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Early Indicators of Academic Difficulties in Children with Neurofibromatosis Type 1

Kelly M. Janke
University of Wisconsin-Milwaukee

EARLY INDICATORS OF ACADEMIC DIFFICULTIES IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1

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Kelly M. Janke

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ABSTRACT

EARLY INDICATORS OF ACADEMIC DIFFICULTIES IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1

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Kelly M. Janke

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Under the Supervision of Bonita Klein-Tasman, Ph.D.

Neurofibromatosis type 1 (NF1) is a genetic neurocutaneous disorder, with an estimated incidence of 1 in 3,000 persons. It is phenotypically variable disorder associated with elevated rates of intellectual disability and learning disabilities, attention problems, speech and language impairment, and executive functioning deficits. Research investigating the presentation of NF1 in preschool-age children is limited, but the data available indicate that cognitive difficulties are present and can be identified at an early age. There is also evidence from the general population that early neuropsychological deficits can be used to predict concurrent and later learning difficulties. The goal of the current study was to characterize the early learning profile of young children with NF1 and to determine which neuropsychological skills may contribute to academic difficulties. The results indicate that early learning difficulties are present and can be identified in young children with NF1. General intellectual functioning was strongly related to academic performance and accounted for many of the relations between neuropsychological and academic skills in the NF1 group. However, some specific neuropsychological skills continued to relate to foundational reading and math skills even when controlling for overall developmental level. These findings provide an indication of

processing domains that may support academic skill development for future longitudinal work. Clinically, the findings suggest that cognitive screenings should be a routine part of care for young children with NF1. If appropriate interventions are implemented at an early age, academic skill development could be altered, preventing subtle learning difficulties from becoming more pronounced over time.

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Introduction

Investigation of the neurocognitive functioning of individuals with genetic syndromes provides a valuable opportunity to learn about gene-brain-behavior relations to further understand the genetic and neural mechanisms that underlie cognitive difficulties in both developmentally delayed or typically developing individuals. Neuropsychological assessments are designed to examine brain-behavior relations and are useful for not only characterizing the impact of a disorder, but also for designing and implementing interventions. Such evaluations are particularly important when working with young children because early interventions have the potential to alter the developmental trajectory of neuropsychological abilities.

Neurofibromatosis-1 (NF1) is the most prevalent single-gene autosomal dominant disorder. As physicians become increasingly aware of the clinical presentation of this disorder, a larger number of young children are being diagnosed. In contrast to genetic disorders with clearly defined cognitive phenotypes, findings regarding the impact of NF1 are more variable. However, research indicates that many of these children experience attention and academic difficulties in addition to significant medical complications (Tonsgard, 2006). Rates of learning disabilities in this population range from 20 to 70% (Payne & North, 2011) and rates of ADHD between 33 to 50% (Templer, Titus, & Gutmann, 2012). Despite the fact that approximately half of the individuals with NF1 will experience such complications that develop before the age of 20 (Riccardi, 1989; Riccardi, 1982), very few developmentally sensitive studies have been designed. In particular, examination of the developmental trajectory of neuropsychological abilities and the relations between these abilities and later functioning is warranted.

This introduction will examine the variable phenotype of children with NF1, with emphasis on what is known about early neuropsychological functioning. The neuroanatomical correlates and medical features of the disorder will also be reviewed. The next section will discuss the early development of neuropsychological and academic skills in typically developing children, which serves as a guide for the study of the cognitive development in young children with NF1. In particular, the predictors and correlates of later academic difficulties will be highlighted.

Medical Features and Diagnostic Criteria

NF1 is an autosomal dominant genetic disorder, with an estimated incidence of 1 in 3,000 persons (North, 1998). It is a highly variable, yet medically progressive disorder that affects all ethnic groups (Seizinger, 1993; Riccardi, 1992). NF1 is associated with a mutation on chromosome 17, which has been classified as a tumor suppressor gene (Jadayel et al., 1990; Stephens et al., 1992; Colman, Williams, & Wallace, 1995; Bader, 1986). Fifty percent of patients inherit the gene from a parent, whereas the other 50 percent are progenitors for the disorder. NF1 has complete penetrance, but the expressivity varies even if family members have the exact same mutation (Carey & McMahon, 1999; von Deimling, Krone, & Menon, 1995).

The diagnosis of this neurocutaneous disorder requires the presence of two or more of the following criteria: (1) Six or more café-au-lait spots; (2) Two or more neurofibromas of any type, or one or more plexiform neurofibroma; (3) Freckling in the axillary or inguinal region; (4) Optic glioma (tumor of the optic pathway); (5) Two or more Lisch nodules (benign iris hamartomas); (6) A distinctive osseous lesion (dysplasia of sphenoid bone or pseudoarthrosis, dysplasia or thinning of long bone cortex); or (7) A

first degree relative with NF1 according to the preceding criteria (NIH Consensus Development Conference, 1988). Therefore, if a child has a parent or sibling with NF1, only one additional symptom must be present to meet criteria.

The most common manifestations of NF1 include café-au-lait spots, axillary freckling, cutaneous neurofibromas, and Lisch nodules [see North, 1998 for an in depth description of these manifestations and a timeline (p. 240) for the detection of symptoms]. Café-au-lait spots are seen in more than 95% of individuals with NF1 and are usually present before the age of two. These macular lesions have symmetrical, even borders and darken with sun-exposure. Skinfold freckling (seen in 65-84%) usually appears by five years of age (North, 1998). These two symptoms allow for early detection of the disorder. Cutaneous neurofibromas and Lisch nodules are also very useful diagnostic tools, but they may not appear until adolescence. Neurofibromas are only present in 14% of patients before the age of 10, but are evident in 85% of patients over the age of 20 (North, 1998). An early onset may be indicative of greater severity of cutaneous symptoms (Riccardi, 1992). They may first appear as a reddened indentation of the skin, and unlike plexiform neurofibromas, cutaneous neurofibromas do not transform into malignant tumors (Gutman et al., 1997). Lisch nodules are dome-shaped lesions on the surface of the iris. Though North (1993) found that only 22% of patients have the nodules by the age of 5, 96% to 100% of patients have lesions by the age of 20 (Huson, Harper, & Compston, 1988; Lubs, Bauer, Formas, & Djokic, 1991).

Macrocephaly and short stature are not pathognomonic signs of NF1, but they are also common medical features that can contribute to the identification of the disease. Approximately 30% of patients have height at or below the third percentile and 45% to

50% of patients have head circumference at or above the 97th percentile (North, 1998). Less frequent complications are seen in nearly every system of the body, and put individuals with NF1 at an increased risk for epilepsy, scoliosis, hypertension, and central nervous system tumors (North, 1998; Gutmann, 1999; Friedman, 1999; Friedman & Riccardi, 1999; Riccardi, 1999). Symptomotology generally increases with age (Riccardi, 1981), and as a result, the lifespan of individuals with NF1 may be somewhat shortened. Recent cohort studies indicate that the heightened mortality rate is primarily due to malignant tumors (Duong et al., 2011; Masocco et al., 2011; Zöller, Rembeck, Akesson, & Angervall, 1995).

Pathogenesis of Cognitive and Behavioral Difficulties

In addition to these significant medical complications, many individuals with NF1 experience neuropsychological difficulties. Given the high rates of cognitive deficits and attention problems in the NF1 population, it is important for research to examine factors such as central nervous system pathology that may contribute to this profile. The significance of brain abnormalities associated with NF1 has not been fully determined. Some of the most common neuroanatomical and molecular correlates and their relations with cognitive functioning are described below.

The Role of Neurofibromin

Affected individuals inherit or develop one mutant copy of the NF1 gene, but the development of more severe clinical symptoms such as malignant peripheral nerve sheath tumors is associated with somatic mutations (i.e., mutations occurring after conception) that render the second copy nonfunctional. Studies examining this loss of heterozygosity seem to confirm the classification of the NF1 gene as a tumor suppressor gene (Thomas,

Kluwe, Chuzhanova, Mautner, Upadhyaya, 2010; Brown, Gianino, & Gutmann, 2010; Colman et al., 1995). The gene codes for a protein called neurofibromin, which regulates Ras activity and therefore plays an important role in cell proliferation (Thomas & De Vries, 2009; Patrakitkomjorn et al., 2008).

Research findings indicate that the NF1 mutation results not only in an increased tumor predisposition, but also learning impairment (Bennett, Thomas, & Upadhyaya, 2009; Costa, Federov, et al., 2002; Costa, Yang, et al., 2001). Neurofibromin plays an important role in regulating GABA release, which in turn, modulates prefrontal-striatal communication and long-term potentiation in the hippocampus (Shilyansky et al., 2010; Cui et al., 2008). Further, increased neurofibromin expression is seen during late embryonic and late post-natal development, and correlates with neuronal differentiation (Geist & Gutmann, 1996). Atypical differentiation could therefore be another contributor to the learning problems associated with NF1.

CNS Tumors

An increased incidence of benign (Carroll & Ratner, 2008; Shannon et al., 1994) and malignant tumors (Hottinger & Khakoo, 2009; Colman et al., 1995) has been observed in individuals with NF1. Optic pathway gliomas are the most prevalent CNS tumor and are present in 15-25% of NF1 patients. Any part of the visual pathway can be affected by optic gliomas, but gliomas are primarily observed in the anterior portion of the pathway (Listernick & Gutmann, 1999). Wright and colleagues (Wright, McNab, & McDonald, 1989) found that some optic gliomas are stable and nonprogressive, while others cause visual functioning to worsen as they increase in size. This activity may be the result of a second somatic mutation of the NF1 gene and therefore the loss of the

tumor suppressor function of neurofibromin. Approximately 30-50% of tumors become symptomatic, typically during early childhood, and may result in eye misalignment, decreased visual acuity, optic atrophy, nystagmus, headache, and nausea (Listernick, Charrow, Greenwald, & Mets, 1994).

MRI Hyperintensities

T2-weighted hyperintensities or "unidentified bright objects" (UBOs) are present in many children with NF1, and represent myelination abnormalities and spongiform change due to glial proliferation (DiPaolo et al., 1995; Barbier et al 2011). The variability in reported frequency (43-79%) is likely related to the age of the study participants (North, 1999). Several studies have reported that these UBOs typically decrease with time and may resolve by adulthood (Aoki et al., 1989; Sevick et al., 1992; Itoh et al., 1994). Sabol and colleagues (2011) found that the presence of T2-hyperintensities is a highly sensitive (81%) and specific (99%) indicator of NF1 for children between the ages of 2 and 7; however, diagnostic sensitivity declined with age given that UBOs were detected in a much small percentage of older participants. Of note, Gill and colleagues (Gill, Hyman, Steinberg, & North, 2006) found that lesions in the thalamus, basal ganglia, cerebellum, and brainstem were less prevalent in older participants, whereas no age-related changes were seen for hemispheric and hippocampal lesions. In a longitudinal study, Feldmann and colleagues (Feldmann, Schuierer, Wessel, Neveling, & Weglage, 2010) also found that lesions of the thalamus and basal ganglia resolve over time, but noted that UBOs were more stable in the cerebellum and capsula interna.

UBOs occur primarily in the cerebellum, basal ganglia, and subcortical white matter (North, 1999; Denckla, 1996). Given that the cerebellum and basal ganglia

contribute to motor functioning, executive functioning, and reading abilities (Denckla, 1996), lesions in these locations may contribute to the neuropsychological deficits observed in the NF1 population. The lesions are not associated with focal neurologic deficits, but may instead be a result of disrupted neuronal circuits (North, 1997).

Finding regarding the relations between UBOs and cognitive deficits have been mixed. Some early studies did not find significant relations between UBOs and cognitive functioning (Duffner, Cohen, Seidel, & Shucard, 1989; Dunn & Roos, 1989; Ferner, Chaudhuri, Bingham, Cox, & Hughes, 1993; Legius et al., 1995; Bawden et al., 1996). However, several study limitations may have contributed to the lack of relations, including a small sample size, inadequate control for intellectual functioning or central nervous system pathology, and the use of a wide age range. The inclusion of both children and adults is problematic given the finding that these lesions may resolve over time. Furthermore, some studies included children as young as 9 months, making it difficult to obtain an accurate estimate of cognitive and developmental level.

Many other studies have indeed found a significant association between T2 hyperintensities and intellectual functioning, visuospatial and visuomotor skills, attention, and executive functioning (North et al., 1994; Hofman, Harris, Bryan, & Denckla 1994; Joy, Roberts, North, & de Silva, 1995; Samango-Sprouse, Vezina, Brasseux, Tilman, & Tifft, 1997). It appears that cognitive and neuropsychological deficits are related to the location of the UBOs, and not just the mere presence or number of the lesions (Chabernaud et al., 2009; Denckla et al., 1996). In particular, a lowering of IQ is associated with T2 lesions of the thalamus, and cognitive performance improves when thalamic lesions resolve over time (Moore, Slopis, Schomer, Jackson, & Levy, 1996;

Goh, Khong, Leung, & Wong, 2004; Hyman, Gill, Shores, Steinberg, & North, 2007; Chabernaud et al., 2009). Basal ganglia lesions are also associated with lower IQ and attention scores, whereas hyperintensities on the right middle cerebellar peduncle are related to sensorimotor deficits (Goh et al., 2004; Feldmann, Schuierer, Wessel, Neveling, & Weglage, 2010).

Macrocephaly and Other Neuroanatomical Correlates

Given that the lost expression of neurofibromin can cause unregulated growth, brain volume abnormalities may also contribute to the cognitive deficits observed in the NF1 population. In a study examining the relationship between cognitive functioning, brain volumes, and hyperintensities (Cutting, Koth, et al., 2000), 47% of the sample was found to have a head circumference one standard deviation above the mean. This is consistent with reports that half of individuals with NF1 have macrocephaly (North et al., 1994; Van Es, North, McHugh, & de Silva, 1996). Cutting and colleagues (2000) found macrocephaly to be related to poorer performance on a measure of vocabulary; however, this finding has not been consistently replicated (Billingsley et al., 2003). The finding that macrocephaly did not correlate with the presence of UBOs suggest that lesions and increased brain volume may be separate consequences of NF1 gene mutations. This is somewhat surprising given that white matter changes are seen both in individuals with UBOs and macrocephaly; however, the presence of UBOs may correlate more with regional brain volume changes rather than an overall increase as measured by head circumference.

MRI studies have indeed found evidence for white and gray matter abnormalities that may contribute to the high rates of macrocephaly and neuropsychological difficulties.

Findings regarding the effects of gray matter volume increases have been mixed. Some studies have observed a relation between increased gray matter and learning disabilities, while others have found that gray matter increases were associated with *better* performance on measures of visuospatial and visuomotor abilities (Moore, Slopis, Jackson, De Winter, & Leeds, 2000; Said et al., 1996). Billingsley and colleagues (Billingsley, Schrimsher, Jackson, Slopis, & Moore, 2002) examined the planum temporale (PT) of children with NF1. In typically developing individuals, the PT is often larger in the left hemisphere (Takao et al., 2011; Cantalupo, Pilcher, & Hopkins, 2003). Although gray matter increases are generally seen in NF1, Billingsley and colleagues found that boys with NF1 had a *smaller* left PT and therefore greater left-right PT symmetry. This greater symmetry was associated with poorer reading and math achievement scores.

White matter (WM) abnormalities have been found to be more consistently related to neuropsychological deficits (Cutting, Choe, et al., 2000; Greenwood et al., 2005), and it is the WM volume increases that appear to underlie the high rate of macrocephaly in the NF1 population (Steen et al., 2001). The WM increases have been most notable in the frontal lobe and corpus callosum. White matter increases resulting in larger corpus callosi is associated with poorer performance on measures of intellectual functioning and academic achievement, visuospatial and visuomotor abilities, and executive functioning (Pride et al., 2010; Moore et al., 2000). Pride and colleagues suggest that an enlarged corpus callosum is a signal of redundant fiber connections that disrupts communication between the hemispheres, resulting in more cognitive difficulties. However, others (Kayl & Moore, 2000; Kayl, Moore, Slopis, Jackson, &

Leeds, 2000) have found that attention problems are associated with a *smaller* corpus callosum.

Neuropsychological and Learning Characteristics

Relations between NF1 gene mutations, intracranial pathology, and the cognitive phenotype remain unclear due to variable cognitive and behavioral phenotype. Although a representative pattern of abilities has not been defined for the NF1 population, research indicates that cognitive and learning difficulties and attention problems are very common (Tonsgard, 2006). The following section summarizes current findings regarding the neuropsychological and academic abilities of individuals with NF1.

Intellectual Functioning

Intellectual disability appears in 4-8% of the NF1 population, which is approximately double the rate present in the general population (North et al., 1997; Ferner, Hughes, & Wenman, 1996). Many studies have observed a slight downward shift of the normal distribution (Moore, Ater, Needle, Slopis, & Copeland, 1994; Billingsley, Slopis, Swank, Jackson, & Moore 2003; Hyman et al., 2005) with mean IQ often still at the low end of the average range. This general lowering of IQ has been found relative to the general population as well as sibling contrast groups (Hyman, Shores, & North, 2005; Sangster, Shores, Watt, & North, 2011). Findings regarding differences between verbal and nonverbal abilities are equivocal. Some studies have found Weschler Verbal IQ to be higher than Performance IQ (Eliason, 1986; Wadsby et al., 1989) while others have observed the opposite (Eldridge et al., 1989; Moore et al., 1994). A majority of studies show no discrepancy between Verbal IQ and Performance IQ (North et al., 1994; Hofman et al., 1994; Moore et al., 1994; Joy et al., 1995; Mazzocco, Turner, Denckla,

Hofman, 1995; Bawden et al., 1996; Ferner et al., 1996; Dilts et al., 1996; Moore et al., 1996; Hyman et al., 2005), indicating that deficits in vocabulary and phonological awareness are just as common as visuospatial deficits. The variable cognitive phenotype highlights the importance of identifying individual patterns of strength and weakness at an early age.

The trajectory of cognitive abilities across the lifespan (i.e., natural history) is largely unknown. Some studies have not observed significant differences between children and adults, and others have noted decline or improvement relative to the age of the participants (Ferner et al., 1996; Moore & Slopis, 1994; Riccardi, 1992). Age-related changes could result from changes in medical severity or be associated with the decreased frequency of hyperintensities in adults with NF1. It is difficult to draw conclusions regarding age effects without implementing a longitudinal design. Cutting and colleagues (2002) found a stable pattern of cognitive strengths and weaknesses for the NF1 group using growth curve analyses. Additional longitudinal studies are warranted to ascertain the natural history of cognitive difficulties and the relations between these difficulties and changes in medical or neurological status.

Academic Functioning

Reported rates of learning disabilities (LDs) for children with NF1 range from 20-70%, compared to 7-10% for the general population (Payne & North, 2011; Descheemacker, Ghesquiere, Symons, Fryns, & Legius, 2005; Sebold, Lovell, Hopkin, Noll, & Schorry, 2004; Rosser & Packer, 2003; Hofman et al., 1994). In a review of recent studies, Levine and colleagues (2006) found evidence for impairment in all academic areas including word reading, reading comprehension, basic math calculations,

math problem solving, and spelling relative to siblings and typically developing children. Hyman and colleagues (2006) sought to clarify the rates of specific learning disabilities (SLDs) using a discrepancy model as well as the cognitive profile associated with specific versus general learning difficulties. Although half of the sample performed poorly on at least one measure of academic achievement, only 20% of the participants were diagnosed with SLDs, which is somewhat lower than findings from previous studies (North, Joy, Yuille, Cocks, & Hutchins, 1995; Brewer, Moore, & Hiscock, 1997). Those with general learning difficulties showed low average performance on nearly all measures of intellectual, academic, and neuropsychological functioning. Children with SLD showed specific academic and neuropsychological deficits despite average intellectual functioning. Specific deficits were seen in academic skills, language and visuospatial abilities, attention, and planning. Hyman et al. (2006) noted that significantly lower verbal IQ scores and attention problems were related to learning difficulties, and that SLDs were present in 37% of males compared to 5% of females. Gender differences have also been observed by Coude and colleagues (Coude, Mignot, Lyonnet, & Munnich, 2006).

The presence of optic glioma or other CNS pathology can also influence the learning profile of children with NF1. Moore and colleagues (1994) compared the performance of children with 1) NF1 only, 2) NF1 + brain tumor, and 3) tumor only to examine the influence of CNS tumors (located on the optic pathway, cerebellum, brainstem) on neuropsychological functioning. On measures of spelling and mathematics, children with a tumor only received significantly better scores. The results suggest that a diagnosis of NF1 puts children at risk for learning difficulties, but a comorbid brain

tumor has mild additional effects. Additional research with a larger sample and more comprehensive assessment of academic skills is warranted. To further clarify the prevalence and nature of learning difficulties in this population, it will be important for researchers to consider the variable cognitive profile and neurological status of individuals with NF1. Furthermore, the lack of consensus regarding the definition and measurement of LDs likely contributes to the variability in reported rates of learning difficulties in the NF1 population.

Visuospatial Abilities

Children with NF1 experience nonverbal learning difficulties in addition to deficits in academic achievement. In fact, early research suggested that the NF1 cognitive phenotype might be best described as a Nonverbal Learning Disability (NVLD), which manifests as visuomotor, visuospatial, tactile-perceptual, and nonverbal problem solving deficits (Harnadek & Rourke, 1994). The nature and pervasiveness of verbal learning difficulties have since been found to be equally problematic (Cutting, Clements, Lightman, Yerby-Hammack, & Denckla, 2004), and there is debate regarding the validity of the NVLD construct more generally (Pennington, 2009; Spreen, 2011). However, the assessment of nonverbal learning difficulties remains important because these deficits can adversely affect academic performance, yet go unnoticed by educators and caregivers.

Impairment of visuospatial abilities in particular is so common that many researchers consider these deficits to be identifying features of NF1 (Moore et al., 1994; North et al., 1995). Children with NF1 consistently perform poorer on the Judgment of Lines Orientation (JLO) compared to unaffected siblings or controls (North et al., 1994; Hofman et al., 1994; Joy et al., 1995; Denckla et al., 1996; Moore et al., 1996;

Schrimsher, Billingsley, Slopis, & Moore, 2003; Billingsley et al., 2003). Acosta, Gioia and Silva (2006) noted that performance on the JLO requires attention, inhibition, and working memory; and it is therefore important to control for these abilities to determine what truly underlies visuospatial deficits. For example, Hyman and colleagues (2005) found that visuospatial deficits remain when controlling for visual scanning and working memory. Similarly, Schrimsher and colleagues (2003) reported that performance on the JLO is a strong predictor of NF1 diagnostic status even after removing the shared variance with ADHD symptomotology. This indicates that visuospatial deficits may uniquely contribute to the learning difficulties observed in the NF1 population.

Motor and Visuomotor Skills

Several studies have observed deficits in both gross and fine motor skills (e.g., Hofman et al., 1994; Moore et al., 1994; North et al., 1995). Moore and colleagues (1994) found that children with NF1 performed below average on a task requiring fine motor coordination and speed; however, they performed above average on finger-tapping tasks that no longer required as much motor coordination. Visuomotor integration (VMI) difficulties have also been noted (North et al., 1995; Cutting et al., 2004). VMI requires integration of several neural structures and therefore the white matter tracts that are often affected in NF1. Visuomotor integration abilities correlate with handwriting skills, reading, and mathematical abilities (Goldstein & Britt, 1994; Kulp, 1999); therefore, these deficits may contribute to the impaired academic functioning observed in the NF1 population. Gilboa and colleagues (Gilboa, Josman, Fattal-Valevski, Toledano-Alhadef, Rosenblum, 2010) found the handwriting of children with NF1 to be impaired compared to typically developing children. It is important for practitioners to consider the role of

motor abilities on cognitive performance given that Hyman and colleagues (2005) found motor coordination to be significantly related to visual-perceptual abilities and motor speed to be highly correlated with measures of processing speed. When motor speed was controlled for, deficits in processing speed were no longer significant.

Speech and Language

Receptive and expressive language deficits. Research indicates that language deficits often co-occur with visuospatial difficulties (Ozonoff, 1999). Receptive and expressive language difficulties have been observed in relation to normative data and sibling control groups (North et al., 1995; Mazzocco et al., 1995; Hyman et al., 2005). Poor performance on vocabulary and naming tests may underlie the higher rates of reading disability in the NF1 population (Denckla, 1996), but few studies have examined specific language skills. Furthermore, the contribution of language abilities above and beyond the role of intellectual functioning is unclear. Hyman and colleagues (2005) found some evidence for receptive and expressive language deficits; however, differences between the children with NF1 and their siblings were no longer significant when controlling for intellectual functioning. Cutting and colleagues (2002) recommend implementing longitudinal research methods to examine language functions such as syntax, semantics and phonology to clarify the nature of these deficits and allow of early interventions.

Speech production and articulation. In a preliminary, and relatively isolated study of the speech production (Robin & Eliason, 1991), children with NF1 were found to have prominent tremors, articulation difficulties, hypernasality, and reduced pitch ranges. Robin and Eliason (1991) suggest that the notably impaired prosody limits their

ability to convey nonverbal cues (e.g., relevant emotional information), and may therefore contribute to the social difficulties experienced by some children with NF1. North and colleagues (1995) observed articulation errors in one quarter of the children in their sample.

Memory and Working Memory

There is evidence of both visual and verbal memory and working memory (WM) impairment in NF1, but relatively few studies have examined memory functioning and findings have been somewhat mixed (Levine, Materek, Abel, O'Donnel, & Cutting, 2006; Acosta et al., 2006). Research using *Drosophila* and mouse models indicates that mutations or deletions of the NF1 gene result in spatial memory and working memory (WM) impairment (Shilyansky et al., 2010; Costa et al., 2002; Ho, Hannan, Guo, Hakker, & Zhong, 2007). A recent study (Ullrich, Ayr, Leaffer, Irons, & Rey-Casserly, 2010) implemented a computerized task based on the Morris Water Maze to examine spatial learning in children with NF1. Ullrich and colleagues (2010) found that the NF1 participants showed more spatial learning and WM difficulties than their siblings. It has been hypothesized that spatial memory impairment in children with NF1 may result from the early neuromotor dysfunction, and subsequently impair the working memory and executive functioning of these children (Denckla, 1996; Samango-Sprouse, 1999).

Other studies have found visual and verbal memory functioning to be spared (Hyman et al., 2005; Mazzocco, 2001; Moore et al., 2000). Deciphering these findings is complex because many factors can influence performance on memory and working measures. Visuospatial difficulties are particularly common in the NF1 population and likely contribute to impaired learning and memory for visual information. Similarly,

difficulties with receptive and expressive language can result in impaired verbal learning and encoding. In addition to an array of contributing cognitive skills, behavioral and emotional functioning can also play a role. For example, Zoller and colleagues (Zoller, Rembeck, & Backman, 1997) found that depressive symptomotology adversely affected memory performance in adults with NF1. Attention abilities are also critical for successful performance on memory and working memory tasks. In fact, Hyman and colleagues (2005) found that children with NF1 did not perform significantly different than typically developing controls on a measure of working memory when accounting for performance on a measure of sustained attention. Further study is therefore needed to clarify the nature of memory difficulties.

Executive Functioning

Executive functioning (EF) is an umbrella construct for human goal-directed, problem-solving behavior that requires inhibition, planning and organization, flexible shifting, self-monitoring, and self-evaluation. EF deficits have been observed in both children and adults with NF1 on standardized laboratory-based measures (Eliason, 1988; Samango-Sprouse et al., 1994, as cited by Samongo-Sprouse, 1999; Hofman et al., 1994; Zoller et al., 1997). A recent study using parent report measures found that children with NF1 show functional EF impairment in day-to-day life (Payne et al., 2011).

Zoller and colleagues (1997) assessed 23 adults with NF1 and 23 controls matched for age, education and gender. They found significant groups differences on tasks of abstraction, problem-solving, and cognitive flexibility. Hyman and colleagues (2005) assessed the planning, abstraction, and verbal fluency abilities of children and adolescents using the Tower of London (Krikorian, Bartok, & Gay, 1994), the Children's

Category Test (Boll, 1997), and the Controlled Oral Word Association Test (Anderson, Lajoie, & Bell, 1995; Yeudall, Fromm, Reddon, & Stefanyk, 1986). The NF1 group scored significantly lower on the measures of planning and abstraction, but these differences were no longer significant when IQ was controlled for. Children with comorbid ADHD did not have significantly more executive functioning deficits than those with NF1 alone. Roy and colleagues (2010) found that children with and without comorbid ADHD exhibit planning deficits above and beyond the role of intellectual functioning. Hofman et al. (1994) also found that children with NF1 had difficulty with organization compared to their unaffected siblings. The NF1 group performed significantly poorer on the Rey-Ostereith Complex Figure (Osterreith, 1944), which assesses planning and perceptual organization by having participants copy a complex design. Samango-Sprouse and colleagues (1994, as cited by Samango-Sprouse, 1999) noted deficits in motor planning and problem-solving strategies in infants and toddlers with NF1.

Deficits have also been seen in response inhibition and flexible set-shifting. Ferner et al. (1996) compared individuals with and without NF1 and found that those with NF1 had difficulty inhibiting responses on automated performance tests including a Continuous Attention test and Stroop test. Chapman and colleagues (Chapman, Waber, Basset, Urion, & Korf, 1996) found that verbal and motor disinhibition was especially common for children with NF1 and learning difficulties. Hofman and colleagues (1994) noted significant deficits in the categories achieved on the Wisconsin Card Sorting Test (Berg, 1948) when comparing children with NF1 to unaffected siblings, which is indicative of difficulties with set-shifting. Rowbotham and colleagues (Rowbotham, Pit-Ten, Sonuga-

Barke, & Huijbregts, 2009) also found that the adolescents with NF1 had substantial difficulty with tasks assessing inhibition and cognitive flexibility.

Attention Problems

Researchers have hypothesized that ADHD may be a part of the NF1 behavioral phenotype because symptoms of inattention are so pervasive (Keyhan et al., 2006). Reported rates of ADHD for the NF1 population range from 30-50%, compared to 3-7% of school-aged children in the general population (Hyman et al., 2005; Schrimsher et al., 2003; Mautner, Kluwe, Thakker, & Leark, 2002; Koth, Cutting, & Denckla, 2000; Moore et al., 1996; APA, 2000). Studies have found children with NF1 to have higher rates of ADHD compared to typically developing controls and unaffected siblings (Hyman et al., 2005; Koth et al., 2000). Whereas the ratio of males to females for ADHD in the general population is approximately 3 to 1 (Willcutt & Pennington, 2000), Hyman and colleagues (2005) observed a more equal ratio for their NF1 sample. Some studies have found that increased distractibility is not always associated with hyperactivity, suggesting that the inattentive subtype might be more common in children with NF1 (Ferner et al., 1996; North et al., 1995; Hofman et al., 1994). Such difficulties with inattention and distractibility can negatively impact academic achievement as well as social skills.

ADHD and academic functioning. Children with comorbid NF1 and ADHD have been found to perform significantly poorer on measures of intellectual functioning compared to children with NF1 alone, ADHD alone, and typically developing controls (Mautner et al., 2002; Koth et al., 2000). As in the general population, attention problems are often comorbid with learning disabilities (Hyman et al., 2005; Wu, Anderson, & Castiello, 2002). In a sample of children with NF1, Hyman and colleagues (2006) found

children with a discrepancy-based SLD and children with learning difficulties related to lower intellectual functioning had higher rates of ADHD (46%) compared to children without learning problems. The highest rate of comorbid ADHD (70%) was observed for children with a reading disability.

ADHD and social functioning. In a study examining the social skills of children with NF1, Barton and North (2004) found that ADHD was a better predictor of poor social functioning than low academic achievement (LA) and SLDs. Although the LA/SLD group scored lowest on tests of IQ and achievement, parents and teachers reported that the ADHD group had the most social, internalizing, and externalizing problems as well as the poorest social competence. One third of the sample had both social and attention problems in the borderline/clinical range. Other characteristics of ADHD, such as emotional dysregulation and difficulty interpreting social cues, may also contribute to poorer social functioning (Maedgen & Carlson, 2000). Cutting and colleagues (2002) therefore recommend designing longitudinal studies to examine the influence of ADHD over time.

Neuropsychological Functioning in Young Children

Research investigating the early neuropsychological profile of children with NF1 and the developmental course of cognitive and academic skills is limited; however, the studies that have assessed young children have found evidence of delays starting in infancy (Riccardi, 1992; Soucy, Gao, Gutmann, & Dunn, 2012) . The MRI findings of Samango-Sprouse and colleagues (1997) indicate that the presence of UBOs is associated with deficits in intellectual and neuromotor development in children between the ages of 18 and 72 months. Deficits in motor planning and problem-solving strategies (Samango-

Sprouse et al., 1994, as cited by Samango-Sprouse, 1999) and language development (Lorenzo, Barton, Acosta, & North, 2010) have also been noted in infants and toddlers with NF1.

The findings of Legius and colleagues (Legius, Descheemaeker, Fryns, & Van Den Berghe, 1994) should be interpreted with caution given the very small sample of young children; however, they found that children between the ages of 17 months and 4 years (N = 7) exhibited delayed language and motor development. Children between the ages of 4 and 6 (N = 7) had average IQ scores, but their verbal IQ scores were significantly higher than their performance IQ scores. Their pattern of cognitive strengths and weaknesses was quite similar to the group of children aged 6 – 16 (N = 31). More recently, Sangster and colleagues (2011) demonstrated a general lowering of IQ compared to a typically developing sample and sibling contrast group with a larger sample of preschoolers with NF1 (N = 26). The available, albeit somewhat limited, data suggest that risk factors for cognitive and learning difficulties are present and can be identified at a young age. Knowledge of these difficulties would allow for early implementation of interventions to reduce the later impact of these deficits.

Summary

In summary, a wide range of medical, cognitive and behavioral difficulties have been observed in the NF1 population (see Table 1 for a summary of neuropsychological findings). Rates of intellectual disability are approximately double the rate present in the general population and reported rates of learning disabilities range from 30-65%. Findings to date do not fit the classic pattern of LDs, as verbal and nonverbal learning difficulties are both reported. Receptive and expressive language deficits, likely related to

general cognitive functioning, are present. Speech difficulties are also relatively common. Studies have shown that both children and adults with NF1 have difficulty with attention and executive skills.

Though considerable progress has been made in the study of NF1, several limitations should be noted. Many of the studies reviewed in this paper used a wide age range, so it is difficult to get a full sense of the NF1 phenotype at a given age. The natural history of behavioral and cognitive deficits is also unclear, as a majority of the research has not been longitudinally designed. Unfortunately, it is challenging to make direct comparisons across studies or combine data to create larger samples because many different neuropsychological measures have been used. The use of various tests is valuable, however, because if a deficit is truly part of the NF1 phenotype, it should appear across measures.

Future research should examine the cognitive and behavioral functioning of larger samples of young children to get a better picture of the early NF1 phenotype. Ideally, these studies should also be conducted longitudinally to identify predictors of later difficulties and characterize how these impairments manifest over time. Participants should be recruited shortly after diagnosis rather than after they present for other developmental difficulties to avoid selection biases. It will be useful to also recruit unaffected siblings as a comparison group because many of the experimental executive functioning measures do not have adequate standardized norms. Comparison to unaffected siblings also controls for some family environmental factors and allows for the detection of more subtle differences in functioning. Finally, investigators should use an age range for which the same measures can be used consistently.

Early Predictors and Correlates of Later Academic Difficulties

To guide research examining the developmental trajectory of cognitive and academic skills in the NF1 population, it is important to consider some early correlates of academic difficulties that have been seen in the general population. In this section, the early development of neuropsychological skills will first be briefly summarized to provide a sense of which skills can be assessed during early childhood that may relate to academic outcomes. The development of reading, math, and writing skills will then be reviewed.

Early Development of Contributing Neuropsychological Skills

Motor and visuomotor. Motor skills are critical for exploration of the environment, and the attainment of these skills can provide insight regarding a child's overall development (Angulo-Barroso & Wiernan, 2008; Heffelfinger & Mrakotsky, 2006). Gross motor skills include balance, coordination, and ambulation. Infants can typically sit with support at 6 months and begin walking at 12 months. They begin running, jumping, and climbing stairs between ages 1 and 3, and are highly coordinated by the preschool years. Rapid changes in fine-motor dexterity and visuomotor skills (i.e., integration of visuospatial processing and movements to produce actions) also occur during early childhood. Infants progress from a full fist grip to a pincer grip. By the preschool years, children manipulate small objects and complete construction tasks such as interlocking puzzles, copying figures, and making patterns with blocks. Table 3 provides examples of gross motor, fine motor, and visuomotor milestones throughout early childhood.

Attention. Significant changes in the ability to direct and sustain attention occur throughout infancy and the preschool years. Infants are able to disengage their attention to explore the environment between 3 and 6 months, and their attention is then highly related to the novelty of the stimuli until habituation occurs more rapidly around 12 months (Courage, Reynolds, & Richards, 2006; Ruff & Capozzoli, 2003). Ruff and Capozzoli (2003) examined changes in attention between infancy and the preschool years. They found evidence for a transition period around 2 years of age when attention is not as highly related to the novelty of stimuli, but attention is not yet regulated for goal attainment. Distractibility decreased with age, which is likely related to the development of inhibitory control and other cognitive abilities required for goal setting that occurs during the preschool years.

Due to the substantial developmental changes that occur and the high base rates of distractibility and impulsivity during early childhood, it can be difficult to assess for attention problems in preschool age children. Young children may also behave very differently at school or daycare where there is more structure and peer interaction than they do at home where they may feel more comfortable and thus display a greater number of emotional and behavioral difficulties. This often results in discrepant parent and teacher reports (Murray et al., 2007), requiring clinicians to collect data from multiple sources when making diagnostic decisions.

Despite these diagnostic challenges, recent research indicates that symptoms of ADHD are common in preschool age children, with 2-6% of preschoolers meeting criteria for ADHD in epidemiological studies (Greenhill, Posner, Vaughan, & Kratochvil, 2008). The most commonly reported inattentive symptoms are being distracted by

extraneous stimuli, not listening, difficulty sustaining attention, and not following instructions (Posner et al., 2007; Murray et al., 2007). The inattentive subtype is the least common in preschool children; therefore, reports of inattentive symptoms may be especially indicative of psychopathology (Smidts & Oosterlaan, 2007). Massetti and colleagues (2008) found that children diagnosed with the inattentive subtype between the ages of 4 and 6 had significantly lower scores than control on measures of spelling, reading, and mathematics at follow-up assessments.

Hyperactive and impulsive symptoms (H/I) including interrupting, fidgeting, and being on the go are more frequently observed in young children (Lahey et al., 1994; Posner et al., 2007; Murray et al., 2007; Schmidts & Oosterlaan, 2007). Parents and teachers report that preschoolers with ADHD often exhibit high-risk behaviors, are disruptive in class, and have difficulty interacting with both peers and adults. When such ADHD symptomotology is identified at a preschool age, the severity of the disorder is often greater than when first identified at a school age (Kadesjo, Kedesjo, Hafflor, & Gillberg, 2001; Posner et al., 2007). Furthermore, it appears that ADHD symptoms persist over time, but may shift from the predominantly H/I subtype to predominantly inattentive or combined subtypes (Lahey, Pelham, Loney, Lee, & Willcutt, 2005; Greenhill et al., 2008).

Executive Functioning. Executive functioning (EF) is an umbrella construct for the skills needed to problem-solve and to plan and control behavior. Although these are complex skills that continue to develop into adulthood, the building blocks for these skills are present in young children (i.e., response inhibition, working memory, and flexible shifting). By the age of 1, infants are able to begin inhibiting their behavior, and

substantial gains in response inhibition are made between the ages of 3 and 4 (Espy, 1997; Zelazo, 2006; Diamond & Goldman-Rakic, 1986). Rule learning and flexible shifting may develop more slowly, but these abilities typically improve between the ages of 4 and 6 (Epsy, Kaufmann, & Glisky, 1999; Jacques & Zelazo, 2001; Denckla, 1996). Senn, Espy, and Kaufmann (2004) examined how inhibition, working memory, and shifting contribute to problem solving abilities in preschool children. They found that in younger children, inhibition is most predictive of problem solving abilities, whereas working memory had more predictive value for older children.

Language. Young children rapidly acquire an understanding of spoken language and an ability to express themselves verbally and with gestures. Although there is some variability in the age at which milestones are attained, children follow the same developmental sequence. Infants can discriminate between speech sounds soon after birth, and learn to segment speech streams into words between 6 and 12 months (Kuhl, 2004). During the first year, they also begin using canonical babbling (consonant – vowel combinations). By 12 months, children begin producing their first words and babble with intonation. In terms of receptive language, they understand approximately 10 words. There is a burst in the development of receptive and expressive vocabulary and grammar between the ages of 1 and 3, (Heffelfinger & Mrakotsky, 2006). Children begin stringing words together around 2 years of age and can speak in complex sentences by age 4 (Harlaar, Hayious-Thomas, Dale, & Plomin, 2008). Table 2 provides a summary of language milestones in early childhood.

Visuospatial. Early visuospatial abilities include recognition of objects and shapes, localization, and part-whole integration. Research indicates that infants process

spatiotemporal information (e.g., location, motion) differently than featural information (e.g., color, shape), and tend to rely on visuotemporal cues to discriminate objects (Wilcox, Haslup, & Boas, 2010; Van de Walle, Carey, & Prevor, 2000). Localization abilities improve throughout infancy when babies can differentiate between their own actions and the environment and when object permanence emerges (Heffelfinger & Mrakotsky, 2006). Preschoolers are capable of segmenting clearly defined parts and integrating basic parts to form a whole, completing visual matching tasks, discriminating differences in pattern or size, and recognizing numerals (Stiles, Paul, & Ark, 2008; Beery & Beery, 2004). Mental rotations can be performed by 5 years of age (Kosslyn, Digirolamo, Thompson, & Alpert, 1990). Table 2 outlines the development of visuospatial skills.

Memory. Memory abilities include working memory (i.e., phonological loop, visuospatial sketchpad, and the central executive), recognition memory, and long-term declarative and procedural memory. Recognition memory is present in infants, as evidenced by longer looking times at familiar objects (Nelson, 1995). Declarative memory emerges throughout the first two years of life as the hippocampus continues to develop (Richmond & Nelson, 2007). Continued advancement of declarative memory takes place during the preschool years as children rapidly acquire language and concrete concepts. Procedural memory is also developing through repeated practice of self-care tasks and other activities (Heffelfinger & Mrakotsky, 2006). In terms of short-term memory, research indicates that the storage component of the phonological loop is present in early childhood, but that children do not typically use rehearsal strategies to maintain information in short-term memory until age 7 (Gathercole & Hitch, 1993).

Phonological short-term memory is often assessed with digit span tasks. Preschool-age children can remember 2-3 digits, and this increases to adult-like levels by age 12 (Gathercole, 1998). Visuospatial short-term memory can be assessed with a pattern span task, which involves pointing to blocks in the same order as shown by an examiner. Several studies have found that preschoolers can remember 4 block patterns, and that pattern span increases to adult-like levels by late childhood (Gathercole, 1998). The central executive controls attention to maintain and process information in working memory. Substantial developmental changes in this ability also occur throughout the preschool years.

Reading Disorder (RD)

Historical and theoretical background. Historically, reading has been thought of as a very complex skill likened to "the performance of a symphony orchestra" (Anderson et al., 1985, p. 7). Although metacognitive and "higher level" reasoning abilities play some role in reading abilities, research has consistently highlighted the importance of two skills: word recognition, which involves translating text into language by decoding the words, and language comprehension. There is evidence that differences in reading comprehension abilities can primarily be accounted for by differences in these "simple" skills, and the contribution of these skills appears to vary throughout childhood (Hoover and Gough, 1999; Peterson & Pennington, 2010). Specifically, research indicates that 1) oral language abilities are strongly related to print knowledge and phonological awareness in preschool, 2) print knowledge and phonological awareness (i.e., knowledge of sounds) are primary contributors to word reading abilities in early elementary school, and 3) oral language significantly contributes to reading

comprehension later in elementary school (Storch & Whitehurst, 2002). The focus of this section will be on the language basis for developmental reading difficulties. Theories emphasizing systems other than the language system (e.g., visuospatial abilities) generally lack of empirical evidence and will be discussed briefly in a later section.

Development of early language and pre-reading skills and their relations to later reading performance. Recent research has focused on characterizing the development of reading-related skills in early childhood to determine when and how reading problems arise. Findings indicate that the development of oral language abilities precedes and lays a foundation for both word reading and reading comprehension (Whitehurst & Lonigan, 1998). Speech segmentation, or learning the sound patterns that make up words, is a prerequisite for phonological awareness and learning the relations between these sounds and meaning. The ability to segment a speech stream into words typically emerges at the age of 7 – 8 months (Nazzi et al., 2003). During infancy and the preschool years, receptive and expressive vocabulary develops rapidly. Exposure to language and home literacy activities during this period is critical for developing oral language skills. For example, research has highlighted the importance of verbal scaffolding for children's early receptive and expressive language abilities and later decoding skills (Dieterich, Assel, Swank, Smith, & Landry, 2005).

Findings that preschoolers with language difficulties are at an increased risk for RD later in childhood and adolescence (Snowling, Bishop, & Stothard, 2000; Catts, Fey, Tomblin, & Zhang, 2002) suggest that their reading abilities may develop at a slower rate than those without language difficulties, causing them to fall farther and farther behind (i.e., cumulative reading trajectory). Skibbe and colleagues (2008) sought to characterize

the pattern of growth in reading abilities for children with language difficulties identified in preschool. The children with language difficulties started with poorer pre-reading skills, but showed an accelerated growth rate in reading abilities. Although these results favor the compensatory trajectory (Leppanen et al., 2004), the children with language difficulties did not fully catch up to their peers, highlighting the importance of early evaluation and intervention.

Scarborough (1990, 1991) found oral language skills during early childhood to be the best predictors of which children would later be diagnosed with RD. At ages 2.5 – 3, syntax and articulation best distinguished children with RD and typical reading abilities, while syntax and vocabulary best distinguished these children at ages 3.5 – 4. Other studies, however, have not found early oral language skills to be directly predictive of later reading abilities (Kendeou, can den Broek, White, & Lynch, 2009; Muter, Hulme, Snowling, & Stevenson, 2004). A meta-analysis examining the predictive relations between emerging literacy skills in preschool/kindergarten and reading outcomes in elementary school found oral language skills to be moderately ($r = .33$) related to decoding abilities and reading comprehension (National Early Literacy Panel, 2009). The predictive power of oral language was inconsistent when controlling for other cognitive abilities. When specific oral language skills were examined, measures of language comprehension and grammar were moderately to highly ($r = .47$ - $.70$) correlated with decoding abilities and reading comprehension. Definitional vocabulary was more strongly related to reading outcomes compared to simple measures of receptive and expressive vocabulary.

Although findings are somewhat mixed regarding the predictive power of preschool oral language skills, it appears that oral language supports the development of phonological processing skills, which *are* predictive of reading abilities in elementary school. Oral language skills and phonological awareness are highly related during the preschool years, and research with school age children has found both concurrent and longitudinal relations between phonological processing and vocabulary (Cooper, Roth, Speece, & Schatschneider, 2002; Wagner et al., 1997). According to the lexical restructuring model, it becomes more efficient for children to recognize smaller segments, such as phonemes, than individual words as their vocabulary increases (Lonigan, 2007). A limited vocabulary may therefore delay the development of phonological skills.

Phonological processing can be divided into three interrelated skills: 1) phonological awareness, 2) phonological memory, and 3) phonological retrieval or lexical access. Lonigan and colleagues (2009) demonstrated that all three areas of phonological processing can be assessed in preschoolers, and that the structure and contribution of these skills is stable over time. Deficits in phonological processing result in word recognition difficulties. When children lack adequate phonological processing abilities, they rely more heavily on contextual cues to guess the word rather than decode it (Lonigan, 2007). Longitudinal research, described below, clearly indicates that phonological processing skills in preschool are predictive of later reading outcomes.

Phonological awareness is the ability to recognize and manipulate sounds, beginning with awareness of larger units (i.e., first words, then syllables and rhyme units) and then smaller units (i.e., phonemes). Carroll and colleagues (Carroll, Snowling,

Hulme, Stevenson, 2003) noted that awareness of syllables and rhyme units at ages 3 – 4 was predictive of phoneme awareness when the children were nearing age 5. These phonological awareness skills are significantly related to decoding abilities even when general intellectual functioning, receptive language, memory skills, and socioeconomic status are controlled for (Lonigan et al., 2009). Deficits in phonological awareness precede reading instruction and phonological awareness training can improve reading outcomes (Catt & Hogan, 2003), indicating that phonological awareness plays a causal role in reading difficulties. Furthermore, there is a reciprocal relationship between phonemic awareness and letter knowledge, and both skills uniquely predict decoding skills (Muter et al., 2004; Lonigan, Burgess, & Anthony, 2000; Carroll et al., 2003). Letter knowledge and phoneme awareness during the preschool years promotes the development of phoneme-grapheme correspondence, which is a foundational reading skill (Treiman, Weatherston, & Berch, 1994).

Children later diagnosed with RD also have difficulty with phonological memory, the ability to temporarily store phonological information; however, this skill does not consistently contribute to word reading abilities independent of phonological awareness. In a study examining phonological processing in preschoolers, phonological memory loaded onto one factor with phonological awareness (Lonigan et al., 2009). Given that phonological memory is not a unique contributor, it is possible that reading abilities depend on the quality of phonological representations more generally (Peterson & Pennington, 2010).

Lexical access, the ability to quickly and accurately retrieve phonological information, is typically assessed with rapid automatized naming (RAN) tasks. Children

with RD perform poorer on RAN than typical readers, and phonological memory in preschoolers is predictive of later reading abilities (Catts & Hogan, 2003). Given findings that phonological awareness and lexical access are both unique contributors to reading abilities, more severe reading deficits may be observed when a child has difficulty with both (Wolf, Bowers, & Biddle, 2000; Semrud-Clikeman, Guy, Griffin, & Hynd, 2000; Catts, Hogan, & Fey 2003). Of note, Puolakanaho and colleagues (2008) found that early phonological and language skills are much more predictive of second grade reading *accuracy* than they are of reading *fluency*. Contrary to some previous findings, they did not observe a strong relation between RAN and reading fluency, indicating that the mechanisms underlying reading fluency may be less clear.

A meta-analysis of the relations between phoneme awareness, RAN, and reading abilities revealed moderate correlations (Swanson et al., 2003). Although the importance of early language and phonological processing abilities has been demonstrated, the results of this study indicate that reading outcomes are influenced by other contributing factors. The following section highlights the other skills that promote the development of reading abilities.

Contribution of other neuropsychological skills to RD. Many educators and parents associate reading reversal errors with developmental dyslexia. The emphasis on these errors, despite little empirical evidence that they are good indicators of decoding problems, has led to hypotheses that visual-perceptual deficits contribute to reading difficulties (Catts & Hogan, 2003). Longitudinal research has shown that preschool visual-perceptual skills are weak predictors of later reading abilities, and many individuals with RD do not have visual-perceptual deficits (Scarborough, 1998; Peterson

& Pennington, 2010). Some studies have found that when visual deficits *are* present, they co-occur with language impairment (Catts & Hogan, 2003). It is therefore possible that these deficits are indicative of cortical disruption more generally, placing the individual at risk for reading difficulties.

The relations between attention and reading have also been frequently examined. School age children with RD are more likely than those with age-appropriate reading abilities to meet criteria for ADHD, particularly the Predominantly Inattentive subtype (Willcutt & Pennington, 2000). Willcutt and colleagues (Willcutt, Betjemann, Wadsworth, et al., 2007) extended these findings to preschoolers, noting that inattentive symptoms were significantly related to concurrent pre-reading skills. Longitudinal research indicates that preschoolers who display ADHD symptoms are at an increased risk for phonological awareness and letter naming deficits and for RD diagnosis in elementary school (Walcott, Scheemaker, & Bielski, 2010; Boetsch, Green, & Pennington, 1996). There is evidence that both preschool and school age children experience more severe academic difficulties when ADHD is comorbid with RD compared to either disorder alone (Pisecco, Baker, Silva, & Brooke, 2001; Willcutt, Betjemann, Pennington, et al., 2007)

Executive skills, including self-regulation and motivation more generally, are important for success in reading as well. Blair and Razza (2007) found that self-regulation in preschool was a significant predictor of early reading skills in kindergarten when controlling for general intellectual functioning, and that teacher-reported inhibitory control was positively related to letter knowledge. Several studies have also examined the role of working memory. Verbal working memory is consistently related to concurrent

and later reading abilities, whereas findings regarding visuospatial working memory have been mixed (Kibby, Marks, Morgan, & Long, 2004; Nevo & Breznitz, 2011). Hirvonen and colleagues (2010) noted that performance on reading tasks in preschool and early elementary school predicted task focused behavior in later elementary school even after controlling for task focused behavior in preschool. As would be expected, children who are successful readers are reinforced to continue reading, whereas those who have difficulty will likely avoid reading tasks and have difficulty catching up to their peers.

Conclusion. Overall, findings indicate that there are many risk factors for later reading problems. Deficits in phonological processing are predictive of later reading difficulties and appear to play a causal role in RD. It appears that phonological deficits interact with language abilities in that early language skills support the development of phonological processing, and language abilities contribute to reading comprehension later in childhood (Peterson & Pennington, 2010; Lonigan et al., 2009). General intellectual functioning, attention, and executive functioning also support literacy development. Comprehensive assessments examining skills that directly contribute to reading and the skills that indirectly support reading development can clarify the nature of a child's reading difficulties.

Mathematics Disorder (MD)

Historical and theoretical background. Researchers from both developmental and neuropsychological backgrounds have made important contributions to the study of MDs. Developmental and educational psychologists have examined how children generally acquire mathematical competence, and neuropsychologists have explored group differences in math performance and the cognitive correlates that contribute to different

outcomes. Findings from both approaches must be integrated for a comprehensive understanding of the typical development of math abilities, the neurocognitive skills that contribute to and may alter the trajectory of math abilities, and the indicators of math difficulties that require intervention. In an attempt to relate the developmental trajectory of math abilities to neuropsychological skills, Geary (1993) proposed three MD subtypes, with different math deficits and accompanying cognitive profiles: (1) the Semantic Memory MD, which is characterized by co-occurring RD and poor retrieval of mathematical knowledge; (2) the Procedural MD, involving execution errors and undeveloped problem solving strategies; and (3) the Visuospatial MD, characterized by difficulty with place values or signs and understanding other relevant spatial relations.

Overall, findings have not supported this model, but indicate that the core deficit in MD is the ability to accurately and efficiently compute basic math problems regardless of comorbid verbal or visuospatial difficulties (Barnes, Fuchs, & Ewing-Cobbs, 2010). There is currently debate regarding the origin of this core MD deficit. One model posits that MDs result from specific quantitative processing deficits (domain-specific), whereas the other model suggests that math difficulties result from deficits in many interrelated cognitive systems (domain-general). Review of developmental and neuropsychological findings indicates that an integrative approach may be most appropriate. This conclusion will be discussed in greater detail below after summarizing how young children acquire math skills and discussing the cognitive and math skills that contribute to later math achievement.

Development of early math abilities and relations to later math performance. It appears that both procedural and conceptual knowledge develops prior to formal math

education in elementary school, and that this early knowledge contributes to later academic success in mathematics. Some of the earliest number skills to develop are number discrimination and estimation, counting, number transformation (e.g., basic addition and subtraction problems), and the ability to recognize and use number patterns (Jordan, Kaplan, Olah, & Locuniak, 2006).

Research indicates that infants are already capable of basic number discrimination and approximation (Bisanz, Sherman, Rasmussen, & Ho, 2004; Xu & Spelke, Goddard, 2005). The debate lies in whether this ability represents core number knowledge per se, or more general cognitive skills that lay the foundation for number-specific knowledge. It is believed that infants create an internal representation or mental model of a set and directly compare this representation to another set (Carey, 2001; Bisanz et al., 2004). The object representations of the subitizing system do not have cardinal value (i.e., final number counted represents the number of items in the set) but do require 1-to-1 correspondence between the perceived objects and object representations (Carey, 2001). Infant discrimination abilities are generally limited to a 1:2 ratio, whereas adults can discriminate at a ratio of 7:8 (Xu et al., 2005; Pica, Lemer, Izard, Dehaene, 2004). Halberda and Feigenson (2008) found that the ability to discriminate between finer ratios increases steadily during the preschool years, but does not reach adult levels until later childhood. This developmental trajectory suggests that number discrimination first relies on general cognitive abilities such as working memory and attention, and then specific number skills learned in elementary school may contribute to the greater precision seen with age.

Between the ages of two and four, children develop an understanding of ordinal relations (i.e., concept that the addition of an object results in a larger set and the removal of an object results in a smaller set), which allows them to begin counting and completing very basic number transformations (Bisanz et al., 2004). Counting abilities are important for the completion of early math problems and are related to knowledge of counting principles, including one-to-one correspondence between the numbers and objects being counted, stable order of counting numbers, order irrelevance (i.e., items can be counted in any order), and cardinality. LeFevre and colleagues (2006) demonstrated that the development of procedural abilities increases steadily, reaching nearly adult levels by second grade, whereas the development of conceptual counting knowledge is nonlinear and moderated by procedural abilities.

Preschool age children are capable of solving basic addition and subtraction problems, and are more accurate when completing nonverbal problems compared to verbal or story problems. This suggests that young children continue to reply on mental models to solve math problems, highlighting the importance of cognitive skills such as attention and working memory. Children also use external representations to count and add (e.g., counting on fingers), and then learn strategies such as counting from the larger addend. Strategy use becomes more efficient with practice, and older children can retrieve number information while other, less efficient procedures become backup strategies (Bisanz et al., 2004). Children between the ages of 4 and 5 can use number patterns to help solve math problems and can accurately compare set sizes to reference points. By the age of 6, children can visualize a number line, which helps them relate number words to magnitudes (Jordan et al., 2006).

Early number knowledge of preschool-age children can be used to predict which children will experience math difficulties in elementary school (Mazzocco & Thompson, 2005; Aunola, Leskinen, Lerkkanen, & Nurmi, 2004; Jordan, Kaplan, Ramineni, & Locuniak, 2009). Mazzocco and Thompson (2005) found that an understanding of number conservation and the ability to read numbers, make magnitude comparisons, and solve basic mental addition problems in kindergarten was highly predictive of MD diagnosis in elementary school. Rapid naming abilities and performance on spatial tasks did not improve the predictive power of the statistical model. Jordan and colleagues (2006) examined the development of math abilities during kindergarten and found three distinct patterns: (1) children with strong number competence at the beginning and end of kindergarten, (2) children who began kindergarten with poor number competence but made gains throughout the year, and (3) children with poor number competence who did not make progress. These growth patterns were predictive of math achievement at the end of grades 1 – 3, even when controlling for demographic variables and other cognitive skills (Jordan et al., 2009). Furthermore, kindergarten number knowledge predicted the rate of growth in math achievement between first and third grade.

Elementary school-age children with MD show impaired procedural and conceptual counting knowledge compared to typically achieving peers, and also have difficulty developing more efficient arithmetic strategies and retrieving basic math facts (Geary & Hoard, 2005). The findings described above indicate that early number competence is important for later math achievement; however, several authors (e.g., Ansari et al., 2003; Halberda & Feigenson, 2008) suggest that development of number specific skills depends on development of domain general abilities. LeFevre and

colleagues (2010) developed a longitudinal model to examine *how* early cognitive and math skills contribute to later math outcomes. Their findings indicate that linguistic abilities, spatial attention, and quantitative skills independently contribute to concurrent early number knowledge, which in turn predicts later math achievement. The following section reviews the contribution of the executive, visuospatial, and language systems to math skill development.

Contribution of neuropsychological skills to MD. Recent research has highlighted the contribution of executive skills such as inhibitory control and cognitive flexibility to both concurrent and later math performance (Bull & Scerif, 2001; Lee, Ng, & Ng, 2009). Inhibitory control has been found to contribute to preschool math skills above and beyond other executive skills (Espy et al., 2004; Blair & Razza, 2007). Furthermore, longitudinal research indicates that performance on measures of inhibitory control, planning, and set shifting at ages 4-5 are significantly related to math abilities in elementary school, when controlling for reading abilities and IQ (Clark et al., 2010; Bull et al., 2008). Executive skills continue to make a significant contribution to math performance in adolescence (Latzman, Elkovitch, Young, & Clark, 2010). Given that EF is a multifaceted construct, future research should elucidate the specific executive skills that contribute to different math abilities at different developmental stages.

The importance of working memory (WM) for many types of math skills has also been consistently demonstrated. Although nonverbal reasoning, processing speed, phonological processing, and memory have been found to contribute to problem solving abilities, there is evidence that WM and sustained attention are the most robust predictors (Swanson & Beebe-Frankenberger, 2004; Fuchs et al., 2005). The shorter WM span of

children with MD likely contributes to inefficient strategy use, a deficit that is also seen in children with math difficulties (Geary, Hoard, Byrd-Crave, Nugent, & Numtee, 2007). Findings indicate that the contribution of WM may differ with age in that young children rely on visuospatial WM to solve nonverbal math problems, whereas older children rely on both visuospatial and verbal WM (Holmes & Adams, 2006; McKenzie, Bull, & Gray, 2003; Rasmussen & Bisanz, 2005). Although the relations between visuospatial skills and basic arithmetic are weak, foundational visuospatial abilities may prepare children to learn math specific skills (Barnes et al., 2010). For example, the use of mental models to solve nonverbal math problems requires visuospatial WM (Rasmussen & Bisanz, 2005). Visuospatial WM at ages 4-5 is a significant predictor of later math performance even after controlling for reading abilities at ages 7-8, suggesting that this skill can predict later math achievement specifically rather than a general learning capacity (Bull et al., 2008).

Fine-motor skills and finger gnosis may help young children compensate for a reduced working memory capacity (Barnes et al., 2011). Finger gnosis training has been used to promote early number skills (Gracia-Bafalluy & Noel, 2008). Barnes and colleagues (2011) found that fine-motor skills and visuospatial abilities predicted object-based arithmetic in both typically developing children and children with spina bifida.

Verbal WM, and language abilities more generally, become important for solving word problems and for retrieving math knowledge and strategies (Fuchs et al., 2005; Barnes et al., 2010). In younger children, phonological awareness is a unique predictor of oral counting abilities and counting knowledge (Barnes et al., 2011). MD and RD frequently co-occur, indicating that deficits in the phonological loop may contribute to

both disorders. Comorbidity of these disorders results in more severe deficits in math performance; however, a bulk of the evidence indicates that regardless of the presence of absence of RD, the core deficit of MD remains the ability to accurately and efficiently solve basic math problems (Fuchs et al., 2004; Barnes et al., 2006).

Conclusion. It appears that both domain-specific and domain-general abilities contribute to successful math performance. The importance of general and specific skills may vary according to an individual's developmental trajectory. For example, attention and working memory are likely important for the acquisition of math skills at all ages; however, these cognitive systems are particularly important for very young children, and the development of these cognitive skills lays the foundation for number specific skills. There is also evidence that the contribution of domain-general skills is related to a child's pattern of relative strength and weakness. Those with neurodevelopmental disorders may rely more heavily on the contribution of relatively intact cognitive systems. For example, children with Williams syndrome have relatively preserved language abilities and a profound weakness in visuospatial skills. Ansari and colleagues (2003) found that language abilities were more predictive of counting abilities for children with Williams syndrome, whereas visuospatial skills made a greater contribution in typically developing children. It is therefore important to consider how the phenotype of neurodevelopmental disorders may impact the nature and course of learning difficulties.

The Current Study

NF1 is neurogenetic disorder associated with variable phenotypic findings including higher rates of intellectual disability and learning disabilities, attention problems, speech and language impairment, and executive functioning deficits. Research

investigating the cognitive and behavioral phenotype of young children with NF1 is very limited, particularly related to academic skill development. There is evidence from the general population that early neuropsychological deficits can be used to predict concurrent and later learning difficulties. Such research with the NF1 population can be used to identify early indicators of learning difficulties so appropriate interventions can be implemented. The goal of the current study was to determine if young children with NF1 display early signs of learning difficulties and to characterize relations between cognitive functioning and foundational academic skills. The following research questions will be addressed:

Question 1: Do Preschool-Aged Children with NF1 Show Difficulty on Measures of Early Academic Skills?

Rates of learning disabilities for school-aged children with NF1 range from 20 to 70% (Payne & North, 2011). Research from the general population indicates that children diagnosed with LDs in elementary school show signs of learning difficulties during the preschool years. Although general abilities like working memory and attention also contribute to the development of academic skills, specific early number knowledge of preschool-age children has been consistently shown to predict math outcomes, and phonological processing skills are predictive of reading outcomes (Aunola et al., 2004; Jordan et al., 2009; Lonigan et al., 2009). It is expected that one third to one half of the NF1 sample will have difficulty with pre-academic skills, with performance one or more standard deviations below the mean.

Question 2: What are the Relations between Concurrent Neuropsychological Skills and Pre-Reading Abilities?

Research has consistently demonstrated that preschool language abilities support the development of phonological processing (Cooper et al., 2002; Wagner et al., 1997). It is expected that receptive and expressive language and verbal working memory will be correlated with performance on the measure of phonological processing. Although some studies have found that RAN performance uniquely contributes to reading success, other researchers have suggested that processing speed more generally contributes to performance on both measures of RAN and reading abilities (Li et al., 2009). It is likely that RAN performance will be more strongly related to processing speed compared to early language abilities. Data from the Differential Ability Scales—Second Edition (DAS-II) standardization sample are consistent with this (Elliot, 2007). In the sample of 3- to 6-year-olds, Phonological Processing was more highly related to verbal tasks, while Rapid Naming showed stronger relations with Speed of Information Processing.

Findings from the general population indicate that attention difficulties, particularly inattentive symptoms, are related to both concurrent pre-reading skills and an increased risk for phonological awareness and letter naming deficits in elementary school (Willcutt, Betjemann, Wadsworth et al., 2007; Walcott et al., 2010; Boetsch et al., 1996). It is expected that measures of attention will be related to performance on early reading tasks.

Question 3: What are the Relations between Concurrent Neuropsychological Skills and Early Number Knowledge?

Recent research findings indicate that early number competence is important for later math achievement, and that the development of number specific skills depends on the development of domain general abilities including visuospatial, fine-motor, executive

and language skills (LeFevre et al., 2010; Halberda & Feigenson, 2008; Barnes et al., 2011). It is expected that measures of working memory, fine-motor abilities, and visuospatial skills will be correlated with early number knowledge. Receptive language abilities likely contribute, particularly to performance on math word problems (Barnes et al., 2010). The relations between performance on Early Number Concepts and attention and early executive skills will also be examined. Findings from the general population have demonstrated the importance of working memory and inhibitory control for math skill development (Bull & Scerif, 2001; Swanson & Beebe-Frankenberger, 2004). In the DAS-II standardization sample, moderate correlations (r = .45 - .55) were seen for the relations between Early Number Concepts and performance on nonverbal reasoning, spatial, auditory attention, and receptive language tasks (Elliot, 2007).

Participants and Procedure

Demographic information for the participants is provided in Table 4. The sample consisted of 50 children with NF1 between the ages of 3 and 7, and 42 control children without NF1 also between ages 3 and 7. This age range was chosen to capture the development of foundation academic skills during the preschool years, as well as grades K-2, which are critical years for acquiring foundational academic skills. The contrast group was made up of 26 siblings and 16 typically developing children from the community. The groups did not differ significantly in age ($t(90) = -.989$, $p = .325$), gender distribution (chi square $(1, 92) = .035$, $p = .852$), minority representation (chi square $(1, 92) = 1.17$, $p = .280$), socioeconomic status ($t(90) = -1.78$, $p = .079$), or maternal education[1]. Children recruited from the community were included if intellectual

[1] Maternal education was dichotomized to look at differences in completion of 1) binary education and 2) tertiary education. Although the number of mothers who completed high school or some college was

functioning fell within the range observed for the NF group. All siblings remained in the comparison group regardless of overall intellectual functioning given that their inclusion helps control for other environmental and familial factors.

Diagnoses of NF1 were based on the NIH Consensus Conference criteria (NIH Consensus Development Conference, 1988). Mutations were familial for 21 of the children with NF1, and sporadic for 29 of the participants. Children with comorbid diagnoses of autism, epilepsy, and hydrocephalus were excluded from the sample described above and from all analyses. Participants with NF1 were recruited through the Neurofibromatosis Clinic at the Children's Hospital of Wisconsin Genetics Center/Medical College of Wisconsin, the University of Chicago Neurofibromatosis Clinic, and distribution of fliers at regional NF1 symposiums. The children were assessed at the Child Neurodevelopment Research Lab, University of Chicago, or a quiet location in the participants' homes.

Materials

Standardized Measures

Differential Ability Scales—Second Edition (DAS-II). The Early Years form of the DAS-II was used to assess the cognitive strengths and weaknesses of the participants. The DAS-II is an empirically derived measure with a factor structure that fits the Cattell-Horn-Carroll (CHC) model well. The measure yields a General Conceptual Ability (GCA) score derived from subtests with the highest *g* loadings as well as a Verbal Ability and Nonverbal Ability cluster score. For children ages 3½ and older, the Nonverbal Ability scores are divided into Nonverbal Reasoning Ability and Spatial

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greater for the control group, these differences did not reach statistical significance. Binary education: (chi square (1, 91) = 3.43, p = .064, Phi = .194), Tertiary education: (chi square (1, 91) = 2.96, p = .085, Phi = .180).

Ability clusters. Diagnostic subtests also provide a measure of processing speed, working memory, early number concepts, rapid naming and phonological processing abilities. At the subtest level, "abilities scores" are used to describe the level of performance considering both the number of correct responses and the difficulty of the item set administered. These ability scores can be converted to T-scores for each subtest, and standard scores are obtained for the clusters and GCA. The DAS-II is highly correlated with other measures of cognitive abilities and was co-normed with the WIAT-II.

NEPSY-II. The NEPSY-II is a neuropsychological measure that assesses six theoretically derived domains: Attention and Executive Functioning, Language, Memory and Learning, Sensorimotor, Social Perception, and Visuospatial Processing. The measure provides normative data from a representative sample of children between the ages of 3 and 16. Selected subtests of the NEPSY-II were used to assess attention, inhibition, judgment of line orientation, and motor control. Table 5 illustrates the specific subtests that were administered, the constructs measured by the subtests, and the age at which the tests were administered.

Experimental Tasks

A-Not-B and Delayed Alternation (DA). A-not-B and DA are measures of prefrontal functioning for preschoolers (Diamond, 1988; Goldman, Rosvold, Vest, & Galkin, 1971) that were administered to the participants ages 3 – 6. These tasks are used to assess inhibitory control and visual working memory. Consistent with the method used by Espy and colleagues (Espy et al., 1999), children are told to find a reward hidden in one of the two covered wells of the testing board. When completing A-not-B, the reward

is hidden while the child watches. The board is then removed from the table and the examiner counts to 10 aloud to distract the children from the testing board. The child is asked to pick up one cup to find the hidden reward. If the reward is found in the same location for two consecutive trials, the reward is hidden in the other well. If the child is unsuccessful, the reward is hidden in the same well until two correct responses occur consecutively. Ten trials are administered, and scores include the total number of correct responses, the longest run of consecutive correct responses, the number of perseverative responses after the first two consecutive correct criterion is reached, and the longest run of consecutive perseverative errors.

When completing DA, rewards are hidden out of sight (e.g., testing board hidden under table). A pre-trial is completed, in which neither well is baited. After the child displaces the cup to find no reward, the opposite well is baited to begin the first of 16 trials. The reward location is alternated after each correct response. If the child is unsuccessful, the same well is baited until a correct response occurs. Scores include the total number correct, the longest run of consecutive alternations, and the longest perseverative run.

Dimensional Change Card Sort (DCCS). The DCCS (Zelazo, 2006) is a measure of executive function that can be used for a wide age range. Target cards, one with a picture of a red bunny and the other a blue boat, are placed above rectangular containers. The children are then presented with cards showing a red bunny, blue bunny, red boat, or blue boat. In the pre-switch trial, the children are told to sort the cards by color. The post-switch trial measures pre-potent response inhibition by asking children to disregard the color and sort the cards by their shape. Most typically developing 3-year-

olds fail the post-switch phase whereas most 4-and 5-year olds pass this phase. Children who pass the post-switch trial proceed to the border phase, which is a measure of flexibility and working memory. They are asked to sort the cards by color is there is a black border around the card and to sort the cards by shape if the border is absent. A majority of 4-year-olds and approximately half of the 5-year-olds fail the border phase, but most 6-year-olds perform well on this phase.

Parent Report Measures

Attention problems were assessed with both categorical and dimensional measures. The Kiddie Disruptive Behavior Disorder Schedule (KDBDS), a structured parent interview, was used to determine if the participants meet criteria for ADHD. The KDBDS is a developmentally sensitive modification of the Kiddie-SADS (Kaufman et al., 1996), which is a validated semistructured interview for DSM-IV. The reliability of the KDBS for diagnosis of ODD and CD in children as young as 3-5 years old (Keenan et al., 2007) has been demonstrated. The children were considered to meet criteria for the Predominantly Hyperactive/Impulsive Type or the Predominantly Inattentive Type if six or more symptoms from the subtype were endorsed. If 6 or more symptoms were endorsed from both subtypes, the children met criteria for the combined type. Parents had to report that these symptoms occur “some” or “a lot” of the time in at least two settings (home, school, public), and the symptoms must have been present for at least six months. Parents were asked six questions to assess the level of impairment (e.g., “How much do these behaviors interfere with the parent’s ability to take child out in public” or “How much do they interfere with the child’s ability to play and get along with other kids?”); two or more of these questions had to be answered “some” or “a lot.”

The Conners' Parent Rating Scales—Revised (Conners, 2001) served as a more dimensional measure of the presence or absence of attention difficulties. The measure includes 4 scales: Hyperactivity, Cognitive Problems/Inattention, Opposition and ADHD index. Normative data for the Conners are available for individuals between the ages of 3 and 17.

Results

Analyses were conducted with SPSS Statistics 19, and findings were interpreted with respect to both statistical significant and effect size.[2] Given the number of comparisons made, a p-value of .01 was used to determine significant differences, and differences at the .05 level were considered trends. For continuous data, *D* was used for effect size, interpreted as follows: 0 to .14 negligible, .15 to .39 small, .40 to .74 medium, .75 and above large (Cohen, 1988). For categorical data analysis, Phi was used to determine effect size, interpreted as follows: V = less than .10 weak, .11 to .15 moderate, .15 to .25 strong, and .25+ very strong. Rates of difficulties on tasks were examined. A difficulty was operationalized as a score one or more standard deviations below the mean.

Level of Performance on Neuropsychological Measures

The level of performance on the measures of neuropsychological functioning will be briefly described before describing performance on the academic measures and examining the relations between these measures and pre-academic skills. The data will primarily be presented in table form, but some of the main findings will be discussed here.

[2] P-values for group comparisons were spot-checked using the IBM randomization program. Randomization tests use the random assignment procedure to repeatedly rearrange the data and calculate test statistics for each permutation. The resulting p-value is the proportion of permutations with test statistics at or above the value obtained experimentally. Results were equivalent using both methods, so the p-values obtained with the SPSS analyses are reported below.

DAS-II. Significant group differences were seen on the GCA, Verbal Abilities, and Nonverbal Reasoning Abilities cluster scores. A significant difference was not observed for the Spatial Abilities composite. At the subtest level, significant group differences were seen for Verbal Comprehension, Naming Vocabulary, Matrices, Pattern Construction, Copying, Digits Forward, and Speed of Information Processing. Trends toward significance were seen for the two remaining subtests given, Picture Similarities and Digits Backward (see Table 6).

NEPSY-II. Significant group differences were seen on Imitating Hand Positions, and trends toward significance on the measures of visuomotor coordination, inhibitory control (Statue), and fine-motor skills of the non-dominant hand (Fingertip Tapping). Group differences were not detected on the measures of auditory attention, visuospatial skills (Arrows), or other motor tasks (Fingertip Tapping Repetition, Sequences, Dominant Hand). Data are presented in Table 7.

Experimental Tasks of Executive Functioning. Performance was examined on the DCCS using the total number of correct sorts across all three trials, and comparing how many children in the NF and control groups passed each phase. A group difference in the total number of correct sorts approached significance ($t(78.73) = -2.396$, $p = .019$, $d = 0.51$). Trends were also seen for group differences in how many children passed the Color phase (Chi square $(1, 81) = 4.23$, $p = .040$, Phi = .229) and the Shape phase (Chi square $(1, 81) = 4.33$, $p = .038$, Phi = .231). A group difference was not observed for the Border phase (Chi square $(1, 81) = .004$, $p = .952$, Phi = .007), as most children in both groups did not pass this phase. Significant group differences were also not observed on A-not-B and Delayed Alternation. Data are presented in Table 8.

Parent Report Measures. A trend toward significance was observed for the ADHD Index and Hyperactivity and Inattention scales when examining group differences on the Conners (see Table 9). The NF and control groups differed significantly on the KDBDS symptom counts. Twenty-two percent of the NF group (N = 11/50) met research criteria for ADHD (Predominantly Inattentive Type 4, Predominantly Hyperactive/Impulsive Type 1, Combined Type 6), compared to 3 of the 40 control participants (7.5%). Two of the control siblings met research criteria for the Combined Type, and 1 sibling for the Predominantly Hyperactive/Impulsive Type. This difference was not significant (Chi square (1) = 3.56, p = .059, Phi = .199), but may become more pronounced with a larger sample size.

Question 1: Do Preschool-Aged Children with NF1 Show Difficulty on Measures of Early Academic Skills?

As indicated in Table 6, means for both the NF1 and control groups fell in the average range on academic tasks. There were, however, differences between the groups in rates of difficulty and level of performance (Tables 6 & 10). Thirty percent of the NF group had difficulty with at least 1 academic task, which is a significantly higher rate of difficulty compared to the control group.

On Early Number Concepts, the NF group's performance was significantly lower than the normative mean (t (49) = -3.70, p = .004, d = .37), while the control group's score was significantly higher than the normative mean (t (41) = 3.79, p < .001, d = .47). This corresponded with a significant group difference in mean score and rates of difficulty. Twenty percent of the NF group (N = 10/50) had difficulty with this task, whereas none of the control children showed a deficit.

On the measure of phonological processing, the control group scored significantly higher than the normative mean (t (25) = 3.15, p = .004, d = .27), and a significant group difference was seen for the NF and control groups (t (51) = -2.79, p = .007, d = .78). A quarter of the NF group had difficulty with this measure (N = 7/27; 25.9%) compared to 1 of the 26 (3.8%) control children. This difference approached significance (Chi square (1) = 5.04, p = .025, Phi = .308).

Less difficulty was seen with the measure of rapid automatized naming. The rates of difficulty fell within a range expected given the normative distribution for both the NF (N = 2/24, 8.3%) and control (N = 2/25, 8%) groups. A significant group difference was not observed, and the level of performance did not differ substantially from the normative mean.

Relations between performance on these academic tasks and demographic variables were examined. Academic performance did not differ substantially by gender in either group[3] or correlate with SES. A trend was seen for the correlation between age and performance on Phonological Processing for the NF group, but normative performance on the other academic tasks did not correlate with age. For the children with NF1, a familial mutation was associated with lower scores on ENC compared to children with sporadic mutations (t (48) = -2.63, p = .011), but differences were not significant for Phonological Processing (t (25) = -1.83, p = .079), GCA (t (48) = -1.50, p = .139), SES based on the Hollingshead Index (t (47.34) = -1.083, p = .284), or maternal education.[4]

[3] Of the 15/50 children in the NF group who had difficulty on at least 1 academic task, 8 were male and 7 were female. Gender differences were not seen in performance on ENC, PP, or RN using independent sample t-tests in the NF or control groups.

[4] Binary education: (Chi square (1, 50) = .516, p = .473, Phi = .102), tertiary education: (chi square (1, 50) = .739, p = .390, Phi = .122)

General intellectual functioning was significantly related to performance on Early Number Concepts and Phonological Processing for both groups. ANCOVA results for Early Number Concepts indicate that intellectual functioning accounts for a significant proportion of the variance in scores ($F(1, 90) = 27.80$, $p < .001$); however, there was also a trend toward significance for group differences ($F(1, 90) = 4.16$, $p = .044$). Results suggest that group differences do not remain on the measure of phonological processing above and beyond the role of intellectual functioning and age-related changes (GCA: $F(1, 51) = 34.97$, $p < .001$, Age: $F(1, 51) = 4.59$, $p = .037$, Group: $F(1, 51) = .382$, $p = .540$).

Question 2: What are Relations between Concurrent Neuropsychological Skills and Pre-Reading Abilities?

Relations between neuropsychological functioning and performance on Phonological Processing and Rapid Naming were examined (see Tables 12 & 13). These tasks were only administered to children ages 5 and older (n = 27 in each group). Given the relatively small sample sizes, the stability of these correlations should be interpreted with caution. Spearman's rho was used in place of Pearson correlations for these analyses because the data from small samples may not resemble the normative distribution as closely as would a larger sample.

Phonological Processing. Significant correlations between Phonological Processing and nearly all other DAS-II subtests assessing verbal abilities, nonverbal reasoning, spatial skills, working memory, and processing speed were seen for the NF group.[5] Partial correlations were then used to determine if specific cognitive skills would relate to phonological processing when accounting to intellectual functioning more

[5] Results using Pearson correlations were very similar to these findings with Spearman's rho.

generally. For the subtests included in the General Conceptual Ability composite, mean T-scores excluding the subtest of interest and averaging the remaining core subtests were calculated. Only the relation between processing speed and phonological processing remained significant after intellectual functioning was partialled out. Trends were seen for the measures of verbal working memory and verbal comprehension. In the control group, correlations between Phonological Processing and other DAS-II subtests were not statistically significant at the .01 level. The correlation with verbal working memory remained a trend after controlling for intellectual functioning (see Table 12).

Table 14 summarizes DAS-II performance for the participants who showed a difficulty on Phonological Processing. This table also compares rates of difficulties on these subtests for those who struggled on the phonological task compared to the entire NF group (including those with phonological processing difficulties). For participants who had difficulty on Phonological Processing, rates of difficulty were highest on Verbal Comprehension, Matrices, Copying, and Digits Forward and Backward.

Phonological Processing was not significantly correlated with the NEPSY attention measures or the subtest assessing visuomotor control in either group. In the NF group, significant correlations were observed for relations with Imitating Hand Positions (IHP) and DCCS total score, and trends for relations with Conners' Inattentive scale, Conners' ADHD scale, and the ADHD total symptom count on the KDBDS. Performance on IHP and DCCS was significantly correlated with intellectual functioning, and these relations no longer approached significant when intellectual functioning was partialled out. A trend was also seen for the relation between Phonological Processing and the Inattentive symptom count in the control group.

In sum, performance on the measures of verbal working memory and receptive language related to phonological processing skills even when controlling for general intellectual functioning. Of the children who had phonological processing difficulties, 70% struggled on these language-related measures. Processing speed and parent ratings of inattention also correlated with performance on Phonological Processing.

Rapid Naming. A moderate effect size was observed for the relation between rapid automatized naming and Statue performance in the NF group ($r = .530$, $p = .051$, $N = 14$); however, the relation between RAN and inhibitory control should be examined with a larger sample size. Notably, Rapid Naming was not significantly correlated with Speed of Information Processing in either group.

Question 3: What are the Relations between Concurrent Neuropsychological Skills and Early Number Knowledge?

Early Number Concepts (ENC) was administered to the entire sample (NF group N = 50, Control group N = 42), so Pearson correlations were used to examine relations with neuropsychological skills unless otherwise noted for specific analyses. Performance on ENC was significantly correlated with the measures of expressive and receptive language, nonverbal reasoning (Picture Similarities), and verbal working memory for the NF group. A trend was seen for the Copying task. When using a partial correlation to control for intellectual functioning, the relation with the receptive language measure remained significant, and a trend remained for the relation with Picture Similarities. Performance on Arrows, a visuospatial task that involves judging line orientation, was significantly correlated with early number knowledge when intellectual functioning was partialled out. A significant correlation was seen between DCCS performance and ENC;

however, this relation was no longer significant when controlling for intellectual functioning ($r = .297$, $p = .063$). Similarly, the trend for perseverations on Delayed Alternation was accounted for intellectual functioning.

For the control group, significant relations to ENC were seen with for Picture Similarities and Pattern Construction. The relation with Pattern Construction remained significant when intellectual functioning was partialled out, and a trend remained for Picture Similarities. Trends were seen for the relations between ENC and Digits Forward, Digits Backward, and Imitating Hand Positions. These relations appear to be accounted for by intellectual functioning given that they were no longer significant when IQ was partialled out. The relations with Conners' Inattentive scale and Delayed Alternation performance continued to approach significant ($p < .05$), even when controlling for intellectual functioning. Only 2 participants had several inattentive symptoms endorsed by parents, and while their ENC scores were low relative to the other control participants, their performance still fell within 1 standard deviation of the normative mean.

Discussion

NF1 is disorder with variable phenotypic effects associated with higher rates of intellectual disability and learning disabilities, attention problems, speech and language impairment, and executive functioning deficits. The goal of this study was to add to the limited literature examining preacademic functioning in young children with NF1. There is evidence that cognitive difficulties are present and can be identified at an early age, but very few studies have examined pre-academic skills in NF1. The primary goal of the current study was to describe early academic skills and characterize relations between cognitive functioning and foundational academic skills in young sample of children with

NF1. Findings indicate that early learning difficulties are present and can be identified in young children with NF1. General intellectual functioning was strongly related to academic performance and accounted for many of the relations between neuropsychological and academic skills in the NF1 group. However, some specific neuropsychological domains apppear to support the development of foundation reading and math skills evening when controlling for overall developmental level. In the following section, I summarize the findings from the analyses and discuss how these results relate to the proposed hypotheses. I describe some limitations of the study as well as provide general conclusions and directions for future research.

Question 1: Do Preschool-Aged Children with NF1 Show Difficulty on Measures of Early Academic Skills?

Rates of learning disabilities for school-aged children with NF1 range from 20 to 70% (Payne & North, 2011). Academic difficulties have been seen in all areas including word reading, reading comprehension, basic math calculations, math problem solving, and spelling relative to siblings and typically developing children (Levine et al., 2006; Krab et al., 2008). These findings indicate that the NF phenotype is not associated with a specific academic deficit, but places these children at risk for learning problems more generally. Based on this prior research with older children, it was hypothesized that one third to one half of this sample of younger children would show learning difficulties. In the current study, 30% of the NF participants had difficulty (defined as performance at least 1 SD below the normative mean) with at least one of the academic tasks. Difficulties were seen on measures of both early number knowledge and phonological processing. These findings indicate that like cognitive difficulties (Sangster et al., 2011, Lorenzo et

al., 2010), academic problems in NF1 can be identified at an early age for some children with NF1.

A primary goal of this study was to determine which factors contribute to learning problems (i.e., neuropsychological difficulties, demographic variables) so that young children with NF1 can be effectively screened and receive remedial services to prevent more pronounced academic difficulties. Relations between pre-academic skills and demographic variables were examined. Although some studies have found that males with NF1 have more academic difficulties than females (Soucy, Gao, Gutmann, & Dunn, 2012; Hyman et al., 2006; Coude, Mignot, Lyonnet, & Munnich, 2006), gender differences were not observed in the current sample of young children. Age effects did, however, approach significance when examining performance on Phonological Processing. The correlation with age (i.e., older children performed better on this task) was observed for the NF group only. This improvement could be a result of intervention services received at school. Older children have also been in a structured classroom setting longer, which could have made older participants more accustomed to the testing environment.

Performance on the academic measures did not correlate with socioeconomic status (SES). This was somewhat surprising given that SES disadvantages have been found to adversely affect academic achievement in young children with NF1 (Sangster et al., 2011) and the general population (Luyten, Schildkamp, & Folmer, 2009; Ready, 2010). The families who participated in this study, both in the NF1 and control groups, were of relatively high SES. Stronger relations between environmental factors and academic performance may be seen in a sample of more diverse SES. However, the fact

that academic difficulties are seen even in a sample of relatively high SES families suggests that learning problems are a true part of the NF1 phenotype, rather than a reflection of environmental disadvantages.

Children with familial mutations performed somewhat poorer than those with sporadic mutations on the academic measures, particularly on the measure of early number knowledge. Differences in SES and maternal education level were not statistically significant, but these measures do not fully account for a family history of learning problems. Parents with NF1 who themselves also potentially struggled in school may have more difficulty helping their children develop academic skills at home. These children may therefore enter school slightly behind and need to catch up to peers who have already acquired foundational academic skills at home.

Intellectual functioning accounted for a significant proportion of the variance in academic performance. Research indicates that some school-aged children with NF1 have specific deficits in academic and neuropsychological skills despite average intellectual functioning, while others have general learning difficulties associated with impaired functioning across many domains (Hyman et al., 2006). The following research questions were used to examine relations between specific neuropsychological and pre-academic skills to determine if an overarching deficit (i.e., intellectual functioning) is the primary risk factor, or if specific deficits can clarify the nature of learning problems in young children with NF1.

Question 2: What are the Relations between Concurrent Neuropsychological Skills and Pre-Reading Abilities?

Language. Considering the relations between neuropsychological skills and reading abilities can clarify why a child is struggling in school to aid in both the identification and amelioration of reading problems. Although difficulties with reading skills such as word decoding and recognition are common in school-aged children with NF1, the reported rates of difficulty differ depending on how learning disabilities are defined and assessed. For example, Watt, Shores, and North (2008) found that while only 17% of their sample met criteria for an IQ/AA discrepancy-based reading disability, two thirds of the children were struggling with reading on clinical measures (i.e., performance in the bottom 5%) and based on teacher report. The prevalence of reading problems may be underestimated using a discrepancy model given that children with NF1 often experience difficulty with verbal skills, which can contribute to lower scores on measures of intellectual functioning *and* academic achievement (Mazzocco et al., 1995).

Relations between verbal abilities and foundational reading skills were examined in this study given that research from the general population has consistently demonstrated that phonological processing is the best predictor of Reading Disability diagnoses, and that preschool language abilities support the development of phonological processing (Wilson & Lonigan, 2010; Storch & Whitehurst, 2002; Cooper et al., 2002). As expected, difficulties with receptive and expressive language and verbal working memory co-occurred with phonological processing delays in young children with NF1. Nearly a quarter of the sample had difficulty with the measure of verbal comprehension, and nearly one third struggled with the measure of verbal working memory. Of the children who had phonological processing difficulties, 70% struggled on these language-related measures. Relations between Phonological Processing and the measures of

receptive language and verbal working memory approached significance even when controlling for overall developmental level. This indicates that, as in the general population, the ability to process oral language likely contributes to the development of pre-reading skills for children with NF1. The importance of early language exposure should be emphasized to parents of children with NF1 to minimize the difficulties seen in this population.

Performance on the measure of expressive vocabulary was stronger than on the other language measures, and did not correlate with phonological processing skills significantly after accounting for intellectual functioning. It is, however, possible that variability in expressive language skills would have been greater and related to early reading skills if more complex skills had been assessed. For example, Lorenzo and colleagues (Lorenzo, Barton, Acosta, & North, 2010) found evidence for expressive language delays in toddlers with NF1 when assessing use of irregular words and level of sentence complexity in addition to basic vocabulary skills. It will be important to examine the individual components of language, and confirm if early expressive language abilities are predictive of pre-reading skills as they are in the general population.

Future research should also continue clarifying the neurobiological mechanisms that contribute to reading and language difficulties seen in the NF1 population. Billingsley and colleagues (Billingsley, Slopis, Swank, Jackson, & Moore 2003; Billingsley, Jackson, et al., 2003) found that morphological and functional brain changes relate to language abilities in children with NF1. Specifically, increased gyral volume in the right inferior frontal region was associated with better language abilities, and children with NF1 showed different patterns of activation in the frontal and temporal lobes

compared to typically developing controls during phonological tasks. The authors proposed that atypical frontal lobe function in NF1 may results in abnormal neuronal recruitment for language tasks.

Given findings that the right inferior frontal region supports performance on language measures in NF1, implications of this atypical laterality should be considered further. Billingsey and colleagues (Billingsley, Schrimsher, Jackson, Slopis, & Moore, 2002) found that smaller left planum temporale (PT) volume and greater left-right PT symmetry was associated with poorer reading scores. Relations between PT asymmetry and phonological difficulties have been seen in those with idiopathic RD as well, but is not a completely consistent finding (Habib, 2000). It is important to note that the PT may more involved in initial auditory processing, rather than language-specific processes (Binder et al., 1996), and PT volume/asymmetry is not the best predictor of language laterality (Eckert et al., 2006). Many factors likely play a role in language lateralization including handedness, gender, individual and group differences in total brain volume and morphology, and the specific language processes of interest. Further, there may be periods during development when different or changing lateralization is actually the norm.

It does, however, appears that recruitment of the typically nondominant right hemisphere for language-related tasks may be a compensatory mechanism for those with reading difficulties. Several studies have observed increased right hemisphere activation in individuals with dyslexia, and a subsequent increase in left hemisphere activation following reading intervention (Guttorm et al. 2010). Guttorm and colleagues found that anomalous right hemisphere language processing in newborns was predictive of later pre-

reading skills. Early detection of compensatory right hemisphere activity in NF1 may therefore serve as a useful indicator of which children are in need of language intervention.

There may also be overlap in the mechanisms underlying language and motor impairment in the NF population. Jäncke and colleagues (Jäncke, Siegenthaler, Preis, & Steinmetz, 2007) found that children with developmental language disorders struggled on several motor tasks, indicating that disrupted frontal-temporal communication may contribute to both difficulties. Motor problems are common in NF1. The relation seen between Imitating Hand Positions and Phonological Processing was primarily accounted for by intellectual functioning, but suggests some degree of abnormal connectivity in language and motor areas.

Contribution of other Neuropsychological Skills. Although there is substantial evidence for the language basis of developmental reading disabilities, there may be other contributing mechanisms in the NF population. School-aged children with comorbid RD/NF1 differ from children with idiopathic RD in that they experience visuospatial difficulties in addition to language-based deficits (Cutting & Levine, 2010). In this sample of young children with NF1, visuospatial abilities did not relate to phonological processing skills above and beyond the role of the intellectual functioning; however, visuospatial skills may play a larger role in orthographic processing when the children are older. The magnocellular theory of developmental reading problems suggests that individual with RD have difficulty perceiving and attending to written text due to abnormalities of the magnocellular layers of the lateral geniculate nucleus (Stein, 2001). Some researchers have observed visual attention difficulties in individuals with idiopathic

RD that appear to result from abnormalities of the magnocellar pathways (e.g., Stoet, Markey, & Lopez, 2007), while others question the validity of this model (Skottun & Skoyles, 2006). Ribeiro and colleagues (2012) found that low-level vision processes (including magnocellular processing) are in impaired in NF1. Future research should examine the validity of the magnocellular theory for children with NF1 who are experiencing reading problems to determine if both language and visual aspects of reading should be targeted in intervention programs.

Subcortical UBOs may also disrupt networks important for attention and processing speed. Difficulty processing information efficiently could place children with NF1 at risk for generalized learning problems. Performance on the measure of processing speed was significantly correlated with phonological processing, even when controlling for intellectual functioning. A phonological processing task like phoneme deletion involves holding a word in mind and breaking it down into individual sounds (e.g., when shown the word *blue*, children are expected to say the sounds *b, l, oo*). This task requires the ability to store the speech sounds and efficiently access the component sounds being held in the phonological loop (working memory). In addition to the relation with the verbal WM task described above, the ability to quickly process information also appears to be important for performance on Phonological Processing.

It was expected that processing speed would also correlate with the measure of rapid automatized naming. Some researchers have suggested that processing speed contributes to performance on both measures of RAN and reading abilities, but there is also evidence that RAN is a unique predictor of reading abilities. In a sample of typically developing children, Georgiou and colleagues (Georgiou, Papadopoulos, Fella, & Parrila,

2012) found that RAN accounted for variance in reading abilities above and beyond the role of processing speed and phonological processing skills, indicating that these skills make separable contributions to reading development. Nonetheless, it was surprising that performance on Rapid Naming was not related to Speed of Information Processing in the NF or control groups given that they comprise the processing speed composite. There was some evidence, however, for a relation between RAN and inhibitory control that will need to be replicated with a larger sample. Qualitatively, many of the NF participants made numerous self-corrections, which contributed to the longer completion times. Inhibitory control difficulties may contribute to difficulties with reading fluency. It would be helpful to further examine the relations between verbal inhibition, fluency, and RAN with measure like NEPSY-II Inhibition and Word Generation.

Attention problems are pervasive in the NF1 population, and it was expected performance on the attention measures would relate to phonological processing abilities. Trends were seen for the relations between Phonological Processing and the parent report measures of attention, supporting this hypothesis. Findings from the general population indicate that attention difficulties, particularly inattentive symptoms, are related to both concurrent pre-reading skills and an increased risk for phonological awareness and letter naming deficits in elementary school (Willcutt, Betjemann, Wadsworth et al., 2007; Walcott et al., 2010; Boetsch et al., 1996). Future research should confirm if early attention problems are predictive of later reading abilities in the NF population as well. The current findings suggest that early screening and intervention for attention problems may promote academic skill development.

Question 3: What are the Relations between Concurrent Neuropsychological Skills and Early Number Knowledge?

Difficulties with both math calculations and word problems have been observed in the NF1 population (Levine et al., 2006). Although research from the general population indicates that early number competence is the best predictor of later math achievement, it appears that the development of domain general abilities including visuospatial, fine-motor, executive and language skills supports the development of number-specific skills (LeFevre et al., 2010; Halberda & Feigenson, 2008). The aim of the current study was to examine relations between neuropsychological performance and Early Number Concepts, to determine if these general skills promote early math development in NF1 as well.

Visuospatial Skills. The role of visuospatial skills was of particular interest because visual-spatial difficulties are so common in the NF1 population. Visuospatial skills have been found to relate to math achievement in other neurodevelopmental disorders including 22q11.2 deletion syndrome (Simon, 2008), Williams syndrome (O'Hearn & Luna, 2009), and spina bifida (Barnes et al., 2011). It was expected that the young children in this sample would have difficulty with subtests assessing these skills, and that visuospatial deficits may be a contributor to early math difficulties.

The children in the NF group did struggle on the DAS-II visuospatial tasks compared to the control group and standardized means. Notably, group differences were not seen in overall performance on Arrows. This was somewhat surprising given the consistent finding that children with NF1 perform poorer than unaffected siblings and controls on a similar task, Judgment of Line Orientation (North et al., 1994; Hofman et

al., 1994; Joy et al., 1995; Denckla et al., 1996; Moore et al., 1996; Schrimsher, Billingsley, Slopis, & Moore, 2003; Billingsley et al., 2003). Arrows is a challenging task that requires attention and working memory in addition to visuospatial processing, and a wide range of performance was seen in both groups. Notably, performance on this task was significantly correlated with early number knowledge even when controlling for intellectual functioning for the NF1 group only. For the control group, performance on Pattern Construction, a task requiring spatial and visuomotor skills, was significantly correlated with ENC above and beyond the role of intellectual functioning. This indicates that when visuospatial difficulties are present in young children, these deficits may uniquely contribute to their learning difficulties.

Visuospatial abilities seem to play a greater role in more complex math (e.g., geometry, trigonometry) than in basic calculations; however, they may also support the development of foundational math skills (Barnes et al 2010). For example, understanding cardinality (i.e., last number counted is the total quantity) and completing object-based math problems are likely supported by the use of mental models (Raghubar, Barnes, & Hecht, 2010). Early Number Concepts assesses these basic skills including cardinality, one-to-one correspondence between the numbers and objects being counted, and visually-based counting and addition problems. ENC, like many achievement subtests, provides a total score that groups these skills together; however, the nature of early math difficulties could be described in greater detail if these skills were examined individually. This could be done clinically by examining patterns of performance on the math measure. Additionally, screening tasks for preschoolers and kindergarteners have been developed to examine specific early math skills (VanDerHeyden, Broussard, & Cooley, 2006) such

as free counting, object counting, and number identification. The authors found that performance on these tasks correlated moderately with standardized measures such as the Test of Early Math Ability (TEMA; Ginsburg & Baroody, 1990). Barnes and colleagues (2011) asked participants to tell a puppet if items were being correctly counted to assess one-to-one correspondence, cardinality, and stable order (Briars & Siegler, 1984; Gelman & Galistell, 1978). Object based arithmetic was completed separately; the children watched the examiner add or remove poker chips behind a screen, and were then asked to place poker chips on their matt that would match how many the examiner had. Use of such tasks could pinpoint specific deficits that are common in NF1 more generally, or the areas that need to be remediated for a specific child.

Future studies could also examine if visuospatial abilities contribute to specific pre-math skills, and the causal mechanisms for these relations. It is possible that difficulties with both math and visuospatial skills result from abnormal development and connectivity of the same brain regions. Neuroimaging research has not yet been utilized to examine neural correlates of math performance in the NF1 population. Studies have found that females with Turner syndrome frequently experience math difficulties, and that these difficulties are associated with disrupted frontal-parietal communication (Kesler, Menon & Reiss, 2006). Similar findings have noted that frontal-parietal communication is associated with number sense in the general population as well. The neuroimaging data available suggest that problem solving abilities supported by frontal lobe function are initially very important for math development, and as children learn more specific math skills, the role of the parietal lobe and the frontal-parietal network is strengthened (Emerson & Cantlon, 2012).During math tasks, children show more frontal

activation and somewhat less parietal activation, compared to adults who show the opposite pattern (Rivera, Reiss, Eckert, & Menon, 2005). Emerson and Cantlon (2012) found that the strength of frontal-parietal communication is predicted by age and level of math achievement in typically developing children. If frontal lobe functioning or frontal-parietal communication is disrupted in young children with NF, this may interfere with math skill development

Abnormal frontal-parietal function has been observed during visuospatial processing in the NF1 population. When completing Judgment of Line Orientation, children with NF1 showed left hemisphere activation of the frontal, parietal, and occipital regions. Control children showed more right hemisphere activation during this task, especially in frontal regions (Clements-Stephens, Rimrodt, Gaur, & Cutting, 2008). This atypical activation pattern likely reflects disrupted right hemisphere networks, requiring the recruitment of other brain regions. It is therefore possible that disruption of frontal-parietal communication contributes to difficulties with both spatial orientation and math tasks. Neuroimaging and longitudinal research is needed to determine if a) visuospatial and math difficulties co-occur in some children with NF, but do not necessarily reflect an association between the two skills, b) these deficits frequently co-occur because they share an underlying neural mechanism, or c) visuospatial difficulties, particularly with judging line orientation, predict later math performance. Determining the nature (and potentially direction) of the relation will be important to guide intervention work.

Intervention aimed at improving math problem solving abilities (e.g., teaching strategies such as decomposition) for female children with Turner syndrome has been shown to improve number sense and calculation skills and to increase parietal activity

(Kesler, Sheau, Koovakkattu, & Reiss, 2012). Improvements were also seen in processing speed, cognitive flexibility, and visuospatial processing with this intervention. A similar intervention may be very effective for children with NF1 who are experiencing math and visuospatial difficulties. Research examining the effects of such an intervention on these skills and neurological functioning is warranted.

Working Memory and Problem-Solving Abilities. Recent research has highlighted the contribution of executive skills such as inhibitory control and cognitive flexibility to early number knowledge (Bull & Scerif, 2001; Lee, Ng, & Ng, 2009; LeFevre et al., 2010). There is some indication that subcortical UBOs may disrupt circuits important for executive functioning in NF1 (North, 1997). Studies implementing both mice models and assessing human participants have shown that neurofibromin plays an important role in regulating the prefrontal-striatal pathways critical for working memory (Shilyansky et al., 2010). Given the decreased expression of neurofibromin seen in NF1, it was expected that the NF participants would struggle with early executive skills, and that these difficulties would relate to concurrent foundational math skills.

The NF1 participants had more difficulty with some, but not all of the EF measures. For children in the control group whose overall intellectual functioning was average or above average, performance on a measure of inhibition and working memory independently related to early math skills. Relations between EF and math were also seen in the NF group, but were accounted for by overall developmental level when GCA was partialled out. There is variability across neurogenetic disorders in whether executive functioning deficits are seen above and beyond the role of IQ (Janke & Klein-Tasman, in press). Although level of intellectual impairment is not as severe in NF1 as it is in other

neurodevelopmental disorders, there may still be threshold of intellectual functioning for EF to be a unique predictor of academic functioning.

Relations between ENC and verbal working memory did not remain significant after controlling for intellectual functioning in either group. Findings from the general population indicate that the contribution of WM may differ with age in that young children rely on visuospatial WM to solve nonverbal math problems, whereas older children rely on both visuospatial and verbal WM (Holmes & Adams, 2006; McKenzie, Bull, & Gray, 2003; Rasmussen & Bisanz, 2005). A measure of visuospatial working memory was not administered in the current study. It would be helpful for future research to assess visual WM with developmentally appropriate measures (e.g., Dots Test; Davidson, Amso, Anderson, & Diamond, 2006), and to examine the relations between these skills and early math performance.

Performance on a measure of nonverbal reasoning correlated with ENC in both groups even when controlling for overall developmental level. Picture Similarities required the participants to match pictures based on a common concept or element (e.g., grouping two round items among objects of other shapes). As the task becomes more challenging, determining the relating concept requires more flexibility and "on-the-spot" problem solving, making Picture Similarities a useful measure of fluid intelligence. Research indicates that math performance is associated with fluid intelligence (Spinath, Freudenthaler, & Neubauer, 2010), and that frontal lobe functioning supports fluid intelligence (Saggino, Perfetti, Spitoni, & Galati, 2006). Neuroimaging research with typically developing adolescents has shown that those who are better at thinking flexibility (i.e., better performance on measures of fluid intelligence), recruit neural

resources more flexibly (Preusse, van der Meer, Deshpande, Krueger, & Wartenburger, 2011). Difficulty with the measure of nonverbal reasoning may therefore be an early sign cognitive and neural dysfunction that can disrupt academic skill development.

Language. In the NF1 group, performance on the measure of receptive language was significantly related to Early Number Concepts even after controlling for intellectual functioning. ENC is a verbally mediated task to some degree. For example, several items require understanding of quantity-related words (e.g., *more, less, few*) to answer the questions correctly. A delay in learning or remembering such terminology can cause children with NF1 to fall behind their peers in math achievement. Performance on Early Number Concepts was also significantly correlated with Phonological Processing in both groups. Barnes and colleagues (2011) found that in addition to visuospatial skills, phonological awareness was a unique predictor of oral counting abilities and counting knowledge in typically developing preschoolers and young children with spina bifida. Similarly, Cutting and colleagues (Levine, Rimrodt, Clements-Stephens, & Cutting, 2006) noted relations between visuospatial abilities and phonological processing skills in school-aged children with NF1. These findings and the frequent co-occurrence of MD and RD in the NF1 population are indicative of shared underlying mechanisms that contribute to both reading and math problems. Abnormal frontal lobe function corresponding with deficits in the phonological loop may contribute to both disorders and/or the previously mentioned atypical recruitment frontal-parietal pathways.

Conclusions

Findings from the current study indicate that the learning problems observed in the NF1 population can be identified at an early age for some children. Approximately a

third of the sample had difficulty with at least one of the academic tasks. Difficulties were seen with phonological processing and early number knowledge, which are foundational academic skills predictive of later reading and math achievement. In addition to describing performance on measures of early academic skills, a primary goal of this study was to examine factors that may contribute to learning difficulties. Knowledge of the risk factors for early learning problems will allow children with NF1 to be effectively screened and receive intervention services sooner.

There was some evidence that demographic variables may play a role in academic skill development. Participants with familial mutations performed poorer on Early Number Concepts than children with spontaneous mutations. It is possible that a family history of learning problems contributed to this difference given that SES effects were not observed. In addition to the genetic risk, parents who themselves struggled in school may have difficulty teaching their children pre-academic skills at home. It may be helpful for clinicians working with young children with NF1 to screen for a family history of learning problems, including more subtle difficulties, regardless of a formal LD diagnosis.

There was also a correlation between age and performance on Phonological Processing, with older children performing better on this measure. This finding highlights the need for longitudinal work. Examining the developmental trajectory of their academic skills can provide valuable insights for those working with the NF1 population. It would provide a sense of which common areas of difficulty should be monitored, and how skills may change over time and relate to brain pathology or medical functioning more generally. It is important to keep in mind, however, that group trends may not generalize

to any individual child with NF1. Research has demonstrated that the pattern of intraindividual strength and weakness can be quite variable (Klein-Tasman et al., in prep). Although a positive correlation was seen between age and Phonological Processing performance, some children with NF may experience more learning difficulties with age. Subtle academic difficulties in early childhood could become more problematic over time and place children at risk for later learning problems as tasks become more complex and tax their cognitive resources (Huijbregts, Swaab, & de Sonneville, 2010; Krab et al., 2008). Further, intellectual functioning in not stable during early childhood, and assessments with young children provide only a snapshot of functioning on a given day. Performance on cognitive and academic measure may therefore vary to some degree across the preschool years.

Of clinical utility is the finding that intellectual functioning was strongly related to academic performance, and accounted for many of the relations between neuropsychological and academic skills for the NF group. This suggests that cognitive screenings should be a recommended for young children diagnosed with NF1, as their overall developmental level may be the best indicator of who is at risk for learning problems. Some specific domains did, however, relate to pre-academic skills. Receptive language and verbal working memory, processing speed, and attention correlated with phonological processing abilities, while visuospatial skills and receptive language related to early math skills. A more comprehensive neuropsychological evaluation examining patterns of strength and weakness could therefore help caregivers and teachers play to their strengths and build up cognitive skills that contribute to math and reading development.

Although only cross-sectional data are presented here, the concurrent relations observed provide some indication of which neuropsychological domains may support academic skill development in NF1. It will be important for longitudinal studies to determine the predictive power of specific neuropsychological skills and/or show if general intellectual functioning continues to be a primary determinant of academic attainment as they age.

Future research should also clarify the trajectory of gene-brain-behavior relations given that the disruption of neural organization both pre- and post-natally that occurs in NF1 can dramatically impact expected relations. At the genetic level, neurofibromin plays an important role in regulating GABA release, which in turn, modulates prefrontal-striatal communication and long-term potentiation in the hippocampus (Shilyansky et al., 2010). Disruption of hippocampal functioning has been shown to impair learning; and disruption of frontal-striatal networks can impair attention, working memory, and processing speed (Cui et al., 2008; Costa et al., 2002; Schneider et al., 2010; Genova, Hillary, Wylie, Rypma, & Deluca, 2009). Frontal abnormalities may also contribute to abnormal recruitment of brain areas for visuospatial and language tasks as described above. The timing of when the mutation occurs can impact both neuronal tissue differentiation and the integrity of white matter pathways and molecular regulation.

The frequently studied but not fully understood impact of UBOs also needs to be further examined. Sabol and colleagues (2011) found that the presence of T2-hyperintensities was very common for children with NF1 between the ages of 2 and 7, but are much less frequent in older children. Why or how these age-related changes occur is not yet clear. Gill and colleagues (2006) suggested that the pathology of

hyperintensities differs by region given their findings that the prevalence of UBOs in the basal ganglia, thalamus, cerebellum, and brainstem declined with age, while age-related changes were not seen for hippocampal or hemispheric UBOs. This was, however, a cross-sectional study, so longitudinal work is needed to determine how neurobiological findings (i.e., the timing of when hyperintensities appear, the placement of the UBOs, and if/when hyperintensities resolve) play a role in the variable phenotype observed in children with NF1.

NF1 provides a useful model for understanding potential etiologies of and treatments for learning problems. The lowering of cognitive functioning associated with NF1 is significantly milder than that of other neurogenetic disorders, such that severe intellectual impairment is not common in this population. This allows children with NF1 to be more easily matched for intellectual functioning to same-aged TD peers. Comparison to an appropriate comparison group over time can help determine when and how the development of cognitive and academic skills lags or differs in NF1, and point to potential mechanisms underlying these patterns. The current findings accentuate the need to continue integrating genetic, imaging, and behavioral work, and to examine the functional consequences of atypical neural development longitudinally. It is important not to assume that a genetic mutation directly produces a deficit consistent with the adult phenotype as "genetic mutations are more likely to affect low-level cognitive processes that will have differing, cascading effects on different domains as development proceeds over time" (Karmiloff-Smith, 2008, p. 697). Clarifying the nature and course of gene-brain-behavior relations will guide intervention research so appropriate treatments can alter the trajectory of development.

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Table 1

Summary of Neuropsychological Findings

Study	N	Age Range	Findings
			Language
North et al., 1995	40	8-16	Left shift in receptive, expressive, and total language scores on the CELF-R
Denckla, 1996	20	School-aged	Performed poorly on measures of vocabulary and naming
Hyman et al., 2005	81	8-16	Receptive and expressive language deficits on the WAIS and WIAT before controlling for IQ
			Quantitative Abilities
Stine & Adams, 1989	18	6-15	Mean WRAT arithmetic scores was 82.8 (SD = 16)
Mazzocco et al., 1995	19	6-14	Discrepancy-based mathematics disability in 42% of NF1 children
North et al., 1995	105	6-18	11 children has significantly lower math scores
Brewer et al., 1997	81	8-16	Children with specific LDs and general learning difficulties had equally low scores on measures of arithmetic
Hyman et al., 2005	81	8-16	Significantly lower scores on math tasks
			Processing Speed
Hyman et al., 2005	81	8-16	Measures of processing speed were highly correlated with motor speed and when motor speed was controlled for, deficits in processing speed were no longer significant
			Memory
Joy et al., 1995	40	8-16	Memory spared
Zoller et al., 1997	30	32-62	Short-term memory deficits
Hyman et al., 2005	81	8-16	Memory spared

			Executive functioning
Hofman et al., 1994	12	6-13	Difficulty organizing tasks; deficits in flexible set-shifting
Samango-Sprouse et al., 1994	90	M: 34 mos.	Deficits in motor planning and problem-solving strategies
North et al., 1995	40	8-16	Difficulty with problem-solving strategies
Ferner et al., 1996	103	6-75	Deficits in response inhibition
Zoller et al., 1997	30	8-16	Difficulty with inductive reasoning, logical abstraction, attention, and mental flexibility
Hyman et al., 2005	81	8-16	Scored significantly lower on measures of planning and concept formation before IQ was controlled for
			Attention abilities
Mautner et al., 2002	80	Means of groups: 9-11 yrs	IQ scores of children with both NF1/ADHD were lower than the mean scores of those with ADHD alone, NF1 alone, and controls.
Koth et al., 2000	31	6-16	IQ scores of children with NF1 and ADHD were significantly lower than the scores of children with NF1 alone, controls, and unaffected siblings.
Hyman et al., 2005; 2006	81	8-16	Presence of a SLD is a risk factor for ADHD, and children with NF1 and ADHD are at an increased risk for developing a SLD. In a follow up study, the highest rate of comorbid ADHD was observed for children with a literacy disability.
Barton & North, 2004	79	8-16	ADHD was a better predictor of poor social functioning than low academic achievement and SLDs.
Maedgen & Carlson, 2000	47	8-11	Other characteristics of ADHD (e.g., emotional dysregulation & difficulty interpreting social cues) may contribute to poorer social functioning.

			Spatial Abilities/Visualization
North et al., 1995	40	8-16	Deficits in visual-motor integration; deficits in manual dexterity, balance, and ball skills
Schrimsher et al., 2003	101	10.6 +/- 2.6	Poor performance on the JLO (many other studies have found this as well)
Hyman et al., 2005	81	8-16	Visual-spatial deficits remain even when controlling for tracking and working memory
			Fine-Motor Skills
Eldridge et al., 1989	13	6-27	Significantly lower scores on the PANESS; abnormal balance and gait
Hofman et al., 1994	12	6-13	Neuromotor dysfunction (using PANESS)
Moore et al., 1994	79	5-16	Performed below average on task requiring motor coordination and speed, but average on motor tasks not requiring speed
North et al., 1995	40	8-16	Deficits in visual motor integration

Table 2

Summary of Language and Visuospatial Skills Development.

	Language	**Visuospatial Skills**
Birth – 1	Discriminate between phonemes Reduplicated babbling around 6 months Variegated babbling at 10-11 months Says first words and understands 10 words	Can track items Discriminates circles, squares, and triangles Looks at picture that someone points to
1 – 2	Understands "no" Vocabulary rapidly increases from a few words to around 200 words Points to wanted items Says some 2-3 word sentences	Turns pictures right side up Can stack rings in correct order with demonstration Can sort toys
2 – 3	Can identify 5-10 items Uses 3-4 word sentences Uses pronoun "me" Uses approximately 500 words	Can match items of the same color Can point to familiar objects
3 – 4	Uses 4-5 word sentences Can name some colors Uses approximately 1000 words Can follow simple instructions	Sorts items by shape Can arrange a few items in sequence Recognizes some basic colors
4 – 5	Can identify colors and shapes Can define simple words Correctly uses past tense Vocabulary of approximately 1500 words	Matches identical photographs Identifies groups of objects with more or less items Recognizes largely covered familiar objects
5 – 6	Can count Knows spatial relation words Vocabulary of approximately of 2000 words Uses complex sentences	Can group items by two characteristics Matches letters Recognizes numerals Recognizes own name and other simple words

Table 3

Summary of Motor Development.

	Gross Motor	**Fine Motor**	**Visuomotor**
Birth – 1	Sits without support Crawls Walks with hands held Stands briefly without support	Explores objects with hands & mouth Picks up & releases toys Tears paper Uses pincer grasp	Bangs toys together Pulls string to get a toy Independently eats finger food Puts objects inside other objects (e.g., nesting cups)
1 – 2	Walks alone Pushes/pulls toy while walking Sits in "child size" chair Climbs onto furniture Walks up & down steps (nonalternating)	Points with index finger Turns door knobs & book pages (2-3 at a time) Uses spoon with little spilling Grasps pencil in palm	Puts objects in/takes them out of a container Imitates simple gestures Builds 6 block tower Kicks ball forward & throws ball to others Threads shoelace into bead
2 – 3	Jumps or hops in place Walks backward Runs forward well Balances briefly on 1 foot Walks on tiptoes	Holds cup with one hand Turns individual book pages Uses small beads & pegs Screws/unscrews jar lids Grasps pencil between thumb & fingers	Copies vertical/horizontal lines & circles Eats with a fork Pours accurately from 1 container to another Builds 9 block tower Throws overhand
3 – 4	Walks up stairs w/o support (alternating) Pedals tricycle Walks heal to toe on a line Runs forward/backward with agility	Completes simple puzzles Manipulates clay/play dough Buttons/unbuttons 1+ buttons	Cuts a relatively straight line Traces around edges of shape templates Colors mostly within the lines Kicks large ball while it's rolling
4 – 5	Climbs ladder/goes down slide w/o aid Walks down stairs w/o support (alternating) Turns somersaults Jumps rope	Feels & identifies objects w/o looking Uses mature pencil grip Touches thumb tip to each finger Screws/unscrew nuts & bolts Laces shoes	Copies squares & draws simple objects Zips most zippers & strings small beads Brushes teeth & dresses/undresses independently Cuts out squares & large circles Prints a few capital letters
5 – 6	Walks backward heel to toe Hops in straight line Skips with alternating feet	Feels & identifies different textures Shows preference for one hand Cuts well with scissors	Copies triangles Connects dots with straight lines Cuts along outline of simple shapes Prints name with & then w/o a model Catches small ball to chest, then with 2 hands Rides bike

Table 4

Demographic Variables.

	NF1 (n = 50)	Typically Developing (n = 42)
Gender:		
Male	30	26
Female	20	16
Age (Mean, SD)	61.92 months (SD = 18.36)	65.55 months (SD = 16.45)
Ethnicity		
Caucasian	37	35
African-American	6	2
Latino	3	1
Asian	1	2
Other	3	2
Maternal Level of Education		
High School & Below	10 (20%)	4 (9.5%)
Higher Education	40 (80%)	38 (90.5%)
Hollingshead SES Index	32.06 (SD = 17.03)	38.33 (SD = 16.68)

Table 5

Age Ranges for Standardized Measures.

Measure	Construct	Age				
		3	4	5	6	7
DAS-II						
VC	Receptive language	*	*	*	*	*
NV	Expressive language	*	*	*	*	*
PS	Nonverbal reasoning/induction	*	*	*	*	*
M	Nonverbal reasoning/induction	*	*	*	*	*
PC	Spatial relations	*	*	*	*	*
C	Visualization	*	*	*	*	*
RDF	Auditory STM/memory span	*	*	*	*	*
RDB	Working memory			*	*	*
ENC	Pre-numerical/numerical concepts	*	*	*	*	*
PP	Phonetic coding			*	*	*
SoIP	Perceptual speed: scanning			*	*	*
RN	Perceptual speed: complex			*	*	*
NEPSY-II						
AW	Visuospatial abilites			*	*	*
AA	Auditory attention, WM			*	*	*
FT	Finger dexterity			*	*	*
IHP	Fine-motor coordination	*	*	*	*	*
ST	Inhibition, self-monitoring	*	*	*	*	

VC: Verbal Comprehension; NV: Naming Vocabulary; PS: Picture Similarities; M: Matrices; PC: Pattern Construction; C: Copying; RDF: Recall of Digits Forward; RDB: Recall of Digits Backward; ENC: Early Number Concepts; PP: Phonological Processing; SoIP: Speed of Information Processing; RN: Rapid Naming
AW: Arrows; AA: Auditory Attention; RS: Response Set; FT: Fingertip Tapping; IHP: Imitating Hand Positions; ST: Statue

Table 6

Group Differences between NF1 and Control groups on the DAS-II and differences from normative mean.

	NF1				TD						
Cluster/*Subscale*	*N*	*Mean*	*(SD)*		*N*	*Mean*	*(SD)*		*T*	*P*	*D*
GCA	50	94.28	12.52	++	42	107.38	9.67	++	-5.53	< .001 **	1.17
Verbal	50	98.20	13.07		42	108.95	8.83	++	-4.53	< .001 **	0.96
Nonverbal Reasoning	50	94.04	13.01	++	42	102.81	12.48		-3.28	.001 **	0.69
Spatial	50	93.31	10.94	++	41	100.12	25.66		-1.58	.118	0.36
Verbal Comprehension	50	46.60	8.04	++	42	52.62	6.09	++	-3.99	< .001 **	0.84
Naming Vocabulary	50	50.86	9.86		42	57.60	6.09	++	-4.00	< .001 **	0.82
Picture Similarities	50	47.60	8.00	+	42	51.21	7.63		-2.21	.030 *	0.47
Matrices	42	45.95	7.63	++	39	51.64	10.32		-2.84	.006 **	0.64
Pattern Construction	50	49.38	9.52		42	54.83	7.99	++	-2.94	.004 **	0.62
Copying	42	42.36	7.62	++	39	51.87	8.53		-5.30	< .001 **	1.19
Digits Forward	50	45.00	10.60	++	41	51.83	7.65		-3.46	.001 **	0.74
Digits Backward	26	43.92	10.37	++	25	50.96	12.70		-2.17	.035 *	0.61
Speed of Info. Processing	23	48.65	7.15		19	55.11	6.03	++	-3.12	.003 **	0.99
Early Number Concepts	50	46.30	8.68	++	42	54.62	7.89	++	-4.77	< .001 **	1.01
Phonological Processing	27	47.22	11.86		26	55.08	8.21	++	-2.79	.007 **	0.78
Rapid Naming	24	53.00	7.34		25	53.96	9.40	+	-.397	.693	0.12

Significantly different from normative data in one-sample t-test + $p < .05$; □ $p < .01$
Significant group differences * $p < .05$; ** $p < .01$

Table 7

Group Differences between NF1 and Control groups on the NEPSY-II and differences from normative mean.

	NF1				TD					
Subtest	*N*	*Mean*	*(SD)*		*N*	*Mean*	*(SD)*	*t*	*P*		*D*
Arrows	27	8.81	3.01		19	10.32	3.13	-1.64	.109		0.50
Auditory Attention											
Total Correct	25	8.92	2.84	+	20	9.65	2.03	-.967	.339		0.30
Combined	25	8.60	2.90		20	9.50	2.24	-1.14	.260		0.35
Fingertip Tapping											
Repetitions	26	11.00	2.21	+	23	11.91	1.88	-1.55	.129		0.45
Sequences	26	9.46	3.29		23	10.91	2.33	-1.76	.085		0.51
Dominant	26	10.27	2.56		23	11.43	1.85	-1.81	.077		0.53
Nondominant	26	9.69	2.71		23	11.00	1.62	-2.02	.050	*	0.59
Imitating Hand Positions	50	7.02	2.62	++	40	8.75	1.88	-3.51	.001	**	0.75
Statue	30	6.77	4.20	++	15	9.67	3.75	-2.26	.029	*	0.73
Visuomotor Completion											
Time	38	11.24	2.96	+	36	10.28	3.71	1.23	.222		0.29
Combined	38	7.63	3.47	++	35	9.66	3.55	-2.47	.016	*	0.59

Significantly different from normative data in one-sample t-test + $p < .05$; □ $p < .01$
Significant group differences * $p < .05$; ** $p < .01$

Table 8

Group Differences between NF1 and Control groups on the Experimental Executive Functioning Tasks.

	NF1			TD					
Task	*N*	*Mean*	*(SD)*	*N*	*Mean*	*(SD)*	*t*	*P*	*D*
A not B									
Total Correct	41	9.00	1.18	26	8.96	0.96	.139	.890	0.04
Correct Run	41	7.95	2.34	26	7.88	2.25	.115	.909	0.03
Total Perseverations	41	0.54	8.87	26	0.58	0.81	-.190	.850	0.01
Perseverative Run	41	0.41	0.63	26	0.46	0.65	-.293	.770	0.08
Delayed Alternation									
Total Correct	41	10.73	2.07	25	11.24	2.74	-.853	.397	0.22
Correct Run	41	4.85	3.11	25	6.16	4.78	-1.22	.231	0.35
Perseverative Run	41	1.54	0.74	25	1.46	0.81	.904	.370	0.11
DCCS									
Total Correct	49	13.71	7.51	32	17.09	5.12	-2.40	.019 *	0.51

Significant group differences * $p < .05$; ** $p < .01$

Table 9

Group Differences between NF1 and Control Groups on Parent-Report Measures and Differences from Normative Mean.

	NF1			TD						
Scale	*N*	*Mean*	*(SD)*	*N*	*Mean*	*(SD)*	*t*	*P*		*D*
Conners										
Opposition	49	51.36	10.05	39	52.75	11.05	-0.50	.619		0.13
Inattention	49	58.49	12.98 ++	39	53.10	12.40	1.99	.050	*	0.43
Hyperactivity	49	56.69	13.39 ++	39	50.90	11.71	2.15	.035	*	0.46
ADHD Index	49	57.14	11.02 ++	39	52.58	10.33	2.00	.049	*	0.43
KDBDS										
Inattention Count	50	2.78	2.80	40	0.95	1.65	3.86	< .001	**	0.78
Hyperactivity Count	50	3.30	2.58	40	1.75	2.11	3.07	.003	**	0.66
Total Symptom Count	50	6.08	4.90	40	2.70	3.44	3.83	< .001	**	0.79

Significantly different from normative data in one-sample t-test + $p < .05$; □ $p < .01$ for Conners scores only
Significant group differences * $p < .05$; ** $p < .01$

Table 10

Frequency of Performance 1 Standard Deviation or More Below the Mean on Academic Tasks.

Subtest	NF1	TD	df	Chi-square	p-value		Effect Size
Early Number Concepts	10/50	0/42	1, 92	9.42	.002	**	.320
Phonological Processing	7/27	1/26	1, 53	5.04	.025	*	.308
Rapid Naming	2/24	2/25	1, 49	.002	.966		.006
1+ Academic Difficulty	15/50	3/42	1, 92	7.58	.006	**	.287

* $p < .05$, ** $p < .01$

Table 11

Relations between Academic Performance and Demographic Variables in the NF and Control Groups.

Demographic Variable	Early Number Concepts			Phonological Processing			Rapid Naming		
	N	*Pearson*	*P*	*N*	*Spearman*	*P*	*N*	*Spearman*	*P*
SES									
NF	50	.102	.480	27	.196	.328	24	-.272	.199
Control	42	-.057	.721	25	.258	.213	24	.036	.869
Age									
NF	50	.139	.334	27	.388	.045 *	24	-.219	.303
Control	42	.048	.763	26	-.014	.947	25	-.209	.316
GCA									
NF	50	.521	< .001 **	27	.615	.001 **	24	.128	.552
Control	42	.436	.004 **	26	.413	.036 *	25	.069	.742

* p < .05; ** p < .01

Table 12

Relations between Neuropsychological Tasks and Phonological Processing in NF and Control Groups.

		NF1						TD				
Subtest	*IQ?*	*N*	*rho*	*P*		*partial*	*P*	*IQ?*	*N*	*rho*	*P*		*partial*	*P*
DAS-II														
Verbal Comprehension	++	27	.610	.001	**	.442	.035 *		27	.441	.021	**	--	--
Naming Vocabulary	++	27	.700	<.001	**	.361	.090		27	.404	.037	*	--	--
Picture Similarities	++	27	.477	.012	*	-.143	.514		27	.169	.399		--	--
Matrices	++	27	.278	.160		-.088	.689		27	.194	.332		--	--
Pattern Construction	++	27	.489	.010	**	.229	.294		27	.441	.021	*	--	--
Copying	++	27	.315	.109		-.163	.459		27	.277	.161		--	--
Digits Forward	++	27	.528	.005	**	.277	.211		27	.296	.134		--	--
Digits Backward	++	26	.759	<.001	**	.477	.025 *		25	.473	.017	*	--	--
Speed of Info. Proc.		23	.593	.003	**	(.582)	(.004) **		20	.298	.202		--	--
NEPSY-II														
Arrows		27	.251	.207		--	--	+	16	-.025	.921		-.066	.800
AA Total Correct		25	.151	.473		--	--		21	-.043	.853		--	--
AA Combined	+	25	.210	.313		.204	.376		20	.134	.572		--	--
FTT Repetitions		26	-.253	.212		--	--		23	.044	.842		--	--
FTT Sequences		26	.286	.156		--	--		23	-.169	.441		--	--
FTT Dominant		26	.184	.369		--	--		23	-.097	.660		--	--
FTT Nondominant		26	-.027	.896		--	--		23	-.082	.709		--	--
Imitating Hand Positions	+	27	.533	.004	**	.023	.951	+	25	.222	.287		-.321	.194
Statue		17	.166	.523		--	--		8	-.255	.543		--	--
VMP Completion Time		19	.228	.348		--	--		20	.139	.559		--	--

VMP Combined		19	.070	.775	--	--	21	.159	.502	--	--
Conners											
Opposition		27	-.151	.452	--	--	25	-.159	.447	--	--
Inattention		27	-.384	.048 *	--	--	25	-.054	.796	--	--
Hyperactivity		27	-.264	.184	--	--	25	.082	.696	--	--
ADHD Total		27	-.429	.026 *	--	--	25	-.126	.550	--	--
KDBDS											
IA Symptom Count		27	-.324	.099	--	--	24	-.418	.042 *	--	--
HI Symptom Count		27	-.366	.060	--	--	24	-.335	.109	--	--
Total Symptom Count		27	-.402	.038 *	--	--	24	-.256	.228	--	--
DCCS											
Total Correct Sorts	++	26	.524	.006 **	.040	.857	22	.225	.313	--	--
A not B											
Correct		20	.323	.165	--	--	14	.106	.719	--	--
Perseverative Run		20	-.115	.628	--	--	14	-.158	.590	--	--
Delayed Alternation											
Correct	++	20	.222	.346	-.205	.400	14	.211	.470	--	--
Perseverative Run	+	20	-.319	.171	-.101	.682	14	-.060	.840	--	--

Subtest correlated with IQ: + $p < .05$; ++ $p < .01$
Trend/significant relation with Phonological Processing: * $p < .05$; ** $p < .01$

Table 13

Relations between Neuropsychological Tasks and Rapid Naming in NF and Control Groups.

		NF1						TD				
Subtest	*IQ?*	*N*	*rho*	*P*	*partial*	*P*	*IQ?*	*N*	*rho*	*P*	*partial*	*P*
DAS-II												
Verbal Comprehension	++	24	.106	.620	.254	.242		26	.236	.245	--	--
Naming Vocabulary	++	24	.183	.392	-.060	.787		26	.039	.852	--	--
Picture Similarities	++	24	.124	.562	-.111	.613		26	-.014	.944	--	--
Matrices	++	24	.254	.249	.171	.436		26	-.032	.878	--	--
Pattern Construction	++	24	.054	.804	-.002	.993		26	-.024	.908	--	--
Copying	++	24	.147	.494	.012	.955		26	.223	.275	--	--
Digits Forward	++	24	-.248	.242	-.433	.056		26	-.195	.341	--	--
Digits Backward	++	23	.139	.528	.137	.564		25	.231	.266	--	--
Speed of Info. Proc.		21	.108	.642	--	--		20	.115	.628	--	--
NEPSY-II												
Arrows		24	.161	.453	--	--	+	18	.147	.548	.062	.806
AA Total Correct		22	.126	.576	--	--		21	.263	.249	--	--
AA Combined	+	22	.320	.147	.345	.125		20	.443	.050	--	--
FTT Repetitions		23	-.001	.997	--	--		22	.197	.379	--	--
FTT Sequences		23	.118	.591	--	--		22	.306	.165	--	--
FTT Dominant		23	-.008	.970	--	--		22	.270	.224	--	--
FTT Nondominant		23	.159	.467	--	--		22	.298	.178	--	--
Imitating Hand Positions	+	24	-.024	.913	-.183	.403	+	24	.226	.288	.067	.791
Statue		14	.530	.051	--	--		7	-.064	.892	--	--
VMP Completion Time		17	-.088	.736	--	--		20	-.085	.723	--	--

VMP Combined		17	.153	.557	--	--		20	.044	.854	--	--
Conners												
Opposition		24	.138	.521	--	--		24	-.031	.887	--	--
Inattention		24	-.167	.436	--	--		24	-.025	.908	--	--
Hyperactivity		24	.095	.660	--	--		24	-.219	.303	--	--
ADHD Total		24	.001	.997	--	--		24	-.108	.614	--	--
KDBDS												
IA Symptom Count		24	.038	.858	--	--		24	-.072	.743	--	--
HI Symptom Count		24	.251	.238	--	--		24	.169	.440	--	--
Total Symptom Count		24	.182	.395	--	--		24	.030	.440	--	--
DCCS												
Total Correct Sorts	++	24	.110	.607	-.014	.950		21	-.187	.417	--	--
A not B												
Correct		18	.035	.890	--	--		13	.365	.205	--	--
Perseverative Run		18	.146	.563	--	--		13	-.391	.187	--	--
Delayed Alternation												
Correct	++	18	.303	.222	.222	.392		13	-.051	.870	--	--
Perseverative Run	+	18	-.051	.840	-.195	.454		13	.132	.667	--	--

Subtest correlated with IQ: + $p < .05$; ++ $p < .01$
Trend/significant relation with Rapid Naming: * $p < .05$; ** $p < .01$

Table 14

Patterns of Cognitive Difficulties for NF Participants who had Difficulty with Phonological Processing in Comparison to the Full Sample.

Participant #	VC	NV	PS	PC	Mat	Cop	DF	DB	SIP
9003	Yes	--	--	--	Yes	Yes	--	Yes	n/a
9013	Yes	--	--	Yes	Yes	Yes	Yes	Yes	Yes
9018	--	--	--	--	--	--	--	Yes	--
9024	Yes	Yes	--	--	Yes	Yes	Yes	Yes	n/a
9028	Yes	Yes	Yes	--	Yes	Yes	Yes	--	--
9063	Yes	--	Yes	Yes	Yes	Yes	Yes	Yes	--
9065	--	--	--	--	--	Yes	Yes	--	Yes
PP Difficulty	5/7 71%	2/7 29%	2/7 29%	2/7 29%	5/7 71%	6/7 86%	5/7 71%	5/7 71%	2/5 40%
Full Sample (5-7 yr. olds)	6/27 22%	2/27 7%	5/27 19%	2/27 7%	9/27 33%	9/27 33%	7/27 26%	8/26 31%	2/23 9%

VC: Verbal Comprehension; NV: Naming Vocabulary; PS: Picture Similarities; PC: Pattern Construction; Mat: Matrices; Cop: Copying; DF: Recall of Digits Forward; DB: Recall of Digits Backward; SIP: Speed of Information Processing; PP: Phonological Processing; Yes: had difficulty with this subtest (operationalized as performance 1 or more standard deviations below the mean)

Table 15

Relations between Neuropsychological Tasks and Early Number Concepts in NF and Control Groups.

		NF1						TD				
Subtest	*IQ?*	*N*	*r*	*P*		*partial*	*P*	*IQ?*	*N*	*r*	*P*		*partial*	*P*
DAS-II														
Verbal Comprehension	++	50	.532	<.001	**	.387	.006 **		42	.072	.650		--	--
Naming Vocabulary	++	50	.379	.007	**	.187	.199		42	.214	.173		--	--
Picture Similarities	++	50	.473	.001	**	.304	.034 *		42	.455	.002	**	--	--
Matrices	++	42	.128	.421		-.158	.323		39	.164	.319		--	--
Pattern Construction	++	50	.269	.059		.038	.794		42	.502	.001	**	--	--
Copying	++	42	.385	.012	*	.186	.245		39	.083	.617		--	--
Digits Forward	++	50	.468	.001	**	-.049	.827		41	.316	.044		--	--
Digits Backward	++	26	.611	.001	**	.169	.453		25	.618	.001	**	--	--
Speed of Info. Proc.		23	.069	.753		--	--		19	.330	.168		--	--
NEPSY-II														
Arrows		27	.543	.003	**	(.497)	(.010) **	+	19	.119	.639		-.109	.678
AA Total Correct		25	.348	.088		--	--		20	.236	.315		--	--
AA Combined	+	25	.354	.082		.219	.303		20	.384	.095		--	--
FTT Repetitions		26	-.350	.080		--	--		23	-.272	.209		--	--
FTT Sequences		26	.340	.089		--	--		23	-.184	.400		--	--
FTT Dominant		26	-.019	.927		--	--		23	-.151	.490		--	--
FTT Nondominant		26	.029	.890		--	--		23	-.315	.143		--	--
Imitating Hand Positions	+	50	.263	.065		.076	.606	+	40	.367	.020	*	.243	.141
Statue		30	.233	.216		--	--		15	-.003	.992		--	--
VMP Completion Time		38	-.146	.383		--	--		35	.022	.900		--	--

VMP Combined		38	.108	.518	--	--	35	-.104	.551	--	--
Conners											
Opposition		49	-.162	.267	--	--	40	-.173	.286	--	--
Inattention		49	-.158	.277	--	--	40	-.388	.013 *	--	--
Hyperactivity		49	-.112	.443	--	--	40	-.247	.124	--	--
ADHD Total		49	-.140	.336	--	--	40	-.317	.047 *	--	--
KDBDS											
IA Symptom Count		50	-.035	.809	--	--	40	-.450	.004 **	--	--
HI Symptom Count		50	-.090	.535	--	--	40	-.150	.356	--	--
Total Symptom Count		50	-.067	.643	--	--	40	-.307	.054	--	--
DCCS											
Total Correct Sorts	++	49	.408	.004 **	.297	.063	32	.269	.137	--	--
A not B											
Correct Run		41	.160	.317	--	--	26	-.030	.884	--	--
Perseverative Run		41	-.039	.809	--	--	26	-.098	.634	--	--
Delayed Alternation											
Correct Run	++	41	.186	.244	.083	.612	25	.446	.025 *	--	--
Perseverative Run	+	41	-.355	.023 *	-.285	.075	25	-.100	.633	--	--

Subtest correlated with IQ: + $p < .05$; ++ $p < .01$
Trend/significant relation with Phonological Processing: * $p < .05$; ** $p < .01$
Pearson correlations: N = 30+
Spearman's rho: N < 30

Table 16

Patterns of Cognitive Difficulties for NF Participants who had Difficulty with Early Number Concepts.

Participant #	VC	NV	PS	PC	Mat	Cop	DF	DB	SIP
9013	Yes	--	--	Yes	Yes	Yes	Yes	Yes	Yes
9024	Yes	Yes	--	--	Yes	Yes	Yes	Yes	n/a
9028	Yes	Yes	Yes	--	Yes	Yes	Yes	--	--
9030	Yes	--	Yes	Yes	n/a	n/a	Yes	n/a	n/a
9045	--	--	--	--	--	--	--	n/a	n/a
9046	Yes	--	Yes	--	Yes	Yes	Yes	n/a	n/a
9053	--	--	--	Yes	--	Yes	Yes	n/a	n/a
9060	--	--	--	--	--	Yes	Yes	n/a	n//a
9067	--	--	--	Yes	--	Yes	--	n/a	n/a
9068	--	--	--	--	--	Yes	Yes	n/a	n/a
ENC Difficulty	5/10 50%	2/20 20%	3/10 30%	4/10 40%	4/9 44%	8/9 89%	8/10 80%	(2/3) (66%)	(1/3) (33%)
Full Sample	11/50 22%	3/50 6%	8/50 16%	9/50 18%	13/42 31%	16/42 38%	15/50 30%	8/26 31%	2/23 9%

VC: Verbal Comprehension; NV: Naming Vocabulary; PS: Picture Similarities; PC: Pattern Construction; Mat: Matrices; Cop: Copying; DF: Recall of Digits Forward; DB: Recall of Digits Backward; SIP: Speed of Information Processing; ENC: Early Number Concepts; Yes: had difficulty with this subtest (operationalized as performance 1 or more standard deviations below the mean)

Kelly M. Janke
VITA

Business Address:
Children's Hospitals and Clinics of Minnesota
Psychology, 17-217
55404
2525 South Chicago Avenue
Minneapolis, Minnesota
612-813-6870
kelly.janke@childrensmn.org

Home Address:
1110 E. 15th St.
Minneapolis, MN

(269) 290-3670

Education

Expected Ph.D.	*University of Wisconsin-Milwaukee*, Milwaukee, WI Program: Clinical Psychology Cumulative GPA: 4.0 Degree Expected: May, 2013
M.S.	*University of Wisconsin-Milwaukee*, Milwaukee, WI Program: Clinical Psychology GPA: 4.0 Degree Awarded: December, 2009
B.A.	*Calvin College*, Grand Rapids, MI Program: Psychology Degree Awarded: May 2007 GPA: 3.98

Awards and Honors

University of Wisconsin – Milwaukee

- UWM Graduate School Dissertation Fellowship (2011– 2012)
- Psi Chi Regional Research Award (2010)
- UWM Graduate School Fellowship (2009 – 2010)
- Graduate School Travel Award (2008)
- Student Association Group Travel Grant (2007)
- Chancellor Fellowship (2007 – 2009)

Calvin College

- Datatel Scholars Foundation Scholarship (2005 –2006)
- Blake, Elise and Macy Morren Memorial Nursing Scholarship (2005 – 2006)
- Academic All-American (2005)
- Academic All-MIAA (2004 – 2007)
- Deans List (2003 – 2007)

Service and Leadership

- Clinical Training Committee student representative (2008 – 2010)
- Curriculum Review Committee student representative (2008 – 2013)
- Division 40 Association of Neuropsychology Students in Training Chapter Representative (2009 – 2012)

Professional Activities

- Ad hoc co-reviewer with Bonita Klein-Tasman, Ph.D. for *Journal of Developmental and Physical Disabilities*
- Ad hoc co-reviewer with Bonita Klein-Tasman, Ph.D. for *Clinical Neuropsychologist*

Membership in Professional Associations

- American Psychological Association
- International Neuropsychological Society
- Midwest Neuropsychological Group
- Psi Chi
- Sigma Xi
- Society of Pediatric Psychology APA Division 54
- UW-Milwaukee Health Psychology Graduate Students' Club

Professional Development

Neuroanatomical Dissection: Human Brain and Spinal Cord (2012)
Marquette University, College of Health Sciences

- Completion of 3-day functional neuroscience course including dissection laboratories

Microsoft Access Short Course (2011)
University of Wisconsin – Milwaukee

- Completion of Access 2010 workshop on database management and data reporting

Clinical Experience

Predoctoral Psychology Intern (2012-2013)
Children's Hospitals and Clinics of Minnesota
Director of Clinical Training: Sharon Berry, Ph.D.
Primary Supervisors: Karen Wills, Ph.D., ABPP, Paula Pitterle, Ph.D., Sherrie Kamm, Ph.D.

- Responsibilities: Neuropsychological assessment including intakes, test administration and scoring, report writing, and feedback; consultation to pediatric

medical services; participation on the hematology-oncology psychosocial team; therapy for children, adolescents, and families; participation in professional development activities (grand rounds, didactics, journal club, community presentations)

Graduate Assistant (2007 – present)
University of Wisconsin—Milwaukee, Child Neuropsychology Clinic
Supervisor: Bonnie Klein-Tasman, Ph.D.

- Responsibilities: Neuropsychological evaluations for children and adolescents with learning disabilities, ADHD, autism spectrum disorders, and other genetic and neurodevelopmental disorders; scoring; report writing; feedback; and supervision of research assistants

Pediatric Neuropsychology Psychometrist (2011 – 2012)
Medical College of Wisconsin – Neurology/Neuropsychology Department
Supervisors: Amy Heffelfinger, Ph.D., ABPP, Jennifer Koop, Ph.D., ABPP, Kristin Phillips Smith, Ph.D., Robert Newby, Ph.D., ABPP

- Responsibilities: Neuropsychological evaluations for children and adolescents, supervision of practicum students, observation of parent-child interactions, scoring, and report writing

Pediatric Neuropsychology Extern (2010 – 2011)
Medical College of Wisconsin – Neurology/Neuropsychology Department, Preschool and Infant Neuropsychological Testing (PINT) Clinic
Supervisors: Amy Heffelfinger, Ph.D., ABPP, Jennifer Koop, Ph.D., ABPP, Kristin Phillips Smith, Ph.D.

- Responsibilities: Neuropsychological evaluations, observation of parent-child interactions, scoring, report writing, participation in weekly group supervision and MCW didactic opportunities

Adult Neuropsychology Extern (2010 – 2011)
Medical College of Wisconsin – Neurology/Neuropsychology Department, Adult Neuropsychology Clinic
Supervisors: Sara Swanson, Ph.D., ABPP, David Sabsevitz, Ph.D., ABPP, Julie Bobholz, Ph.D., ABPP, Jennifer Geiger, Ph.D.

- Responsibilities: Neuropsychological evaluations for individuals with TBIs, dementias, movement disorders, cancer, and comorbid psychiatric disorders; consultation with multidisciplinary teams; scoring; report writing

Student Therapist (2009 – 2012)
University of Wisconsin—Milwaukee, Psychology Clinic
Supervisors: Doug Woods Ph.D., Shawn Cahill, Ph.D., Robyn Ridley, Ph.D.

- Training in adult and child outpatient therapy. Presenting concerns include: mood disorders, anxiety and repetitive behavior disorders including Obsessive Compulsive Disorder, tic disorders, and Trichotillomania. Interventions include: exposure/response prevention, habit reversal training, cognitive-behavioral

therapy, parent training, designing and implementing a group therapy treatment program for children with Trichotillomania and their parents.

Empirically Supported Interventions Practicum Student (2008 – 2009)
University of Wisconsin—Milwaukee, Psychology Clinic
Supervisor: Shawn Cahill, Ph.D.

- Training: APA-Division 12 Empirically Supported Interventions including exposure and response prevention, stress and anxiety management, structured problem solving, cognitive restructuring, and behavioral activation strategies

Clinical Psychology Assessment Trainee (2008 – 2009)
University of Wisconsin—Milwaukee, Psychology Clinic
Supervisors: David Osmon, Ph.D., ABPP; Bonnie Klein-Tasman, Ph.D.

- Training: Administration of diagnostic, psychoeducational, neuropsychological, and projective assessment batteries; scoring; report writing; classroom observation; and feedback

Clinical Psychology Practicum Student (2007 – 2008)
University of Wisconsin—Milwaukee, Psychology Clinic
Supervisors: David Osmon, Ph.D., ABPP; Bonnie Klein-Tasman, Ph.D.

- Training: Clinical interviews, report writing, and diagnostic and psychoeducational assessments.

Mental Health Nursing Student (2005)
Supervisor: Margaret Harvey, R.N., Ph.D.

- Hope Behavioral Network, Grand Rapids, MI. Duties: Constructing individualized psychiatric care-plans for residents and leading educational group sessions.
- Forest View Hospital, Grand Rapids, MI. Duties: Interviewing acute patients with psychiatric diagnoses on the adult and adolescent unit, creating care plans, and discussing discharge needs.

<u>Supervision Experience</u>
University of Wisconsin-Milwaukee

- Psychology 821: Practicum in Assessment (Fall 2010 – Spring 2011). Supervision of graduate students completing psychodiagnostic and neuropsychological assessments.
- Training and supervision of undergraduate research assistants in neuropsychological assessment

Medical College of Wisconsin

- Supervision of graduate student externs in the Preschool and Infant Neuropsychological Testing Clinic

<u>Publications</u>

Janke, K. M. & Klein-Tasman, B. P. (in press). Intellectual disability syndromes. S. J. Hunter and E. P. Sparrow (Eds.), *Executive Function and Dysfunction: Identification, Assessment and Treatment* (pp. 109-122). New York: Cambridge University Press.

Janke, K. M. & Klein-Tasman, B. P. (2011). Down Syndome. In J. S. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of Clinical Neuropsychology.* New York: Springer.

Klein-Tasman, B. P. & **Janke, K. M.** (2010). Intellectual disability across the lifespan. In S. J. Hunter and J. Donders (Eds.), *Principles and practice of lifespan developmental neuropsychology* (pp. 221-238). New York: Cambridge University Press.

Donders, J. & **Janke, K. M.** (2008). Criterion validity of the WISC-IV after pediatric traumatic brain injury. *Journal of the International Neuropsychological Society, 14(04),* 651-655.

Manuscripts and Chapters under Review

Klein-Tasman, B. P., **Janke, K. M.**, Luo, W., Casnar, C. L., Hunter, S. J., Tonsgard, J., Trapane, P., van der Fluit, F., & Kais, L. A. (submitted). *Cognitive and behavioral phenotype of young children with neurofibromatosis-1: An examination of psychosocial and inter- and intra-individual patterns of cognitive functioning.*

Manuscripts in Preparation

Janke, K. M., Klein-Tasman, B. P., Garwood, M. M., Davies, W. H., Holman, K. S. (in preparation). *Contributions of executive functioning to academic performance in adolescents with neurofibromatosis-1.*

Janke, K. M., Klein-Tasman, B. P., Hunter, S. J., Tonsgard, J., Casnar, C. L., & Kais, L. A. (in preparation). *Early indicators of academic difficulties in children with neurofibromatosis type 1.*

Janke, K. M., Klein-Tasman, B.P., Berlin, K., Davies, W. H., & Kais, L. A. (in preparation). *Intellectual, neuropsychological, and academic functioning of individuals with neurofibromatosis-1: A meta-analysis.*

Published Abstracts

Janke, K. M., Klein-Tasman, B. P., Hunter, S. J., Tonsgard, J. H., & Schuett, M. J. (2012). Relations between Cognitive Functioning and Early Academic Skills in Preschool-Aged Children with NF1 [Abstract]. *Journal of the International Neuropsychological Society, 1 (S1),* 45. DOI: S1355617712000537

Kais, L. A., **Janke, K. M**., & Klein-Tasman, B. P. (2011). Inattention and Impulsivity in Young Children with Neurofibromatosis-1 [Abstract]. *Journal of the International Neuropsychological Society, 17(S1)*, 126. DOI: 10.1017/S1355617711000415

Janke, K. M., Holman, K. S., Klein-Tasman, B. P., & Garwood, M. M. (2010). Role of Executive Functioning in Academic Achievement for Adolescents with NF1 [Abstract]. *Journal of the International Neuropsychological Society, 16(S1)*, 209. DOI: 10.1017/S1355617710000226

Janke, K. M., Kais, L. A., & Klein-Tasman, B. P. (2010). Cognitive and Early Learning Profile of Preschool Age Children with NF1 [Abstract]. *Journal of the International Neuropsychological Society, 16(S1)*, 209. DOI: 10.1017/S1355617710000226

Janke, K. M., Magargee, E. M., & Klein-Tasman, B. P. (2009). "Hot" and "Cool" Executive Functioning in Children and Adolescents with Williams Syndrome [Abstract]. *Journal of the International Neuropsychological Society, 15(S1)*, 111. DOI: 10.1017/S1355617709090420

Janke, K. M., Phillips, K. D. & Klein-Tasman, B. P. (2008). Question-Asking Behavior in Children and Adolescents with Williams Syndrome: Anticipation of Positive and Negative Events. Frontiers in Human Neuroscience. Conference Abstract: 12th International Professional Conference on Williams Syndrome. DOI: 10.3389/conf.neuro.09.2009.07.041

<u>Paper Presentations</u>

Klein-Tasman, B. P., **Janke, K. M**., Trapane, P. (2010, February). Interdisciplinary Pediatric Behavioral Health Research Conference: Milwaukee, WI.

Janke, K. M. & Klein-Tasman, B. P (2009, April). *An examination of "hot" and "cool" executive functioning in children and adolescents with Williams syndrome.* Presented at the Association for Graduate Students in Psychology, Milwaukee, WI.

Zwier-Janke, K. M. (2006, May). *Differences in the frequency of binge drinking between athletes and non-athletes.* Paper presented at the Calvin College Undergraduate Research Conference, Grand Rapids, MI.

<u>Presentations at National/International Meetings</u>

Janke, K. M., Casnar, C., van der Fluit, F., Haberman, D.A., Brei, N. G., Hunter, S. J., & Klein-Tasman, B. P. (2013, February). Concurrent relations between early neuropsychological and academic skills in young children with NF1 and typically developing peers. Poster accepted for presentation at the 41st Annual Meeting of the International Neuropsychological Society: Waikoloa, Hawaii.

Walther, M. R., Bauer, C. C., **Janke, K. M.**, Woods, D. W., Flessner, C. A., Franklin, M. E., & Golomb, R. (2012, November). *Trichotillomania in school-aged children: acceptability, feasibility, and preliminary efficacy of behavior therapy*. Poster session presented at the 46th Annual Convention for the Association for Behavioral and Cognitive Therapies, National Harbor, MD.

Klein-Tasman, B. P., Schuett, M. J., Kais, L. A., Hunter, S. J., Tonsgard, J., **Janke, K. M.**, & Casnar, C. L. (2012, June). Parent Perspectives on Executive Functioning in Preschoolers with NF1: Comparison to Typically Developing Controls and Teacher Ratings. Poster session presented at the Annual Neurofibromatosis Conference: New Orleans, Louisiana.

Klein-Tasman, B. P., Kais, L., Trapane, P., Hunter, S., Tonsgard, J., & **Janke, K. M.** (2011, June). *Attention and Inhibition in Young Children with NF1: A Multimethod Study*. Poster session presented at the Annual Neurofibromatosis Conference: Jackson Hole, Wyoming.

Klein-Tasman, B. P., Berka, S., Kais, L. A., Trapane, P., Tonsgard, J., Hunter, S., & **Janke, K.** (2011, June). *Social Skills in Young Children with NF-1: Relations to Intellectual Functioning and Attention Problems.* Poster session presented at the Annual Neurofibromatosis Conference: Jackson Hole, Wyoming.

Thomspon, S. R., Klein-Tasman, B. P., Woods, D. W., & **Janke, K. M.** (2010, November). *Exploring the Utility of a Functional Analysis and Functional Interview in Constructing an Intervention to Reduce Question-Asking in Williams Syndrome.* Poster session presented at the 44th Annual Convention of the Association for Behavioral and Cognitive Therapies: San Francisco, CA.

van der Fluit, F. D., **Janke, K. M.,** Erdman, E. K., & Klein-Tasman, B. P. (2010, May). *The Use of New ADOS Diagnostic Algorithms in Young Children with Williams Syndrome.* Poster session presented at the 9th International Meeting for Autism Research: Philadelphia, PA.

Janke, K. M., Kais, L. A., Fine, K. M., Klein-Tasman, B. P., Davies, W. H., Trapane, P. (2009, June). *Early Indicators of Cognitive and Learning Difficulties in Children with NF-1.* Poster session presented at the Annual Neurofibromatosis Conference: Portland, OR.

Janke, K. M., Holman, K. S., Garwood, M. M., Klein-Tasman, B. P., Davies, W. H., Trapane, P. (2009, June). *Contribution of Executive Functioning to Academic*

Achievement in Adolescents with NF-1. Poster session presented at the Annual Neurofibromatosis Conference: Portland, OR.

Fine, K. M., Klein-Tasman, B. P., **Janke, K. M**., Magargee, E. T., Davies, W. H., Trapane, P. (2009, June). *Adaptive and Psychosocial Functioning of Young Children with NF-1: Preliminary Findings.* Poster session presented at the Annual Neurofibromatosis Conference: Portland, OR.

Janke, K. M. & Donders, J. (2008, June). *Validity of the WISC-IV after pediatric traumatic brain injury.* Poster session presented at the American Academy of Clinical Neuropsychology Conference: Boston, MA.

Janke, K. M., Phillips, K. D., & Klein-Tasman, B. P. (2008, April). *Anticipatory anxiety and question-asking behavior in children and adolescents with Williams syndrome*. Poster session presented at the Child Health Psychology Conference: Miami, FL.

Presentations at Regional Meetings

Berka, S. M., **Janke, K. M.,** Kais, L.A., & Klein-Tasman, B. P. (2011, February) *Social Skills and Intelligence in Young Children with NF-1*. Poster submitted for presentation at the Interdisciplinary Pediatric Behavioral Health Research Conference: Milwaukee, WI.

Kais, L. A., **Janke, K. M.**, & Klein-Tasman, B. P. (2010, April). *Inhibition and Attention in Young Children with NF-1*. Poster session presented at the Midwest Psychological Association: Chicago, IL.

Dziadosz, J. H., **Janke, K. M.,** & Klein-Tasman, B. P. (2010, March). *The Relationship between Intellectual Ability and Executive Functioning in Young Children with NF1*. Poster session presented at the Wisconsin Psychological Association Convention: Madison, WI.

Kais, L. A., **Janke, K. M.**, Klein-Tasman, B. P., & Trapane, P. (2010, February). *Inattention and Impulsivity in Young Children with NF-1*. Poster session presented at the Interdisciplinary Pediatric Behavioral Health Research Conference: Milwaukee, WI.

Research Experience

Behavior Therapy for Pediatric Trichotillomania
Role: Research therapist (2011-2012)
University of Wisconsin—Milwaukee, Psychology Clinic

- Project description: Effectiveness study of a family-based treatment for young children (ages 5-9) with Trichotillomania. The manual includes psychoeducation, differential attention, reward systems, and modified habit reversal training.

- Responsibilities: Implementation of study manual, scoring questionnaire data, scheduling and case management.

Patience and Planning in Typically Developing Children
Role: Graduate Research Assistant (2009-2012)
University of Wisconsin—Milwaukee, Child Neurodevelopment Research Lab

- Project description: Examination of developing patience and planning, cognitive functioning, and fine-motor skills in typically developing children; comparison group for research about patience and planning in children with NF1 and Williams syndrome.
- Responsibilities: Administration of neuropsychological battery; scoring; training of undergraduate research assistants.

Intellectual, Neuropsychological, and Academic Functioning of Individuals with Neurofibromatosis-1: A Meta-Analysis
Role: Co-investigator (2008-present)
University of Wisconsin—Milwaukee

- Project description: A meta-analysis investigating the extent to which those with NF1 experience intellectual, academic, and neuropsychological difficulties compared to controls, and identifying potential moderating variables.
- Responsibilities: Literature review and data analysis; manuscript preparation

Association between Headache Experiences and Individual and Family Functioning in Adolescents with Neurofibromatosis-1
Role: Graduate Research Assistant (2007-present)
Children's Hospital of Wisconsin; University of Wisconsin—Milwaukee

- Project description: Examination of how headache pain influences the social, emotional, and academic functioning of adolescents with Neurofibromatosis-1
- Responsibilities: Administration of neuropsychological battery; scoring; data analysis; manuscript preparation

Anticipatory Anxiety and Question-Asking Behavior in Children and Adolescents with Williams Syndrome
Role: Graduate Research Assistant (2007-2012)
University of Wisconsin—Milwaukee, Child Neurodevelopment Research Lab

- Project description: Examination of repetitive question-asking and anticipatory anxiety related to both positive and negative events
- Responsibilities: Administration of neuropsychological battery; data analysis; development of an online parent measure to examine anticipatory anxiety and question-asking behavior in children and adolescents with Williams Syndrome.

Emotion Regulation and Dysregulation in Children and Adolescents with Williams Syndrome
Role: Graduate Research Assistant (2007-2009)
University of Wisconsin—Milwaukee, Child Neurodevelopment Research Lab

- Project description: Examination of the relationship between emotion regulation and cognitive abilities, behavior, and executive functioning
- Responsibilities: Administration of neuropsychological battery; scoring

Early Indicators of Emotional, Cognitive, and Learning Difficulties in Neurofibromatosis Type 1
Role: Graduate Research Assistant; Study Coordinator (2007-present)
University of Wisconsin—Milwaukee, Child Neurodevelopment Research Lab

- Project description: A longitudinal study aimed at characterizing the cognitive and behavioral phenotype of young children with Neurofibromatosis-1 as well as identifying risk factors of later learning or emotional problems that allow to early intervention
- Responsibilities: Administration of neuropsychological battery; scoring; report writing; data analysis; preparation of grant proposals; training of undergraduate research assistants; manuscript preparation

Neuropsychology Intern (2006)
Mary Free Bed Rehabilitation Hospital
Supervisor: Jacobus Donders, Ph.D., ABPP

- Project description: Examination of the validity and clinical utility of using neuropsychological measures such as the WISC-IV to assess the functioning of individuals after traumatic brain injury.
- Responsibilities: Data entry and analysis; manuscript preparation

Research Assistant (2004)
Supervisor: Jeff Tatum, J.D.

- Responsibilities: Researched and collected legal data concerning the Terri Schiavo case to examine how bioethics and related laws change over time.

<u>Teaching Experience</u>

University of Wisconsin-Milwaukee

- Psychology 260 Child Psychology Instructor (Spring 2012)
- Guest Lecturer for Psychology 260: Child Psychology (Spring 2010, Summer 2010, Spring 2011, Summer 2011)
- Guest Lecturer for Psychology 801: 1st year Practicum (Fall 2008, Fall 2009)
- Teaching Assistant for Psychology 260: Child Psychology (Fall 2007 – Spring 2008). Taught topics in child development at weekly discussion sections, developed and administered quizzes and exams, assisted with grading.

Calvin College

- Anatomy and physiology tutor