic fluency, they had spared abilities for magnitude comparison and enumeration. While only a couple of domain-specific abilities were examined as part of this study, these findings potentially suggest that domain-specific abilities may not be the primary driver of poor mathematic performance in children with NF1.

Cognitive Contributors to Academic Difficulties in School Age Children with NF1.

Given the wide range of cognitive deficits that are possible for children with NF1, it is important to determine which cognitive abilities may impact learning. Intellectual functioning is the most commonly examined and lower intellectual functioning has been associated with poorer reading and math abilities (Coutinho et al., 2016; Janke et al., 2014; North et al., 1995; Watt et al., 2008). Several studies have examined the impact of attention on academic functioning for children with NF1 and found that children with NF1 and ADHD perform worse on academic tasks when compared to children with NF1 only (Barton & North, 2007; Pride et al., 2012). EF has also been associated with math calculation and reading tasks (Janke et al., 2014). EF abilities such as inhibition, working memory, and cognitive flexibility were associated with academic performance and should be examined further in children with NF1. Visuospatial abilities have been shown to be associated with reading comprehension and math problem solving abilities in children with NF1 (Mazzocco et al., 1995). Additionally, when compared to unaffected children with RD, children with NF1 and RD had poorer visuospatial abilities, which suggests that there may be a difference in the neuropsychological profile of children with NF1 with RD when compared to unaffected children with RD (Cutting et al., 2010). There were no significant differences in oral language ability when children with NF1 with and without RD were compared to unaffected children with and without RD, which may have been due to having groups that were matched on intellectual functioning (Cutting et al., 2010). Overall, these findings suggest that cognitive features that are associated with NF1 may impact learning abilities in children with NF1. However, the evidence is fairly limited across the different cognitive domains and further study is warranted.

Overall, the current literature on academic functioning in children with NF1 suggests that reading and math problems are common and that children with NF1 should be screened for academic difficulties. Knowledge about the domain-specific abilities associated with academic difficulties is limited. Phonological awareness may be associated with basic reading problems for children with NF1; this relationship would be expected based on evidence suggesting the importance of phonological awareness in reading ability for typically developing children (for review see Melby-Larvåg et al., 2012). Domain-specific abilities associated with math performance have not been adequately probed and further investigation is warranted. Neuropsychological factors such as intellectual functioning, attention, executive functioning, and visuospatial functioning appear to impact learning problems in children with NF1, but more exploration of these areas is needed. Several problems with the current literature of academic functioning in school age children with NF1 are notable. Specifically, the estimates of specific learning disability in children with NF1 are often based on the old approaches to classification, comparison groups are not always matched for intellectual functioning, and the age range of children in studies often is wide making it more difficult to determine how academic functioning may change with development.

Preacademic and Academic Functioning in Young Children with NF1. Research about pre-academic functioning in children with NF1 is limited, but suggestive that pre-academic difficulties can be observed in young children with NF1. Limited research has been conducted on foundational number knowledge (Janke, 2013; Klein-Tasman et al., 2014). These studies that were conducted using an overlapping sample have suggested that young children with NF1 have mean scores in the average range on a task assessing foundational number knowledge. However, approximately 20-30% perform at one standard deviation or below the mean and young children with NF1 perform poorer when compared to the normative mean and unaffected children.

Pre-literacy abilities including phonological processing abilities such as phonological awareness, RAN, and phonological memory have been previously examined (Arnold et al., 2018; Janke, 2013). Janke (2013) found the phonological processing score was in the average range; however, children with NF1 had poorer performance compared to the unaffected group. Approximately one-quarter of children with NF1 demonstrated deficits on the phonological processing task. Young children with NF1 have shown poorer phonological awareness compared to unaffected groups (Arnold et al., 2018). Even though phonological awareness abilities showed average abilities, approximately one-third of young children with NF1 had composite scores below the average range (Standard score <90). Arnold and colleagues (2018) also found that performance on phonological memory in young children with NF1 was significantly worse than controls. Mean performance for the phonological memory composite score was in low average range with approximately half of children with NF1 having composite scores that were below the average range (Standard score <90).

Mixed findings have been found for RAN deficits in young children with NF1; however, only two studies have examined RAN so further investigation is warranted. Janke (2013) found no significant differences for young children with NF1 when compared to both the normative mean and an unaffected group when assessing RAN using the Differential Ability Scales, Second Edition (DAS-II). Notably, the RAN score was in the average range. Additionally, only 8% of children in both groups had difficulties 1SD or more below the mean. Mazzocco (2001) also found no significant differences for RAN of colors for young children with NF1 in comparison to age, sex, and IQ matched controls. Arnold and colleagues (2018) found no significant differences between young children with NF1 compared to an unaffected group on the each of the subtests of the Comprehensive Test of Phonological Processing (CTOPP); however, young children with NF1 performed poorer on the Rapid Naming composite score. Notably, approximately half of the young children with NF1 scored below the average range (Standard score <90) on the CTOPP RAN composite. Differences between the findings in these studies may be due to the different measures that were used. For example, the DAS-II does not have multiple RAN subtests and it appears that subtle difficulties on the CTOPP may have had an additive effect.

Young children with NF1 also have average letter knowledge abilities even though they have poorer performance when compared to age, sex and maternal education matched unaffected children (Lorenzo et al., 2013). However, young children with NF1 showed significant difficulties compared to unaffected children on a task that required them to sound out letters or combinations of letters (Arnold et al., 2018). This may suggest that the added complexity of having to sound out groups of letters is difficult for young children with NF1 where they may be able to rely on rote memory to identify single letters.

There are few studies examining academic functioning specifically in young children with NF1. The extant studies are problematic due to small sample sizes (Mazzocco, 2001) or use of screening measures with a very small number of items per domain, rather than a comprehensive assessment of academic functioning (Soucy et al., 2012; Wessel et al., 2013). Mazzocco (2001) found that young children with NF1 (ages 5 and 6) did not have significantly different math and reading abilities compared to unaffected children when groups were matched for age, sex, and IQ. Soucy and colleagues (2012) examined math/premath and reading/prereading in a wide age range of young children with NF1 (7 months to 8 years) using the Parents' Evaluation of Developmental Status – Developmental Milestones which is a screening form for developmental delays across 6-8 developmental domains. Each domain is assessed through a multiple-choice question posed either to the parent or directly to the child based on the domain and the age of the child. Children are considered delayed in a domain if their score is below the 16th percentile. Based on this screener, young children with NF1 showed statistically significant delays in math/premath (31% of children had delays). Delays for children with NF1 on the reading/prereading domain (28%) were not significant. Due to the wide age range in the study conducted by Soucy and colleagues (2012), it is difficult to determine potential academic difficulties specifically in early school age children. However, Wessel and colleagues (2013) examined potential changes over time using the same measure, in an overlapping sample. Considered delays in math/premath and reading/prereading were found to increase with age. While 17-25% of children with NF1 were considered delayed during the infant and/or preschool years (0-5 years old), 54-62% were considered delayed during the school years (6-8 years old). Results of these studies should be interpreted with caution due to concerns about the measure of pre-academic/academic functioning; The Parents' Evaluation of Developmental Status – Developmental Milestones is a criterion-based screening measure as opposed to a norm-referenced measure which is typically examined in studies of pre-academic/academic functioning in youth with NF1. Furthermore, the screening measure bases its scores on a very small number of items, and therefore the measure cannot have strong psychometric properties.

Few studies have examined pre-academic functioning and academic functioning in young children with NF1. While the few that exist suggest that pre-academic and academic deficits can be observed starting at a young age, further investigation is needed. Most studies examining academic functioning have a wide age range so it is unclear when problems with academic functioning may become more evident although there is some evidence that problems may increase during early childhood (Wessel et al., 2013).

Longitudinal Studies of Academic Functioning in NF1. To my knowledge, there is only a single study examining pre-academic/academic functioning longitudinally in children with NF1, and this study should be interpreted with caution given the methodology used. Wessel and colleagues (2013) measured development in youth with NF1 using the Parents' Evaluation of Developmental Status - Developmental Milestones screener at three age groups: infant (0-2 years), preschool (3-5 years), and school age (6-8 years). Pre-math/math was examined at all three time points while pre-reading/reading was only measured during preschool and school age time points. For children with longitudinal data, the initial time point was compared to the second time point. For pre-math/math, 17% and 31% of children with NF1 were considered delayed at the initial and second time points, respectively. For pre-reading/reading, 14% and 21% of children with NF1 were considered delayed at the initial and second time points, respectively. Frequency of considered delays did not significantly differ between initial and second time points for pre-reading/reading and pre-math/math abilities. Notably, 7-11% of children with pre-math/math and pre-reading/reading delays at the initial time point also had delays at their second time point. This study potentially suggests that it may be possible to identify learning difficulties in young children with NF1 using a very brief screening measure and detected early difficulties may persist as children develop. However, as previously noted, these results need to be interpreted with caution given the concerns with the measure of pre-academic/academic functioning used in this study. Further examination of longitudinal academic abilities in children with NF1 is warranted as the only known study uses a screening measure to examine pre-academic and academic functioning making it difficult to compare to other studies in children with NF1.

Summary of Pre-academic and Academic Functioning in Children with NF1

The literature examining academic functioning in children with NF1 suggests that reading and math abilities are a common concern. Additionally, common areas of cognitive difficulty in NF1 have been shown to potentially impact school age academic functioning (e.g., intellectual functioning, executive functioning). There are some indications that difficulties with pre-math and pre-reading difficulties can be identified in young children with NF1 although the research is currently limited. Only a single study examined pre-academic/academic abilities in children with NF1 longitudinally and found that considered delays did not change over time; however, this study used a criterion-based screening measure rather than a norm-referenced measure.

Based on the academic literature regarding children with NF1, there are several significant limitations to the current literature that need to be addressed. First, there is limited cross-sectional research that examines the cognitive correlates associated with academic functioning in children with NF1. Second, there are a limited number of studies that examine pre-academic functioning and early school age academic functioning specifically. Third, there is only a single study that examines pre-academic/academic functioning over time and this study needs to be interpreted with caution due to methodological concerns. Finally, to my knowledge there is no literature that looks at early school age predictors of later academic functioning.

Overall Summary and Rationale

Academic challenges are the most commonly reported problem for children with NF1 despite the cognitive profile for NF1 often indicating other common areas of difficulty such as intellectual functioning, attention, executive functioning, visuospatial abilities, and language. Notably, intellectual functioning, attention, executive functioning, visuospatial abilities have been shown to have concurrent relations with academic functioning in school age children with NF1. Despite the common occurrence of academic problems in children with NF1, there is limited information about pre-academic functioning and the pre-academic/academic functioning trajectory. In particular, there are no known studies that examine predictors of later academic functioning in children with NF1.

As there are no known studies of pre-academic and neuropsychological predictors of later academic functioning in children with NF1, potential predictors were based on findings from the typically developing literature. Based on a review of the literature, there is evidence to suggest that school age reading and math ability may be predicted by both pre-academic and neuropsychological predictors (intellectual functioning, attention, executive functioning, language, and visuospatial abilities) for preschool/early school age children.

Based on examination of the literature of pre-academic/academic functioning in children with NF1 and predictors of school age academic performance in typically developing children, potential predictors of school age academic functioning were determined for children with NF1. This study aims to both replicate the findings of school age academic functioning of children with NF1 from previous studies as well as to examine predictors of later academic functioning for the first time.

Aims and Hypotheses

Aim 1: Replicate the previous findings in the literature that examine academic performance of late school age children with NF1.

1a: Children with NF1 will have poorer academic performance when compared to the normative mean and have rates of difficulty similar to those found in previous studies.

1b: It is hypothesized that intellectual functioning, attention, working memory, and oral language abilities will be able to predict reading abilities in children with NF1.

1c: It is also hypothesized that intellectual functioning, attention, working memory, and visuospatial abilities will predict math abilities in children with NF1.

Aim 2: Examine the association between pre-academic functioning and later academic functioning in children with NF1.

2a: It is hypothesized that a pre-math measure will be associated with later math ability.

2b: It is also hypothesized that pre-reading measures will be correlated with later reading abilities.

Aim 3: Investigate whether neuropsychological variables in the early school age years predict later school age academic functioning in children with NF1.

3a: It is hypothesized that intellectual functioning, attention, working memory, and oral language abilities will be associated with later reading abilities in children with NF1.

3b: It is also hypothesized that intellectual functioning, attention, working memory, and visuospatial abilities will be associated with later math abilities in children with NF1.

Aim 4 (Exploratory): Examine which early school age pre-academic and/or neuropsychological predictors are best able to significantly predict later reading and math abilities in children with NF1. As Aim 4 is more exploratory in nature, there are not previous studies from which to directly draw evidence to hypothesize the predictors which are going to be most likely to predict later academic functioning. However, based on the prior information about pre-academic and neuropsychological associations with academic functioning in children with NF1 and in typically developing children, it is hypothesized that three predictors will be able to significantly predict later reading and math abilities in children with NF1.

Aim 5 (Exploratory): Examine the relation between how a set of late school age neuropsychological variables as well as a set of early school age pre-academic or neuropsychological variables are associated with the set of late school age academic variables. Since Aim 5 is also more exploratory in nature, there are also no prior studies examining this to base hypotheses on. However, it is hypothesized that there will be a significant relationship between the sets of pre-academic (early school age) or neuropsychological variables (early school age and late school age) and late school age academic variables.

Method

Participants

Participants initially took part in a study to examine the cognitive and behavioral phenotype of preschool and early school age (ESA) children with NF1 (n = 62; ages 3 to 8). Children with NF1 and their families were recruited from NF clinics in the Milwaukee (Neurofibromatosis Clinic at the Children's Hospital of Wisconsin Genetics Center/Medical College of Wisconsin) and Chicago (University of Chicago Neurofibromatosis Clinic) areas, and flyer distribution at regional NF1 symposiums. Children with NF1 were asked to return each year for a follow-up appointment until age 8. Thus, participants have a varying number of follow-up appointments due to willingness to return for follow-up appointments and the age at which they entered the study.

We also examined the cognitive and behavioral phenotype of late school age (LSA) children with NF1 (n = 40; ages of 9 to 13; Table 1). Children with NF1 and their families who previously participated in the earlier study were contacted about participation via a flyer in the mail and by phone to answer potential study questions. New participants were recruited through several Midwestern Neurofibromatosis clinics and a study flyer being posted on the Neurofibromatosis Research Registry. Twenty-seven of the children in the LSA sample also participated in the prior ESA study.

Children with NF1 who completed visits both during the ESA and the LSA time points were included if they had both a full set of pre-academic functioning data at the ESA time point and academic functioning data at the LSA time point. Twenty-four children with NF1 had full sets of pre-academic data at the ESA time point (Table 2). These children were between the ages of 5 and 7. Notably, the full set of pre-academic measures used for this study could only all be administered starting at age 5. Three children with NF1 (ages 3-5) did not have full sets of pre-academic measures completed at the ESA time point and were excluded from the analyses. ESA pre-academic functioning and neuropsychological variables were examined at multiple time points for some children with NF1. As some participants had multiple ESA visits, the data from the first visit with complete data for the pre-academic functioning measures were used for analyses. Inclusion criteria included diagnosis of NF1 from a physician and having English as the main language spoken in the home. Exclusion criteria also included any major surgery within the past 6 months and having another medical condition that is not typically associated with NF1. Notably, two children were included in the study who had medical treatment that may have impacted their cognition; however, these participants were included to capture the variability in pre-academic/academic performance that may be associated with children with NF1.

Measures

All measures included in this study are normed published measures that have adequate reliability and validity data.

Intellectual Functioning

Intellectual functioning was assessed using the Differential Abilities Scales, Second Edition (DAS-II; Elliot, 1990) at both the ESA and LSA time points. The DAS-II Early Years version was administered to children at the ESA time point and the DAS-II School-Age version was administered at the LSA time point. The DAS-II yields a General Conceptual Ability (GCA) score, which is similar to an intelligence quotient and is comprised of subtests assessing Nonverbal Reasoning, Verbal and Spatial abilities. The GCA composite score provided is a Standard Score (Mean = 100, SD = 15), with higher scores indicating better intellectual functioning.

Attention

The Kiddie-Disruptive Behavior Disorder Schedule (KDBDS; Kaufman et al., 1996) and the Schedule for Affective Disorders and Schizophrenia for School Aged Children – Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997)- ADHD section were used to assess for symptoms of ADHD at the ESA and the LSA time points, respectively. Specifically, parents were interviewed about symptoms of ADHD to determine whether children met diagnostic criteria for ADHD. Diagnostic criteria are met for ADHD subtypes if parents endorsed six or more items for either predominantly hyperactive-impulsive or inattentive subtypes. If parents endorsed six or more items for both hyperactive/impulsive and inattentive symptoms, then children meet criteria for the combined presentation. For the KDBDS, children needed to have symptoms that occurred “some” or “a lot” of the time in at least two settings. Symptoms also needed to be present for at least six months. Additionally, at least two questions about level of impairment needed to be rated as “some” or “a lot.” For the K-SADS-PL, an item was considered endorsed if symptom was rated as moderate or severe.

The revised Conners’ Parent Rating Scale (CPRS-R; Conners, 1997) was used to assess parent rated attention abilities at the ESA visit. Specifically, the Cognitive Problems/Inattention (CPRS-R CPI), Hyperactivity (CPRS-R HYP), and ADHD Index (CPRS-R ADHD) scales were used to examine attention abilities in this study. Each scale provides a T score (Mean = 50, SD = 10), with higher scores indicating poorer attention abilities.

The Conners 3rd Edition Parent Short Form (Conners–3; Conners, 2008) was used to assess parent reported attention abilities at the LSA time point. Specifically, the Conners–3 Inattention and Hyperactivity/Impulsivity (H/I) scales were used to examine attention abilities in this study. The Conners–3 scales each provide a T score (Mean = 50, SD = 10); poorer attention ability is indicated by higher T scores.

The Recall of Digits-Forward (DF) subtest of the DAS-II (Elliot, 1990) was used as a performance-based measure of attention at both the ESA and LSA time points. This subtest provides a T score (Mean = 50, SD = 10), with higher scores indicating better attention abilities.

The Flanker Inhibitory Control and Attention Test (Flanker; Zelazo et al., 2013) was used as a performance-based measure of attention and inhibitory control at the LSA time point. Flanker scoring takes into account accuracy and reaction time. When accuracy is above 80%, reaction time and accuracy are considered in combination. However, accuracy alone is considered when its score is less than or equal to 80%. This subtest provides a Standard Score (Mean = 100, SD = 10), with higher scores indicating better attention and inhibitory control. Four children had missing data for the Flanker task.

Working Memory

The Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P; Gioia et al., 2003; age 5) and Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000; ages 5-7) Working Memory scale (WM) were used to assess parent rated working memory for the ESA time point. At the LSA time point, the BRIEF Working Memory scale was used to assess working memory for all children. These scales provide a T score (Mean = 50, SD = 10), with higher scores indicating poorer working memory.

The Recall of Digits-Backward (DB) subtest of the DAS-II (Elliot, 1990) was used as a performance-based measure of working memory at both the ESA and LSA time points. This subtest provides a T score (Mean = 50, SD = 10), with higher scores indicating better working memory abilities. Three children had missing data for this task at the ESA time point either due to difficulties understanding task instructions or because the DB task was not administered during that visit.

Language Abilities

The subtests comprising the DAS-II Verbal index were used to assess language functioning in children with NF1 (Elliot, 1990). The Naming Vocabulary (NV) and Verbal Comprehension (VC) subtests were examined for children administered the DAS-II Early Years form at the ESA time point and the Word Definitions (WD) and Verbal Similarities (VS) subtests were examined for children administered the DAS-II School-Age form at the LSA time point. These subtests provide a T score (Mean = 50, SD = 10), with higher scores indicating better language abilities.

Visuospatial Functioning

The subtests of the DAS-II Spatial index were used to examine visuospatial abilities (Elliot, 1990). The Copying (CO) and Pattern Construction (PC; DAS-II Early Year form) subtests were used to assess visuospatial functioning at the ESA time point and the Recall of Designs (RD) and PC subtests (DAS-II School-Age form) were used for the LSA time point. All subtests provide a T score (Mean = 50, SD = 10), with higher scores indicating better visuospatial performance.

The NEPSY Second Edition (NEPSY-II) Arrows subtest was also used to assess visuospatial functioning at the ESA time point (Korkman et al., 2007). This subtest provides a Scaled Score (Mean = 10, SD = 3), with higher scores indicating better visuospatial abilities.

Early School Age Pre-Academic Functioning

ESA pre-academic functioning was assessed using the Early Number Concepts (ENC), Phonological Processing (PP), and Rapid Naming (RN) subtests of the DAS-II (Elliot, 1990). ENC was used as a measure of pre-math ability, while PP and RN were used as assessments of pre-reading abilities. Each subtest provides a T score (Mean = 50, SD = 10), with higher scores indicating better pre-academic functioning.

Late School Age Academic Functioning

LSA reading-related and mathematics abilities were examined using the Wechsler Individual Achievement Test, Third Edition (WIAT-III; Breaux, 2009). The Word Reading (WR), Pseudoword Decoding (PD), and Reading Comprehension (RC) subtests were used to assess LSA reading-related abilities. The Math Problem Solving (MPS) and Numerical Operations (NO) subtests were used to examine LSA mathematical abilities. The WIAT-III subtests provide Standard Scores (Mean = 100, SD = 10). Higher scores on the WIAT-III indicate better academic performance.

Procedure

At each time point, parents were mailed consent forms and questionnaires ahead of the visit to complete. Research appointments took place at the Child Neurodevelopment Research Lab (CNRL) at the University of Wisconsin–Milwaukee, Pediatric Neuropsychology Clinic at the University of Chicago Hospitals, participants' homes, or in a quiet hotel conference room near participants' homes. Visits took approximately 3 to 4 hours to complete and included a developmentally appropriate battery of neuropsychological assessments.

Data Analytic Plan

Standardized scores for ESA pre-academic, LSA academic, and ESA and LSA neuropsychological variables were used due to the variety of ages at each time point. The normality of all variables was assessed, and non-parametric statistics were used as needed. Outliers were identified as needed using visual inspection and analyses were rerun without the outliers; results are reported without outliers if they were different from analyses that included outliers. Due to the small sample size, both statistical significance and effect sizes were analyzed. Statistical significance values were interpreted as follows: *p*-values < .05 were considered statistically significant. Spearman's rho effect size (Cohen, 1988) are interpreted as follows: small = 0.1 – 0.3; medium = 0.3 – 0.5; large = 0.5 – 1. Kendall rank correlations were also assessed when they seemed appropriate and compared to Spearman correlations findings; associations did not significantly differ between Spearman and Kendall rank correlations for analyses. False discovery rate corrections were used within a given analysis (Benjamini & Hochberg, 1995; Pike, 2011).

Only a subset of the children from the ESA time point returned for the LSA study. Thus, it is important to investigate whether there are differences between children who returned at LSA time point from those who did not. As not all children who returned for the LSA time point will be included in the analyses for this study (n = 3 were excluded due to incomplete data), we will specifically investigate the differences between children who returned for the LSA time point and will be included in analyses (n = 24) and children who did not return (n = 23; ESAonly). T-tests and chi-squares were used to examine demographic, intellectual functioning, and pre-academic differences between the two groups.

Relations with demographic variables were explored for all predictor and outcome variables at ESA and LSA time points. Potential age, gender, intellectual functioning, and SES effects were examined for all variables using Spearman correlations and t-tests as appropriate. For all demographic analyses, outliers were included in the analyses.

In order to assess Aim 1 (examination of LSA academic performance), academic outcomes and predictors were compared to the normative mean using a one-sample t-test for all children who were seen at the LSA time point (n = 40). The percentage of children who are one standard deviation below the normative mean was also assessed to examine LSA academic difficulties. Spearman correlations were used to examine the ability of neuropsychological variables to concurrently predict LSA academic outcome variables. For each math subtest, individual predictors of intellectual functioning, attention, working memory, and visuospatial abilities were analyzed. For each reading-related subtest, the individual predictors of intellectual functioning, attention, working memory, and oral language were examined.

To examine Aim 2 (association between ESA pre-academic measures and LSA academic functioning), Spearman correlations between ESA pre-academic measures and LSA academic variables were analyzed for children with NF1 who participated in both ESA and LSA visits (n = 24). Specifically, the correlation between pre-math ability (DAS-II ENC) and each math subtest was assessed. For reading-related subtests, correlations were examined with both the pre-reading (DAS-II PP and RN) scores individually.

To assess Aim 3 (association between ESA neuropsychological variables and LSA academic performance), Spearman correlations between ESA neuropsychological variables and LSA academic measures were examined for the subset of children who were seen at both ESA and LSA time points (n = 24). For each math subtest, correlations between ESA intellectual functioning, attention, working memory, and visuospatial abilities were analyzed. For each reading-related subtest, correlations between ESA intellectual functioning, attention, working memory, and oral language were examined.

To assess Aim 4 (exploratory examination of the ESA pre-academic and neuropsychological variables that best predict LSA academic functioning), the ESA pre-academic and neuropsychological variables with the strongest associations with LSA academic functioning, based on the results of Aims 2 and 3, were entered in a hierarchical regression model. Due to the small sample size, we limited the number of predictors in each regression model to three predictors. Predictors with the strongest association were entered into the regression first.

To assess Aim 5 (exploratory examination of the association of a set of ESA pre-academic variables, ESA neuropsychological variables or LSA neuropsychological variables with a set of LSA academic variables), canonical correlations were examined. There may be individual differences in how pre-academic and neuropsychological variables relate to academic variables. Thus, if individual differences are present then canonical correlation between pre-academic or neuropsychological variables and the academic variables may better reveal associations compared to hierarchical regression. First, we examined the association between

LSA neuropsychological variables and LSA academic variables. Second, we investigated the relation between ESA pre-academic variables and LSA academic variables. Third, we examined the association between ESA neuropsychological variables and LSA academic variables. Canonical loadings higher than .6 were considered to contribute highly to the pre-academic, neuropsychological, and academic dimensions.

Results

Participant Demographics

Demographic information was collected for the 24 children with NF1 who were seen at both the ESA and LSA time points (Table 2). On average, the LSA time point occurred approximately four years after the ESA time point. Similar numbers of boys and girls returned for the LSA time point. On the Hollingshead Four-Factor Index of Socioeconomic Status (SES; Hollingshead, 1975), children had similar SES levels at both the ESA and LSA time points. The sample consisted of mostly children who had sporadic cases of NF1 instead of a family history of NF1. Children who returned for the LSA time point primarily identified their race/ethnicity as Caucasian. Mean intellectual functioning was in the average range at both time points. At the ESA time point, zero children met ADHD criteria for the Primarily Inattentive subtype, three met criteria for the Primarily Hyperactive/Impulsive subtype, and three met criteria for the Combined subtype. At the LSA time point, five children met ADHD criteria for the Primarily Inattentive subtype, zero met criteria for the Primarily Hyperactive/Impulsive subtype and three met criteria for the Combined subtype. At the ESA time point, two children were taking ADHD medications. Five children were taking ADHD medications at the time of the LSA study visit.

Demographic information was also collected for all 40 children with NF1 who were seen at the LSA time point (Table 1). Children with NF1 seen at this time point were comprised of similar numbers of boys and girls. More children with sporadic cases of NF1 were seen at the LSA time point. The sample was comprised of children who primarily identified their race/ethnicity as Caucasian. Intellectual functioning of children who were seen at the LSA time point was in the average range. When assessing how many children with NF1 met criteria for ADHD, seven children met criteria for the Primarily Inattentive subtype, one participant met criteria for the Primary Hyperactive/Impulsive subtype and five children met criteria for the Combined subtype. Ten children were reported to be taking medications for ADHD at the LSA time point.

Attrition Analyses

Attrition analyses examined differences between the ESA (those seen both in ESA and LSA timepoints) and ESAonly groups for demographic, intellectual functioning, and pre-academic differences. Twenty-three children ages 5 to 7 (*M* = 6.10, *SD* = 0.89) did not return for the LSA time point and were included in the ESAonly group. This group was comprised of 13 (57%) boys and 10 (43%) girls. Ten children (43%) had a familial history of NF1 and 13 (57%) children had sporadic cases of NF1. Mean SES for the ESAonly group was 40.19 (*SD* = 13.27); two children in the ESAonly group did not have SES data available. Children in the ESAonly group primarily identified their race/ethnicity as Caucasian (n = 17); one child identified as African American, four as Latino, zero as Asian, and one as Mixed.

There were no significant group differences for any of the demographic variables: age (*t*(45) = -0.152, *p* = .880), gender ($\chi 2(1) = 0.016$, *p* = .900), SES (*t*(43) = 1.231, *p* = .225), NF classification ($\chi 2(1) = 2.772$, *p* = .096), race/ethnicity ($\chi 2(1) = 0.181$, *p* = .671). Race/ethnicity was collapsed into two categories (Caucasian versus non-Caucasian) to analyze group differences due to the small number of children who classified their race/ethnicity as African

American, Latino, Asian, or Mixed. Notably, normality was violated for age for the ESAonly group; however, there were still no significant age differences between groups when non-parametric statistics were analyzed.

There were no significant differences in intellectual functioning between the ESA and ESAonly (*M* = 92.78, *SD* = 16.36) groups (*t*(45) = 1.420, *p* = .163), with both groups performing in the average range. The ESA group performed in the average range on pre-academic tasks: DAS-II ENC (*M* = 50.96, *SD* = 9.77), PP (*M* = 49.96, *SD* = 8.36), and RN (*M* = 52.63, *SD* = 6.49). ESAonly group performed in the low average to average range on pre-academic tasks: DAS-II ENC (*M* = 43.30, *SD* = 12.85), PP (*M* = 41.43, *SD* = 14.12), and RN (*M* = 51.56, *SD* = 9.47). Notably, DAS-II PP data was not available for two children in the ESAonly group and DAS-II RN data was not available for five children in the ESAonly group. Analysis of pre-academic variables suggested that the ESA group performed significantly better on DAS-II ENC (*t*(45) = 2.306, *p* = .026) and PP (Welch *t*(31.578) = 2.422, *p* = .021) tasks compared to the ESAonly group. When an independent samples t-test was run to assess group differences for DAS-II ENC, it was noted that there were outliers and normality was violated for the ESA group. Thus, the analysis was rerun removing the outliers using a Welch t-test (*t*(29.730) = 2.617, *p* = .014); results did not significantly differ from analyses that included outliers. Significant group differences were not found for DAS-II RN (*t*(40) = 0.435, *p* = .666). Notably, when an independent samples t-test was run to assess group differences for DAS-II RN, there were outliers. The analysis was rerun removing the outliers using an independent samples t-test (*t*(38) = -0.617, *p* = .541), suggesting that results did not significantly differ from analysis that included outliers.

Demographic Analyses

Relations between demographic variables (age, gender, intellectual functioning, SES) were analyzed for all behavioral, cognitive, and pre-academic/academic variables at the ESA (Table 3) and LSA (Table 4 and Table 5) time points. At the ESA time point (Table 3), there were no significant relations with age and SES. There were no significant gender differences at the ESA time point. Significant Spearman correlations were found between intellectual functioning (DAS-II GCA) and DAS-II DB and PP. Spearman correlations between DAS-II GCA and NV, VC, CO, and PC were not analyzed as these subtests are components of the DAS-II GCA score.

At the LSA time point for participants who were seen at both the ESA and LSA time points (n = 24; Table 4), no significant associations were found between LSA behavioral, cognitive, and academic variables and age or SES. Using a Welch t-test, boys had significantly higher Conners–3 Inattention scores compared to girls. Significant Spearman correlations were found between intellectual functioning (DAS-II GCA) and DAS-II DB, Flanker, and WIAT-III NO, MPS, WR and PD. Spearman correlations between DAS-II GCA and WD, VS, RD, and PC were not analyzed as these subtests are components of the GCA score.

At the LSA time point, relations between demographic variables and all behavioral, cognitive, and academic variables were also examined for all participants who were seen at the LSA time point (n = 40; Table 5). No significant associations were found between age and behavioral, cognitive, and academic variables. No significant associations were found between SES and behavioral, cognitive and academic variables. Boys had significantly poorer parent rated inattention ability (Conners–3 Inattention) compared to girls. However, boys had significantly better performance than girls on the Flanker, DAS-II RD, and WIAT-III MPS. Intellectual functioning (DAS-II GCA) was significantly associated with DAS-II DF, Flanker and DAS-II DB. Spearman correlations between overall intellectual functioning (DAS-II GCA) and its component subtests (DAS-II WD, VS, RD, and PC) were not analyzed. Spearman correlations between DAS-II GCA and WIAT-III academic subtests are examined as part of Aim 1 and the results are presented below.

Aim 1 Results

Description of Academic Functioning at Late School Age

When academic abilities at LSA were compared to the normative mean (Table 6), children with NF1 performed significantly below the normative mean for WIAT-III MPS, NO, WR and PD. However, academic abilities at LSA did not differ significantly from the normative mean for WIAT-III RC. WIAT-III MPS had one outlier but when the analysis was run again without the outlier, the results still remained significant ($t(38) = -4.352$, $p = < .001$). Notably, the mean scores for all academic tasks were in the average range. More than 1/4 and up to approximately 1/3 (27.5-35%) of children had performance one standard deviation below the mean for WIAT-III MPS, NO, WR, and PD; however, only 7.5% of children with NF1 performed one standard deviation below the mean for WIAT-III RC.

Relations Between Late School Age Neuropsychological Variables and Late School Age Academic Functioning

Associations between neuropsychological variables and WIAT-III academic variables were assessed (Table 7).

Reading-Related. DAS-II GCA, DF, DB, WD, and VS were significantly correlated with WIAT-III PD; all significant correlations had medium to large effect sizes and survived FDR correction. DAS-II GCA, DF, WD, and VS were significantly correlated with WIAT-III RC. Significant Spearman correlations between DAS-II GCA, WD, and VS and WIAT-III RC had medium to large effect sizes and continued to be significant after FDR correction. The significant Spearman correlation between DAS-II DF and WIAT-III RC had a medium effect size and was no longer significant after FDR correction. Flanker in addition to DAS-II GCA, DF, WD, and VS were significantly correlated with WIAT-III WR; significant Spearman correlations between DAS-II GCA, DF, WD, and VS and WIAT-III WR with medium to large effect sizes and remained significant after FDR correction. The correlation between Flanker and WIAT-III WR had a medium effect size and did not remain significant after FDR correction. Notably, DAS-II DB was initially significantly correlated with WIAT-III WR ($r_s(38) = .344$, $p = .030$), but was no longer significant when an outlier was removed.

Mathematics. Flanker as well as DAS-II GCA, DF, DB, and RD were significantly correlated with both WIAT-III NO and MPS. DAS-II PC was also significantly correlated with WIAT-III NO. All significant Spearman correlations had a medium or large effect size and remained significant after FDR correction. There were no significant differences in the analyses when outliers were removed.

Aim 2 Results: Relations Between Early School Age Pre-Academic Abilities and Late School Age Academic Functioning

The associations between pre-academic functioning at ESA and academic functioning at LSA were examined (Table 8).

Reading-Related

DAS-II PP was significantly correlated to all reading-related tasks (WIAT-III PD, RC, WR). All significant Spearman correlations had large effect sizes. DAS-II RN was not significantly correlated to any of the academic tasks. There were no differences in the analyses when outliers were removed for DAS-II PP and RN analyses. Notably, all significant Spearman correlations between ESA DAS-II PP and LSA reading-related tasks remained significant after FDR correction.

Mathematics

DAS-II ENC was significantly correlated to math tasks (WIAT-III NO and MPS). There were no differences in the analyses when outliers were removed for DAS-II ENC analyses. All significant Spearman correlations had large effect sizes and remained significant after FDR correction.

Aim 3 Results: Relations Between Early School Age Neuropsychological Variables and Late School Age Academic Functioning

Associations between ESA neuropsychological variables and LSA academic performance were also examined (Table 9).

Reading-Related

DAS-II DB and VC were significantly associated with WIAT-III PD. The effect sizes for the significant Spearman correlations between both DAS-II DB and VC with WIAT-III PD were large and remained significant after FDR correction. DAS-II GCA, NV, and VC were significantly correlated with WIAT-III RC. All effect sizes for significant Spearman correlations were medium and were no longer significant after FDR correction. DAS-II GCA, DF, DB, NV, and VC were significantly associated with WIAT-III WR. Notably, if one participant was removed who may be an outlier, there was a significant relation between CPRS-R CPI and WIAT-III WR ($r_s(21) = -.421$, $p = .045$). The effect size for the significant Spearman correlation between DAS-II DF and WIAT-III WR was medium, while the effect sizes for the Spearman correlations between DAS-II GCA, DB, NV, and VC and WIAT-III WR were large. Significant

Spearman correlations for both medium and large effect sizes remained significant after FDR correction.

Mathematics

DAS-II GCA, DF, DB, and PC were significantly correlated with WIAT-III NO and MPS. While there was a significant relation between DAS-II PC and WIAT-III MPS, it is important to note that there were some discontinuities, and the relation seems to be heavily influenced by a couple of participants. The effect size was medium for the association between DAS-II DF and WIAT-III NO, but a large effect size was noted for the correlations between DAS-II GCA, DB, and PC and WIAT-III NO. The effect size was medium for the association between DAS-II GCA and PC and WIAT-III MPS while a large effect size was noted for the correlations between DAS-II DF and DB and WIAT-III MPS. Notably, correlations with large effect sizes were still significant after FDR correction while the correlations with medium effect sizes were not significant after FDR correction.

Aim 4 Results: Early School Age Pre-Academic and Neuropsychological Predictors of Late School Age Academic Functioning (Exploratory Hierarchical Regression Analyses)

The pre-academic and neuropsychological variables with the three highest correlations with each academic task were used for hierarchical multiple regression analyses. Notably, when DAS-II GCA and one of the components that makes up DAS-II GCA (e.g., NV) were both one of the three highest correlations, only correlations with DAS-II GCA were used. Notably, the assumption of homoscedasticity was violated for all hierarchical multiple regression analyses. Since DAS-II DB had one of the three highest correlations with all WIAT-III academic variables, hierarchical multiple regression analyses were examined using a sample of 21 children with NF1, as three children were missing data for DAS-II DB.

Reading-Related

A hierarchical multiple regression using DAS-II PP, DB and VC (predictors entered individually in this order) was analyzed to predict WIAT-III PD. The full hierarchical multiple regression model of DAS-II PP, DB, and VC significantly predicted WIAT-III PD, $R^2 = .551$, $F(3, 17) = 6.968$, $p = .003$, adjusted $R^2 = .472$. DAS-II PP alone was a significant predictor of WIAT-III PD ($F(1, 19) = 12.898$., $p = .002$, $R^2 = .404$). The addition of DAS-II DB ($F(1, 18) = 3.554$, $p = .076$, R^2 change = .098) and DAS-II VC ($F(1, 17) = 1.854$, $p = .191$, R^2 change = .049) did not lead to a statistically significant increase in R^2.

A hierarchical multiple regression using DAS-II PP, GCA, and DB was analyzed next (predictors entered individually in this order) to predict WIAT-III RC. The full hierarchical multiple regression model of DAS-II PP, GCA, and DB did not significantly predict WIAT-III RC, $R^2 = .312$, $F(3, 17) = 2.566$, $p = .089$, adjusted $R^2 = .190$. DAS-II PP alone was a significant predictor of RC ($F(1, 19) = 5.866$, $p = .026$, $R^2 = .236$). The addition of DAS-II GCA ($F(1, 18) = 1.219$, $p = .284$, R^2 change = .048) and DAS-II DB ($F(1, 17) = .674$, $p = .423$, R^2 change = .027) did not lead to statistically significant increases in R^2.

Next, a hierarchical multiple regression using DAS-II PP, DB, and VC (predictors entered individually in this order) to predict WIAT-III WR was analyzed. The full hierarchical multiple regression model of DAS-II PP, DB, and VC significantly predicted WIAT-III WR, $R^2 = .649$, $F(3, 17) = 10.498$, $p = < .001$, adjusted $R^2 = .588$. DAS-II PP alone was a significant predictor of WIAT-III WR ($F(1, 19) = 15.596$, $p = < .001$, $R^2 = .451$). The addition of DAS-II DB ($F(1, 18) = 2.160$, $p = .159$, R^2 change = .059) did not lead to a statistically significant increase in R^2. The addition of DAS-II VC ($F(1, 17) = 6.779$, $p = .019$, R^2 change = .140) did lead to a statistically significant increase in R^2. Due to concerns about high leverage points, analyses were rerun removing four high leverage points. The only notable change when the high leverage points were removed was that DAS-II VC no longer led to a statistically significant increase in R^2. However, this additional analysis has lower power so the difference from the original analysis should be interpreted with caution.

Mathematics

A hierarchical multiple regression using DAS-II DB, ENC, and GCA (predictors entered individually in this order) to predict WIAT-III NO was analyzed. The full hierarchical multiple regression model of DAS-II DB, ENC, and GCA significantly predicted WIAT-III NO, $R^2 = .671$, $F(3, 17) = 11.571$, $p < .001$, adjusted $R^2 = .613$. DAS-II DB alone was a significant predictor of WIAT-III NO ($F(1, 19) = 26.140$, $p = < .001$, $R^2 = .579$). The addition of DAS-II ENC ($F(1, 18) = 3.075$, $p = .097$, R^2 change = .061) and DAS-II GCA ($F(1, 17) = 1.591$, $p = .224$, R^2 change = .031) did not led to a statistically significant increase in R^2.

A hierarchical multiple regression using DAS-II DB, ENC, and DF (predictors entered individually in this order) was analyzed to predict WIAT-III MPS. The full hierarchical regression model of DAS-II DB, ENC, and DF significantly predicted WIAT-III MPS, $R^2 = .841$, ($F(3, 17) = 29.940$, $p < .001$, adjusted $R^2 = .813$). DAS-II DB alone was a statistically significant predictor of WIAT-III MPS ($F(1, 19) = 39.719$, $p = < .001$, $R^2 = .676$). The addition of DAS-II ENC ($F(1, 18) = 10.869$, $p = 004.$, R^2 change = .122) led to a statistically significant increase in R^2. The addition of DAS-II DF ($F(1, 17) = 4.551$, $p = .048$, R^2 change = .043) also led to a statistically significant increase in R^2.

Aim 5 Results: Relations Between Pre-Academic and Neuropsychological Abilities and Academic Functioning (Exploratory Canonical Correlation Analyses)

Exploratory canonical correlations were investigated to assess relations between the pre-academic and neuropsychological variables with academic tasks. Tasks that were components of the GCA were not used as part of the analyses. Additionally, parent reported questionnaires were not included in the analyses due to the lack of association between these variables in the earlier analyses.

A statistically significant relationship was found between the LSA neuropsychological variables (DAS-II GCA, DF, DB, and Flanker) and LSA academic variables (WIAT-III PD, RC, WR, NO, MPS) on only the first canonical dimension (*F*(20.0/90.5) = 3.234, *p* < .001; Table 10). This analysis was also run without outliers and the analysis continued to show a significant relationship between the academic and neuropsychological variables. For the neuropsychological variables, DAS-II GCA contributed the most. For the academic dimension, WIAT-III NO, MPS, WR, and PD contributed the most.

When examining the canonical correlation between ESA pre-academic variables (DAS-II ENC, PP, RN) and LSA academic variables (WIAT-III PD, RC, WR, NO, MPS), only one of the canonical dimensions were statistically significant (*F*(15.0/44.6) = 2.524, *p* = .009; Table 11). For the pre-academic dimension, DAS-II PP and ENC contributed highly but not RN. The academic dimension was mostly influenced by WIAT-III NO, MPS, WR, and PD but not RC. Notably, when an outlier was removed from the analysis, the canonical correlation no longer yielded a statistically significant model.

When examining the canonical correlation between ESA neuropsychological variables (DAS-II GCA, DF, DB) and the LSA academic variables (WIAT-III PD, RC, WR, NO, MPS), there was a statistically significant relation for only one of the canonical dimensions (*F*(15.0/36.3) = 3.274, *p* = .002; Table 12). DSA-II GCA and DB contributed the most to the

ESA neuropsychological dimension. The LSA academic dimension was mostly influenced by the WIAT-III MPS, NO, WR, and PD variables but not RC. Results remained significant when an outlier was removed.

When compared to the earlier analyses that investigated the association between individual pre-academic or neuropsychological variables and academic tasks (Aims 1-3), there are several notable similarities between the results. First, both sets of analyses indicate that we are able to correlate LSA academic performance with concurrent or earlier neuropsychological variables as well as earlier pre-academic variables. Furthermore, DAS-II GCA, DB, PP, ENC all emerge as strong contributions to canonical correlations analyses and these variables also have strong correlations with academic tasks when the associations are examined individually.

Discussion

This aim of the current investigation was to replicate studies of concurrent neuropsychological correlates of academic functioning in late school age children with NF1 as well as to investigate for the first time relations between early school age pre-academic and neuropsychological abilities and later school age academic functioning in children with NF1. Due to the preliminary nature of this study and small sample size, findings will be interpreted as significant even if they did not survive FDR correction. The findings of this study replicated past concurrent relations between neuropsychological correlates and late school age academic functioning generally as predicted. Due to the higher chance of academic difficulties in children with NF1, it is important to learn what factors contribute to risk for academic problems. Study findings suggested that of the pre-academic variables, phonological processing and foundational number knowledge were associated with late school age reading-related and math abilities respectively as predicted. Furthermore, early school age intellectual functioning, performance-based attention, performance-based working memory abilities were also related to late school age academic abilities generally as predicted. Additionally, early school age visual spatial abilities were found to be related to late school age math abilities and early school age oral language abilities were found to be associated with late school age reading abilities. Questionnaire measures did not show any significant associations with any academic tasks when looking at longitudinal and concurrent relations with the exception of a possible relation between early school age inattention (CPRS-R CPI) and late school age word reading if a potential outlier was removed.

In the remainder of the Discussion, study findings and their association to the past literature are reviewed. In particular, the importance of domain specific and domain general abilities are discussed. Longitudinal and concurrent predictors of academic functioning in NF1 are highlighted. Additionally, the implications for clinical practice, limitations, future directions and overall study conclusions are discussed.

Reading Abilities Findings in Relation to Previous Literature

Participants who were assessed in both the late school age years had mean performance in the average range on word reading and reading comprehension tasks consistent with prior literature in children with NF1 (e.g., Clements-Stephens et al., 2008; Hyman et al., 2005). In the current study, late school age word reading and pseudoword decoding (but not reading comprehension) were below the normative mean, which is consistent with prior studies indicating poorer basic reading and reading comprehension compared to unaffected siblings and controls (e.g., Clements-Stephens et al., 2008; Cutting et al., 2000; Hyman et al., 2005; Mazzocco et al., 1995).

Compared to past literature, rates of reading difficulties observed here (7.5-27.5%) were within the range of findings for past studies; however, it is important to note that a wide range of difficulties has been found in previous studies approximately 10-45% (e.g., Chaix et al., 2018; Coutinho et al. 2016; Dilts et al., 1996; De Winter et al., 1999; Hyman et al., 2005; North et al., 1994; North et al., 1995). Notably, reading comprehension difficulties in this study were much lower than found in some studies in the past literature. For example, some past studies have shown that approximately half the sample had impaired performance on reading comprehension tasks (North et al., 1994; North et al., 1995). This indicates that, our sample may have had less effect on reading comprehension abilities than prior literature potentially due to a variety of reasons such as small sample size, attrition, and age at the time of study participation.

When assessing the concurrent relations between late school age neuropsychological variables and reading-related variables, intellectual functioning, performance-based attention, performance-based working memory, oral language were associated with reading-related abilities, generally as hypothesized. Contrary to expectations, relations to one of the performance-based attention variable (Flanker) were more sparsely observed than expected; Flanker was not significantly related to pseudoword decoding or reading comprehension, although a significant relation to word reading was observed. Also contrary to expectations, performance-based working memory was not associated with word reading or reading comprehension. Overall, however, concurrent relations were largely consistent with prior studies in children with NF1 examining the aforementioned neuropsychological variables in relation to reading-related abilities. Specifically, intelligence has been associated with reading abilities in children with NF1 (e.g., Coutinho et al., 2016; Janke et al., 2014). Attention has also been associated with reading abilities as children with both NF1 and ADHD performed worse on reading tasks than children with NF1 alone suggesting that attention can impact reading performance in children with NF1 (Barton and North, 2007; Pride et al., 2012). While language variables were associated with academic variables in this study, the impact of language abilities on reading tasks in children with NF1 is unclear. When children with NF1 were IQ matched to unaffected controls and idiopathic reading groups, oral language deficits were not found for children with NF1 (Cutting et al., 2010).

During early school age, phonological processing and rapid naming abilities were in the average range consistent with prior literature with young children with NF1 (e.g., Janke, 2013). In a sample of young children with NF1 that overlaps substantially with the current sample, phonological processing abilities were poorer when compared to the unaffected group, but differences for rapid automatic naming were not found when comparing young children with NF1 to the normative mean and unaffected controls (Janke, 2013). We assessed the relation between pre-reading abilities in the early school age years and late school age reading-related abilities. Phonological processing was associated with late school age reading-related abilities as predicted. However, the other pre-reading ability in the early school age years, rapid naming, showed no significant relations with any of the late school age reading-related abilities. The relation to phonological abilities is similar to past findings (e.g., Lonigan et al., 2000). With regard to rapid naming, Cirino and colleagues (2018) found that RAN abilities in typically developing children who were in kindergarten were associated with reading performance in the first grade. Additionally, Cronin (2013) also found that rapid naming of objects during preschool and kindergarten was associated with reading abilities through the fifth grade. Differences between the associations found in the past literature may be due to the different assessment measures used to assess rapid naming or they may be due to a real difference in the relations between rapid naming in children with NF1 when compared to typically developing children. The current study suggests that phonological abilities are an important building block for reading abilities in children with NF1. Furthermore, phonological awareness has been identified as an area of weakness in children with NF1 when compared to matched unaffected children regardless of reading impairment (Chaix et al., 2018). Thus, it appears that difficulties with phonological awareness may be a core feature of the NF1 cognitive profile and children with NF1 may be more vulnerable to phonologically-based reading disorders than to orthographically-based reading disorders, or that orthographic reading disorders are more prominent in NF1 at a later age. Further examination of the relation between rapid naming and later reading abilities across different gaps of time may be important.

When assessing the correlations between early school age neuropsychological variables and late school age academic functioning, patterns of associations varied across reading-related tasks. Early school age intellectual functioning was associated late school age word reading and reading comprehension abilities but not non-word reading. Early school age performance-based attention (DAS-II DF) was only associated with late school age word reading. Early school age performance-based working memory was associated with most late school age reading-related academic tasks except for reading comprehension. Early school age language tasks were associated with late school age reading-related tasks as predicted. However, verbal reasoning (DAS-II NV) was not associated with non-word reading. These findings are consistent with past literature that suggests that later reading ability in typically developing children is associated with earlier intellectual functioning (e.g., Horbach at el., 2018; Peng et al., 2019) and language abilities (e.g., Duff et al., 2015). In this study, performance-based attention was associated with later word reading, but not reading comprehension. Prior research has suggested that teacher ratings of attention are indirectly related to later reading comprehension through word reading (Miller et al., 2014). Thus, it may be that we do not see a direct relationship between attention and reading comprehension in this study but may have found an indirect effect if that had been investigated. Working memory has been associated with later word decoding and reading comprehension abilities in typically developing children (Novo et al., 2001) while other studies have examined composites of executive functioning to predict later reading abilities (e.g., Blair & Razza, 2007; Ribner et al., 2017). This study only found a relation between word reading and working memory, but did not find a relation between reading comprehension and working memory. This may be due to the longer length of time between assessment of working memory and reading comprehension, less impairment observed in reading comprehension in this study, or it may be that a composite of EF would be more beneficial to predicting later reading comprehension.

Reading comprehension was less impacted and had different interrelations with other measures in this sample compared to the other academic variables. More research should be conducted in reading comprehension abilities in children with NF1 as difficulties have been inconsistently found in past literature. Notably, past literature has hypothesized that mixed findings in reading comprehension difficulties may be related to intellectual functioning and small sample size (e.g., Mazzocco, 2001). In this sample, intellectual functioning was in the average range and did not significantly differ from the normative mean which may be a reason that reading comprehension was less impacted. Future research may also want to investigate whether greater reading comprehension difficulties emerge in later adolescence as paragraphs become more conceptually challenging. Additionally, visuospatial abilities have been shown to be associated with reading comprehension abilities in children with NF1 (Mazzocco et al., 1995) and this should be explored further in future research.

Prior literature in children with NF1 suggests that the impact of domain-specific abilities (e.g., phonological abilities) for reading disorders is unclear due to mixed findings across past studies (Orraca-Castillo et al., 2014; Watt et al., 2008). Watt and colleagues (2008) found that 50% of children with NF1 met criteria for phonological dyslexia while 13% were classified as mixed dyslexia. However, Orraca-Castillo and colleagues (2014) found that 13% of children with NF1 met criteria for surface dyslexia and 21% met criteria for mixed dyslexia. Additionally, 6% of children with NF1 met criteria for surface dyslexia in addition to developmental dyscalculia and 9% of children with NF1 met for mixed dyslexia in addition to developmental dyscalculia. The findings of the current study indicate that phonological processing, a domain-specific ability, is an important predictor of later reading abilities, consistent with past studies indicating challenges with phonological awareness abilities in children with NF1 (e.g., Cutting et al., 2000; Mazzocco et al., 1995). Domain-general abilities such as intellectual functioning, language and working memory may not be as important for predicting reading abilities since the addition of these variables did not typically add significantly to the prediction above phonological processing abilities.

Mathematical Abilities Findings in Relation to Previous Literature

Participants who were assessed in the late school age years had mean performance in the average range on math calculations and math problem solving tasks which is consistent with prior research suggesting that math abilities are in the low average to average range (e.g., Cutting et al., 2000; De Winter et al., 1999; Hyman et al., 2005; Mazzocco et al., 1995). In the current study, performance on late school age math calculations and math problem solving suggested abilities were below the normative mean. This is consistent with the prior research in children with NF1 that suggests that math performance is poorer in children with NF1 compared to unaffected siblings and controls (e.g., Billingsley et al., 2003; Dilts et al., 1996; Mazzocco et al., 1995). The rates of math difficulties in past academic literature for children with NF1 (approximately 20-40%; De Winter et al., 1999; Hyman et al., 2005; North et al., 1994; North et al., 1995) were fairly comparable to the findings of this study (30-35%).

When assessing the concurrent relations between late school age neuropsychological variables and late school age math performance, the results suggested that neuropsychological variables of intellectual functioning, performance-based attention, performance-based working memory, and visuospatial abilities were associated with math abilities, generally as hypothesized. However, the visuospatial variable (DAS-II PC) was not related to math problem solving which was contrary to our predictions. The finding that there is a relation between intelligence and math abilities is consistent with prior research (e.g., Janke et al., 2014). The role of attention observed in this study is also consistent with past findings examining children with NF1; children with NF1 and ADHD had worse math abilities than children with NF1 alone suggesting that attention has some impact on academic performance in this population (Barton and North, 2007; Pride et al., 2012). The associations found between working memory and visual spatial skills and math abilities are also consistent with prior studies in children with NF1. For example, Janke and colleagues (2014) found that parent reported working memory was associated with math calculations in children with NF1. Additionally, Mazzocco and colleagues (1995) found that visual spatial abilities were associated with math problem solving in children with NF1. Notably, Mazzocco and colleagues (1995) did not find that visual spatial abilities were associated with math calculations; however, this may be due to the different visual spatial task used in that study (Judgment of Line Orientation).

Pre-math abilities in this study were in the average range which was consistent with prior findings using a substantially overlapping sample of participants suggesting that pre-math abilities are in the average range for young children with NF1 (Janke, 2013). However, is notable that foundational number knowledge showed difficulty in comparison to the normative mean even though performance was in the average range for young children with NF1 (Janke, 2013). We assessed the relation between pre-math ability in the early school age years and late school age mathematics performance. Early school age pre-math ability was associated with late school age math calculations and math problem solving abilities as predicted. This is consistent with the literature that finds that foundational number knowledge in young children is associated with later math abilities in typically developing children (e.g., De Smedt et al., 2013). Notably, the current study did not seek to examine the difference in association between symbolic number skills and non-symbolic skills and later math abilities which may be a beneficial area of investigation for future research.

Early school age intellectual functioning, performance-based attention (DAS-II DF), performance-based working memory, and certain visuospatial abilities (DAS-II PC) were associated with late school age math problem solving and math calculations. The association between early intellectual functioning (e.g., Geary, 2011), working memory (e.g., Toll et al., 2016), attention (e.g., Becker et al., 2018), and visual spatial abilities (e.g., Peng et al., 2016) and later math abilities are consistent with the relations found in prior literature with typically developing children.

There is only a single known study in children with NF1 that examines the domain-specific abilities in relation to math fluency concurrently (Orraca-Castillo et al., 2014). Children with NF1 had poor math fluency abilities, but spared domain-specific abilities (enumeration and magnitude comparison), which suggests that domain-specific abilities may not be the most important for math abilities in children with NF1. This is in line with the findings of this study that working memory, a domain-general predictor, was the most significant predictor of later math calculations and that pre-mathematical abilities did not add significantly to the prediction. For math problem solving, working memory continued to be the most important predictor while pre-mathematical abilities did significantly add to the prediction. Thus, it appears that domain-specific abilities may play a greater role in math problem solving abilities in children with NF1 even though domain-general abilities may be a more significant predictor; however, further examination is needed.

Exploratory Analyses

When multiple regression was used to predict each academic task from the three highest correlated pre-academic/neuropsychological variables, models predicting word reading, pseudoword decoding, math calculations, and math problem solving accounted for reasonable amounts of variance, but the predictors were not significantly associated with reading comprehension. Notably, the violation of the assumption of homoscedasticity for the hierarchical multiple regression analyses does suggest these findings should be interpreted with caution. Problems with homoscedasticity may be related to small sample size or it may be a real limitation of the hierarchical multiple regression findings. Canonical correlation results suggest that there are associations between select early school age and late school age pre-academic and/or neuropsychological variables and late school age academic performance. Across the several canonical correlations, all academic tasks except for reading comprehension tended to contribute highly to the academic dimension. Additionally, intellectual functioning, performance-based working memory, phonological processing, and pre-math abilities emerged as strong contributors to the neuropsychological dimension. Notably, the canonical correlations generally had higher values which may indicate that significant individual differences exist in the relations between the pre-academic and neuropsychological variables to the academic variables. Therefore, it is possible that Spearman correlations which are group-oriented relations may be underestimating associations. The aformentioned methods have not been used previously in the NF1 literature to predict academic functioning. Therefore, these analyses should be replicated in future studies.

Discussion of Concurrent and Longitudinal Predictors of Academic Functioning in Children with NF1

Overall, late school age intellectual functioning emerged as an important concurrent predictor of math and reading performance as it typically had either the highest or second highest effect size relative to other neuropsychological variables (attention, working memory, visual spatial, oral language). This finding is consistent with past findings of the association between intellectual functioning and academic performance in children with NF1 (e.g., Janke et al., 2014). Even in early childhood, some pre-academic variables (i.e., foundational number knowledge and phonological processing) are associated with intellectual functioning in children with NF1 (Janke, 2013), and this association between pre-academic/academic variables and intellectual functioning appears to continue to be relevant as children with NF1 develop.

At the early school age timepoint, working memory appeared to be a particularly important variable in relation to both late school age reading and math abilities. The effect sizes for the association between early school age working memory and late school age academic variables were consistently the largest among the neuropsychological variables (except for reading comprehension). This is notable given the prior research that suggests that working memory is an area of weakness in NF1 (e.g., Payne et al., 2011). In particular, young children with NF1 show poorer working memory when compared to their normative peers based on parent and teacher report (Casnar & Klein-Tasman, 2017). However, parent reported working memory was not associated with late school age academic functioning in this study. Thus, it may be important moving forward to assess for associations with later academic functioning using early school age performance-based measures of working memory instead of (or in addition to) parent reported measures of working memory.

Limitations and Future Directions

While there are many strengths and innovations of this study related to its longitudinal design and the novelty of some of the analytic approaches used, there are also study limitations which should be acknowledged. First, the sample size is quite small. Participant attrition is a one of the greatest difficulties with longitudinal analyses and more than 50% of children who were seen during the early school age time point did not return for the late school age time point. Notably, children who did not return for the late school age time point had poorer pre-academic functioning compared to those who did return on several tasks. Therefore, the findings should be considered preliminary and further research is needed to replicate results as the sample may not fully represent those with greater difficulties. Additionally, children were only included in this study if they had complete sets of the pre-academic measures. Notably, two of the three pre-academic measures used in this study are not available for children under the age of 5, which further decreased the sample size. Due to the preliminary nature of this investigation and the small sample size, analyses are presented with and without correction. Notably, it appeared that the sample size provided for adequate power for analyses with a large effect size, as many medium effect sizes were either not significant or did not survive FDR correction. While FDR correction helps to correct for type I error that may be present due to the high number of analyses run, it is important not to discount those significant findings that did not survive correction without future analysis using a larger sample size. Additionally, due to the small number of participants seen at both visits, analyses erred on the side of leaving in potential outliers especially when it was unclear if the data points would be considered outliers if we had a larger sample. Finally, while the regression analyses were exploratory in nature, it is important to note that the assumption of homoscedasticity was violated for all hierarchical multiple regression analyses. This should be taken into account when interpreting these findings. Issues with homoscedasticity may have been related to the small sample size.

Another limitation in this study is the lack of an unaffected comparison group. Due to the novel nature of the associations between early school age pre-academic and neuropsychological variables and late school age academic functioning, hypothesized predictors were based on findings for typically developing children. While many of the associations established were as hypothesized, an unaffected comparison group would help to clarify how the relations between the early school age pre-academic and neuropsychological variables and late school age academic functioning may be the same or different from typically developing children. Since some of the assessment measures utilized are not commonly found in the typically developing academic literature (e.g., DAS-II), without an unaffected comparison group, it is unclear if the construct may not be an appropriate predictor of academic functioning or whether the assessment measure itself may be a poor predictor of academic functioning. Additionally, it would be beneficial to examine if there are associations found between pre-academic/neuropsychological variables and academic functioning in children with NF1 that are not generally found in typically developing children.

Further, it can be difficult to make comparisons to past literature due to the variability in pre-academic and academic variables in the literature. The DAS-II pre-academic variables that were used in this study appear to be seldom used in both the typically developing as well as the NF1 literature. Academic variables across the typically developing and NF1 academic literature also vary; however, the WIAT academic performance variables were more often found in the NF1 and typically developing literature. In future studies, it would be beneficial to examine a wider range of pre-academic (e.g., Comprehensive Test of Phonological Processing) and academic variables (e.g., Woodcock-Johnson Tests of Achievement, Wide Range Achievement Test) to assess whether differences may exist depending on the assessment measure used.

Given the association between working memory variables in the early school age and later academic functioning, it is a limitation of this study that additional EF-related tasks were not assessed. In particular, it may be helpful to analyze additional working memory as well as selective attention abilities which are thought to develop in the preschool years (Welsh et al., 2013). However, it is important to note that there are several critical developmental windows for EF development which occur later in childhood and adolescence (Welsh et al., 2013) so the association between EF and academic functioning may be more important later in child development. Further research is needed to be investigate the importance of EF in predicting academic functioning at different ages in children with NF1. It should be noted that assessment of EF tasks in the early childhood can be challenging. There is a wide variability of EF performance for young children and there continue to be a limited number of tasks that are available to assess EF for younger children, many of which are more experimental in nature.

Implications for Clinical Practice

The implications for clinical practice are notable due to the high prevalence of learning problems in children with NF1. These findings suggest it is important to assess for pre-academic and neuropsychological variables in young children with NF1 as it appears that these are valid indicators of vulnerability to later learning problems in children with NF1. Furthermore, early assessment of these abilities allows for earlier intervention for children with NF1. This may be particularly important because support for neuropsychological abilities (e.g., attention, working memory) that may impact academic performance may have implications for school performance in general. For example, difficulties with attention are likely to impact a children's ability to learn but there are behavioral and medication intervention strategies which can support attention as well as overall learning.

The findings of this study suggest that there is a similarity of the relations between early pre-academic and neuropsychological variables and later academic abilities in children with NF1 with the typically developing population. This is particularly important as it suggests that academic interventions used in typically developing populations would likely also be beneficial in children with NF1. This is further supported by studies that have shown the efficacy of mainstream reading interventions in children with NF1 (Arnold et al., 2016; Barquero et al., 2015). Arnold et al. (2016) found that use of a phonics-based training program in children with NF1 was effective for improving reading and reading-related abilities. Notably, the greatest improvements were made in older children and those with stronger verbal working memory. Barquero et al. (2015) examined the effectiveness of two reading interventions training children in sound-symbol correspondences and phonological awareness with either greater kinesthetic or visual spatial demands and showed that children with NF1 and reading deficits responded better to the kinesthetic intervention. Notably, children with an idiopathic reading deficit responded similarly to both interventions. The findings of both studies suggest that phonics and kinesthetic based approaches to reading intervention may be particularly important for teaching reading in children with NF1. Based on the findings of this study that there is a strong association between early school age phonological abilities and later reading abilities, phonics-based reading interventions are strongly recommended for children with NF1. Further research to assess usefulness of interventions used in the typically developing populations for children with NF1 is warranted especially for academic domains other than reading.

In summary, this study aimed to assess the associations between neuropsychological variables and academic functioning concurrently, to replicate past findings in the NF1 literature with older children, as well as to add to the literature by investigating relations for academic functioning with preacademic functioning and neuropsychological variables (both individually and collectively) in early school age children with NF1 for the first time. Results indicated that math and reading-related abilities in late school age children with NF1 are associated with both concurrent and earlier neuropsychological variables that tend to show similar patterns with variables although the strength of those associations vary some based on whether they are concurrent or longitudinal relations. Early school age intellectual functioning, language, phonological processing, and working memory as well as concurrent intellectual functioning, attention, and language were most associated with late school age reading ability. Early school age intellectual functioning, attention, working memory, pre-math and visual spatial abilities in addition to concurrent intellectual functioning, attention, working memory, and visual spatial abilities were most associated with late school age math performance. During the later school years, intellectual functioning appears to be a particularly important concurrent predictor of academic performance in children with NF1. During the early school years, phonological processing and performance-based working memory abilities appeared to be particularly important predictors of late school age academic functioning. Notably, early school age domain general abilities (performance based working memory) appear to be important for late school age math abilities in children with NF1. However, early school age domain specific abilities (phonological processing) appear to be more important for late school age reading abilities. This study suggests that there is merit in assessing for early pre-academic and neuropsychological variables in early school age children with NF1 to aid in determining which children may be at risk for later academic difficulties. Furthermore, similar relations between early school age pre-academic and early school age and concurrent neuropsychological variables with late school age academic functioning in children with NF1 as is seen in the typically developing population suggests that intervention strategies used in typically developing populations are likely to also be appropriate for children with NF1.

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Table 1

Demographic Information About Participants Seen at the Late School Age Timepoint

	Participants (N = 40)
Age	*M* = 10.94 (*SD* = 1.58)
Gender	
Boys/Girls	22 (55%)/18 (45%)
SES	*M* = 46.13 (*SD* = 12.42)
NF1 Classification	
Familial/Sporadic	13 (32.5%)/27 (67.5%)
Race/Ethnicity	
Caucasian	33 (82.5%)
African American	4 (10%)
Latino	0 (0%)
Asian	1 (2.5%)
Mixed	2 (5%)
DAS-II GCA	*M* = 93.90, *SD* = 13.24
ADHD Diagnosis	13 (32.5%)
ADHD Medications	10 (25%)

Note. Attention-deficit/hyperactivity disorder (ADHD); Differential Abilities Scales, Second Edition (DAS-II); General Conceptual Ability (GCA); Hollingshead Four-Factor Index of Socioeconomic Status (SES); Neurofibromatosis type 1 (NF1).

Table 2

Demographic Information About Participants Seen at Both Early School Age and Late School Age Timepoints

	Participants (N = 24)
Age	
ESA	*M* = 6.07 (*SD* = 0.69)
LSA	*M* = 10.81 (*SD* = 1.61)
Gender	
Boys/Girls	14 (58%)/10 (42%)
SES	
ESA	*M* = 44.67 (*SD* = 11.13)
LSA	*M* = 45.36 (*SD* = 10.54)
NF1 Classification	
Familial/Sporadic	5 (21%)/19 (79%)
Race/Ethnicity	
Caucasian	19 (79%)
African American	3 (13%)
Latino	0 (0%)
Asian	1 (4%)
Mixed	1(4%)
DAS-II GCA	
ESA	*M* = 98.75, *SD* = 12.25
LSA	*M* = 95.00, *SD* = 15.40
ADHD Diagnosis	
ESA	6 (25%)
LSA	8 (33%)
ADHD Medications	
ESA	2 (8%)
LSA	5 (21%)

Note. Attention-deficit/hyperactivity disorder (ADHD); Differential Abilities Scales, Second Edition (DAS-II); Early school age (ESA); General Conceptual Ability (GCA); Hollingshead Four-Factor Index of Socioeconomic Status (SES); Late school age (LSA); Neurofibromatosis type 1 (NF1).

Table 3

Relations Between Demographic and Behavioral, Cognitive, and Pre-Academic Measures During Early School Age (n = 24)

	Age *rho* (*p*)	DAS-II GCA *rho* (*p*)	SES *rho* (*p*)	Male Mean (*SD*)	Female Mean (*SD*)	Gender
DAS-II GCA	.008 (.970)	-	-.020 (.927)	100.50 (11.66)	96.30 (13.25)	*t*(22) = 0.822, *p* = .420
CPRS-R CPI	-.310 (.140)	-.293 (.165)	-.181 (.398)	53.64 (10.54)	59.90 (16.37)	*t*(22) = -1.142, *p* = .266
CPRS-R HYP	.361 (.083)	.212 (.320)	-.202 (.343)	54.29 (12.51)	54.60 (12.98)	*t*(22) = -0.060, *p* = .953
CPRS-R ADHD	.028 (.895)	-.138 (.520)	-.268 (.206)	55.36 (10.73)	57.70 (12.65)	*t*(22) = -0.490, *p* = .629
BRIEF-P/BRIEF WM	-.076 (.726)	-.169 (.430)	-.151 (.482)	57.71 (12.45)	57.00 (12.88)	*t*(22) = 0.137, *p* = .893
DAS-II DB[a]	.285 (.211)	.527 (.014)	.138 (.551)	48.36 (10.74)	44.30 (9.86)	*t*(19) = 0.900, *p* = .379
DAS-II DF	-.086 (.691)	.301 (.153)	.141 (.512)	53.21 (6.48)	47.70 (7.06)	*t*(22) = 1.981, *p* = .060
DAS-II NV	.258 (.223)	-	.008 (.971)	57.29 (11.56)	51.80 (8.09)	*t*(22) = 1.288, *p* = .211
DAS-II VC	-.087 (.686)	-	.206 (.335)	50.64 (5.96)	46.40 (6.47)	*t*(22) = 1.661, *p* = .111
DAS-II CO	-.220 (.301)	-	.043 (.843)	43.29 (5.82)	44.30 (7.70)	*t*(22) = -0.368, *p* = .716
DAS-II PC	.290 (.169)	-	.033 (.878)	56.71 (8.70)	50.70 (9.62)	*t*(22) = 1.598, *p* = .124
NEPSY-II Arrows	-.171 (.424)	.025 (.906)	-.138 (.519)	9.86 (2.11)	8.00 (2.49)	*t*(22) = 1.973 *p* = .061
DAS-II ENC	-.117 (.587)	.281 (.183)	.294 (.162)	53.64 (11.51)	47.20 (5.03)	*t*(22) = 1.652, *p* = .113
DAS-II PP	.306 (.146)	.503 (.012)	-.119 (.581)	50.64 (8.07)	49.00 (9.10)	*t*(22) = 0.466, *p* = .646
DAS-II RN	.173 (.419)	.356 (.088)	-.186 (.383)	53.00 (6.47)	52.10 (6.82)	*t*(22) = 0.329, *p* = .746

Note. Behavior Rating Inventory of Executive Function (BRIEF); Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P); Copying (CO); Differential Abilities Scales, Second Edition (DAS-II); Early Number Concepts (ENC); General Conceptual Ability (GCA); Hollingshead Four-Factor Index of Socioeconomic Status (SES); Naming Vocabulary (NV); NEPSY Second Edition (NEPSY-II); Pattern Construction (PC); Phonological Processing (PP); Rapid Naming (RN); Recall of Digits-Backward (DB); Recall of Digits-Forward (DF); Revised Conners' Parent Rating Scale ADHD Index (CPRS-R ADHD); Revised Conners' Parent Rating Scale Cognitive Problems/Inattention (CPRS-R CPI); Revised Conners' Parent Rating Scale Hyperactivity (CPRS-R HYP); Verbal Comprehension (VC); Working Memory scale (WM).

[a] DAS-II DB data unavailable for three children.

Table 4

Relations Between Demographic and Behavioral, Cognitive, and Academic Measures During Late School Age (n = 24)

	Age *rho* (*p*)	DAS-II GCA *rho* (*p*)	SES *rho* (*p*)	Male Mean (*SD*)	Female Mean (*SD*)	Gender
DAS-II GCA	-.179 (.403)	-	.063 (.768)	98.36 (16.17)	90.30 (13.64)	*t*(22) = 1.281, *p* = .213
Conners–3 Inattention	-.379 (.068)	.032 (.883)	.212 (.321)	71.14 (12.71)	58.70 (8.53)	*t*(21.954) = 2.869, *p* = .009[b]
Conners–3 H/I	-.159 (.459)	.206 (.333)	.154 (.471)	61.14 (12.46)	54.30 (11.56)	*t*(22) = 1.366, *p* = .186
DAS-II DF	-.117 (.587)	.398 (.054)	.247 (.245)	45.93 (10.18)	44.20 (7.15)	*t*(22) = 0.461, *p* = .650
Flanker[a]	-.232 (.312)	.590 (.005)	.158 (.494)	91.09 (13.20)	84.87 (13.07)	*t*(19) = 1.073, *p* = .297
BRIEF WM	-.182 (.394)	-.230 (.279)	-.069 (.750)	57.71 (8.44)	56.10 (10.80)	*t*(22) = 0.411, *p* = .685
DAS-II DB	-.191 (.371)	.554 (.005)	.223 (.296)	41.64 (8.86)	41.10 (5.74)	*t*(22) = 0.169, *p* = .867
DAS-II WD	-.021 (.921)	-	.069 (.748)	51.86 (9.72)	47.90 (12.25)	*t*(22) = 0.883, *p* = .387
DAS-II VS	-.341 (.103)	-	.216 (.310)	51.57 (8.86)	48.70 (9.78)	*t*(22) = 0.750, *p* = .461
DAS-II RD	-.157 (.465)	-	-.231 (.278)	46.86 (7.61)	41.60 (8.14)	*t*(22) = 1.621, *p* = .119
DAS-II PC	-.101 (.638)	-	.132 (.540)	49.71 (6.82)	46.10 (7.32)	*t*(22) = 1.241, *p* = .228
WIAT-III NO	-.286 (.175)	.730 (< .001)	.010 (.961)	96.93 (13.93)	91.20 (17.18)	*t*(22) = 0.902, *p* = .377
WIAT-III MPS	-.126 (.557)	.740 (< .001)	.211 (.322)	98.29 (20.08)	86.50 (12.79)	*t*(22) = 1.630, *p* = .117
WIAT-III WR	-.032 (.881)	.747 (< .001)	-.256 (.228)	93.79 (14.01)	88.50 (13.83)	*t*(22) = 0.916, *p* = .370
WIAT-III PD	.103 (.631)	.755 (< .001)	-.111 (.607)	91.57 (11.57)	89.50 (12.96)	*t*(22) = 0.411, *p* = .685
WIAT-III RC	-.305 (.147)	.386 (.062)	-.105 (.624)	100.79 (12.60)	97.70 (10.65)	*t*(22) = 0.629, *p* = .536

Note. Behavior Rating Inventory of Executive Function (BRIEF); Conners 3rd Edition Parent Short Form (Conners–3); Differential Abilities Scales, Second Edition (DAS-II); Flanker Inhibitory Control and Attention Test (Flanker); General Conceptual Ability (GCA); Hollingshead Four-Factor Index of Socioeconomic Status (SES); Hyperactivity/Impulsivity (H/I); Math Problem Solving (MPS); Numerical Operations (NO); Pattern Construction (PC); Pseudoword Decoding (PD); Reading Comprehension (RC); Recall of Designs (RD); Recall of Digits-Backward (DB); Recall of Digits-Forward (DF); Verbal Similarities (VS); Wechsler Individual Achievement Test, Third Edition (WIAT-III); Word Definitions (WD); Word Reading (WR); Working Memory scale (WM).

[a] Flanker data unavailable for three children.

[b] Welch t-test

Table 5

Relations Between Demographic and Behavioral, Cognitive, and Academic Measures During Late School Age (n = 40)

	Age ***rho*** (*p*)	DAS-II GCA ***rho*** (*p*)	SES ***rho*** (*p*)	Male Mean (*SD*)	Female Mean (*SD*)	Gender
DAS-II GCA	-.194 (.230)	-	.077 (.636)	96.91 (14.45)	90.22 (10.87)	*t*(38) = 1.622, *p* = .113
Conners –3 Inattention	-.189 (.243)	-.195 (.229)	.245 (.128)	71.86 (12.93)	61.94 (11.92)	*t*(38) = 2.499, *p* = .017
Conners –3 H/I	.019 (.906)	.043 (.792)	.208 (.198)	63.59 (13.29)	58.39 (14.56)	*t*(38) = 1.180, *p* = .245
DAS-II DF	-.183 (.258)	.465 (.003)	.263 (.101)	46.91 (10.48)	43.28 (8.53)	*t*(38) = 1.183, *p* = .244
Flanker[a]	-.100 (.561)	.506 (.002)	.227 (.183)	91.85 (13.91)	83.18 (10.57)	*t*(34) = 2.061, *p* = .047
BRIEF WM	.063 (.699)	-.197 (.224)	.095 (.560)	59.23 (9.82)	58.56 (11.19)	*t*(38) = 0.202, *p* = .841
DAS-II DB	-.077 (.638)	.535 (< .001)	.124 (.446)	43.45 (10.09)	43.00 (5.44)	*t*(33.387) = .181, *p* = .857[b]
DAS-II WD	-.032 (.845)	-	.020 (.901)	50.68 (9.29)	48.89 (9.34)	*t*(38) = 0.606, *p* = .548
DAS-II VS	-.305 (.056)	-	-.035 (.832)	49.64 (8.66)	48.44 (7.86)	*t*(38) = 0.451, *p* = .654
DAS-II RD	-.163 (.316)	-	-.160 (.324)	48.00 (7.82)	41.00 (7.00)	*t*(38) = 2.952, *p* = .005
DAS-II PC	-.233 (.148)	-	.049 (.764)	47.91 (7.27)	43.72 (7.09)	*t*(38) = 1.833, *p* = .075
WIAT-III NO	-.220 (.173)	-	.107 (.511)	97.82 (13.72)	89.50 (15.16)	*t*(38) = 1.820, *p* = .077
WIAT-III MPS	-.111 (.495)	-	.275 (.086)	96.55 (17.64)	86.56 (11.57)	*t*(38) = 2.064, *p* = .046
WIAT-III WR	-.034 (.837)	-	-.064 (.695)	93.45 (15.51)	90.17 (12.89)	*t*(38) = 0.718, *p* = .477
WIAT-III PD	-.022 (.895)	-	.025 (.876)	93.27 (13.03)	89.17 (12.32)	*t*(38) = 1.016, *p* = .316
WIAT-III RC	-.232 (.150)	-	.082 (.616)	98.73 (12.10)	97.78 (9.34)	*t*(38) = .273, *p* = .787

Note. Behavior Rating Inventory of Executive Function (BRIEF); Conners 3rd Edition Parent Short Form (Conners–3); Differential Abilities Scales, Second Edition (DAS-II); Flanker Inhibitory Control and Attention Test (Flanker); General Conceptual Ability (GCA); Hollingshead Four-Factor Index of Socioeconomic Status (SES); Hyperactivity/Impulsivity (H/I); Math Problem Solving (MPS); Numerical Operations (NO); Pattern Construction (PC); Pseudoword Decoding (PD); Reading Comprehension (RC); Recall of Designs (RD); Recall of Digits-Backward (DB); Recall of Digits-Forward (DF); Verbal Similarities (VS); Wechsler Individual Achievement Test, Third Edition (WIAT-III); Word Definitions (WD); Word Reading (WR); Working Memory scale (WM).

[a] Flanker data unavailable for four children.

[b] Welch t-test

Table 6

Descriptive Statistics: Academic Score Comparison to Normative Mean and Rates of Difficulty for Academic Performance

	Mean (*SD*)	One Sample t-test	*p*	N (%) of Scores 1 SD Below the Mean (scores <85)
WIAT-III NO	94.08 (14.80)	-2.532	.015	12 (30%)
WIAT-III MPS	92.05 (15.85)	-3.172	.003	14 (35%)
WIAT-III WR	91.98 (14.31)	-3.547	.001	11 (27.5%)
WIAT-III PD	91.43 (12.72)	-4.263	< .001	11 (27.5%)
WIAT-III RC	98.30 (10.82)	-.993	.327	3 (7.5%)

Note. Math Problem Solving (MPS); Numerical Operations (NO); Pseudoword Decoding (PD); Reading Comprehension (RC); Wechsler Individual Achievement Test, Third Edition (WIAT-III); Word Reading (WR).

Table 7

Concurrent Relations Between Neuropsychological Variables and Academic Functioning in Late School Age

	WIAT-III PD *rho* (*p*)	WIAT-III RC *rho* (*p*)	WIAT-III WR *rho* (*p*)	WIAT-III NO *rho* (*p*)	WIAT-III MPS *rho* (*p*)	WIAT-III PD *q*	WIAT-III RC *q*	WIAT-III WR *q*	WIAT-III NO *q*	WIAT-III MPS *q*
DAS-II GCA	.695 (< .001)	.483 (.002)	.689 (< .001)	.777 (< .001)	.685 (< .001)	< .001	.009	< .001	< .001	< .001
Conners–3 Inattention	-.182 (.260)	-.163 (.314)	-.170 (.294)	-.124 (.444)	.050 (.760)	.334	.404	.378	.500	.760
Conners–3 H/I	-.041 (.800)	-.139 (.392)	.148 (.363)	.080 (.625)	.204 (.208)	.800	.441	.408	.625	.267
DAS-II DF	.394 (.012)	.346 (.029)	.470 (.002)	.555 (< .001)	.586 (< .001)	.022	.065	.006	< .001	< .001
Flanker [a]	.306 (.070)	.269 (.112)	.364 (.029)	.386 (.020)	.420 (.011)	.105	.168	.052	.036	.023
BRIEF WM	-.114 (.485)	-.064 (.693)	.088 (.589)	-.156 (.336)	-.107 (.512)	.546	.693	.589	.432	.576
DAS-II DB	.474 (.002)	.306 (.055)	.292 (.072) [b]	.576 (< .001)	.543 (< .001)	.006	.099	.108	< .001	< .001
DAS-II WD	.531 (< .001)	.427 (.006)	.724 (< .001)	-	-	< .001	.018	< .001	-	-
DAS-II VS	.425 (.006)	.583 (< .001)	.408 (.009)	-	-	.014	< .001	.020	-	-
DAS-II RD	-	-	-	.483 (.002)	.389 (.013)	-	-	-	.005	.023
DAS-II PC	-	-	-	.344 (.030)	.300 (.060)	-	-	-	.045	.090

Note. Behavior Rating Inventory of Executive Function (BRIEF); Conners 3rd Edition Parent Short Form (Conners–3); Differential Abilities Scales, Second Edition (DAS-II); Flanker Inhibitory Control and Attention Test (Flanker); General Conceptual Ability (GCA); Hyperactivity/Impulsivity (H/I); Math Problem Solving (MPS); Numerical Operations (NO); Pattern Construction (PC);

Pseudoword Decoding (PD); Reading Comprehension (RC); Recall of Designs (RD); Recall of Digits-Backward (DB); Recall of Digits-Forward (DF); Verbal Similarities (VS); Wechsler Individual Achievement Test, Third Edition (WIAT-III); Word Definitions (WD); Word Reading (WR); Working Memory scale (WM).

[a] Flanker data unavailable for four children.

[b] Results are presented with outliers removed for this analysis

Table 8

Relations Between Pre-Academic Functioning in Early School Age and Academic Functioning in Late School Age

	WIAT-III PD *rho* (*p*)	WIAT-III RC *rho* (*p*)	WIAT-III WR *rho* (*p*)	WIAT-III NO *rho* (*p*)	WIAT-III MPS *rho* (*p*)	WIAT-III PD *q*	WIAT-III RC *q*	WIAT-III WR *q*	WIAT-III NO *q*	WIAT-III MPS *q*
DAS-II ENC	-	-	-	.612 (.001)	.632 (< .001)	-	-	-	.001	< .001
DAS-II PP	.633 (< .001)	.571 (.004)	.650 (< .001)	-	-	< .001	.008	< .001	-	-
DAS-II RN	.327 (.119)	.150 (.483)	.321 (.126)	-	-	.119	.483	.126	-	-

Note. Differential Abilities Scales, Second Edition (DAS-II); Early Number Concepts (ENC); Math Problem Solving (MPS); Numerical Operations (NO); Phonological Processing (PP); Pseudoword Decoding (PD); Rapid Naming (RN); Reading Comprehension (RC); Wechsler Individual Achievement Test, Third Edition (WIAT-III); Word Reading (WR).

Table 9

Relations Between Neuropsychological Variables in Early School Age and Academic Functioning in Late School Age

	WIAT-III PD *rho* (*p*)	WIAT-III RC *rho* (*p*)	WIAT-III WR *rho* (*p*)	WIAT-III NO *rho* (*p*)	WIAT-III MPS *rho* (*p*)	WIAT-III PD *q*	WIAT-III RC *q*	WIAT-III WR *q*	WIAT-III NO *q*	WIAT-III MPS *q*
DAS-II GCA	.364 (.080)	.480 (.018)	.575 (.003)	.606 (.002)	.457 (.025)	.209	.086	.009	.010	.083
CPRS- R CPI	-.159 (.457)	.056 (.794)	-.315 (.134)	.049 (.820)	-.181 (.398)	.596	.794	.201	.820	.569
CPRS- R HYP	-.150 (.485)	-.256 (.228)	.149 (.488)	.205 (.336)	.023 (.914)	.596	.410	.595	.642	.914
CPRS- R ADHD	-.135 (.530)	-.185 (.387)	-.114 (.595)	.050 (.818)	-.223 (.294)	.596	.581	.595	.820	.569
DAS-II DF	.254 (.231)	.125 (.559)	.452 (.027)	.410 (.047)	.599 (.002)	.416	.719	.049	.118	.010
BRIEF-P/ BRIEF WM	-.047 (.829)	-.095 (.660)	-.129 (.548)	.135 (.531)	-.156 (.466)	.829	.743	.595	.759	.583
DAS-II DB[a]	.622 (.003)	.347 (.123)	.611 (.003)	.639 (.002)	.720 (< .001)	.027	.277	.009	.010	.002
DAS-II NV	.351 (.093)	.475 (.019)	.517 (.010)	-	-	.209	.086	.023	-	-
DAS-II VC	.539 (.007)	.416 (.043)	.582 (.003)	-	-	.032	.129	.009	-	-
DAS-II CO	-	-	-	.051 (.813)	.121 (.573)	-	-	-	.820	.637
DAS-II PC	-	-	-	.571 (.004)	.417 (.043)	-	-	-	.013	.108
NEPSY-II Arrows	-	-	-	.186 (.385)	.201 (.347)	-	-	-	.642	.569

Note. Behavior Rating Inventory of Executive Function (BRIEF); Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P); Copying (CO); Differential Abilities Scales, Second Edition (DAS-II); General Conceptual Ability (GCA); Math Problem Solving (MPS); Naming Vocabulary (NV); NEPSY Second Edition (NEPSY-II); Numerical Operations (NO); Pattern Construction (PC); Pseudoword Decoding (PD); Reading Comprehension (RC); Recall of Digits-Backward (DB); Recall of Digits-Forward (DF); Revised Conners' Parent Rating Scale ADHD Index (CPRS-R ADHD); Revised Conners' Parent Rating Scale Cognitive Problems/ Inattention (CPRS-R CPI); Revised Conners' Parent Rating Scale Hyperactivity (CPRS-R HYP); Verbal Comprehension (VC); Wechsler Individual Achievement Test, Third Edition (WIAT-III); Word Reading (WR); Working Memory scale (WM).

[a] DAS DB data unavailable for three children.

Table 10

Canonical Correlations Between Late School Age Neuropsychological and Late School Age Academic Variables

	Canonical Loadings
WIAT-III RC	-.522
WIAT-III MPS	-.927
WIAT-III WR	-.796
WIAT-III PD	-.734
WIAT-III NO	-.910
DAS-II DB	-.591
DAS-II DF	-.546
DAS-II GCA	-.976
Flanker	-.445

Note. Differential Abilities Scales, Second Edition (DAS-II); Flanker Inhibitory Control and Attention Test (Flanker); General Conceptual Ability (GCA); Math Problem Solving (MPS); Numerical Operations (NO); Pseudoword Decoding (PD); Reading Comprehension (RC); Recall of Digits-Backward (DB); Recall of Digits-Forward (DF); Wechsler Individual Achievement Test, Third Edition (WIAT-III); Word Reading (WR).

Table 11

Canonical Correlations Between Early School Age Pre-Academic Variables and Late School Age Academic Variables

	Canonical Loadings
WIAT-III RC	-.516
WIAT-III MPS	-.866
WIAT-III WR	-.849
WIAT-III PD	-.781
WIAT-III NO	-.939
DAS-II ENC	-.810
DAS-II PP	-.835
DAS-II RN	-.214

Note. Differential Abilities Scales, Second Edition (DAS-II); Early Number Concepts (ENC); Math Problem Solving (MPS); Numerical Operations (NO); Phonological Processing (PP); Pseudoword Decoding (PD); Rapid Naming (RN); Reading Comprehension (RC); Wechsler Individual Achievement Test, Third Edition (WIAT-III); Word Reading (WR).

Table 12

Canonical Correlations Between Early School Age Neuropsychological Variables and Late School Age Academic Variables

	Canonical Loadings
WIAT-III RC	.265
WIAT-III MPS	.971
WIAT-III WR	.730
WIAT-III PD	.684
WIAT-III NO	.891
DAS-II DB	.704
DAS-II DF	.572
DAS-II GCA	.949

Note. Differential Abilities Scales, Second Edition (DAS-II); General Conceptual Ability (GCA); Math Problem Solving (MPS); Numerical Operations (NO); Pseudoword Decoding (PD); Reading Comprehension (RC); Recall of Digits-Backward (DB); Recall of Digits-Forward (DF); Wechsler Individual Achievement Test, Third Edition (WIAT-III); Word Reading (WR).