August 2019

A Longitudinal Investigation of Social Functioning in Children with Neurofibromatosis Type 1

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A LONGITUDINAL INVESTIGATION OF SOCIAL FUNCTIONING IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1

by

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A Thesis Submitted in

Partial Fulfillment of the

Requirements for the Degree of

Master of Science

in Psychology

at

The University of Wisconsin, Milwaukee

August 2019

ABSTRACT

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The University of Wisconsin – Milwaukee, 2019
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Social difficulties are commonly reported by parents and teachers of children with neurofibromatosis type 1 (NF1) and can impact a child's social relationships. Investigations of social functioning in children with NF1 during early childhood are scarce, with most studies focusing on school age. This study aims to characterize the emergence of social skills challenges for children with NF1, with a special focus on the stability of social skills longitudinally and the interrelations of social skills with ADHD symptomatology and cognitive function. Participants included children with NF1 who were assessed longitudinally during early childhood from the ages of 3-6 years (T1; n = 50; *M*= 3.96, *SD*= 1.05) and from early childhood to school age (n = 25) and their parents. Forty children (T2; ages 9-13; *M*= 10.90, *SD*= 1.59) were assessed during school age. Young children and school age children with NF1 experienced social skills difficulties in comparison to the normative mean. Social skills were relatively stable throughout early childhood and school age with no differences in mean social skills across age. Social skills at the end of early childhood predicted school age social skills. ADHD symptomatology showed significant negative relations with social skills concurrently and early childhood inattentive symptoms predicted school age social skills. GCA showed a weak relation to social skills during early childhood. Cognitive functioning was not related to social skills concurrently during school

age or across time. Overall, these findings contribute to the limited NF1 social functioning literature, especially in early childhood, and help provide a target for early and effective intervention.

TABLE OF CONTENTS

I. Introduction....1
Behavioral Phenotype of NF1....2
Social Functioning in NF1....4
Relations of ADHD Symptomatology....6
Relations of Cognitive Function....7
Study Rationale....9

II. Methods....10
Participants....10
Procedures....10
Measures....11

III. Research Questions and Analytic Strategy....14
Research Question 1....14
Research Question 2....16

IV. Results....17
Individual Differences....18
Emergence and Stability of Social Difficulties....18
Relations with Social Functioning....20
Attrition....21

V. Discussion....22
Prevalence of Social Difficulties....23
Relations of Social Functioning....29
Limitations and Future Directions....32

VI. Conclusions....34

References....47

LIST OF FIGURES

Figure 1. Social functioning compared to normative data.....36

LIST OF TABLES

Table 1. Studies in the area of social functioning in children with NF1 37

Table 2. Summary of number of participants by age during school age 41

Table 3. Summary of young children by age and visit number.....42

Table 4. Participant demographic data.....43

Table 5. Descriptive statistics for early childhood and school age.....44

Table 6. Descriptive statistics by age group for longitudinal participants.....45

Table 7. Correlations with ADHD symptomatology and cognitive function 46

INTRODUCTION

Parents and teachers of children with neurofibromatosis type 1 (NF1), a genetically-based neurodevelopmental disorder, frequently report difficulties with social functioning (Barton & North, 2004; Noll et al., 2007; Huijbregts & de Sonneville, 2011; Huijbregts et al., 2015; Loitfelder et al., 2015). Literature within the typically developing child population evidences the impact of poor social skills on a child's social relationships and school outcomes. Poorly accepted children are reportedly lonelier than other children and display particular behavioral characteristics such as being shyer, less prosocial, more aggressive, and more disruptive than their peers (Cassidy & Asher, 1992). Buhs and Ladd (2001) found that socially rejected children were more likely to be treated poorly by peers, report more loneliness, have less classroom participation and express desires to avoid school, highlighting the impact of social functioning on social and academic outcomes. Relevant to the longitudinal nature of social functioning, early social difficulties are associated with poor peer acceptance, social isolation and perception of social incompetence during middle childhood (Hymel, Rubin, Rowden & LeMare, 1990). Specifically, children who perceive themselves as socially incompetent and are perceived by peers as unpopular, sensitive and isolated during early childhood have been found to experience greater loneliness in middle childhood (Hymel et al., 1990). Additionally, children who experience social difficulties such as making friends or getting along with peers are at risk for later conduct problems, mental health problems and substance abuse (Bierman & Wargo, 1995; Coie, Lochman, Terry & Hyman, 1992; Boivin, Hymel & Bukowski, 1995; Woodward & Fergusson, 1999). Relationships between social skills and academic achievement have also been noted in the literature such that children with early peer relationship problems showed increased risk for under-achievement and school-related difficulties (Ladd, 1990; Woodward & Fergusson,

2000; Buhs & Ladd, 2001; DeRosier & Lloyd, 2010; Caemmerer & Keith, 2015). Given that social difficulties are commonly reported by parents and teachers of children with NF1, examining social functioning in children with NF1, especially using a longitudinal design, may provide data that helps to pinpoint an appropriate age for intervention and to mitigate potential negative outcomes.

Recent examinations of social functioning in children with NF1 have indicated elevated levels of difficulty compared to normative data and unaffected controls. While some studies have included children in middle childhood through late childhood and adolescence, detailed characterization of social skills in early childhood has not been explored. This study will comprehensively examine and characterize the emergence and stability of social skills challenges in young children and school age children with NF1 as well as identify the developmental trajectory of social skills into the school age years. A further aim of this research is to examine the relations of ADHD symptomatology and cognitive functioning with social skills, due to the lack of literature and inconsistent findings in the literature, respectively. To emphasize the importance of the current study, I will first briefly describe the behavioral phenotype associated with NF1. Second, I will review the current literature on social functioning of children with NF1. Third, I will describe the relation between ADHD symptomatology and social functioning, as attention deficits are commonly observed in children with NF1. Lastly, I will discuss relevant literature among children with NF1 on the association of cognitive and social functioning.

Behavioral Phenotype of NF1

NF1 is an autosomal dominant genetic disorder with a prevalence rate of 1 in 3,500 births (Huson & Hughes, 1994). NF1 is caused by a genetic mutation or a deletion of the NF1-gene, occurring on the long arm of chromosome 17q11.2. The NF1 gene is responsible for encoding

the tumor suppressor protein, neurofibromin (Friedman, 1999). Two or more of the following symptoms are required to meet diagnostic criteria: (1) 6 or more café au lait spots, (2) skinfold freckling, (3) 2 or more cutaneous neurofibromas, (4) a plexiform neurofibroma, (5) 2 or more iris Lisch nodules, (6) an optic glioma, (7) a characteristic body lesion, or (8) a first degree relative with NF1 (National Institutes of Health, 1987). The manifestations of NF1 are highly variable and include a number of medical, cognitive and psychosocial difficulties. Medical problems include cardiovascular abnormalities such as congenital heart disease, vasculopathy and hypertension (Nguyen et al., 2013), orthopedic problems, headaches, and epilepsy (Tonsgard, 2006). In addition to medical problems, cognitive difficulties can include visuospatial and visuomotor deficits such as fine and gross motor coordination problems (Johnson et al., 2010; Lorenzo, Barton, Acosta & North, 2011), delayed language skills (Lorenzo et al., 2011), learning difficulties associated with a lowering of IQ and problems with academic achievement (Hyman, Shores & North, 2006). There is significant symptom overlap of NF1 with other disorders such as attention-deficit hyperactivity disorder (ADHD) (Koth, Cutting & Denckla, 2000; Kayl, Moore, Slopis, Jackson & Leeds, 2000; Mautner, Kluwe, Thakker & Leark, 2002) and learning disorders (Hyman et al., 2006) as well as an association with autism spectrum disorders (ASD) (Garg et al., 2013a; Plasschaert et al., 2014). Investigations of general quality of life among children with NF1 have shown significantly lower scores than normative data in the preschool years (Oostenbrink et al., 2007), school age and adolescent years (Graf, Landolt, Mori & Boltshauser, 2006; Krab et al., 2009) and adults (Wolkenstein, Zeller , Revuz, Ecosse & Leplège, 2001; Page et al., 2006).

Social Functioning in NF1

Previous research about children with NF1 indicates that impairments in social functioning are commonly reported by both parents and teachers. Table 1 summarizes the current literature on social functioning in children with NF1. Broadly, children with NF1 have poorer social functioning, based on self and parent report, compared to unaffected controls (Allen, Willard, Anderson, Hardy & Bonner, 2016; Cipolletta, Spina & Spoto, 2017). Specifically, children with NF1 show difficulties in social skills and have poorer social outcomes in comparison to same-aged peers (Barton & North, 2004; Huijbregts & de Sonneville, 2011; Huijbregts et al., 2015; Loitfelder et al., 2015). In a study conducted by Barton and North (2004), social skills and social outcomes were investigated for children with NF1 as a group as well as compared to unaffected siblings. Social skills were assessed using the Social Skills Rating System (SSRS) while social outcomes were evaluated with the Child Behavior Checklist (CBCL) and Teacher's Report Form (TRF). Children with NF1 had poorer social skills compared to normative data based on parent and teacher report and had stronger social skills compared to normative data based on self-report. Higher ratings of social skills were correlated with less social problems and increased social competence for children with NF1 and their unaffected siblings. This study also found that children with NF1 have poorer social outcomes compared to unaffected siblings including more social problems and less social competence (Barton & North, 2004). In similar studies using the SSRS, children with NF1 display poorer social skills compared to unaffected controls (Loitfelder et al., 2015; Huijbregts & de Sonneville, 2011; Huijbregts et al., 2015). Additionally, children with NF1 display more social problems compared to unaffected controls (Johnson, Saal, Lovell, & Schorry, 1999; Dilts et al., 1996; Loitfelder et al., 2015; Huijbregts et al., 2015; Allen et al., 2016; Cipolletta et al., 2017) as well

as normative data (Johnson et al., 1999; van der Vaart et al., 2016) and have less social competence compared to unaffected controls (Johnson et al., 1999; Lewis, Porter, Williams, North & Payne, 2016). Parents reported a higher than expected proportion of above average social problems for children with NF1 using normative data (Dilts et al., 1996). Relevant to the longitudinal nature of the proposed investigation, one study found that older individuals with NF1 report more effects on their social functioning than younger individuals with NF1 (Wolkenstein et al., 2001), providing support for greater concern regarding social difficulties with age.

In contrast, there is some available literature to suggest that children with NF1 do not have impairments in social functioning (Dilts et al., 1996; Barton & North, 2004; Klein-Tasman et al., 2014; Sangster, Shores, Watt and North, 2011; Martin et al., 2012). One early study conducted by Dilts and colleagues (1996) using SSRS parent and teacher report did not find a difference in social skills between children with NF1 and unaffected siblings. However, this finding may be due to the high percentage of learning and communication difficulties present in the sample. Barton and North (2004) also found that self, parent and teacher report of social skills, using the SSRS, for children with NF1 did not differ significantly from unaffected siblings. Martin and colleagues (2012) found that children with NF1 did not differ in social skills compared to normative data using the BASC-2. In two studies on young children with NF1, ages 3-6 years old, social skills were not significantly different from unaffected controls based on parent report (Sangster et al., 2011; Klein-Tasman et al., 2014). Notably, the studies of young children with NF1 have used the BASC-2 which is primarily a screening measure rather than a comprehensive measure of social functioning. Overall, the current available literature on social functioning in children with NF1 lacks consistent findings, although the majority of evidence

supports vulnerability to social challenges in school age children with NF1. Additionally, there are only two studies available for young children and no studies available with longitudinal investigations.

Relations between ADHD Symptomatology and Social Functioning in NF1

A secondary aim of this investigation is to examine the relation of ADHD symptomatology and social functioning in children with NF1. Attention deficits are widely recognized as part of the cognitive phenotype of individuals with NF1. A notable elevated prevalence of 30-50% of individuals with NF1 meet DSM criteria for ADHD (Koth et al., 2000; Kayl et al., 2000; Mautner et al., 2002; Barton & North, 2004). Individuals with NF1 have more inattention and hyperactivity/impulsivity difficulties compared to unaffected controls (Dilts et al., 1996; Johnson et al., 1999; Barton & North, 2004; Hyman, Shores & North, 2005; Johnson, Wiggs, Stores & Huson, 2005; Gilboa, Rosenblum, Fattal-Valevski, Toledano-Alhadef & Josman, 2011; Huijbregts & de Sonneville, 2011; Payne, Hyman, Shores & North, 2011; Huijbregts et al., 2015; Loitfelder et al., 2015; Cipolletta et al., 2017) and normative data (Johnson et al., 1999; Isenberg, Templer, Gao, Titus & Gutmann, 2013).

Social functioning has been found to be associated with ADHD symptomatology for individuals with NF1. In a study by Barton and North (2004), attention problems were significantly correlated with social skills such that poorer social skills were evident with more attention problems for children with NF1. Social problems have been found to be significantly correlated with attention problems in children with NF1 (van der Vaart et al., 2016), and Allen and colleagues (2016) noted a trend that more inattention was associated with greater social problems. Additionally, children with NF1 and co-morbid ADHD had poorer social competence, poorer social skills and more social problems than children with NF1 only and children with NF1

and co-morbid learning deficits (Barton & North, 2004; Mautner et al., 2002). These findings highlight the relation between ADHD symptomatology and social functioning in NF1 and support the novelty of the current investigation as it is the first to examine this relation in young children with NF1 as well as longitudinally from early childhood to school age.

Relations between Cognitive and Social Functioning in NF1

In addition to examining relations with ADHD symptomatology, the secondary aim of the current investigation also includes exploring the relation between cognitive and social functioning in children with NF1. A general lowering of cognitive functioning is commonly observed in individuals with NF1, with the majority falling in the low average to average range for overall IQ (Ferner, Hughes & Weinman, 1996; Cutting, Clements, Lightman, Yerby-Hammack & Denckla, 2004; Klein-Tasman et al., 2014). Individuals with NF1 have lower verbal, performance and full-scale IQ than unaffected controls (Dilts et al., 1996; Barton & North, 2004; Hyman et al., 2005; Payne et al., 2011; Sangster et al., 2011; Loitfelder et al., 2015; Lewis et al., 2016) and normative data (Barton & North, 2004; Sangster et al., 2011).

Investigations of the association between cognitive and social functioning in children with NF1 have yielded inconsistent results. Studies of social skills, social problems and social competence have not found significant correlations with full scale IQ in children with NF1 (Barton & North, 2004; Allen et al., 2016; Lewis et al., 2016). Similarly, verbal IQ and social skills (Barton & North, 2004) as well as performance IQ and social problems have not been significantly correlated (van der Vaart et al., 2016). When examining children with NF1 and comorbid ASD, verbal IQ was not significantly different across groups, indicating social impairments are not explained by cognitive function (Garg et al., 2013a).

Conversely, there is some evidence for a relation between cognitive functioning and aspects of social functioning. Children with NF1 with lower verbal IQ and lower performance IQ had more problems with social skills (Martin et al., 2012) while van der Vaart and colleagues (2016) found that social problems were significantly correlated with total verbal intelligence. In a study of young children with NF1, ages 3-6 years, a trend was observed such that stronger social skills were evident in children with stronger intellectual functioning (Klein-Tasman et al., 2014). The presented findings highlight the relevant association of cognitive function with social functioning and provide support for the importance of the current investigation.

In this investigation, the emergence and stability of social skills challenges in young children and school age children with NF1 was examined and the extent to which ADHD symptomatology and cognitive functioning are related to social skills was demonstrated. Given that available literature has shown social difficulties for young children and school age children with NF1, it was hypothesized that young children and school age children with NF1 will show poorer social skills in comparison to normative data. Within early childhood, social skills at age 3 or 4 years in children with NF1 will be significantly correlated with social skills at age 6 years. Social skills will remain stable throughout early childhood and throughout school age for children with NF1. Additionally, relevant to the longitudinal nature of this investigation, school age children (T2) will have poorer social skills than young children (T1) with NF1 and social skills will be significantly correlated from early childhood to school age. The frequency of social difficulties experienced by children with NF1 will be higher during the school age years. Lastly, related to the second study aim, ADHD symptomatology and cognitive functioning will be significantly correlated with social skills concurrently during early childhood (T1) and school age (T2) as well as longitudinally across time. Overall, this work contributes to a better

understanding of when social skills difficulties emerge, the frequency at which social skills challenges occur for young children and school age children and the persistence of social skills difficulties over time in NF1.

Study Rationale

Previous literature has shown that in the general population social difficulties result in a variety of negative outcomes including negative behavioral characteristics (Cassidy & Asher, 1992), poorer peer acceptance, social isolation, perceptions of self as socially incompetent (Hymel et al., 1990), increased risk for conduct, mental health and substance use problems (Bierman & Wargo, 1995; Coie et al., 1992; Boivin, Hymel & Bukowski, 1995; Woodward & Fergusson, 1999), and worse school outcomes (Ladd, 1990; Woodward & Fergusson, 2000; Buhs & Ladd, 2001; DeRosier & Lloyd, 2010; Caemmerer & Keith, 2015). Given the significant impact of social functioning, the planned areas of research are important for increased awareness among parents and teachers of children with NF1, to help with identifying which children are most at risk for developing social skills difficulties, and to aid in identification and implementation of early and effective intervention related to social skills challenges. Although there has been assertion of an association between NF1 and social difficulties in the literature, to date there have been limited studies focusing on social functioning in the young children. Similarly, no examination of social functioning longitudinally in children with NF1 has been conducted. ADHD symptomatology and cognitive functioning as potential predictors of social challenges have, respectively, been scarcely investigated and lack consistent findings in children with NF1. Additional understanding in the aforementioned areas will support the development of specific and targeted intervention strategies based on empirical research to mitigate negative outcomes associated with social skills difficulties.

METHODS

Participants

Participants included children with a confirmed clinical diagnosis of NF1 and their parents. Fifty children (19 females, 31 males) ages 3-6 years (*M*= 3.96, *SD*= 1.05) were assessed at least once in the Early Cognitive and Behavior Characteristics in Neurofibromatosis-1 (T1) early childhood study (see Table 2 for age and visit distribution). Forty children (18 females, 22 males) ages 9-13 years (*M*= 10.90, *SD*= 1.59) were assessed in the School-Age Outcomes in NF1: Attention, Social, and Academic Functioning (T2) school age study (see Table 3 for age distribution). Twenty-five children (11 females, 14 males) were assessed longitudinally and seen in both studies, ages 3-6 years (*M*= 4.12, *SD*= 1.09) and ages 9-13 years *(M*= 10.40, *SD*= 1.35). The mean amount of time between T1 and T2 for the longitudinal sample is 6.28 years (*SD*= 0.76).

Within the early childhood study, participants were enrolled to participate between ages 3 and 8 and then were assessed yearly from enrollment, yielding time points at ages 3-8 years depending on enrollment age. At some point early on in the study, a decision was made to discontinue enrollment of 7 and 8-year olds and instead focus on enrolling only in the early childhood period of 3 through 6 years; due to the small sample size at these ages, participants ages 7 and 8 years old were excluded from this investigation. As mentioned, a subset of the early childhood sample also participated in the school age study, providing longitudinal data.

Procedure

Participants for the early childhood study were recruited from several Midwestern Neurofibromatosis Clinics who were informed about the study and provided fliers. Families that indicated interest in participating were instructed to call the lab or were approached by study

personnel for detailed information about the study. A flier describing the study was emailed to families within driving distance who had expressed interest in being contacted about possible research opportunities through the National Neurofibromatosis Research Registry. For the school age study, similar recruitment methods were used in addition to mailing fliers describing the study to previous research participants who had consented to be informed of future studies in the lab. Inclusion criteria included (1) a confirmed clinical diagnosis of NF1 by a physician, (2) age 3-8 years (for early childhood study) and/or 9-13 years (school age study), and (3) first and main language spoken in the home is English. Exclusion criteria included (1) any comorbid conditions not commonly associated with NF1 and (2) a recent (within 6 months) significant surgery.

Participants who met eligibility criteria were scheduled for an evaluation at the Child Neurodevelopment Research Lab (CNRL) at the University of Wisconsin – Milwaukee or in a quiet hotel conference room near their home. Participants were consented over the phone and had the opportunity to ask questions prior to participating. Consent forms and questionnaire measures were mailed to participants for parental completion prior to the assessment appointment. Each participant was administered an age-appropriate neuropsychological battery, including cognitive measures, by a trained member of the study team. Assessment sessions lasted approximately four hours for all participants during the early childhood and school age studies. Among the study battery, parents completed measures of social functioning (Social Skills Rating System; Social Skills Improvement System) and ADHD symptomatology (Conners Parent Rating Scales – Revised Short Form; Conners 3rd Edition - Parent Short Form) at each assessment.

Measures

Social Functioning:

Social Skills Rating System (*SSRS*; Gresham & Elliott, 1990).

The SSRS is a parent report questionnaire measure of social skills in childhood and adolescence. Adequate internal consistency, test-retest reliability and validity have been demonstrated for the SSRS (Gresham & Elliott, 1990). The SSRS Social Skills scale assesses the presence of positive social behaviors and was used to examine social skills during early childhood (T1). Standard scores have a mean of 100 and a standard deviation of 15. Higher scores represent more positive social behaviors. The SSRS Social Skills scale includes Cooperation, Assertion, Responsibility, and Self Control subscales. These subscales do not yield scaled scores, but instead only interpretative categories which were not used in this investigation. Parents are asked to rate the child on each item using a 3-point scale including "Never," "Sometimes" and "Very Often." The SSRS was used with young children with NF1 ages 3-6 years. The Preschool form was used for children ages 3-5 years and the Elementary form for children in K-1st grades.

Social Skills Improvement System (*SSIS*; Gresham & Elliott, 2008).

The SSIS is an updated questionnaire measure of the SSRS that was administered to parents and examines social skills in childhood and adolescence. Adequate internal consistency, test-retest reliability and validity have been demonstrated for the SSIS (Gresham & Elliott, 2008). The SSIS has a moderate to strong correlation with the SSRS depending on form and subscale. The SSIS Social Skills scale was used to examine social skills during school age (T2). Standard scores have a mean of 100 and a standard deviation of 15. Higher scores represent more positive social behaviors. The SSIS Social Skills scale also includes subscales in Communication, Cooperation, Assertion, Responsibility, Empathy, Engagement and Self Control but as with the

SSRS, these subscales were not used in this investigation. On the SSIS, parents are asked to rate the child on each item using a 4-point scale including "Never," "Seldom," "Often" and "Almost Always." The SSIS was used with school age children with NF1 ages 9-13 years. The Elementary form was used for children grades K-6th grade and the Secondary form for children grades 7th- 8th.

ADHD Symptomatology:

Conners Parent Rating Scales – Revised Short Form (*CPRS-R*; Conners, 1997).

The CPRS-R is a parent report questionnaire used to assess attention difficulties for children ages 3-17 years. The CPRS-R has demonstrated good reliability and validity (Conners, 1997). This measure provides T-scores on four indices: Hyperactivity, Cognitive Problems/Inattention, Opposition and ADHD Index. T-scores have a mean of 50 and a standard deviation of 10. Higher scores represent more ADHD symptomatology. The Hyperactivity, Cognitive Problems/Inattention and ADHD Index were used to examine ADHD symptomatology during early childhood (T1).

Conners 3rd Edition - Parent Short Form (*Conners-3*; Conners, 2008)

The Conners-3 is an updated questionnaire measure of the CPRS-R that was administered to parents and assesses attention difficulties for children ages 6 -18 years. The Conners-3 has demonstrated good reliability and validity (Conners, 2008). T-scores are provided for each of the following subscales: Inattention, Hyperactivity/Impulsivity, Learning Problems, Executive Functioning, Aggression and Peer/Family Relations. T-scores have a mean of 50 and a standard deviation of 10. Higher scores represent more ADHD symptomatology. The Inattention and Hyperactivity/Impulsivity scales were used to examine ADHD symptomatology during the school age years (T2).

Cognitive Function:

Differential Ability Scales-Second Edition (*DAS-II*; Elliott, 2007).

The DAS-II was used to assess cognitive abilities including verbal reasoning, nonverbal reasoning and spatial abilities. The DAS-II demonstrates excellent internal consistency, test-retest reliability and validity. An overall General Conceptual Ability (GCA) standard score as well as standard scores in the above three domains are provided by the DAS-II and were used to examine cognitive function. Standard scores have a mean of 100 and a standard deviation of 15. Higher scores represent higher cognitive abilities. The Early Years version was used for young children ages 3-6 years and the School Age version was used for ages 9-13 years.

RESEARCH AIMS & ANALYTIC STRATEGY

Research Aim 1: *Characterize the emergence and stability of social skills challenges in young children and school age children with NF1*

Research Aim 1a Analytic Strategy: To characterize the emergence and stability of social skills challenges in young children: a) a one-sample t-test was conducted to compare SSRS social skills standard scores of children with NF1 ages 3-6 years, as a group at visit 1, to normative data; b) a one-sample t-test was conducted to compare SSRS social skills standard scores of children with NF1 at each age 3-6 years to normative data; c) a one-way ANOVA was used to compare mean SSRS social skills standard scores each year from ages 3-6 years, with appropriate follow up tests; d) a Spearman bivariate correlation was also conducted to determine whether social skills, as indicated by the SSRS, at the beginning of early childhood are associated with social skills at the end of early childhood. This analysis was exploratory in nature to aid in further characterization of the stability of social functioning within early childhood for children with NF1. Participants with a visit at age 3 or 4 years and a visit at age 6 years were

used for this analysis. For these participants, ages 3 or 4 years were used for an early timepoint within early childhood and age 6 years was used for a later timepoint in early childhood (n=18).

Young children with NF1, at T1 visit 1, will have poorer social skills compared to normative data (*Hypothesis 1a*). Children with NF1 will have poorer social skills compared to normative data at each age from 3 to 6 years (*Hypothesis 1b*). Social functioning in children with NF1 will remain stable, such that social skills remain constant, throughout early childhood (*Hypothesis 1c*). Social skills at age 3 or 4 years in children with NF1 will be significantly associated with social skills at age 6 years (*Hypothesis 1d*).

Research Aim 1b Analytic Strategy: To characterize social skills in the school age years cross-sectionally, a one-sample t-test was conducted to compare SSIS social skills standard scores of school age children with NF1 as a group to normative data. A Spearman bivariate correlation was also conducted to determine whether social skills, as indicated by the SSIS social skills standard score at T2, is associated with age. These analyses were confirmatory to determine if the findings of the current investigation are consistent with the available literature for school age children with NF1. School age children with NF1 (T2) will have poorer social skills compared to normative data (*Hypothesis 1e*). Social skills will remain stable throughout school age for children with NF1 (*Hypothesis 1f*).

Research Aim 1c Analytic Strategy: Visit one data during early childhood was used for longitudinal analyses with school age. To test whether the severity of social skills challenges changes from early childhood to school age, a paired samples t-test was conducted to compare the mean social skills standard scores from T1 (SSRS) to T2 (SSIS). A Spearman bivariate correlation was also conducted to evaluate whether social skills during early childhood (T1; SSRS) are associated with social skills in school age (T2; SSIS). A McNemar's test was

conducted to evaluate whether the frequency of social skills difficulties changes over time from early childhood (T1) to school age (T2). Difficulty was represented by social skills standard scores below 85 on the SSRS and SSIS. Standard scores below 85 were classified as below average in the SSRS and SSIS examiner's manuals.

Social skills in children with NF1 ages 3-6 years (T1) will be significantly higher than social skills during ages 9-13 years (T2) (*Hypothesis 1g*). Social skills in children with NF1 ages 3-6 years (T1) will be significantly correlated with social skills during ages 9-13 years (T2) (*Hypothesis 1h*). The frequency of social skills difficulties at visit 1 for children with NF1 ages 3-6 years (T1) will be significantly lower than the frequency of social skills difficulties at ages 9-13 years (T2) (*Hypothesis 1i).*

Research Aim 2: *Examine the relations of ADHD symptomatology and cognitive function with social skills*

Research Aim 2a Analytic Strategy: ADHD symptomatology was examined using the CPRS-R (T1) and Conners-3 (T2). The Hyperactivity, Cognitive Problems/Inattention and ADHD Index scales on the CPRS-R were used for T1 analyses. The Inattention and Hyperactivity/Impulsivity scales on the Connors-3 were used for T2 analyses. Social skills standard scores on the SSRS and SSIS were used for T1 and T2 analyses, respectively. To examine the relation between ADHD symptomatology and social skills, Spearman bivariate correlations were conducted. Correlations examined whether ADHD symptomatology in early childhood (T1; CPRS-R) were associated concurrently with social skills in early childhood (T1; SSRS) and separately across time with social skills in the school age years (T2; SSIS). Additionally, ADHD symptomatology in the school age years (T2; Connors-3) was tested for an association concurrently with social skills in the school age years (T2; SSIS). ADHD

symptomatology in early childhood and school age will be significantly negatively correlated with social skills in children with NF1 (*Hypothesis 2a*).

Research Aim 2b Analytic Strategy: Cognitive function was examined using the General Conceptual Ability (GCA) standard score from the DAS-II. Social skills standard scores on the SSRS and SSIS were used for T1 and T2 analyses, respectively. Exploratory investigations included examining the verbal, nonverbal and spatial domains of cognitive functioning from the DAS-II. To examine the relation between cognitive function and social skills, Spearman bivariate correlations were conducted. Correlations examined whether cognitive functioning in early childhood (T1; DAS-II) was associated concurrently with social skills in early childhood (T1; SSRS) and separately across time with social skills in the school age years (T2; SSIS). Additionally, cognitive functioning in the school age years (T2; DAS-II) was tested for an association concurrently with social skills in the school age years (T2; SSIS). Cognitive functioning in early childhood and school age will be significantly positively correlated with social skills in children with NF1 (*Hypothesis 2b*).

RESULTS

The data were analyzed using IBM SPSS for Windows, version 25. A p value of $< .05$ indicated significance. Findings are interpreted with respect to both statistical significance and effect size. Interpretations of Cohen's d are as follows: negligible effect = 0 – .14; small effect = .15 – .39; medium effect = .40 – .74; large effect = .75 and above. Interpretations of Spearman's *rho* correlation effect size (Cohen, 1988) are as follows: small = .1 – .3; medium = .3 – .5; large = .5 – 1.

Individual Differences

The demographic information for participants at each time point is described in Table 4. No group differences in social skills were found by sex within early childhood, school age and for the SSRS within the subset of longitudinal participants (T1: $t(48) = -1.71$, $p = .09$, $d = 0.51$; T2: $t(38) = -1.84$, $p = .074$, $d = 0.59$; Long. SSRS: $t(23) = -0.78$, $p = .44$, $d = 0.31$). However, females were significantly higher than males in social skills on the SSIS for longitudinal participants (Long. SSIS: $t(23) = -2.70$, $p = .013$, $d = 1.12$), with a large effect size. No significant differences in social skills were evident for familial compared to sporadic NF etiology classification (T1: $t(48) = -1.52$, $p = .136$, $d = 0.43$; T2: $t(15.64) = -0.86$, $p = .403$, $d = 0.32$; Long. SSRS: $t(23) = 0.62$, $p = .54$, $d = 0.26$; Long. SSIS: $t(23) = -0.93$, $p = .36$, $d = 0.37$). Social skills were weakly significantly correlated with SES during early childhood ($rho(50) = .29$, $p = .022$) but were not significantly correlated during school age ($rho(40) = -.03$, $p = .43$) or for the subset of participants we examined longitudinally (Long. SSRS: $rho(25) = .25$, $p = .11$; Long. SSIS: $rho(25) = -.006$, $p = .49$).

Emergence and Stability of Social Skills Challenges in Young and School Age Children

Research Aim 1a: A summary of descriptive statistics for young children with NF1 is provided in Table 5. One-sample t-test revealed young children with NF1 had significantly lower social skills compared to normative data ($t(49) = -4.41$, $p < .001$, $d = 0.67$). Figure 1 illustrates social skills compared to normative data within early childhood and across age groups. Children ages 3, 4 and 5 years had significantly lower social skills compared to the normative mean ($t(21) = -6.37$, $p < .001$, $d = 1.28$; $t(29) = -3.01$, $p = .005$, $d = 0.60$; $t(32) = -2.94$, $p = .006$; $d = 0.56$) while children age 6 years did not significantly differ from normative data using one sample t-tests ($t(27) = -0.92$, $p = .37$, $d = 0.19$). There was a statistically significant difference between

age groups as determined by one-way ANOVA ($F(3, 109) = 3.23$, $p = .025$). LSD post hoc tests revealed that the children with NF1 age 3 years had statistically significantly weaker social skills compared to children with NF1 age 6 years ($p = .002$, $d = 0.98$). Social skills at ages 3 or 4 years were strongly significantly correlated with social skills at age 6 years ($rho(18) = .71$, $p = .001$).

Research Aim 1b: Table 5 illustrates a summary of descriptive statistics for school age children with NF1. School age children with NF1 had significantly lower social skills compared to the normative mean using a one-sample t-test ($t(39) = -3.38$, $p = .002$, $d = 0.54$), as illustrated in Figure 1. Social skills within the school age years were not significantly correlated with age ($rho = .049$, $p = .38$).

Research Aim 1c: Table 6 provides a summary of descriptive statistics for children with NF1 assessed longitudinally at both timepoints. A paired samples t-test revealed social skills in early childhood did not differ significantly from social skills in school age for children with NF1 ($t(24) = 0.97$, $p = .34$, $d = 0.23$). With standard scores of <85 classified as a difficulty and ≥85 classified as no difficulty, social skills difficulties were observed for 32.0% of young children and 24.0% of school age children with NF1. An exact McNemar's test indicated no statistically significant difference in the proportion of social skills difficulties from early childhood to school age for children with NF1 ($p = .69$). Social skills were not significantly correlated across time from early childhood (using T1 visit one data) to school age ($rho = .30$, $p = .08$), with a small to medium effect size.

To further explore longitudinal relations, early childhood was grouped into two age groups: 1) 3- and 4-year-olds and 2) 5- and 6-year-olds. These analyses included participants at any visit number rather than visit one only. 16 participants were represented in both age groups. Social skills during early childhood for 3- and 4-year-olds were not significantly correlated with

social skills during school age (*rho(*17*)* = .32, *p* = .104), with a small to medium effect size. Social skills of 5- and 6-year-olds were significantly correlated with social skills during school age (*rho(*24*)* = .56, *p* = .002).

Relations of ADHD symptomatology and cognitive function with social skills

Table 7 summarizes Spearman bivariate correlations conducted to examine relations between social skills and both ADHD symptomatology and cognitive functioning.

Research Aim 2a: Hyperactivity, Cognitive Problems/Inattention and the ADHD Index on the CPRS-R during early childhood had significant negative correlations, ranging from weak to moderate strength, with SSRS social skills during early childhood (*rho*(50) = -.46, *p* < .001; *rho*(50) = -.25, *p* = .04; *rho*(50) = -.37, *p* = .004). Cognitive Problems/Inattention on the CPRS-R during early childhood was significantly negatively correlated with SSIS social skills during school age with a medium effect size (*rho*(25) = -.39, *p* = .026). Hyperactivity and the ADHD Index on the CPRS-R during early childhood were not significantly correlated with SSIS social skills during school age (*rho*(25) = -.05, *p* = .42; *rho*(25) = -.29, *p* = .081), with a negligible and small effect size, respectively. Inattention and Hyperactivity/Impulsivity on the Conners-3 during school age were significantly negatively correlated with SSIS social skills during school age, with corresponding strength in the moderate range (*rho*(40) = -.42, *p* = .004; *rho*(40) = -.35, *p* = .013).

Research Aim 2b: GCA during early childhood was weakly significantly correlated with SSRS social skills during early childhood (*rho*(50) = .26, *p* = .034). Verbal, nonverbal and spatial reasoning during early childhood were not significantly correlated with social skills during early childhood (*rho*(50) = .15, *p* = .14; *rho*(50) = .21, *p* = .068; *rho*(38) = .22, *p* = .097). Cognitive functioning during early childhood was not significantly correlated with SSIS social

skills in school age (GCA: *rho*(25) = -.06, *p* = .39; V: *rho*(25) = -.19, *p* = .18; NV: *rho*(25) = .15, *p* = .24; S: *rho*(21) = .15, *p* = .26), with effect sizes ranging from negligible to small. Cognitive functioning during school age was not significantly correlated with SSIS social skills in school age (GCA: *rho*(40) = .025, *p* = .44; V: *rho*(40) = -.05, *p* = .37; NV: *rho*(40) = .01, *p* = .48; S: *rho*(40) = .09, *p* = .29) with negligible effect sizes.

Attrition:

Given the longitudinal nature of this study, analyses were conducted to evaluate whether differential attrition is evident within this sample. No significant differences were found for sex, SES, NF classification or GCA among individuals with a visit at T2 and those that did not have a visit at T2 (χ^2(1, N = 50) = .76, *p* = .38; *t*(48) = -.53, *p* = .560, *d* = 0.15; χ^2(1, N = 50) = 2.12, *p* = .15; *t*(48) = -.92, *p* = .36, *d* = 0.26). Notably, social skills were significantly higher for those who did return at T2 (*t*(48) = -3.05, *p* = .004, *d* = 0.86). Hyperactivity and the ADHD Index of the CPRS-R during early childhood were significantly lower for those that did return at T2 compared to those that did not return at T2 (*t*(34.4) = 3.35, *p* = .002, *d* = 0.95; *t*(44.2) = 2.57, *p* = .014, *d* = 0.73). There was no significant difference for Cognitive Problems/Inattention on the CPRS-R (*t*(48) = 1.14, *p* = .26, *d* = 0.32).

For an analysis of stability during early childhood, 18 individuals with a visit at age 3 or 4 years and a visit at age 6 years were examined. No significant differences were found for sex, SES, NF classification, GCA, social skills or ADHD symptomatology among young children used for this analysis and those who were excluded as they did not have a visit at age 6 years (χ^2(1, N = 50) = 1.25, *p* = .26; *t*(48) = -1.12, *p* = .27, *d* = 0.35; χ^2(1, N = 50) = 1.25, *p* = .27; *t*(48) = -.29, *p* = .78, *d* = 0.11; *t*(48) = 0.24, *p* = .81, *d* = 0.19; CPI: *t*(48) = 1.95, *p* = .058, *d* = 0.604; Hy: *t*(47.77) = 2.00, *p* = .051, *d* = 0.607; ADHD: *t*(46.3) = 1.78, *p* = .081, *d* = 0.58).

DISCUSSION

The primary aim of this investigation was to characterize the emergence and stability of social skills challenges in children with NF1 in the early childhood and school age periods. As hypothesized, young children and school age children with NF1 showed poorer social skills compared to normative data. Hypothesis 1b was partially supported in that young children with NF1 ages 3, 4 and 5 years had significantly lower social skills compared to normative data. As expected, social skills were relatively stable throughout early childhood with the exception of children with NF1 ages 3 years having significantly lower social skills compared to children with NF1 age 6 years. Related to the stability of social skills within young children, social skills at an early timepoint were strongly positively correlated with a later timepoint during early childhood. Similarly, within the school age years, social skills were not correlated with age, indicating social skills are likely stable over time during the school age years. Regarding social skills longitudinally, social skills were neither significantly different from early childhood to school age nor significantly correlated. However, when early childhood was divided into two age groups, social skills at the end of early childhood (5 and 6 years old) were moderately positively correlated with school age social skills, indicating that social skills at the end of early childhood are more predictive of social skills during school age than are social skills at the beginning of early childhood. Approximately 1/3 of young children and 1/4 of school age children with NF1 displayed social skills difficulties with no significant difference in the proportion of social skills difficulties at each timepoint.

A secondary aim of this investigation was to examine the relations of ADHD symptomatology and cognitive functioning with social skills. As hypothesized, ADHD symptomatology was negatively correlated with social skills concurrently, with weak to

moderate strength depending on the scale, for young children and school age children with NF1. Cognitive Problems/Inattention in early childhood predicted school age social skills while Hyperactivity and the ADHD Index did not show relations over time. Within cognitive function, GCA was positively correlated to a weak degree with social skills for young children concurrently. However, contrary to predictions, social skills relations with cognitive function were not evident across time or concurrently during school age.

Prevalence of Social Difficulties

Previous research about social functioning for children with NF1 indicates difficulties are evident in social functioning broadly as well as in the specific areas of social skills, social problems and social competence. The results of the current study are consistent with one prior research study that uses the SSRS and demonstrates that school age children with NF1 have poorer social skills compared to normative data (Barton & North, 2004). Similar studies that have used the SSRS with a comparison group have found children with NF1 have poorer social skills compared to unaffected controls (Huijbregts & de Sonneville, 2011; Huijbregts et al., 2015; Loitfelder et al., 2015). In contrast to the studies above that found poorer social skills using the SSRS, two studies using the SSRS did not find impairments in social skills compared to unaffected controls (Dilts et al., 1996; Barton & North, 2004). Therefore, the SSRS shows varying patterns of social skills for children with NF1, with the majority of studies finding impairments.

In the social functioning literature, there is evidence of varying terminology that focuses on social skills and functions, as outlined in Beauchamp and Anderson (2010), some of which are compatible and others that are distinct. This suggests that measures of social skills, social problems and social competence may in fact tap different constructs of social functioning and

should be evaluated independently. For instance, social problems have often been evaluated using the CBCL and studies support that children with NF1 experience more social problems compared to normative data (Johnson et al., 1999; van der Vaart et al., 2016) and unaffected controls (Dilts et al., 1996; Johnson et al., 1999; Barton & North, 2004; Huijbregts et al., 2015; Loitfelder et al., 2015; Allen et al., 2016; Cipolletta et al., 2017). The CBCL also examines social competence as does the Social Competence with Peers Questionnaire (SCPQ). The majority of studies have found that children with NF1 have poorer social competence compared to unaffected controls (Johnson et al., 1999; Barton & North, 2004; Noll et al., 2007; Lewis et al., 2016). However, one study found no difference in social competence compared to unaffected controls using the CBCL (Dilts et al., 1996). Additionally, the Behavior Assessment System for Children (BASC) and BASC-2 have been used as a measure of social skills. These measures have generally indicated that children with NF1 do not have poorer social skills compared to normative data (Martin et al., 2012) or unaffected controls (Sangster et al., 2011; Klein-Tasman et al., 2014). In the current study, social skills during early childhood were poorer compared to normative data, which is distinct from these previous research findings. The social functioning literature in NF1 highlights the need for continued research to determine which social functioning measure is most sensitive to identifying social deficits in children with NF1. It is clear that a consensus within the research community is needed in this area in order to more consistently evaluate social functioning and to better characterize social deficits in children with NF1.

Within the current study, an association was found between social skills during early childhood and SES such that children from families with higher SES had better social skills. Relations to SES are not consistently examined in the literature. However, this result is in

contrast to some other studies that examine aspects of social functioning in children (Graf et al., 2006) and adults with NF1 (Pride et al., 2013) which have not found a relation with SES. Nevertheless, it may be that children from a family with higher SES are more likely to participate in activities that foster social skills such as sports teams and events with other children as well as be enrolled in daycare or preschool, leading to this relation between social skills and SES.

An exploratory examination of the social skills items most frequently endorsed by parents during early childhood and school age years for children with NF1 was conducted and revealed that compromising in conflict situations and introducing themselves to other people are relative weaknesses for children with NF1 across time. Specifically, during early childhood, managing conflict and communication in social settings emerged as areas of relative weakness while social connections, ability to communicate with parents, showing interest in a variety of things and following instructions were areas of relative strength. During school age, themes of managing conflict and emotions in response to others appeared as relative weaknesses while social communication was a relative strength. However, it should be noted that without a contrast group in the current investigation, these areas of strengths and weaknesses are strictly relative, rather than normative, for children with NF1.

One study by Martin and colleagues (2012) found that 13% of their sample of 53 children with NF1 were in the at-risk or clinically significant range for social skills as measured by the BASC-2 based on parent report and 11% based on teacher report. Barton and North (2004) found that 25% of their sample of 79 children with NF1 had social competence difficulties in the borderline/clinical range based on parent report using the CBCL. In young children with NF1, ages 3-6 years (with a sample overlapping with the current study), using the BASC-2, 8% of a

sample of 40 children were one standard deviation or more away from the mean for social skills (Klein-Tasman et al., 2014). The current study found 32% of young children and 24% of school age children with NF1 of a sample of 25 displayed social skills difficulties based on parent report suggesting that many children with NF1 do not have significant social skills difficulties. Further examination of the percentage of social skills difficulties revealed that 4% of young children and 8% of school age children showed social skills difficulties greater than 2 standard deviations below the mean which illustrates that social skills deficits may be subtle. The exploratory item analysis illustrated that the majority of social skills evaluated on the SSRS and SSIS did not emerge as consistent weaknesses. Additionally, it is likely that these social skills challenges may be variable such that strengths and weaknesses in social skills are specific to the individual rather than a pattern of performance that is representative of all children with NF1. Findings from the literature on social functioning in NF1 as well as from the exploratory item analysis conducted in this investigation illustrate that deficits in social skills may be mild, subtle and variable.

Within the NF1 literature, an association with autism spectrum disorders (ASD) has been found for individuals with NF1 (Garg et al., 2013a; Garg et al., 2013b; Plasschaert et al., 2014). ASD is characterized by deficits in social communication and social interaction including specific impairments in social-emotional reciprocity, nonverbal behaviors used in social interactions as well as having relationships with others (American Psychiatric Association, 2013). Within recent studies on children with NF1, 13-33% of children with NF1 meet criteria for ASD (Walsh et al., 2013; Garg et al., 2013a; Garg et al., 2013b; Plasschaert et al., 2014). Similarly, studies have shown that children with NF1 often have many symptoms of ASD but these symptoms are subthreshold and do not meet criteria for a diagnosis, with 26.6-30% falling in the mild to moderate autism spectrum range (Walsh et al., 2013; Garg et al., 2013b;

Plasschaert et al., 2014). Additionally, poorer socialization was evident on the Autism Diagnostic Observation Schedule – Generic (ADOS-G), Autism Diagnostic Interview-Reviews (ADI-R) and Vineland Adaptive Behavior Scale (VABS-II) for children with NF1 and ASD compared to children with NF1 and subthreshold ASD and non-ASD (Garg et al., 2013a). In one study that compared children with NF1 and children with ASD, children with NF1 had significantly milder social deficits than children with ASD (Adviento et al., 2014). For children and adolescents with ASD, mean social skills standard scores on the SSRS and SSIS in the literature range from below average to average based on parent report, with the majority of studies reporting social skills in the below average range (Estes, Rivera, Bryan, Cali & Dawson, 2011; Neuhaus, Bernier and Beauchaine, 2014; Carlisle, 2015; Jamison & Schuttler, 2015; Laugeson, Gantman, Kapp, Orenski & Ellingsen, 2015; Berkovits, Eisenhower & Blacher, 2017). The mean social skills standard scores from the current investigation are solidly in the average range for children with NF1, providing further evidence that children with NF1 likely experience subtle difficulties in social skills compared to those evident for children with ASD.

Studies of social functioning in adults with NF1 evidence that social difficulties continue into adulthood. One study found that social skills deficits are present within adulthood, with more severe social difficulties for males. More specifically, adults have reduced awareness of their deficits in social skills and less prosocial behavior based on family and peer report (Pride, Crawford, Payne & North, 2013). Another study with adults with NF1 found that 30% of a sample of adults with NF1 reported that having NF1 made forming new relationships difficult and 12% of parents of these adults with NF1 reported that their adult child had trouble forming relationships (Benjamin et al., 1993). Additionally, a study by Hummelvoll and Antonsen (2013) reported negative experiences/bullying during childhood was related to current low self-

confidence in adults with NF1. These findings are important within the context of the current investigation as they provide evidence that social difficulties are likely to continue into adulthood, confirm the value of longitudinal investigations and the necessity for early intervention once social difficulties emerge.

Impairments in social functioning have also been found to be associated with NF1 severity and physical manifestations of NF1 for adults (Wolkenstein et al., 2001; Page et al., 2006; Hummelvoll & Antonsen, 2013), indicating a role of health and appearance on an individual's social functioning. Additionally, Hummelvoll and Antonsen (2013) reported that female adults with NF1 expressed concern about the visibility of NF1 manifestations such as facial and cutaneous neurofibromas. In studies with children with NF1, relations of social functioning with NF1 severity and appearance have not been found (Barton & North, 2004; Noll et al., 2007). Barton and North (2004) found no significant differences in social skills, social competence and social problems by parent and teacher report based on NF1 severity classification. However, based on self-report, children with moderate/severe NF1 had significantly poorer social skills than children with minimal/mild NF1. Noll and colleagues (2007) found no significant relations with physical appearance and peer reported best friend nominations and ratings of reciprocated friendships. Research on NF1 describes the progressive nature of NF1 such that physical manifestations including café-au-lait spots appear in the first few months of life, skinfold freckling develops around 3-5 years of age (Korf, 1992) and cutaneous and plexiform neurofibromas arise in early adulthood and increase with age (Huson, Harper & Compston, 1988; Jett & Friedman, 2010). These studies, in line with the research on the progressive nature of NF1, suggest that the relation of social functioning with NF1 severity and physical manifestations may become more pronounced within adulthood and highlight the

importance of further investigation of social functioning in relation to NF1 severity and appearance.

Investigations of quality of life for children with NF1 have evidenced poorer overall quality of life and health-related quality of life compared to unaffected controls (Graf et al., 2006; Cipolletta et al., 2017) and indicated a reduced quality of life related to social functioning (Cipolletta et al., 2017; Graf et al., 2006). More specifically, parents report concerns regarding their child's quality of life related to emotional states, social life and overall quality of life while children report worse perceptions of quality of life related to physical health, emotional states, social life, school activities and overall quality of life (Cipolletta et al., 2017). Similarly, Graf and colleagues (2006) found that children with NF1 had poorer health-related quality of life in the areas of motor, cognitive, social and emotional functioning compared to unaffected controls based on self and parent report. Due to the many cognitive, medical and psychosocial difficulties experienced by children with NF1, the impact of these difficulties on quality of life, specifically related to social functioning, is an important consideration when working with this population.

Relations with Social Functioning

The results of the current investigation that poorer social skills were present with more ADHD symptomatology are generally consistent with prior research that has found social skills to be significantly correlated with attention problems (Barton & North, 2004). This investigation is one of only a few studies to evaluate the relation between ADHD symptomatology and social functioning concurrently and the first to investigate this relation longitudinally. Investigations of children with NF1 and co-morbid ADHD have illustrated poorer social competence, poorer social skills and more social problems than children with NF1 only and children with NF1 and co-morbid learning deficits (Barton & North, 2004; Mautner et al., 2002). Although not directly

measured within this investigation, social problems, a relevant aspect of social functioning, have been found to be significantly correlated with attention problems in children with NF1 (van der Vaart et al., 2016). The current findings of relations with inattention and social skills concurrently and longitudinally is consistent with the trend observed by Allen and colleagues (2016) such that more inattention was associated with greater social problems.

Understanding the relation between ADHD symptomatology and social functioning within children with NF1 is important as typically developing children with attention difficulties commonly experience social impairments (Bagwell, Molina, Pelham Jr, & Hoza, 2001; Nijmeijer et al., 2008). It is evident that children with NF1 and co-morbid ADHD symptomatology are more likely to experience social skills difficulties, indicating that children with NF1 who present with attention problems are at-risk for social difficulties and their social functioning also warrants consideration and assessment. Providers should supply social skills training resources and recommendations to aid in increasing social abilities for these at-risk children.

In regard to cognitive function, prior research examining relations with social functioning yields inconsistent findings. In this study, overall cognitive functioning showed weak, but significant, concurrent relations with social skills during early childhood. These findings are consistent with one study, of which has an overlapping sample with the current investigation, that found a trend suggesting children with stronger intellectual functioning had stronger social skills (Klein-Tasman et al., 2014). Additionally, the results from our school age children are similar to previous research in older children with NF1 that found no correlation between various aspects of social functioning, including social skills, social problems and social competence, and full-scale IQ (Barton & North, 2004; Allen et al., 2016; Lewis et al., 2016). More specifically, in the current study, verbal reasoning was not related to social skills concurrently for school age

children which is consistent with previous research by Barton and North (2004) that found verbal IQ and social skills were not significantly correlated. The results of this investigation, as well as the current literature, seem to suggest that relations between cognitive and social functioning are mildly apparent during early childhood but this association dissipates with age such that cognitive function has more of an impact on social functioning when children are young and this impact is not sustained into the school age years. It may be important for providers to evaluate social functioning during early childhood when difficulties in cognitive function are evident.

The findings of this investigation correspond well to the socio-cognitive integrations of abilities (SOCIAL) model proposed by Beauchamp and Anderson (2010). This model suggests multiple dimensions, such as biological functioning, cognitive functions, and internal and external factors, interact to determine an individual's social function. The first component of the model includes internal (personality, temperament, physical attributes) and external factors (family environment, SES, culture) as well as brain development and integrity that act as mediators to shape social function emergence. Within this component, internal and external factors interact bidirectionally with the ongoing development of the brain to influence cognitive function, which is the second component of the model. This second component involves three cognitive domains (attention-executive, communication and socio-emotional) that directly determine an individual's social function. There is a bidirectional relationship between these two components in that changes in cognitive processes can impact an individual's internal and external factors such as biology and environment as well as brain development. In summary, all of the components of the model interact to influence an individual's social function and any component of the model could be altered during development. These alterations can influence an individual's social function directly or indirectly as well as in a positive or negative manner,

ultimately impacting an individual's development of social skills (Beauchamp & Anderson, 2010). In this investigation, I examined the influence of ADHD symptomatology and cognitive function on social skills of children with NF1. Consistent with the SOCIAL model, the results indicate that ADHD symptomatology is directly influencing the social skills of children with NF1 while cognitive function seems to be causing alterations in social skills during early childhood and development for children with NF1 with less of an impact later in life. Additionally, this model indicates that internal and external factors, such as NF1 and socioeconomic status, have the capacity to shape the emergence of social function which is consistent with the finding that children from families with higher SES had better social skills. The SOCIAL model includes physical attributes as a mediator of social function which we have discussed here in relation to NF1 severity and the physical manifestations of NF1 as important for future research. The SOCIAL model posits that social function has many interacting influences and provides avenues for future research to continue to investigate the various influences on social function within children with NF1.

Limitations and Future Directions

The present study is the first to report on social skills longitudinally in children with NF1. This investigation also provides further evidence for social skills difficulties during early childhood and school age as well as relations with ADHD symptomatology. However, there are limitations in the design of this investigation. First, the sample of children in the current study is relatively small given the focus on three different groups: young children, school age and children who were assessed at both of those timepoints. A larger sample of children at each timepoint would ensure adequate representation of all ages within each timepoint. Similarly, the sample size available for longitudinal analyses is quite small with 25 children. Second, the

current investigation relies on parent report of social skills and ADHD symptomatology, which may introduce response bias on these constructs for children with NF1. Third, the current study is limited by a lack of a contrast group, which would have been useful in determining the presence of social skills difficulties, the persistence of difficulties over time and social strengths and weaknesses as well as relations with ADHD symptomatology and cognitive functioning in unaffected controls. Fourth, related to differential attrition, the findings suggest that the current investigation could be examining a less impaired group of individuals with NF1 in regard to social functioning and ADHD symptomatology. More specifically, it appears that children with NF1 who have less difficulty in these areas were more likely to continue in the study and return during school age while children with NF1 who have more difficulties in these areas were more likely to drop out.

Future research on social functioning in children with NF1 should include examination of relations of social skills with NF1 severity and appearance. This would include investigating characteristic symptoms of NF1 such as café-au-lait spots, cutaneous neurofibromas, plexiform neurofibromas, posture (scoliosis) and tibial dysplasia to determine contributions to social skills difficulties. In addition, future longitudinal work on social functioning using linear mixed model growth curves will be important to provide information about the trajectories of social difficulties in children with NF1. This method also will allow to flexibly account for missing data due to attrition in this sample. Lastly, future research may include a follow up study in order to examine social skills of adolescents with NF1. This would include recruiting participants that partook in the early childhood study and/or the school age study to provide another longitudinal datapoint. This would aid in further characterization of social skills among individuals with NF1 and would allow for further investigation of social skills over time.

CONCLUSIONS

The current study is the first to report on social skills longitudinally and one of the first to characterize social skills during early childhood in children with NF1. This study also examined the relations of ADHD symptomatology and cognitive function with social skills. Children with NF1 experience social difficulties during early childhood and school age in comparison to normative data. Social skills were relatively stable throughout early childhood and school age, however children with NF1 age 3 years showed poorer social skills than children with NF1 age 6 years when examining age group. Social skills were neither significantly different from early childhood to school age nor significantly correlated. The frequency of social skills difficulties did not change over time. When early childhood was further divided by age, social skills at the end of early childhood (5 and 6 years) predicted school age social skills while social skills at the beginning of early childhood (3 and 4 years) did not. The findings from this investigation provide evidence that there does not appear to be an increase in social skills difficulties over time in children with NF1, from the parents' perspective, but that difficulties in social skills that begin at an early age persist throughout early childhood. However, these difficulties are likely mild, subtle and variable. ADHD symptomatology had negative correlations with social skills concurrently, suggesting ADHD symptomatology may be contributing to social skills difficulties. Inattention during early childhood predicted school age social skills. GCA was weakly related to social skills for young children concurrently. However, social skills relations with cognitive function were not evident concurrently during school age or across time. These findings add evidence to the argument that cognitive functioning is not a driving factor in the social functioning for children with NF1.

This investigation contributes to the limited social functioning literature in children with NF1 by characterizing social skills in early childhood and by investigating social skills longitudinally. In addition, given the significant impact of social functioning, it is expected that the detailed characterization of social skills for young children with NF1 will inform targeted interventions, with implementation at a young age.

Figure 1. Social functioning compared to normative data

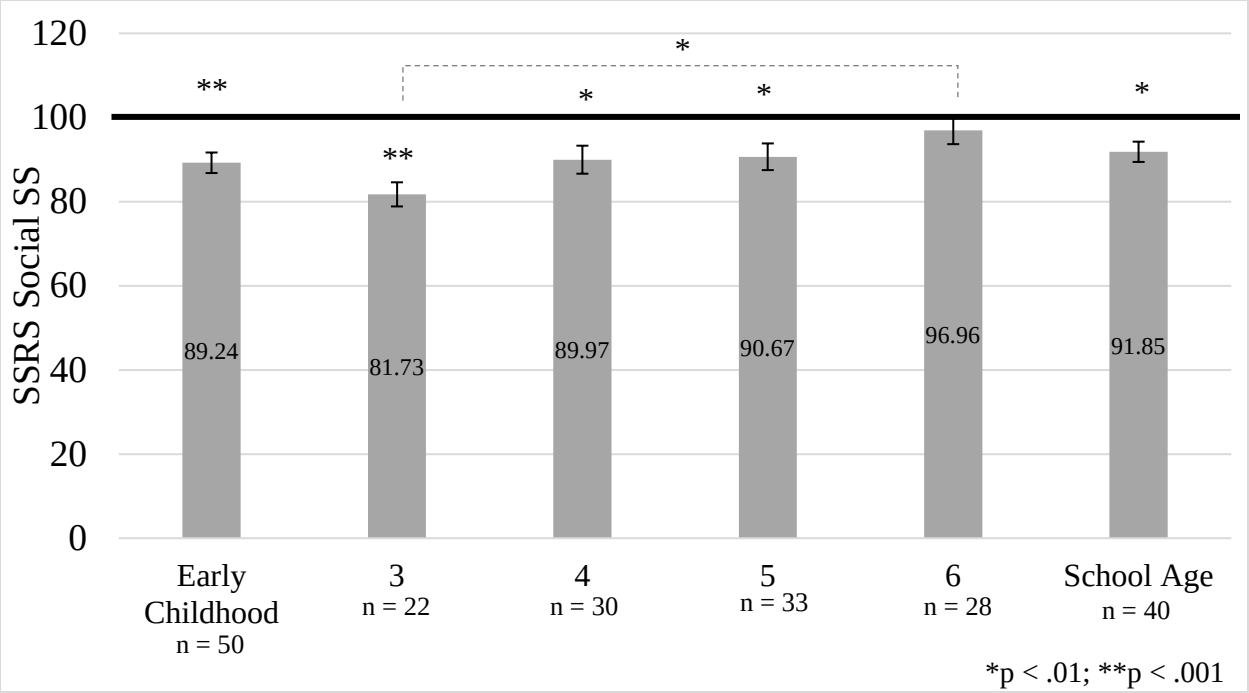

Table 1. Studies in the area of social functioning in children with NF1

Authors	Participants	Measures	Findings
Dilts et al. (1996)	Ages 6-17 years 20 children with NF1 • 8 males, 12 females • Range: 6 years, 2 months to 16 years, 11 months • Median: 10 years, 10 months 20 sex-matched siblings • Range: 6 years, 4 months to 17 years, 3 months • Median: 12 years, 6 months	Social Skills Rating System (SSRS) • SSRS-Parent • SSRS-Teacher Child Behavior Checklist (CBCL) – Parent • Social Competence Scales • Problem Behavior Teacher Report Form • Problem Behavior	Children with NF1 did not differ significantly on measures of social skills from controls. Children with NF1 had more social problems than controls, based on parent and teacher report, but did not differ significantly on social competence scales.
Johnson et al. (1999)	Ages 5-18 years 43 children with NF1 • 23 males, 20 females • Mean age: 11.4 years 22 unaffected siblings • 12 males, 10 females • Mean age: 10.6 years	Child Behavior Checklist (CBCL) – Parent and Teacher	Children with NF1 display more social problems compared to unaffected controls as well as normative means based on parent and teacher report. Children with NF1 have less social competence compared to unaffected controls based on parent report. Specifically, they have less close friends, less time per week with friends and less ability to get along with siblings.

Barton & North (2004)	Ages 8-16 years 79 children with NF1 • 42 males, 37 females • Mean age: 11.5 years • SD: 2 years, 4 months 46 unaffected siblings • 19 males, 27 females • Mean age: 12 years, 1 month • SD: 2 years, 6 months	Social Skills Rating System (SSRS) • Self, parent and teacher report Child Behavior Checklist (CBCL) • Social Problem scores • Social Competence scores Teachers Report Form (TRF) • Social Problem scores	Children with NF1 had significantly poorer social skills compared to normative data based on parent and teacher report. Children with NF1 showed better social skills compared to normative data based on self-report. There was no significant difference found on subscales or total social skills for children with NF1 and unaffected siblings based on self, parent and teacher report. Children with NF1 have poorer social outcomes compared to unaffected siblings including more social problems and less social competence.
Graf et al. (2006)	Ages 7-16 years 46 children with NF1 • Mean age: 11.6 years	TNO-AZL Child Quality of Life Questionnaire (TACQOL) – Child and Parent Forms	Children with NF1 had significantly lower social functioning compared to normative data based on self and parent report. However, there was weak correlation between child and parent report.
Noll et al. (2007)	Ages 7-15 59 children with NF1 • 35 males, 24 females 59 classroom peers (comparison) • Same race/gender • Closest date of birth	Revised Class Play (RCP) • Peer, teachers and self-report Peer/social acceptance: • Peer reported best friend nominations and reciprocated friendships • Classmate ratings of how much they liked another individual Child Behavior Checklist (CBCL) • Social competence	Children with NF1 displayed less leadership behavior, were more sensitive and were more isolated compared to peers based on peer and teacher report. Children with NF1 displayed more prosocial behavior compared to peers based on teacher report. Children with NF1 were selected less often as a best friend, had fewer reciprocated friendships and were less well liked compared to peers based on peer report. Children with NF1 displayed lower total social competence compared to peers based on parent report.

Huijbregts & de Sonneville (2011)	30 children with NF1 • 12 boys, 18 girls • Mean age: 11.7 years (SD: 3.3) • Range 6.9-17.4 years 30 healthy controls • 11 boys, 19 girls • Mean age: 12.5 years (SD: 3.1) • Range 6.0-17.3 years	Social Skills Rating System (SSRS)	Children with NF1 display poorer social skills than healthy controls (before and after control for cognitive abilities).
Sangster et al. (2011)	26 children with NF1 • 17 males, 9 females • Mean age: 5 years, 3 months (SD: 5.88 months) 21 peer comparisons • 11 males, 10 females • Mean age: 4 years, 8 months (SD: 5.57 months)	Behavior Assessment System for Children (BASC) - Parent	Social skills of young children with NF1 were not significantly different from a peer comparison group.
Martin et al. (2012)	Ages 6-18 years 53 children with NF1 and plexiform neurofibromas • 35 males, 18 females • Mean age: 12.4 years	Behavior Assessment System for Children – 2nd Edition (BASC-2) • Parent and Teacher Forms	Children with NF1 did not differ in social skills compared to normative data. 13% in the "at-risk/clinically significant" range for social skills based on parent report and 11% in the "at-risk/clinically significant" range for teacher report.
Klein-Tasman et al. (2014)	Ages 3-6 years 40 children with NF1 • 26 males, 14 females • Mean age: 4 years, 6 months 37 unaffected controls • 25 males, 12 females • Mean age: 4 years, 8 months	Behavior Assessment System for Children – 2nd Edition (BASC-2) • Parent and Teacher Forms	Social skills of young children with NF1 were not significantly different from unaffected controls.
Huijbregts et al. (2015)	15 children with NF1 • 9 male, 6 female • Mean age: 12.9 (SD: 2.6) • Median: 13.1 years • Range: 9.3 years 18 healthy controls • 8 male, 10 female • Mean age: 13.8 (SD: 3.6) • Median: 12.4 years • Range: 9.9 years	Social Skills Rating System (SSRS) – Parent Child Behavior Checklist (CBCL) - Parent	Children with NF1 display poorer social skills compared to healthy controls. Children with NF1 have more social problems compared to healthy controls.

Loitfelder et al. (2015)	14 children with NF1 • 8 male, 6 females • Mean age: 12.49 years (SD: 2.65) 30 healthy controls • 23 males, 7 females • Mean age: 12.30 years (SD: 2.94)	Social Skills Rating System (SSRS) – Parent Child Behavior Checklist (CBCL) - Parent	Children with NF1 showed poorer social scores (on all domains of the SSRS) than healthy controls (before controlling for executive function). After controlling for executive function, children with NF1 showed poorer scores only in the assertion domain Children with NF1 display more social problems compared to healthy controls.
Allen et al. (2016)	Ages 8-16 years 23 children with NF1 • 15 males, 8 females • Mean age: 12.11 years (SD: 2.24) 23 typically developing peers • 11 males, 12 females • Mean age: 12.9 years (SD: 1.94)	Child Behavior Checklist (CBCL) – Parent Pediatric Quality of Life Inventory (PedsQL) - Parent	Children with NF1 display more social problems compared to healthy controls. Children with NF1 had poorer social functioning based on self and parent report.
Lewis et al. (2016)	23 children with NF1 • 8 males, 15 females • Mean age: 10.04 years (SD: 2.12) 23 typically developing controls • Age-matched • 14 males, 9 females • Mean age: 9.92 years (SD: 1.97)	Social Competence with Peers Questionnaire (SCPQ) - Parent	Children with NF1 displayed less social competence compared to typically developing controls.
van der Vaart et al. (2016)	Ages 8-16 years 84 children with NF1 • 39 males, 45 females • Mean age: 11.5 years	Child Behavior Checklist (CBCL) – Self, Parent and Teacher	Children with NF1 display more social problems compared to normative data based on self, parent and teacher report.
Cipolletta et al. (2017)	Ages 6-17 years 60 children with NF1 • 31 males, 29 females • Mean age: 11.27 years (SD: 3.02) 60 healthy controls • 32 males, 28 females • Mean age: 11.65 years (SD: 3.16)	Child Behavior Checklist (CBCL) – Parent Pediatric Quality of Life Inventory (PedsQL) - Parent	Children with NF1 display more social problems compared to healthy controls. Children with NF1 had poorer social life based on self and parent report.

Table 2. Summary of young children by age and visit number

Visit Number	Age				Age Ranges (N per visit)
	3	4	5	6	3-8
1	22	14	8	6	50
2	0	16	15	5	36
3	0	0	10	10	20
4	0	0	0	7	7
Total # of visits by age/range	22	30	33	28	113

Table 3. Summary of number of participants by age during school age

Age						
9	**10**	**11**	**12**	**13**	**14**	**N**
10	10	7	3	6	4	40

Table 4. Participant demographic data

			Longitudinal	
	Early Childhood	**School Age**	**T1 V1**	**T2**
Variable	**n= 50**	**n= 40**	**n= 25**	
Mean Age (*SD*)	3.96 (1.05)	10.9 (1.59)	4.12 (1.09)	10.40 (1.35)
Sex (Frequency/%)				
Females	19 (38)	18 (45)	11 (44)	
Males	31 (62)	22 (55)	14 (56)	
Classification (Frequency/%)	Familial: 19 (38) Sporadic: 31 (62)	Familial: 13 (32.5) Sporadic: 27 (67.5)	Familial: 7 (28) Sporadic: 18 (72)	
Ethnicity (Frequency/%)				
Caucasian	37 (74)	33 (82.5)	20 (80)	
African-American	5 (10)	4 (10)	3 (12)	
Latino	5 (10)	-	-	
Asian	1 (2)	1 (2.5)	1 (4)	
Mixed Ethnicity	2 (4)	2 (5)	1 (4)	
Hollingshead SES Index Mean (SD)	41.92 (14.86)	46.13 (12.43)	43.04 (14.26)	44.99 (10.82)

Table 5. Descriptive statistics of study measures for children in early childhood (n=50) and school age (n = 40)

Early Childhood			School Age		
Scale	**Mean**	**SD**	**Scale**	**Mean**	**SD**
Social Functioning			*Social Functioning*		
SSRS	89.24	17.26	SSIS	91.85	15.25
ADHD Symptomatology			*ADHD Symptomatology*		
CPRS-R			Conners-3		
Hyperactivity	54.04	10.94	Inattention	67.23	13.04
Cognitive Problems/ Inattention	56.84	12.16	Hyperactivity/ Impulsivity	61.33	13.98
ADHD Index	55.46	10.52			
Cognitive Function			*Cognitive Function*		
DAS-II			DAS-II		
GCA	93.02	11.87	GCA	93.90	13.24
Verbal	96.00	12.8	Verbal	98.65	13.20
Nonverbal	93.54	12.59	Nonverbal	94.08	15.56
Spatial	92.5	12.59	Spatial	91.82	11.36

Table 6. Descriptive statistics of measures by age group for longitudinal participants (n=25)

	Early Childhood			School Age	
Scale	**Mean**	**SD**		**Mean**	**SD**
Social Functioning					
SSRS	96.24	16.58	SSIS	92.76	13.51
ADHD Symptomatology					
CPRS-R			Conners-3		
Hyperactivity	49.32	6.05	Inattention	66.08	12.75
Cognitive Problems/ Inattention	54.88	10.91	Hyperactivity/ Impulsivity	59.00	11.81
ADHD Index	51.84	8.38			
Cognitive Function					
DAS-II					
GCA	94.56	9.87		94.60	14.09
Verbal	98.76	11.22		99.72	14.74
Nonverbal	93.88	11.99		93.80	17.95
Spatial	94.10	9.91		92.76	10.89

Table 7. Correlations between social functioning standard scores and ADHD symptomatology and cognitive function by age group

	Early Childhood		**School Age**	
	Social Functioning			
	SSRS		SSIS	
Scale	*rho*	*p*	*rho*	*p*
ADHD Symptomatology				
CPRS-R				
Hyperactivity	-.46	<.001***	-.05	.42
Cognitive Problems/Inattention	-.25	.04*	-.39	.026*
ADHD Index	-.37	.004**	-.29	.081
Conners-3				
Inattention		-	-.42	.004**
Hyperactivity/Impulsivity		-	-.35	.013*
Cognitive Function – T1				
General Conceptual Ability (GCA)	.26	.034*	-.06	.39
Verbal	.15	.14	-.19	.18
Nonverbal	.21	.068	.15	.24
Spatial	.22	.097	.15	.26
Cognitive Function – T2				
General Conceptual Ability (GCA)		-	.025	.44
Verbal		-	-.05	.37
Nonverbal		-	.01	.48
Spatial		-	.09	.29
*p < .05; **p < .01; ***p < .001				

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