Autism Spectrum Disorder Symptomatology in Children with Neurofibromatosis Type 1

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AUTISM SPECTRUM DISORDER SYMPTOMATOLOGY IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1

by

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Social problems are a common concern of parents of children with Neurofibromatosis type 1 (NF1). There has been a recent surge of research examining the prevalence of autism spectrum disorders (ASD) and ASD symptomatology in children with NF1. Findings from this relatively new body of research are mixed. The primary aim of this study was to examine ASD symptomatology in children with NF1 using a comprehensive assessment of ASD symptoms. A second aim was to examine possible variables that may contribute to socio-communicative difficulties. Participants included 25 children with NF1 between the ages of 9 and 13, along with their parent. Standardized parent-report questionnaires were used to assess social responsiveness and restrictive and repetitive behaviors (RRB; Social Responsiveness Scale, Second Edition: SRS-2) and ASD symptomatology (Social Communication Questionnaire: SCQ). Diagnostic assessment measures for ASD were used to examine the frequency and severity of ASD symptomatology (Autism Screening Interview: ASI, and Autism Diagnostic Observation Scale, Second Edition: ADOS-2). Selected measures were used to assess intellectual functioning, attention, social cognition, and pragmatic language. Overall, results indicate that 30% of parents observed mild to moderate social responsiveness difficulties and RRB on the SRS-2. However,
no children met diagnostic criteria for ASD based on the combination of ASI and ADOS-2 classifications and very few RRB were reported by parents or observed by clinicians. Relations between social responsiveness and intellectual functioning, social information processing, and pragmatic language were found. Performance on a pragmatic language task uniquely explained 38% of the social responsiveness difficulties reported by parents. Results indicate that children with NF1 are demonstrating elevated ASD symptomatology per parent and clinician report; however, those difficulties are largely not severe nor pervasive enough to meet criteria for ASD.
To
my parents,
my brothers,
and my friends
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Autism Spectrum Disorder Symptomatology in Children with Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) is one of the most common genetic disorders, presenting in approximately 1 in 3,500 live births. NF1 is a highly variable condition with a large number of medical, cognitive, and psychosocial sequelae. During childhood, medical features of the disease most often include the presence of café-au-lait spots and skinfold freckling. However, the most common manifestations reported by parents of children with NF1 are difficulties in cognition and psychosocial functioning. Previous research has focused on exploring the neuropsychological phenotype of children with NF1 and examining broad domains of psychosocial functioning. A growing body of literature has recently begun to examine the social functioning of children with NF1, and more specifically, exploring possible variables that may contribute to poor social functioning. Additionally, there has been a recent surge of research examining the prevalence of autism spectrum disorders (ASD) in children with NF1. Findings from this relatively new body of research are mixed, with some studies reporting high rates of ASD and ASD symptomatology in children with NF1 and some studies reporting only mild social difficulties. Therefore, the primary aim of this study was to examine ASD symptomatology in children with NF1 using a comprehensive assessment of ASD symptoms. In addition, this study aimed to examine possible variables that may contribute to socio-communicative difficulties, such as intellectual functioning, attention, social cognition, and pragmatic language skills.

In this introduction, the current literature on the social difficulties and ASD symptomatology often reported in children with NF1 will be examined. First, I will provide general background information about NF1. I will briefly describe medical features and the
common cognitive and behavioral characteristics of individuals with NF1. Second, I will review research examining social difficulties and risk factors that may contribute to poor social outcomes in children with NF1. Third, I will provide general background information about ASD. I will briefly describe the diagnostic criteria and symptoms associated with ASD. Fourth, current research examining the overlap between NF1 social difficulties and ASD symptomatology will be explored. Finally, I will provide a brief summary and rationale for the current study.

**Literature Review**

**Neurofibromatosis Type 1**

Neurofibromatosis type 1 is an autosomal dominant disorder with an incidence of approximately 1 in 3,500 live births (Huson & Hughes, 1994; North, Riccardi, Samango-Sprouse, & Ferner, 1997). NF1 is caused by a mutation of the *NF1* gene on the long arm of chromosome 17q11.2, which is responsible for encoding neurofibromin. NF1 has an autosomal dominant pattern of inheritance, although half of all cases result from a spontaneous mutation. Diagnosis requires the presence of two or more of the following criteria: (1) 6 or more café au lait spots, (2) axillary or inguinal freckling, (3) 2 or more cutaneous neurofibromas, (4) 1 plexiform neurofibroma, (5) 2 or more iris Lisch nodules, (6) an optic glioma, (7) a characteristic body lesion, or (8) first degree relative with NF1 (NIH Consensus Development Conference, 1987). The most common manifestations to first appear in childhood are café au lait spots and axillary freckling. A study of children with NF1 by Cnossen et al. (1998) reported that as many as 96.7% of children diagnosed with NF1 displayed six or more café au lait spots by 3 years of age. Freckling was found in 85.3% of children with NF1 by the 4 years of age (Cnossen et al.,
Recent advances in genetic testing have made it possible to confirm diagnosis in approximately 95% of individuals diagnosed clinically with NF1 (Tonsgard, 2006).

**Neuropsychological Phenotype of Children with NF1**

NF1 is a highly variable condition with a large number of medical, cognitive, and psychosocial difficulties and while physical medical features are indeed problematic for many children with NF1, the most common complaints from parents of children with NF1 are not medical in nature, but rather neuropsychological and behavioral. Children with NF1 are at higher risk for cognitive problems, as well as learning and attention difficulties. Several studies have found that although children with NF1 have cognitive abilities that fall in the average range, the IQ curve is shifted to the left (with a mean around 90) when compared to unaffected children (Hyman, Shores, & North, 2005; North, Joy, Yuille, Cocks, & Hutchins; 1995). Additionally, it has been suggested that as many as 50-65% of children with NF1 have a learning disability, with variability in the nature of the learning disability (Brewer, Moore, & Hiscock, 1997; Hyman et al., 2005; Krab et al., 2008; North et al., 1995). Based on current literature, up to half of children with NF1 have visuospatial ability difficulties, with performance falling one standard deviation or more below population norms even after controlling for intellectual functioning and attention difficulties (Hyman et al., 2005; Levine, Materek, Abel, O'Donnell, & Cutting, 2006; Schrimsher, 2003). Fine motor coordination impairment and low motor speed have been reported in 20-30% of children with NF1 (Casnar, Janke, van der Fluit, Brei, & Klein-Tasman, 2014; Hyman et al., 2005; Levine et al., 2006). Executive functioning and attention skills have also been shown to be an area of difficulty for children with NF1 (Casnar & Klein-Tasman, 2016; Hyman et al., 2005; Ferner, Chaudhuri, Bingham, Cox, & Hughes, 1993; Huijbregts, Swaab, & de Sonneville, 2010; Payne, Hyman, Shores, & North, 2011; Pride, Payne, & North, 2012;
Rowbotham, Pit-ten Cate, Sonuga-Barke, & Huijbregts, 2009). Hachon, Iannuzzi, and Chaix (2011) report that 30-50% of children with NF1 meet the diagnostic criteria for ADHD. Finally, in regards to psychosocial functioning, research suggests that children with NF1 have more difficulties than unaffected children on measures of internalizing and externalizing disorders (Barton & North, 2004; Graf, Landolt, Mori, & Boltshauser, 2006; Johnson, Saal, Lovell, & Schorry, 1999; Noll et al., 2007).

Social Functioning in Children with NF1

Early studies examining parental report of general psychosocial functioning found that children with NF1 are frequently teased, more often rejected by their peers, have difficulties forming friendships, and have more difficulty getting along with siblings than typically developing children (Benjamin et al., 1993; Dilts, Carey, Kircher, & Hoffman, 1996; Johnson et al., 1999; North et al., 1995). Barton and North (2004) examined parent, teacher, and self-report of social skills in children with NF1 compared to unaffected siblings. No significant differences between groups were found; however, children with NF1 had poorer social skills compared to normative data. Noll et al. (2007) investigated social behavior and peer relationships in children with NF1 using classroom peer and teacher ratings. Results indicated that children with NF1 had fewer friendships, were selected less often as a best friend, and were less well liked than their classroom peers. Their teachers and peers also rated them as having fewer leadership skills and being more sensitive and isolated. However, it is important to note that teachers reported more prosocial behaviors in children with NF1 relative to their peers.

The reasons for poor social functioning in children with NF1 are not well understood. Several researchers have examined possible risk factors for poor social skills and social outcome in NF1 (Barton & North, 2004; Eeghen, Ueland, & Johansen, 2012; Huijbregts et al., 2010;
Huijbregts & Sonneville, 2011; Noll et al., 2007). Barton and North (2004) attempted to parse out possible factors that could contribute to poor social functioning, such as, intellectual functioning, learning disabilities, low academic achievement, ADHD, physical symptoms associated with NF1, and pattern of inheritance. Barton and North (2004) reported finding no significant relations between the risk factors examined, with the exception of ADHD. These authors found that children with comorbid NF1 and ADHD had poorer social skills than any other subgroups examined (NF-Alone, NF-Low Academic/LD). Walsh et al. (2013) found similar significant relations between ADHD symptoms, social information processing, and social communication in their study. Additionally, Noll et al. (2007) also examined the relation between social problems and neurological involvement (which included conditions such as ADHD, LD, Borderline IQ, seizures, etc.) in their peer and teacher rating study and found neurological severity to be significantly related to social problems. These finding suggest that attention difficulties and learning problems, which are found in higher frequency in the NF1 population, may be affecting children with NF1’s ability to facilitate positive social interactions and foster successful peer relationships.

Few studies have explored how social information processing skills may relate to social difficulties. Huijbregts et al. (2010) examined the relation between social information processing and cognitive control in 32 children with NF1 compared to 32 unaffected children. Children with NF1 had difficulties identifying fear and anger. They also had more difficulty on profile facial recognition and matching facial emotions. Results also indicated that while cognitive control played a large role in impaired facial processing, children with NF1 still had difficulty with bottom-up encoding of social stimuli. Additionally, Huijbregts et al. (2010) found that many of the significant group differences remained after excluding children with a known diagnosis of
ADHD from the analysis. The authors suggest that these findings may indicate that attention deficits do not determine social information processing difficulties in NF1 and that despite a well-documented association between ADHD and cognitive control deficits, there appears to be NF1-specific neuronal abnormalities that causes problems with cognitive control and social processing. Huijbregts and Sonneville (2011) found similar results when investigating relations between cognitive ability (including processing speed and cognitive control), social information processing, and socio-emotional problems in 30 children with NF1 compared to 30 healthy control children. Children with NF1 had poorer cognitive control, slower processing speed, and lower social information processing scores compared to healthy controls. For children with NF1, cognitive abilities best explained variability in emotional problems and social responsiveness, whereas social information processing deficits best explained variability in conduct and peer relations problems. However, group differences in autistic traits, peer problems, social skills, and hyperactivity-inattention symptoms remained even after controlling for cognitive ability and social processing. This suggests that children with NF1 are demonstrating difficulties with both top-down processing (cognitive control) and bottom-up (social information processing) of social information.

In sum, these studies seem to suggest that the social difficulties described by parents and teachers of children with NF1 may at least be in part due to certain risk factors or aspects of cognitive processing. Attention difficulties, intellectual ability, learning disorders, and social cognition skills all appear to explain away some of the social difficulties reported by parents and teachers, yet social difficulties consistently remain. However, findings from these studies should be interpreted with caution. Many studies utilized a small sample size that stretched across a broad age range. Small sample sizes could limit the power necessary to detect moderating
factors. Additionally, many studies relied on medical record review in determining diagnosis of ADHD, LD and other variables. Although medical records often include formal neuropsychological testing, assessment procedures are often quite varied and could have been completed at different ages. A more uniform, systematic assessment of risk factors is needed. Finally, from a more theoretical standpoint, since successful social functioning requires the collaboration of many distinct, but related, cognitive processes, it is difficult to tease apart what exact processing skills are responsible for which exact deficit. However, what is clear from the research described above is that parents and teachers are concerned about the social functioning of children with NF1 and more research is needed to identify the social behaviors that are most problematic and the associated risk factors that may play an important role in those difficulties.

**Autism Spectrum Disorders**

Autism Spectrum Disorder is a developmental disorder characterized by significant and persistent impairments in social communication, social interaction, and restricted and repetitive patterns of behavior or interests. Current general population prevalence rates for ASD are estimated to be 1:68 children, with males showing a greater incidence (1:42) than females (1:189; Centers for Disease Control and Prevention [CDC], 2014). Symptoms are evident in early childhood and core symptoms are suggested to be apparent by 12 months of age (Maestro et al., 2002; Werner, Dawson, Osterling, & Dinno, 2000; Werner & Dawson, 2005). Most researchers agree that ASD is a complex disorder in which both environmental and genetic factors play a role in who develops the disorder (Mazina et al., 2015). Evidence from twin and sibling studies provides strong support for the involvement of genetic risk factors in the development of ASD (Bailey et al., 1995; Folstein & Rutter, 1977; Smalley, Asarno, & Spence, 1988). Many genome-wide linkage studies of ASD have been conducted in order to explore
possible genetic underpinnings; however, results from these studies have shown limited success (Yuen et al., 2015). Several single-gene disorders have been associated with an increased risk for ASD or expression of ASD symptomatology, including fragile X syndrome, Rett syndrome, tuberous sclerosis, and NF1 (CDC, 2014). Research examining ASD symptomatology in these single-gene disorders provides a platform for future research aimed at characterizing the possible genetic risk factors and cognitive mechanisms for the development of ASD.

DSM-5 diagnosis of ASD requires the presence of deficits in two core domains. The first domain includes deficits in social communication and social interaction (SCI) that must be present across multiple contexts. Symptoms described in this domain include (1) deficits in social-emotional reciprocity; (2) deficits in nonverbal communicative behaviors used for social interaction; and (3) deficits in developing, maintaining, or understanding social relationships. The second domain includes the presence of restricted repetitive patterns of behavior, interest, or activities (RRB). Symptoms described in this domain include (1) stereotyped or repetitive motor movements, use of objects, or activities; (2) insistence on sameness, inflexibility to routines, or ritualized patterns of verbal or nonverbal behavior; (3) highly restricted, fixated interest that are abnormal for developmental level; and (4) hyper- or hypo-activity to sensory import or unusual interested in sensory aspects. At least two symptoms must be present in this domain in order to meet diagnostic criteria for ASD. Additionally, the criteria specify that symptoms must be present in early development, cause clinically significant impairment, and are not better explained by an intellectual disability or global developmental delay (American Psychiatric Association, 2013). The DSM-5 diagnostic criteria also include a severity specifier that was intended to help clinicians succinctly describe the current symptomatology.
Diagnostic procedures for ASD are often quite varied depending on provider preferences and provider resources. Typically, an ASD diagnosis is made by a clinical psychologist, psychiatrist, or neurologist and includes an interview with a caregiver regarding early development and ASD symptomatology, behavioral observations made by the clinician, and formal assessment. It is important to note that the diagnosis of ASD in individuals with a genetic condition can be especially challenging. Many genetic syndromes present with socio-communicate difficulties that overlap with ASD symptoms; however, the presence of these behaviors themselves does not necessarily warrant a comorbid ASD diagnosis. The complex, and often unusual, cognitive and behavioral phenotypes that are characteristic of numerous genetic disorders may result in individuals reaching and/or exceeding ADI-R and ADOS-2 cutoffs artificially (Moss & Howlin, 2009). This could be especially true if the genetic syndrome is associated with intellectual disability (Kaufman, Ayub, & Vincent, 2010). Therefore, it is important to disentangle the association between ASD and genetic symptomatology meticulously at both the diagnostic and behavioral level.

Much of the previous research examining ASD symptomatology in children with NF1 utilized DSM-IV diagnostic criteria and/or ASD diagnostic classifications based on an algorithm which was developed by the National Institute of Child Health and Human Development Collaborative Programs of Excellence in Autism (CPEA; Lainhart et al., 2006). The DSM-5 criteria for ASD are thought to be stricter and more thorough compared to the DSM-IV criteria and CPEA guidelines (Grzadzinski, Dick, Lord, & Bishop, 2016; Lainhart et al., 2006; Young & Rodi 2014). The DSM-IV identified a set of Pervasive Developmental Disorders that were considered to fall under the ASD umbrella, including Autistic Disorder, Asperger's Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). Besides the removal
of Asperger's Disorder and PDD-NOS as separate disorders, the new DSM-5 criteria made significant changes to the specific criteria needed for a diagnosis of ASD. For example, in the DSM-5 criteria, evidence of impairment needs to be present for all three symptoms listed in the SCI domain and at least 2 of the 4 symptoms listed in the RRB domain. The old DSM-IV criteria required the presence of a total of six (or more) symptoms from the Social Interaction (SI), Social Communication (SC), and RRB domains, with at least two from the SI, one from the SC, and one from the RRB domains. Therefore, a child only needed to show evidence of one RRB, as opposed to the two that are required for a diagnosis of Autism from the DSM-5. Furthermore, an individual could be diagnosed with PDD-NOS based on a range of symptomatology that might or might not include RRBs.

CPEA diagnostic guidelines for Autism, Asperger’s Disorder, and broad-ASD were developed for research purposes to ensure standardized diagnostic classifications across research sites and are based upon scores from the ADI-R, ADOS, and Best Estimate Clinical (BEC) diagnosis as determined by a clinician (CPEA; Lainhart et al., 2006). According to CPEA guidelines, for a diagnosis of Autism or Asperger’s Disorder an individual must meet specific ADI-R classification cutoffs, ADOS classification of “Autism” or Autism Spectrum”, and/or BEC, which is similar to the diagnostic criteria in the DSM-5. However, the classification criteria threshold for broad-ASD is not restricted to DSM-5 diagnostic criteria. Additionally, the CPEA approach relaxed the empirically-developed diagnostic algorithms for the ADI-R and ADOS. In order to meet for a diagnosis for broad-ASD an individual only needs to meet ADI-R cutoffs in 1 in the following 3 ways: 1) Meet cutoffs on the SI and SC domains, 2) Meet cutoffs on either the SI or SC domains and score with 2 points of the cutoff of the other, or 3) Score within 1 point of both the SI and SC domains (see Appendix A for a complete explanation of
CPEA diagnostic criteria). None of these methods requires the presence of RRB symptoms. This means that no RRB would need to be evident in order to meet diagnostic criteria for broad-ASD, which is in stark contrast to the diagnostic criteria presented in DSM-5. Additionally, subthreshold scores on the SI and SC domains would also suffice for a diagnosis of ASD according to CPEA guidelines.

**Autism Spectrum Disorder Symptoms in Children with NF1**

Recently, there has been a surge of research examining prevalence rates of ASD within the NF1 population. As described above, it has been well established that children with NF1 show impairments in social functioning per parent and teacher report (Benjamin et al., 1993; Dilts, Carey, Kircher, & Hoffman, 1996; Huijbregts et al., 2010; Huijbregts and Sonneville, 2011; Johnson et al., 1999; North et al., 1995). Additionally, early ASD prevalence studies and case studies indicated an increased rate of NF1 in the ASD population. These early studies found relatively low to moderate levels of co-occurrence, ranging from 0.6 to 6% (Fombonne, Du Mazaubrun, Cans, & Grandjean, 1997; Gillberg & Forsell, 1984; Mouridsen, Andersen, Sorensen, Rich, & Isager, 1992; Williams & Hersh, 1998). These studies were the first to demonstrate a relation between NF1 and ASD, but were limited by their variability in design and potential sampling bias.

More recently, several studies have examined the relations between NF1 social difficulties and ASD symptomatology more systematically. The majority of this research has been done using social responsiveness and RRB screening measures, such as the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005) and the Children Social Behavior Questionnaire (CSBQ; Luteijn, Jackson, Volkmar, & Minderaa, 1998), and/or by utilizing ASD-specific screening measures, such as the Social Communication Questionnaire (SCQ; Rutter,
Bailey, & Lord, 2003), Modified Checklist of Autism for Toddlers (M-CHAT; Robins, Fein, Barton, & Green, 2001) and the Childhood Asperger Syndrome Test (CAST; Scott, Baron-Cohen, Bolton, & Brayne, 2002). Currently, these studies report elevated levels of ASD symptomatology in 11-29% of individuals with NF1 (Walsh et al., 2013; Garg et al., 2013a; Garg et al., 2013b; Tinker et al., 2014; Adviento et al., 2013; Plasschaert et al., 2014).

Walsh et al. (2013) examined parental report of ASD symptomatology using the SRS in 66 school-aged children and found significantly elevated symptomatology. Walsh et al. (2013) noted that 14% of the sample reached clinically significant levels (T-score <75) of ASD symptomatology. The authors indicated that the most commonly reported ASD symptoms were in the Autistic Mannerisms domain (elevated in 44% of the sample), which assesses RRB, such as, problems with flexibility, transitions, and perseverative behaviors. Impairments on the Social Communication, Motivation, Awareness, and Cognition domain scores were also present for 30% of the sample. Garg et al. (2013b) also used the SRS to assess ASD symptomatology in 109 school-aged children with NF1 and found that 29% of the children scored in the severe range and 26% scored in the mild to moderate range using the SRS Total Score by parent report. Sixty-eight percent of children in this study scored in the mild, moderate, or severe range by their parents on the Autistic Mannerism domain. However, rates of difficulties were significantly lower on a subset of children in which teacher report of SRS scores were available. According to teacher report, only 6% of children scored in the severe clinical range and 25% scored in the mild to moderate range on the SRS Total Score. Additionally, only 26% of children with NF1 were reported to have elevated scores (T-score >60) on the Autistic Mannerisms domain by their teachers, suggesting that teachers are seeing fewer social responsiveness difficulties, RRB, and less ASD symptomatology within the school setting.
Tinker et al. (2014) examined ASD symptomatology in 40 school-aged children with NF1 using the CAST, an autism specific screening questionnaire. Tinker et al. (2014) were interested in examining prevalence rates using a comparison to general population norms provided by Williams et al. (2005). Tinker et al (2014) reported that 5 out of 40, or 13%, screened positive on the CAST, which was not significantly different from the Williams et al. (2005) general population data (6%). However, the authors did note that children with NF1 had higher mean and median scores when compared to control norms. The authors proposed that results could suggest that school-aged children with NF1 may exhibit more ASD symptoms, without actually meeting threshold for a true diagnosis of ASD. The authors examined the questions that were most often endorsed and found that both social communication and RRB were reported by parents.

Adviento et al. (2013) assessed ASD symptomatology using the SCQ and SRS in a sample of 66 school-aged children and adults with NF1, along with a sample of children and adults with other RASopathies (e.g. Noonan (NS), Costello (CS), and cardio-faco-cutaneous (CFC) syndromes). On the SCQ, 11% of participants with NF1 had scores above the threshold indicative of a possible ASD diagnosis. The NF1 group had the lowest reported rates of ASD symptomatology on the SCQ within the sample of RASopathies, with 54% of CFC, 26% of CS, and 21% of NS participants meeting or exceeding the threshold. On the SRS, mean scores for participants with NF1 were within the normal range ($M = 57, SD = 16$) per parent report; however, approximately 13% received scores in the severe clinical range and 30% received scores in the mild to moderate range. This was, again, the lowest score compared to the other RASopathies (CFC: $M = 74, SD = 13$; NS: $M = 65, SD = 17$; CS: $M = 61, SD = 10$). Adviento et
al. (2013) also indicated that 7 out of 66 (11%) NF1 participants exceeded cutoff on both the SCQ and SRS.

Finally, a recent study by Plasschaert et al. (2014) examined ASD symptomatology using the CSBQ and SRS in a sample of 82 school-aged children with NF1. The authors reported that the mean total score for both the CSBQ and the SRS were significantly higher than the normative mean (CSBQ: NF1 raw = 24.8, SD = 16.3; Normative raw = 10.2, SD = 9.0; SRS: NF1 M = 69.94, SD = 19.29). Thirty percent of children with NF1 scored in the mild to moderate range and an additional 33% scored in the severe clinical range on the SRS Total Score. Plasschaert et al. (2014) noted that the Social Cognition domain was the most severely affected (elevated in 66% of the sample), followed by subclinical elevations in the Social Communication (57%) and Autistic Mannerisms (58%) domains. Age was significantly correlated to symptomatology, with more social difficulties reported with increasing age. Plasschaert et al. (2014) found significantly less social problem behaviors reported in children with NF1 before the age of 8. The authors also noted that males were reported to have significantly more social problems than females on both measures.

Only one study has examined ASD symptomatology in young children with NF1. Tinker et al. (2014) examined parental report of ASD symptomatology using the M-CHAT on a sample of toddlers with NF1. The M-CHAT is a widely used ASD screening measure and was developed for children between the ages of 16 to 48 months. The M-CHAT utilizes a cutoff score to specify a positive screen, which indicates a need for further evaluation. Tinker et al. (2014) compared the M-CHAT scores to general population norms provided by Robins et al. (2001) and Miller et al. (2011). Tinker et al. (2014) did not find an increased rate of ASD in their sample of NF1 toddlers using the M-CHAT. In fact, 0 out of 20 toddlers with NF1 screened
positive, compared to 5% from Robin et al. (2001) and 6% from the Miller et al. (2011) general population studies. These findings are different from previous research examining ASD symptomatology in school-aged children (Adviento et al., 2013; Garg et al., 2013b; Plasschaert et al., 2014; Walsh et al., 2013), suggesting that young children with NF1 are not at a significantly increased risk for ASD. The authors proposed a couple different ways of interpreting the results of their study. One interpretation suggested that children with NF1 show certain characteristics that put them at a higher risk for ASD symptoms, but they do not have an increased risk for a diagnosis of ASD when compared to the general population. The authors also proposed that it is possible that children with NF1 may not manifest ASD symptoms until later in life (e.g. school-age); however, this would be in stark contrast to what is known regarding the early development of socio-communicative difficulties and RRB in children with ASD (Maestro et al., 2002; Werner, Dawson, Osterling & Dinno, 2000; Werner & Dawson, 2005). Finally, Tinker et al. (2014) suggest that it may be that the M-CHAT is not a sensitive ASD screening measure for children with NF1.

Studies examining the overlap between NF1 and ASD symptomatology using questionnaire data are essential for better understanding parent and teacher perspectives of socio-communicative difficulties in children with NF1. To date, several studies have specifically examined this overlap and, unfortunately, the findings are still mixed. The studies described above have several limitations that may make interpretation difficult and may contribute to the variability in findings. Most studies reviewed used published, normative data as their comparison control group. Doing this could mask subtle difficulties that may still be significant for children with NF1. Also, when examining finding by their geographical location, it appears that European studies (Garg et al., 2013b; Plasschaert et al., 2014) tend to report higher rates of severe
difficulties compared to American studies (Walsh et al., 2013; Tinker et al., 2014; Adviento et al., 2013). It is unclear whether there may be cultural factors at play that affect the type and/or frequency of social difficulties and RRB that parents of children with NF1 are reporting. Additionally, as Payne (2013) points out, it is important to keep in mind that while questionnaires can provide us with useful information about symptoms, they do not indicate disorder. While the SRS has demonstrated good psychometric properties, recent studies suggest that elevated scores on the SRS are strongly correlated to problem behavior, more generally (Charman et al., 2007; Hus, Bishop, Gotham, Huerta, & Lord, 2012). Therefore, it is possible that there is an increased risk of false positives for children with NF1 given they often display a wide-range of problem behaviors that overlap with other neurodevelopmental disorders, such as attention difficulties and externalizing and internalizing problems.

**ASD in NF1 using Comprehensive Evaluations**

Only four studies have examined NF1 and ASD symptomatology using comprehensive autism diagnostic evaluation. A follow-up, population-based prevalence study by Garg et al. (2013a) investigated ASD diagnosis using the Autism Diagnostic Interview-Revised (ADI-R: Lord, Rutter, & Le Couteur, 1994) and the Autism Diagnostic Observation Schedule-Generic (ADOS-G: Lord et al., 2000) in a sample of children with NF1. The ADI-R is a standardized parent interview used to help aide in the diagnosis of ASD. The ADOS-G is a semi-structured observational assessment of socio-communication, social interaction, and play skills. It is important to note that the ADOS-G diagnostic algorithm does not include assessment of RRB, which has been identified as a core and necessary symptom cluster of ASD according to the DSM-5 (American Psychiatric Association, 2013). ASD diagnostic classification was based on CPEA diagnostic guidelines (CPEA; Lainhart et al., 2006). Participants included 47 children
from the Garg et al. (2013b) screening study. The authors indicated that 30% of children with NF1 met criteria for ASD, 28% met criteria for broad ASD, and 43% were identified as non-spectrum. After adjusting for probability of responding rates from the first study (Garg et al., 2013b), whole-population prevalence in NF1 was identified as 25% for ASD and 21% for broad ASD. The authors did not find a significant difference in intellectual functioning between the three groups. Severity of everyday adaptive functioning, and severity of socialization and communication impairment on the ADOS-G and ADI-R were ordered across the three groups as would be expected, with most impairment in the ASD group. However, RRB (based on the ADI-R) and deficits in everyday socialization skills (based on the Vineland Adaptive Behavior Scale) were particularly associated with the ASD group. The authors collapsed the ASD and broad ASD groups to compare with the non-spectrum children. Results indicated no significant differences in age, SES, familial NF1 status, NF1 physical severity, or special educational services between ASD children and non-spectrum children. Garg et al. (2013a) noted that there was a significantly higher male to female ratio in the ASD group.

Adviento et al. (2013) also conducted a follow-up study that examined ASD symptoms in three children with NF1 who screened positive for ASD (on at least one screening measure) in their ASD screening study described above. The authors also evaluated one negative control participant, with below-threshold scores on both screening measures. A comprehensive assessment that examined intellectual functioning, adaptive functioning, and ASD symptoms using the ADI-R and the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2: Lord, Rutter, Risi, Gotham, & Bishop, 2012) was conducted. Results were provided for each participant. The negative control participant, who did not initially screen positive for ASD, received a classification of non-spectrum on both the ADI-R and ADOS-2. Two of the 3 children
who initially screened positive for ASD received classifications of autism or autism spectrum on both the ADI-R and ADOS-2. The third child, who initially screened positive for ASD, received a classification of non-spectrum on the ADI-R and ADOS-2 and was diagnosed with Social Anxiety Disorder. Final determination of an ASD diagnosis was based on clinical impressions and generally matched ADI-R and ADOS-2 classifications. The most frequent impairments on the ADOS-2 across all the RASopathies were in speech abnormalities, limited inquiry into the thoughts, feelings or experiences of others, and limited sharing of information about oneself, poor recognition of others emotions, poor insight into typical social relationships, and deficits in imaginative use of objects (Adviento et al., 2013).

Plasschaert et al. (2014) also conducted a follow-up study examining ASD symptoms in a subset of children with NF1. Selection was based on results from screening measures and clinical impression. ASD diagnosis was determined using DSM-IV-TR diagnostic criteria and made by a multidisciplinary team of educational psychologists, a speech therapist, and a child psychiatrist. Thirty-one children with NF1 underwent a comprehensive ASD evaluation that included assessment of intellectual functioning and administration of the ADOS-2. Results indicated that 27 of the 33 children evaluated received an ASD diagnosis. When taking into consideration all of the children screened in the initial study, Plasschaert et al. (2014) concluded that a minimum prevalence estimate of 26% of ASD was found in NF1. No significant difference in the proportion of familial versus sporadic cases of NF1 was found; however, a higher male to female ratio was reported in the ASD group. The authors indicated that according to ADOS-2 analysis, 15% of the group presented with minimal ASD symptoms, 48% presented with moderate ASD symptoms, and 4% presented with severe ASD symptoms. However, results of this study should be interpreted with caution, as 14% of the children who were diagnosed with ASD did not have
ADOS-2 scores available. Additionally, detailed information about ADOS-2 scores and how clinical diagnosis was determined was not adequately described in the article.

Finally, Garg et al. (2015) examined ASD symptomatology in 36 children with a comorbid diagnosis of NF1 and ASD (NF1+ASD). In this study, Garg et al. (2015) described the behavioral phenotype of children with NF1 together with a diagnosis of ASD (based on meeting or exceeding the cutoff scores on the SRS and ADOS-2 algorithm items). Results indicate that generally, children with NF1+ASD demonstrated a similar behavioral phenotype to the ASD/autism groups provided in the ADOS-2 manual (Lord et al., 2012). However, children with NF1+ASD had better eye contact, fewer RRB, and better language skills compared to the ASD/autism groups. Results also noted a discrepancy between parent-reported and clinician-observed RRB symptoms, with 67% of parents reporting severe elevations in RRB on the SRS and clinicians observing RRB in only a few children with NF1. The authors suggested that given these findings, the new DSM-5 diagnosis of Social (Pragmatic) Communication Disorder (SCD) may more accurately describe the social impairments seen in the NF1+ASD group (American Psychiatric Association, 2013).

Overall, while these recent comprehensive studies are important for better understanding the overlap of ASD and NF1, they are not without limitations. One limitation includes the potential overestimation of prevalence rates due to response bias during both the screening stage and during the comprehensive assessment stage. Additionally, few studies reported data regarding specific ASD symptom frequency and severity. Having more information about the most commonly reported symptoms and level of severity would be important clinical information for parents and caregivers of children with NF1 and would also characterize the nature of difficulties typically observed for those who exceed cutoff. Finally, some of the studies
reviewed above relied on DSM-IV diagnostic criteria for ASD that did not require symptoms from the RRB domain to be endorsed, which could lead to an overestimate of diagnoses. Therefore, more research is needed to examine specific ASD behaviors, as well as the frequency and severity of those behaviors, in children with NF1.

Summary and Study Rationale

Social problems are a common concern of parents of children with NF1 (Benjamin et al., 1993; Dilts et al., 1996; Johnson et al., 1999; North et al., 1995). Data on parental report of social difficulties indicate significant elevations in autistic traits, peer problems, and social skill difficulties (Barton & North, 2004; Noll et al., 2007). While difficulties in intellectual functioning, attention, learning problems, and social information processing can explain some of the difficulties in social functioning, they do not explain all of the variance (Eeghen et al., 2012; Huijbregts et al., 2010; Huijbregts & Sonneville, 2011). Studies investigating prevalence rates and symptoms clusters of ASD in NF1 are inconsistent (Adviento et al., 2013; Garg et al., 2013b; Garg et al., 2013a; Plasschaert et al., 2014; Tinker et al., 2014; Walsh et al., 2013). Therefore, a systematic examination of specific ASD symptomatology and its relation to risk factors for social difficulties is much needed. The study design was chosen to utilize both descriptive and exploratory methods in order to broaden and build upon existing literature. The primary aim of the current study was to examine ASD symptomatology in children with NF1 using a comprehensive assessment of ASD symptoms. In addition, this study aimed to examine possible variables that may contribute to socio-communicative difficulties, such as intellectual functioning, attention, social cognition, and pragmatic language skills.
Methods

Research Questions

**Primary Aim:** To explore socio-communicative behavior in children with NF1, and in particular, to examine overlaps in symptoms with ASD.

1a. What is the pattern of parent-reported socio-communicative behavior and RRB in a sample of children with NF1?

1b. Are there parent-reported socio-communicative behaviors or RRB that are more or less problematic for children with NF1?

1c. What is the pattern of clinician-observed socio-communicative and RRB behavior in a sample of children with NF1?

1d. Are there clinician-observed socio-communicative behaviors or RRB that are more or less problematic for children with NF1?

1e. What proportion of children with NF1 meet criteria for an ASD (using both the ADOS-2 and ASI) in a sample of children with NF1?

**Secondary Aim:** To examine possible variables that may contribute to poor socio-communicative behavior and RRB.

2a. Do intellectual functioning, attention, social cognition, and/or pragmatic language skills predict socio-communicative behavior and RRB difficulties?

Hypotheses

It is hypothesized that moderate levels of parent-reported socio-communicative difficulties and RRB will be endorsed on a measure of social responsiveness and RRB, but fewer children with NF1 will meet or exceed the cutoff on ASD-specific screening measures. It is also hypothesized that the majority of children with NF1 will demonstrate few clinician-observed
socio-communicative difficulties or RRB and that there will few items on which more than half of the sample demonstrates significant impairment. Finally, it is expected that variables that may contribute to socio-communicative difficulties and RRB, such as intellectual functioning, attention, social cognition, and pragmatic language, will be related to severity of social responsiveness difficulties. Specifically, it is expected that the children with NF1 with lower performance on these variables will also be the children who are more severely affected by behavioral symptoms overlapping with ASD.

Participants

Participants included (1) 25 children between the ages of 9 and 13 diagnosed with NF1, and (2) one parent of each child participant. Only children whose first and main language spoken in the home was English were included in this study. Children whose first and main language was not English were excluded because study measures and instructions were standardized and normed using English speaking populations. Additionally, children who had recently (within 6 months) had a significant surgery (heart or brain surgery) were excluded from this study, given that the effects of surgery could have an impact on their performance on study measures. Group demographic data is provided in Table 1.

Procedures

Participants were recruited using three methods. First, fliers describing the study were mailed to participants in our database who have participated in prior research with us and who consented to be informed of future studies in our lab. After the fliers were sent, families were called so that a member of the study staff could answer any questions they may have had about the study. Second, potential participants were recruited through the several Midwestern Neurofibromatosis Clinic. NF1 clinic directors shared a description of the study to families with
children between the ages of 9 and 13 with a known diagnosis of NF-1. Parents who were interested in participating or finding out more about the research were provided with a flier and encouraged to contact the PI or study coordinator. Finally, a flier was posted to the national Neurofibromatosis Research Registry and families within driving distance, who had noted their interest in being contacted about possible research opportunities on the Registry, were emailed a description of the study and a flier.

Participants who met eligibility requirements were schedule 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 guided through the consenting process and had an opportunity to ask questions or express concerns before agreeing to participate. Prior to the assessment appointment, the consent form and questionnaires were mailed to the family for parental completion. The questionnaires were designed to examine social difficulties and ASD symptoms. Each child was administered an age-appropriate neuropsychological battery by a trained member of the study team. Assessment sessions lasted approximately 4 hours for all children, including time for breaks to minimize fatigue. All assessment measures were administered to all children in the same order. Parents were interviewed about their child’s behavior during their child’s assessment in an adjacent room.

**Measures**

All measures chosen for this study were developed for use with children 9 to 13 and are widely used in pediatric assessment and research. All neuropsychological measures are norm-referenced and have demonstrated strong psychometric properties, including good reliability and validity. These measures have been used with both typically developing children and children with a variety of developmental disorders. These measures were selected to pick up on both
obvious impairments, as well as more subtle difficulties that are commonly found in children with NF1. A detailed description of each measure is provided below and an overview of the selected measures is listed in Table 2.

**Social Responsiveness Scale – Second Edition (SRS-2: Constantino & Gruber, 2012).** The SRS-2 is a parent questionnaire that measures social responsiveness difficulties and RRB that are associated with ASD and quantifies their severity. The SRS-2 has demonstrated evidence of good inter-rater reliability, high internal consistency, and convergent validity with the ADI-R, ADOS, and SCQ (Constantino & Gruber, 2012). The SRS-2 utilizes T-scores based on a gender-normalized, nationally representative standardization sample. Scores are provided for five treatment subscales, including the Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behavior (RRB) subscales. There are also two DSM-5 compatible subscales, including the Social Communication and Interaction (SCI) and Restricted Interests and Repetitive Behavior (RRB) subscales, which allows for comparison of symptoms to DSM-5 ASD diagnostic criteria. Interpretation is based on a single score, the SRS-2 Total Score, which reflects the sum of responses to all 65 items and serves as a continuous severity index of social responsiveness and repetitive behaviors that are indicative of ASD symptomatology. A Total Score of 76 or higher is considered severe and strongly associated with clinical diagnosis of ASD. Scores of 66-75 are interpreted as indicating moderate impairments and scores of 60-65 indicate mild impairments in social responsiveness. Scores of 59 and below are considered to be within typical limits and are generally not associated with clinically significant ASD symptomatology.

**Social Communication Questionnaire – Lifetime (SCQ; Rutter, Bailey, & Lord, 2003).** The SCQ is a parent-completed screening questionnaire that examines the level of ASD
symptomatology. The SCQ was designed as a companion screening measure for the ADI-R. The SCQ yields a raw score that is compared to a research derived cutoff score. Raw scores that are equal to or greater than the cutoff score (cutoff = 15) indicates the possibility of ASD and, therefore, the need of a more comprehensive evaluation. The SCQ demonstrates good reliability and good agreement with the ADI-R (Berument et al. 1999).

**Autism Symptom Interview (ASI; S. Bishop, personal communication with B. P. Klein-Tasman, Jan. 12, 2015).** The ASI is a newly developed structured interview based on the ADI-R and the SCQ. It was developed by Bishop and colleagues (S. Bishop and C. Lord, personal communication) with publication forthcoming. The ASI is a structured interview conducted with caregivers that assesses the presence and frequency of ASD symptomatology in preschool- and school-aged children. The measure was developed using questions from the ADI-R and SCQ and preliminary data has demonstrated good sensitivity (82%) and specificity (92%) when used in combination with the ADOS-2 classification (S. Bishop and C. Lord, personal communication). Similar to the ADI-R, the ASI utilizes a cutoff score (cutoff = 38) to determine ASD classification, with a range of raw scores from 0-116.

**Autism Diagnostic Observation Schedule – 2nd Edition (ADOS-2; Lord, Rutter, Risi, Gotham, & Bishop, 2012).** The ADOS-2 is a semi-structured, standardized assessment of socio-communication, social interaction, play/imaginative play, and RRB. It is considered the “gold standard” observational assessment for diagnosing ASD and demonstrates good reliability and validity (Lord et al, 2012). Based on observations made during the activities and interactions, rating codes are assigned for several ASD related symptoms. A subset of the codes were converted to algorithm scores that were then summed and used to complete a diagnostic classification (i.e. non-spectrum, autism spectrum, autism) based on empirically-derived cutoff
scores. Scores less than 7 were considered “non-spectrum”, scores between 7 and 9 were considered “autism spectrum”, and scores greater than 9 were considered a classification of “autism.” Additionally, the ADOS-2 provides a comparison score, which was developed as a way of indicating the level or severity of autism spectrum-related symptomatology. The comparison score ranges from 1 to 10, with a score of 1 indicating “minimal-to-no evidence” and 10 indicating “high evidence” of ASD symptomatology.

A graduate student who has been specifically trained to administer the ADOS-2 to “research reliable” standards administered this measure. In order to insure the reliability of scoring, 20% of cases were selected at random to be coded by another “research reliable” graduate student or faculty member. Cohen's κ was run to determine if there was agreement between the two coders on all ADOS-2 scores and codes. There was substantial agreement between the two coders, κ = .72, p < .001. There was agreement on 93% of all ADOS-2 items and 94% agreement on ADOS-2 algorithm items between coders.

**Differential Ability Scales-Second Edition: School-Age Form (DAS-II; Elliot, 1990).**

The DAS-II is a commonly used, comprehensive measure of cognitive abilities for children ages 7-0 to 17-11. The DAS-II is empirically derived and demonstrates excellent internal consistency, test re-test reliability and correlates highly with other commonly used measures of cognitive abilities (Elliot, 1990). The DAS-II provides normative data collected on a large representative national sample and contains excellent floor and ceiling levels, making it appropriate for children with neurodevelopmental disorders. This measure yields an overall composite score called the General Conceptual Ability (GCA) standard score (mean of 100, standard deviation of 15) that is equivalent to a full-scale IQ score. The GCA is broken down into three cluster scores, including Verbal Ability, Nonverbal Reasoning Ability, and Spatial Ability. In this study, participants
completed the core subtests for the School-Age Form (including Word Definitions, Verbal Comprehension, Matrices, Sequential and Quantitative Reasoning, Recall of Designs, and Pattern Construction) to yield a GCA.

**NEPSY – Second Edition: Auditory Attention/Response Set (NEPSY-II; Korkman, Kirk, & Kemp, 2007).** The NEPSY-II is a widely used measure that assesses children’s performance in areas of six theoretically derived domains, including Attention and Executive Functioning, Language, Memory and Learning, Sensorimotor, Social Perception, and Visuospatial function. Administration of selected subtests takes approximately 5-10 minutes and is designed for children 3-16 years old. The Auditory Attention/Response Set (AA/RS) subtest from the Attention domain has two parts; Auditory Attention was designed to assess sustained, selective auditory attention and Response Set was designed to assess shifting and sustained attention skills. This measure yields a combined scaled score (mean of 10, standard deviation of 3) that incorporates performance on the both portions of the task.

**Clinical Evaluation of Language Fundamentals – Fifth Edition: Metalinguistic (CELF-5 ML; Semel, Wiig, & Secord, 2014).** The CELF-5 ML is a standardized measure with good reliability and validity, designed to assess higher-level language skills, such as understanding inferences, conversational speech, multiple word meanings, and non-literal language (Semel, Wiig, & Secord, 2014). The CELF-5 ML was developed for children and adults from 9-21 years. The CELF-5 ML has five subtest including the Metalinguistic Profile, Making Inferences, Conversation Skills, Multiple Meanings, and Figurative Language. Performance scores for Making Inferences (MI) and Conversation Sills (CS) subtests can be used to derive a Meta-Pragmatic Language (MPLI) index score. For this study, the MPLI was used
and the MI and CS subtests were administered in order to examine pragmatic language skills. This measures utilized standard scores for both the subtests and the index.

**Cogstate Research Battery (Cogstate; [http://www.cogstate.com](http://www.cogstate.com)), selected subtests.**
The Cogstate battery is a commercially available, computerized cognitive testing system designed specifically for the use in research studies. Cogstate tasks have been shown to be highly reliable, repeatable, and sensitive. The entire Cogstate testing battery targets a wide range of cognitive domains, including processing speed, attention, executive function, and social-emotional cognition. For this study, the Visual Attention/Vigilance, Attention/Working Memory, and Social Cognition tasks were administered. For the Visual Attention/Vigilance domain, the Identification Task (IT) was completed. This task takes approximately 2 minutes to complete and yields an accuracy score in which higher scores indicate better performance. This task was designed to assess simple visual attention and vigilance/concentration. Within the Attention domain, the One Back Task (OBT) and Two Back Task (TBT) were completed. The OBT and TBT take approximately 4 minutes to complete and produce an accuracy score in which higher scores indicate better performance. These two tasks were designed to assess working memory and sustained visual attention skills. Within the Social Cognition domain, the Social-Emotional Cognition Task (SECT) was completed. The SECT takes approximately 7 minutes to complete and produces an accuracy score in which higher scores indicate better performance. This task was designed to assess emotional facial expression and eye expression recognition.

**Background Questionnaire.** The CNRL Background Questionnaire is a parent-completed questionnaire that was used to collect demographic information, which may aid in analysis of data (examining differences based on, for example, parental education or child medical history).
Results

In this section, the data from parent-reported and clinician-observed measures of socio-communicative difficulties for school-aged children with NF1 are provided. First, descriptive statistics examining group demographics will be provided. Next, descriptive statistics of parent-reported and clinician-observed socio-communicative difficulties, as well as, item-level analysis of ASD symptomatology on the ASI and ADOS-2 will be detailed. Additionally, descriptive statistics of intellectual functioning, attention, social cognition, and pragmatic language skills will be provided. Finally, relations between the severity of ASD symptoms and those variables that may contribute to socio-communicative difficulties will be examined.

The data were analyzed using IBM SPSS for Windows, version 22. When relevant, findings are interpreted with respect to both statistical significance and effect size. The frequencies of scores on individual items will be reported. Since current DSM-5 diagnostic criteria focuses primarily on the presence/absence of symptoms, ASI and ADOS-2 items will be examined with regard to the presence (scores of 1, 2, or 3) or absence (score of 0) of endorsement. Items for which more than half (>50%) of the sample endorsed the presence of a symptom (receives a score/code of 1, 2, or 3) will be especially highlighted and will be considered “common.” Items that were endorsed as present (endorsed by 33-50% of the sample), will also be discussed in order to add to the clinical utility of findings. Spearman’s rho was used when correlational analyses were conducted and interpretations of correlation effect size (Cohen, 1988) are as follows: small = 0.1 – 0.3; medium = 0.3 – 0.5; large = 0.5 – 1. The stability of the correlations must be interpreted with caution given the small sample size.
ASD Symptomatology in Children with NF1

Research Question 1a: What is the pattern of parent-reported socio-communicative behavior and RRB in a sample of children with NF1? A summary of parent-reported SRS-2 scores is detailed in Table 3. One parent did not complete the SRS-2; therefore, all analyses for the SRS-2 were completed using 24 children. Group mean scores fell in the normal range for all domain scores; however, independent one-sample t-tests indicated significantly higher scores than the normative mean on the Social Awareness, $t(23) = 3.05, p > .01$; Social Cognition, $t(23) = 2.38, p = .03$; and Social Communication, $t(23) = 2.66, p = .01$, domains; and on the Social Communication, $t(23) = 2.54, p = .02$; and Total Score, $t(23) = 2.64, p = .02$, indexes. Figure 1 details the distribution of normal (≤ 59), mild (60-65), moderate (66 – 75), and severe (≥ 76) problems reported by parents on the SRS-2. There were no children whose parents reported severe difficulties on the Social Awareness and Social Motivation domains, nor on the RRB, SCI, or Total Score indexes. There were also no domains in which over half of parents reported mild, moderate, or severe social problems. There were no difference in SRS-2 Total Score in relation to age, $r = .34, n = 24, p = .10$; nor sex, $F(1, 22) = 0.15, p = .70$.

Of the 25 children with NF1 whose parents completed the SCQ, zero parents reported ASD symptomatology that met or exceeded the cutoff score (≥ 15). SCQ scores ranged from 0 to 14, with a mean of 4.12, median of 3.00, and mode of 0. Figure 2 details the distribution of SCQ scores. Of the 25 children with NF1 whose parents completed the ASI, 3 (12%) met or exceeded the cutoff score (≥ 38). ASI scores ranged from 5 to 50, with a mean of 21.12, median of 20.00, and mode of 11, 15, 18, 24, and 30 (frequency of 2 each). Figure 3 details the distribution of ASI scores. There were no differences between SCQ and ASI Total Scores in relation to age, SCQ: $r$
Research Question 1b: Are there parent-reported socio-communicative behaviors or RRB that are more or less problematic for children with NF1? The frequencies of scores on ASI individual items are reported in Table 4. There were 7 out of 17 items from the Social Communication domain and 5 out of 7 items from the Peer Interaction domain in which more than half of the children with NF1 demonstrated some degree of difficulty, indicated by a score of 1, 2, or 3. Parent endorsement of awkward social interactions (76%), lack of use of gestures (80%), lack of group play with peers (52%), limited asking for information (76%), perseverative topics of conversations (68%), prefers time alone (60%), lack of nodding (60%), limited socializing with peers (56%), lack of sharing (56%), limited approaching other children (52%), use of odd phrases (60%) and lack of pointing (92%) were common for children with NF1. There were 0 out of 5 items from the RRB domain in which over half of parents of children with NF1 reported as problematic. These findings suggest that difficulties with peer interactions are the most prevalent difficulty and RRB are the least problematic area of impairment reported by parents of children with NF1.

There were eight additional items for the Social Communication and Peer Interaction domains in which one-third to one-half of parents endorsed some level of difficulty, including, inappropriate direct gaze (44%), response to conversational leads (40%), intonation (40%), facial expressions (40%), responses to distress (48%), social responses (48%), and responses to children (44%). There were two items from the RRB domain in which elevations were noted by parents including the initiation of appropriate activities (40%) and sensory aversions (40%). Results indicate that while there was not an overwhelming endorsement of ASD
symptomatology, difficulties in SCI and RRB are reported by parents for a minority of children with NF1.

The ASI is a new measure with sparse research to support its reliability and validity. Therefore, the relation between ASI and SRS-2 Total Scores were examined to explore whether parent report of socio-communicative behaviors was similar across measures. There was a large, significant correlation of .84 ($p < .001$) between the ASI and SRS-2 Total Scores, suggesting that parents are reporting similar behaviors on the ASI and SRS-2.

**Research Question 1c:** What is the pattern of clinician-observed socio-communicative behaviors and RRB in a sample of children with NF1? Of the 25 children with NF1 who were administered Module 3 of the ADOS-2, 24 (96%) were classified “non-spectrum” on the Overall Total Score. Figure 4 details the distribution for ADOS-2 domain scores. There were no differences in ADOS-2 Total Scores in relation to age, $r = .05$, $n = 25$, $p = .82$; however, there was a significance difference in ADOS-2 Total Scores by sex, with males demonstrating more difficulties on the ADOS-2 than females (Males: $M = 2.31$, $SD = .68$; Females: $M = .793$, $SD = .23$), $F(1, 23) = 5.35$, $p = .03$).

**Research Question 1d:** Are there clinician-observed socio-communicative behaviors or RRB that are more or less problematic for children with NF1? The frequencies of scores on ADOS-2 algorithm items are reported in Table 5. There were no items in which over one-third of children with NF1 demonstrated problematic behaviors. Additionally, there were no non-algorithm items in which over one-third of the children with NF1 demonstrated significant problematic behaviors.

**Research Question 1e:** What proportion of children with NF1 meet criteria for an ASD (using both the ADOS-2 and ASI) in a sample of children with NF? No children met or
exceeded cutoff using the algorithms for “ASD” and “autism” classifications on both the ADOS-2 and ASI. While there were no children who met classification for ASD on the ADOS-2 and ASI, there were four (16%) children who met or exceeded cutoff on one ASD screening measure. Table 6 details scores for those four children.

**Relations to Socio-Communicative Behavior in Children with NF1**

**Research Question 2: Do intellectual functioning, attention, social cognition, and/or pragmatic language skills predict socio-communicative behavior and RRB difficulties?**

Table 7 describes group performance on variables that may play a role in social responsiveness and RRB. Children with NF1 generally demonstrated average performance on measures of intellectual functioning, attention, and pragmatic language abilities. One-sample t-tests indicate that children performed significantly below the normative mean on intellectual functioning (GCA: \( t(24) = -3.94, p > .001 \)), attention (AA/RS: \( t(24) = -2.72, p = .01 \)), and understanding inferences (MI: \( t(24) = -2.06, p = .05 \)).

In order to better understand what variables could help explain social responsiveness difficulties and RRB reported by parents of children with NF1, relations between the SRS-2 Total Score and the variables described above were investigated using Pearson product-moment correlation coefficients. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity, and homoscedasticity. The SRS-2 is a well-established measure that has demonstrated good reliability and validity, and given the high correlation found between the SRS-2 and ASI in this study, the SRS-2 was chosen as our primary social impairment measure. The SRS-2 Total Score was chosen over the ADOS-2 Severity Score since there was very little variability in ADOS-2 Severity Scores. The SRS-2 Total Score was also chosen over the ASI Total Score given that the ASI is a new measure that has not been
rigorously researched. ASI correlational analyses were also conducted for thoroughness and can be found in Appendix B. Results were very similar across the two measures; therefore, only the results of SRS-2 analyses are presented here.

Results indicated medium, negative correlations between SRS-2 Total Score and GCA ($r = -.53, n = 24, p = .01$), SECT ($r = -.46, n = 24, p = .02$), and MPLI ($r = -.53, n = 24, p = .01$).

Given the significant correlation between the SRS-2 Total Score and MPLI, additional correlational analyses were investigated utilizing the MLPI subtest scores. Results highlighted a large, negative correlation between the SRS-2 Total Score and MI ($r = -.0, n = 24, p < .01$).

There was no significant correlation between the SRS-2 Total Score and CS ($r = -.34, n = 24, p = .10$).

Multiple linear regression analysis was used to test if intellectual functioning (GCA), social cognition (SECT), and pragmatic language (MI) performance predicted parent-reported social responsiveness difficulties (SRS-2 Total Score). Results indicated that the three predictors explained 36% of the variance (Adjusted $R^2 = .36, F(3, 23) = 5.31, p < .01$). It was found that MI significantly predicted parent report of social responsiveness ($\beta = -.44, p = .03$) and uniquely explained 38% of the variance found in the SRS-2 Total Score.

**Discussion**

The primary aim of this study was to examine parent-reported and clinician-rated levels of ASD symptomatology in children with NF1 using a diagnostic assessment of ASD symptoms. A secondary aim was to examine possible variables that may contribute to socio-communicative difficulties and RRB, such as intellectual functioning, attention, social cognition, and pragmatic language skills. As hypothesized, results indicate that parents of approximately 30% of children with NF1 reported significant social difficulties on a measure of social responsiveness and RRB;
however, few parents endorsed enough ASD symptomatology on ASD-specific screening measures to suggest the presence of an ASD. Additionally, as hypothesized, low rates of ASD symptoms were endorsed on a clinician-observed ASD diagnostic measure. Relations between severity of social responsiveness and RRB and intellectual functioning, social processing, and pragmatic language skills were found. Contrary to our original hypothesis, there was no significant relation between the severity of social responsiveness and RRB and attention. These findings are both similar and dissimilar to previous literature which indicated higher levels of social responsiveness difficulties and RRB and higher rates of ASD in children with NF1 (Adviento et al., 2013; Garg et al., 2013a; Garg et al., 2013b; Garg et al., 2015; Huijbregts & Sonneville, 2011; Plasschaert et al., 2014; Tinker et al., 2015; Walsh et al., 2012). Potential explanations for these findings will be provided below, along with limitations and future directions, and conclusions.

**Parental Report of Social Difficulties and ASD Symptomatology**

The present study found fewer children with marked parent-reported elevations in social responsiveness difficulties and RRB in a sample of children with NF1 than observed in prior research. Previous studies found that 13-33% of parents of children with NF1 endorsed severe (T-score > 75) difficulties, whereas, this study found no children whose SRS-2 Total Score fell in the severe range (See Table 8 for a brief summary of SRS findings from previous studies). Furthermore, rates of severe impairment across all domains of the SRS-2 were very low (see Figure 1), including in the RRB index. Additionally, in contrast to previous studies, our results found that no children met or exceeded cutoff on the SCQ per parent report. Very low levels of ASD symptomatology was reported by parents on the SCQ, with raw scores ranging from 0-14 (see Figure 2). This is different from previous research by Adviento et al. (2013) and Tinker et
al. (2014) in which 11% and 13% of children with NF1, respectively, screened positive for a possible ASD on the SCQ. However, Tinker et al. (2014) noted that while 13% of children with NF1 screened positive on the CAST, this rate did not differ significantly from general population data (5.8%; Williams et al., 2005).

One reason we may have not seen as many severe social responsiveness difficulties and RRB as previous studies is because previous studies included a wider age range of participants, with some studies including toddlers and adults in their sample (see Table 8 for a brief outline of previous SRS study samples). It may be that we would see an increase in severe social responsiveness difficulties and RRB with a younger or older sample of children. However, Plasschaert et al. (2014) found that age was significantly correlated to social responsiveness and ASD symptomatology, with more social responsiveness difficulties reported with increasing age. These authors found significantly less social problem behaviors reported in children with NF1 before the age of 8 and reported that social problems and ASD symptomatology seemed to peak between 11-13 years. Therefore, it seems unlikely that our restricted age range would explain why we did not find elevated levels of severe social responsiveness difficulties in children with NF1. Additionally, this study sample was small compared to previous studies (Ns ranging from 30-109) and larger samples are needed to replicate our findings. Finally, potential ascertainment biases, from this study and/or at the screening and follow-up stage of previous studies, may be contributing to the discrepancy in results.

In sum, in contrast with previous research, results from the current study indicate that while children with NF1 do show mild to moderate levels of social responsiveness difficulties compared to population norms, they do not appear to demonstrate a high frequency of severe social responsiveness difficulties or problematic RRB. Furthermore, results indicate that children
with NF1 may display more ASD symptoms than population norms, which makes them appear to be at a higher risk for a diagnosis of ASD; however, they may not actually meet threshold for a positive screen on ASD-specific screening measures.

**Overall Pattern of Performance on ASD Diagnostic Measures**

Based on item analysis of parent-reported ASD symptomatology using the ASI, difficulties were commonly observed (for more than 50% of the sample) in the Social Communication domain on items such as asking for information, using odd phrases, pointing to objects of interest, using gestures, nodding, and sharing with others, and especially in the Peer Interaction domain, including items such as preferring to spend time alone, approaching children, joining in group play with peers, socializing with peers, and awkward interactions with peers. Additional symptoms within the Social Communication and Peer Interaction domains were endorsed for 33-50% of the sample, including ineffective eye contact when communicating, lack of social chat, respond to questions and conversational leads inappropriately, and inappropriate intonation when speaking. Additionally, parents reported some RRB behaviors in a minority of children with NF1, including poor initiation of activities (40%) and sensory aversions (40%). These findings are particularly important clinical findings because it highlights that while the majority of children with NF1 are not demonstrating significant ASD symptomatology for a diagnosis, especially in the RRB domain, there is a minority of children who have social communication difficulties.

Children with NF1 also showed very few difficulties on the ADOS-2, with the majority of algorithm items receiving a score of 0. Some very mild difficulties were noted on three algorithm items, including slight difficulties with reporting events (32%), use of gestures (20%) and quality of social responses (20%). Overall, this study found very low rates of ASD
symptomatology and many prosocial, socio-communicative behaviors when using a clinician-rated ASD diagnostic measure. Results indicated that severity of ADOS-2 Total Scores was related to sex, with males demonstrating more ASD symptoms than females. This is similar to previous studies that found a higher rate of ASD symptomatology in boys with NF1 (Garg et al., 2013b, Adviento et al., 2013; Plasschaert et al. (2014).

Contrary to previous literature, there were no children who met criteria for diagnosis of ASD when combining the ASI and ADOS-2 results in the current sample. Garg et al. (2013a) found that 30% of their sample of children with NF1 met criteria for ASD and an additional 28% met criteria for broad ASD when using the more relaxed CPEA diagnostic guidelines. Plasschaert et al. (2014) found a minimum prevalence estimate of 27% of ASD in their sample of children with NF1 based on DSM-IV-TR diagnostic criteria. The authors indicated that 15% of the group presented with minimal ASD symptoms, 48% presented with moderate ASD symptoms, and 4% presented with severe ASD symptoms. However, in contrast, Adviento et al. (2013) reported that only 3% of their sample of children with NF1 were diagnosed with ASD or broad ASD after completing a comprehensive evaluation that included the ADOS and ADI-R.

One reason this study may have found fewer children meeting criteria for ASD is due to our stringent diagnostic criteria. For this study, we required that in order to meet criteria for ASD, a child would have to meet or exceed ASD cutoff scores on both the ASI and ADOS-2 and meet criteria based on DSM-5 diagnostic criteria. However, most previous studies relied on DSM-IV-TR ASD diagnostic criteria and/or ADOS-G classification (Adviento et al., 2013; Plasschaert et al., 2014), which did not require the presence of RRB in order to meet criteria of ASD. Additionally, Garg et al., 2013 relied on an ASD diagnostic classification that was based on the CPEA algorithm. This included children who meet criteria for Autism, Asperger’s, and
broad-ASD, who do not necessarily have to meet original cutoff scores on diagnostic measures to fulfill diagnostic criteria (Lainhart et al. 2006; see Appendix A for CPEA diagnostic criteria). However, even with these diagnostic criteria differences in mind, the majority of children with NF1 in this study presented with very “clean” ADOS-2 scores (indicated by the lowest possible severity score of 1). There was a small proportion (12%) of children who had severity scores higher than 1. Two children had severity scores of 3, which falls in the “low evidence of an ASD” category and one child who had a severity score of 5, which falls in the “moderate evidence of an ASD” category. This would suggest that while the majority of children with NF1 present with very few ASD symptoms, some did show evidence of mild to moderate ASD symptomatology. The rate of even mild to moderate ASD symptomatology, however, is considerably lower than the rate of ASD diagnoses in much of the previous literature. Our findings are most consistent with those of Adviento et al. (2013) who found low rates of ASD.

Furthermore, while the results of the current study indicate that children with NF1 are not more likely to screen positive for ASD than children without NF1, we did find some evidence of elevated ASD symptomatology in children with NF1. Thirty-percent of parents reported elevated rates of social responsiveness difficulties and RRB on the SRS-2, and, as noted in the Results section, four children with NF1 met or exceeded cutoff on at least one ASD screening or diagnostic measure (see Table 6). Three children met or exceeded cutoff on the ASI Total Score and one child met classification of Autism Spectrum on the ADOS-2 Overall Score; however, this child did not display any RRB symptoms and therefore did not meet for criteria for ASD. In fact, RRB symptoms were only identified in 1 of the 25 children assessed with the ADOS-2. Given the few RRB symptoms reported by parents of children with NF1 and noted by clinicians during the ADOS-2, it seems possible that the new DSM-5 diagnosis of SCD may more
accurately describe the social impairments seen in the NF1, as suggested by Garg et al. (2015). Children with SCD have significant problems using verbal and nonverbal communication for social purposes, leading to impairments in their ability to effectively communicate, participate socially, maintain social relationships, or otherwise perform academically or occupationally (American Psychiatric Association, 2013).

Overall, our results suggest that children with NF1 demonstrate some socio-communicative difficulties and RRB per parent and clinician report; however, those difficulties are largely not severe nor pervasive enough to meet DSM-5 criteria for ASD. Children with NF1 do not appear to be at a significantly higher risk of developing an ASD. However, given that the social responsiveness difficulties that parents are reporting in children with NF1 are falling largely in the Social Communication and Peer Interaction domains, a diagnosis of SCD may be a more appropriate description of the kind of social difficulties some children with NF1 face. The hallmark difficulties present in SCD include deficits in using communication for social purposes, the inability to match communication style to match the social context, following the rules for conversation, and difficulties in understanding what is not explicitly stated. These deficits in social communication manifest in functional limitations in effective communication, social participation, and developing and maintaining peer relationships (American Psychiatric Association, 2013).

**Relations between Social Responsiveness, RRB, and Related Variables**

Results from this study are similar to previous studies that examined relations between social responsiveness and RRB and intellectual functioning, attention, and social processing. Results indicate that children with NF1 are demonstrating low scores on measures of intellectual functioning, attention, and social information processing when compared to the normative mean.
These findings are congruent with Huijbregts et al. (2010) and Huijbregts and Sonneville (2011) who found that children with NF1 had difficulties on profile facial recognition and matching facial emotions, suggesting that children with NF1 have difficulty with bottom-up encoding of social stimuli. Additionally, results from the current study found that overall intellectual functioning and difficulties with social information processing on the SECT were significantly related to social responsiveness difficulties reported by parents on the SRS-2. Interestingly, contrary to our original hypothesis, attention difficulties were not significantly related to social responsiveness. These findings do still align with the results of Huijbregts et al. (2010) and Huijbregts and Sonneville (2011) which suggested that attention deficits do not determine social information processing difficulties in NF1 and that there appear to be vulnerabilities in both top-down, cognitive control, and bottom-up, social information processing difficulties in NF1.

Results from this study also suggest that children with NF1 are demonstrating impairments in pragmatic language skills, and more specifically, the ability to interpret inferences. Not only did the results of this study find that children with NF1 are performing in the low average range on a making inferences task, but those difficulties uniquely explained 38% of the social responsiveness difficulties reported by parents on the SRS-2. These findings further support the notation that a diagnosis of SCD may be more appropriate to capture the social communication difficulties of children with NF1. Previous studies have found that language skills appear to be an area of weakness in preschool and school-aged children with NF1 (Brei, Klein-Tasman, Schwarz, & Casnar, 2014; Dilts et al., 1996; Hyman et al., 2005; Lorenzo, Barton, Acosta, & North, 2011; Mazzocco et al., 1995); however, no studies have examined the role of pragmatic language abilities specifically in children with NF1. The results of this study do mirror the results found by Pride et al. (2014) which found relations between social dysfunction
and emotion recognition and the ability to understand paradoxical sarcasm in adults with NF1.

More research in this area is needed to see if these findings generalize, given this study utilized a small sample size, and only included two pragmatic language tasks. However, it seems that pragmatic language deficits may help explain why many parents of children with NF1 are reporting social difficulties and that those difficulties are being carried into adulthood.

**Limitations and Future Directions**

The present study provides clinically relevant information about the severity and frequency of ASD symptomatology a sample of children with NF1 and identifies a few variables that may contribute to elevated rates of social responsiveness difficulties and RRB reported by parents. However, there are limitations in the study design that point to areas for improvement in future research in this domain. First, this study utilized a relatively small sample size that may have hindered our ability to identify significant results. Recruiting large cohorts of children with NF1 is difficult because many of the clinical manifestations of NF1 are age-dependent and some children may not be referred to a NF-specific clinic until significant medical manifestations develop. This study attempted to address this barrier by emailing potential participants through the NF Research Registry that may include children whom do not belong to a NF-specific clinic, in order to reach a wider range of potential participants. However, response was generally limited. Future studies employing larger sample sizes would improve power and generalizability of results.

Second, this study relied solely on maternal report of social difficulties. A multi-informant approach that included more fathers, teachers, and peer ratings would help characterize social difficulties in different social contexts and environments. This is especially
important given previous research suggests that teachers are reporting fewer social responsiveness difficulties and RRB in the school setting.

Third, this study restricted participation to only children with NF1 between the ages of 9-13. We chose to only include children in this narrow age range because previous research suggested that social difficulties reported by parents of children with NF1 are most pronounced in children 8 and older (Plasschaert et al., 2014). Given the barriers to recruitment in NF1 research, we hoped that by recruiting children in this age range, we would maximize our inclusion of children with social difficulties, and thus, justify the completion of a comprehensive ASD diagnostic evaluation. However, by restricted the age range we restrict the generalizability of results. Therefore, future research examining ASD symptomatology in children from a wider age range would help better characterize the developmental course of the presence or absence of ASD symptomatology in children with NF1.

Fourth, the majority of children in this study (78%) presented with a sporadic verses familial mode of inheritance. Given that approximately half of NF1 cases are identified as caused by a sporadic mutation and half are caused by familial inheritance, it is generally preferred to have a similar distribution in the mode of inheritance in research. Thus far, there does not seem to be a relation between mode of inheritance and social responsiveness or ASD symptomatology (Adviento et al., 2013; Garg et al., 2013b; Garg et al., 2013a; Plasschaert et al., 2014; Tinker et al., 2014; Walsh et al., 2013); however, the skewed distribution of this study could affect the interpretation of the results. Future studies would benefit from a more even distribution of sporadic verse familial mode of inheritance in order to control for a potential confound.

Fifth, this study relied on the ASI, as opposed to the ADI-R, for our diagnostic measure of parent-reported ASD symptomatology. As noted in the Methods section, the ASI is a relatively
new measure that is still building research support for its reliability and validity. The results of the present study found that the ASI correlated well with the SRS-2, lending support for its reliability. However, there are many important differences between the ASI and ADI-R that must not be overlooked. The ADI-R is a semi-structured interview that is rated by the clinician, based on parent responses to questions. The clinician is allowed to rephrase questions and ask for example behaviors in order to decide on the most appropriate code for that item. The ASI has less flexibility and relies solely on the parent to interpret and select the best code for each item. The ASI does provide more detail, in terms of frequency of behaviors, than other ASD screening measures, which makes it a better measure for examining ASD symptomatology. However, parents may misinterpret items or may not understand the subtle differences in socio-communicative behaviors that the ASI assesses. Therefore, future studies may benefit from including a clinician-rated measure of developmental history and ASD symptomatology, such as the ADI-R, in order to ensure the accuracy of parental understanding of subtle socio-communicative behaviors.

Finally, this study used published normative data as a comparison when examining SRS-2 scores. There may be differences between this study sample with regards to socioeconomic status and intellectual functioning that may have an impact on score interpretation. Future research that utilizes a control group of unaffected children and a comparison group of children with ASD (without NF1) from the community would help control for this limitation.

**Summary**

Social problems are a common concern of parents of children with NF1 and recent studies have demonstrated elevations of ASD symptomatology in school-aged children with NF1. In this study, parent-reported and clinician-observed ASD symptomatology and relations to
risk factors for social responsiveness difficulties and RRB were examined. We explored these symptoms at a global level (using cutoff scores) and detailed level (using item analysis) using the ASI and ADOS-2. Overall, results suggest that parents are observing mild to moderate social responsiveness difficulties in school-aged children with NF1, but report few ASD-specific symptomatology on screening and diagnostic measures. Additionally, clinicians observed few severe or pervasive ASD symptoms on the ADOS-2. Relations between parent report of social responsiveness and intellectual functioning, social information processing, and pragmatic language were found.

Although elevated scores on the SRS-2 were found in our sample of children with NF1, no child met diagnostic threshold for a DSM-5 diagnosis of ASD. This suggests that there are important differences in the socio-communicative characteristics between the social difficulties described by parents of children with NF1 and those described by parents of children with ASD. It remains unclear whether the elevations on the SRS-2 are a result of over-reporting of ASD symptomatology, misinterpreting behaviors as symptoms of ASD, a lack of awareness of subtle socio-communicative behaviors (such as nodding, pointing or gesturing), or whether children with NF1 truly exhibit social deficits similar to those seen in ASD. Regardless, the results of this study indicate that the social difficulties described by parents of children with NF1 may overlap with ASD symptomatology, they are not indicative of a true ASD diagnosis.

**Implications for Clinical Practice**

The results of this study highlight the importance of the use of a comprehensive assessment of socio-communicative difficulties when a child with NF1 presents with social difficulties in clinic. Quick diagnosis of ASD based solely on questionnaire data may lead to misclassification of children with NF1, given ASD symptoms are often endorsed by parents. The social difficulties
described by parents appear to be related to other risk factors, such as pragmatic language
difficulties, social information processing difficulties, or intellectual functioning, rather than to 
true ASD socio-communicative difficulties and RRB. Nonetheless, the results of this study 
underline the need to develop interventions to address the social difficulties seen in children with 
NF1 and that these interventions are not dependent on a diagnosis of ASD. Targeting weaknesses 
in social language and social information processing may be a promising starting point for 
intervention development.
Table 1.

Participant Demographic Data (n = 25)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score/Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>11.36 (1.56)</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Females</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>20 (80)</td>
</tr>
<tr>
<td>African American</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Biracial</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Mother’s Education (%)</td>
<td></td>
</tr>
<tr>
<td>HS Diploma</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Some College</td>
<td>5 (20)</td>
</tr>
<tr>
<td>College Degree</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Post College</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Mean GCA (SD)</td>
<td>90.84 (11.63)</td>
</tr>
<tr>
<td>Current Grade (SD)</td>
<td>5.36 (1.71)</td>
</tr>
<tr>
<td>Special Education (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (52)</td>
</tr>
<tr>
<td>No</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Previous Diagnoses (%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>17 (68)</td>
</tr>
<tr>
<td>ADHD</td>
<td>5 (20)</td>
</tr>
<tr>
<td>MD, Language Disorder</td>
<td>1 (4)</td>
</tr>
<tr>
<td>RD, Language Disorder</td>
<td>1 (4)</td>
</tr>
<tr>
<td>MD, RD, Language Disorder</td>
<td>1 (4)</td>
</tr>
<tr>
<td>NF1 Diagnosis (%)</td>
<td></td>
</tr>
<tr>
<td>Sporadic</td>
<td>18 (72)</td>
</tr>
<tr>
<td>Familial</td>
<td>7 (28)</td>
</tr>
</tbody>
</table>

*Note: MD = Math Disorder; RD = Reading Disorder.*
Table 2.

Summary of Study Measures

<table>
<thead>
<tr>
<th>Domain</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social Responsiveness and RRB</td>
<td>Social Responsiveness Scale-2 (SRS-2)</td>
</tr>
<tr>
<td>Autism Symptomatology</td>
<td>Social Communication Questionnaire (SCQ)</td>
</tr>
<tr>
<td></td>
<td>Autism Symptoms Interview (ASI)</td>
</tr>
<tr>
<td></td>
<td>Autism Diagnostic Observation Schedule-2 (ADOS-2)</td>
</tr>
<tr>
<td>Intellectual Functioning</td>
<td>Differentials Ability Scale-II (DAS-II)</td>
</tr>
<tr>
<td>Vigilance/Concentration</td>
<td>Cogstate: Identification Task (IT)</td>
</tr>
<tr>
<td>Attention/Working Memory</td>
<td>Cogstate: One Back Task (OBT) &amp; Two Back Task (TBT)</td>
</tr>
<tr>
<td></td>
<td>NEPSY-II: Auditory Attention/Response Set (AA/RS)</td>
</tr>
<tr>
<td>Social Cognition</td>
<td>Cogstate: Social-Emotion Cognition Task (SECT)</td>
</tr>
<tr>
<td>Pragmatic Language</td>
<td>CELF-5 MPLI: Making Inferences (MI) &amp; Conversation Skills (CS)</td>
</tr>
<tr>
<td>NF1 Related Factors</td>
<td>Background Questionnaire</td>
</tr>
</tbody>
</table>
Table 3.

*SRS-2 Descriptive Statistics and One-sample t-tests*

<table>
<thead>
<tr>
<th>Domain/Index</th>
<th>M (SD)</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social Awareness</td>
<td>56.25 (10.05) ++</td>
<td>0.63</td>
</tr>
<tr>
<td>Social Cognition</td>
<td>55.58 (11.49) +</td>
<td>0.56</td>
</tr>
<tr>
<td>Social Communication</td>
<td>56.13 (11.27) +</td>
<td>0.61</td>
</tr>
<tr>
<td>Social Motivation</td>
<td>52.00 (11.17)</td>
<td>0.20</td>
</tr>
<tr>
<td>Restricted, Repetitive Behaviors</td>
<td>53.54 (8.71)</td>
<td>0.36</td>
</tr>
<tr>
<td>Social Communication &amp; Interaction Index</td>
<td>55.79 (11.16) +</td>
<td>0.58</td>
</tr>
<tr>
<td>SRS-2 Total Score</td>
<td>55.76 (10.65) +</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Significantly higher than normative mean: + p < .05, ++ p < .01
Table 4.

**ASI Algorithm Item Scores**

<table>
<thead>
<tr>
<th></th>
<th>Absent (score 0)</th>
<th>Present (score 1, 2, 3)</th>
<th>Symptom Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Social Communication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct Gaze</td>
<td>14</td>
<td>56</td>
<td>11</td>
</tr>
<tr>
<td>Social Chat</td>
<td>21</td>
<td>84</td>
<td>4</td>
</tr>
<tr>
<td>Responds to Questions</td>
<td>19</td>
<td>76</td>
<td>6</td>
</tr>
<tr>
<td>Responds to Conversation Leads</td>
<td>15</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>Starting Conversation</td>
<td>17</td>
<td>68</td>
<td>8</td>
</tr>
<tr>
<td>Asking for Information</td>
<td>6</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Perseveration</td>
<td>8</td>
<td>32</td>
<td>17</td>
</tr>
<tr>
<td>Odd Phrases</td>
<td>10</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>Intonation</td>
<td>15</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>Pointing</td>
<td>2</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>Gestures</td>
<td>5</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Nodding</td>
<td>10</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>Inappropriate Facial Expressions</td>
<td>15</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>Sharing</td>
<td>11</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>Response to Distress</td>
<td>13</td>
<td>52</td>
<td>12</td>
</tr>
<tr>
<td>Appropriate Social Responses</td>
<td>13</td>
<td>52</td>
<td>12</td>
</tr>
<tr>
<td>Inappropriate Social Responses</td>
<td>13</td>
<td>52</td>
<td>12</td>
</tr>
<tr>
<td>Peer Interaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Alone</td>
<td>10</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>Approaching Children</td>
<td>12</td>
<td>48</td>
<td>13</td>
</tr>
<tr>
<td>Response to Children</td>
<td>14</td>
<td>56</td>
<td>11</td>
</tr>
<tr>
<td>Group Play with Peers</td>
<td>12</td>
<td>48</td>
<td>13</td>
</tr>
<tr>
<td>Socializing with Peers</td>
<td>11</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>Awkward Interactions</td>
<td>6</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Maintaining Friendships</td>
<td>17</td>
<td>68</td>
<td>8</td>
</tr>
<tr>
<td>Restricted &amp; Repetitive Behaviors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiation of App Activities</td>
<td>15</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>Sensory Aversions</td>
<td>15</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>Unusual Sensory Interests</td>
<td>23</td>
<td>92</td>
<td>2</td>
</tr>
<tr>
<td>Circumscribed Interests</td>
<td>17</td>
<td>68</td>
<td>8</td>
</tr>
<tr>
<td>Routines</td>
<td>18</td>
<td>72</td>
<td>7</td>
</tr>
</tbody>
</table>

*Note:* Items printed in red indicate “common” behaviors (over half of sample endorsed the presence of that behavior). Scores of “0” indicate that parents reported no abnormality in that behavior. Items that required reverse coding have been converted to scores in order to reflect correct symptom severity levels.
Table 5.

*ADOS-2 Algorithm Scores*

<table>
<thead>
<tr>
<th></th>
<th>Absent (score 0)</th>
<th>Present (score 1, 2)</th>
<th>Symptom Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Social Affect</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reporting of Events</td>
<td>17</td>
<td>68</td>
<td>8</td>
</tr>
<tr>
<td>Conversation</td>
<td>21</td>
<td>84</td>
<td>4</td>
</tr>
<tr>
<td>Gestures</td>
<td>20</td>
<td>80</td>
<td>5</td>
</tr>
<tr>
<td>Unusual Eye Contact</td>
<td>24</td>
<td>96</td>
<td>1</td>
</tr>
<tr>
<td>Facial Expressions</td>
<td>23</td>
<td>92</td>
<td>2</td>
</tr>
<tr>
<td>Shared Enjoyment</td>
<td>25</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Quality of Social Overtures</td>
<td>24</td>
<td>96</td>
<td>1</td>
</tr>
<tr>
<td>Quality of Social Responses</td>
<td>20</td>
<td>80</td>
<td>5</td>
</tr>
<tr>
<td>Amount Reciprocal Social Communication</td>
<td>23</td>
<td>92</td>
<td>2</td>
</tr>
<tr>
<td>Overall Quality of Rapport</td>
<td>23</td>
<td>92</td>
<td>2</td>
</tr>
<tr>
<td><strong>Restricted and Repetitive Behavior</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stereotyped/Idiosyncratic Words</td>
<td>24</td>
<td>96</td>
<td>1</td>
</tr>
<tr>
<td>Unusual Sensory Interest</td>
<td>24</td>
<td>96</td>
<td>1</td>
</tr>
<tr>
<td>Hand, Finger, Complex Mannerisms</td>
<td>25</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Excess Interest Unusual/Specific Topics</td>
<td>22</td>
<td>88</td>
<td>3</td>
</tr>
</tbody>
</table>
### Table 6.

**Descriptive Scores for Meeting/Exceeding Cutoff on ASD Screening Domains**

<table>
<thead>
<tr>
<th></th>
<th>SCQ Total (cutoff = 15)</th>
<th>ASI Total (cutoff = 38)</th>
<th>SA Total</th>
<th>RRB Total</th>
<th>ADOS-2 Overall (cutoff = 7/9)</th>
<th>ADOS-2 Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 1</td>
<td>8</td>
<td>38*</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Child 2</td>
<td>14</td>
<td>39*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Child 3</td>
<td>10</td>
<td>50*</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Child 4</td>
<td>2</td>
<td>22</td>
<td>8</td>
<td>0</td>
<td>8*</td>
<td>5</td>
</tr>
</tbody>
</table>

* Denotes met/exceeded cutoff on that domain score
Table 7.

*SRS-2 Total Score Correlations to Related Variables*

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
<th>M</th>
<th>SD</th>
<th>Range</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASI Total Score</td>
<td>Range</td>
<td>21.12</td>
<td>11.26</td>
<td>5-50</td>
<td>.836</td>
<td>&lt;.001***</td>
</tr>
<tr>
<td>GCA Standard</td>
<td>90.84 +</td>
<td>11.63</td>
<td></td>
<td>67-109</td>
<td>-.534</td>
<td>.007**</td>
</tr>
<tr>
<td>Identification Task</td>
<td>Accuracy</td>
<td>1.31</td>
<td>0.22</td>
<td>0.60-1.57</td>
<td>-.256</td>
<td>.227</td>
</tr>
<tr>
<td>AA/RS Combined Scaled</td>
<td>8.16 +</td>
<td>3.39</td>
<td></td>
<td>1-13</td>
<td>-.206</td>
<td>.333</td>
</tr>
<tr>
<td>One Back Task Accuracy</td>
<td>1.15</td>
<td>0.25</td>
<td></td>
<td>0.57-1.57</td>
<td>-.315</td>
<td>.133</td>
</tr>
<tr>
<td>Two Back Task Accuracy</td>
<td>0.99</td>
<td>0.25</td>
<td>0.40-1.27</td>
<td>-.118</td>
<td>.582</td>
<td></td>
</tr>
<tr>
<td>Cogstate SECT Accuracy</td>
<td>0.94</td>
<td>0.20</td>
<td></td>
<td>0.55-1.28</td>
<td>-.464</td>
<td>.023*</td>
</tr>
<tr>
<td>MPLI Standard</td>
<td>98.76</td>
<td>17.01</td>
<td>70-132</td>
<td>-.530</td>
<td>.008**</td>
<td></td>
</tr>
<tr>
<td>Making Inferences Scaled</td>
<td>8.60 +</td>
<td>3.39</td>
<td></td>
<td>3-16</td>
<td>-.600</td>
<td>.002**</td>
</tr>
<tr>
<td>Conversation Skills Scaled</td>
<td>10.92</td>
<td>3.34</td>
<td>4-16</td>
<td>-.341</td>
<td>.103</td>
<td></td>
</tr>
</tbody>
</table>

Significantly higher than normative mean: + p < .05
Significant correlation: * p < .05, ** p < .01, *** p < .001
**Table 8.**

*Summary of SRS-2 Total Scores from Previous Studies*

<table>
<thead>
<tr>
<th>Research Study</th>
<th>N (M/F)</th>
<th>Ages</th>
<th>M (SD)</th>
<th>Levels of Difficulty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huijbregts &amp; Sonneville, 2011</td>
<td>30 (12/18)</td>
<td>6-17</td>
<td>59.4 (23.4)</td>
<td>-- -- --</td>
</tr>
<tr>
<td>Walsh et al., 2012</td>
<td>66 (42/24)</td>
<td>4-48</td>
<td>57.9 (14.2)</td>
<td>60% 27% 13%</td>
</tr>
<tr>
<td>Garg et al., 2013b</td>
<td>109 (50/59)</td>
<td>4-16</td>
<td>63.2 (35.4)</td>
<td>44% 27% 29%</td>
</tr>
<tr>
<td>Adviento et al., 2013</td>
<td>66 (26/40)</td>
<td>2-45</td>
<td>57.0 (16.0)</td>
<td>57% 30% 13%</td>
</tr>
<tr>
<td>Plasschaert et al., 2014</td>
<td>82 (44/38)</td>
<td>5-17</td>
<td>58.3 (32.5)</td>
<td>37% 30% 33%</td>
</tr>
</tbody>
</table>
**SRS-2 Levels of Difficulties**

![SRS-2 Levels of Difficulties](image)

*Figure 1.* Bar chart depicting levels of difficulties reported by parents on the SRS-2 by each domain and index. Comm = Communication; RRB = Restricted, Repetitive Behaviors; SCI = Social Communication & Interaction Index; Total = SRS-2 Total Score.
Figure 2.

Distribution of SCQ Total Scores

* Denotes the SCQ Total Score cutoff score.

Figure 2. Line chart depicting distribution of SCQ Total Scores reported by parents. * Denotes the SCQ Total Score cutoff score.
Figure 3. Line chart depicting distribution of ASI Total Scores reported by parents. * Denotes the ASI Total Score cutoff.
Figure 4. Multiline chart depicting distribution of ADOS-2 domain scores and severity scores. * Denotes Autism Spectrum Disorder cutoff score; ** Denotes Autism cutoff score. SA = Social Affect; RRB = Restricted and Repetitive Behavior.
References


Casnar, C. L., & Klein-Tasman, B. P. (2016). Parent and Teacher Perspectives on Emerging Executive Functioning in Preschoolers with Neurofibromatosis Type 1: Comparison to
Unaffected Children and Lab-Based Measures. *Journal of Pediatric Psychology.*

http://doi.org/10.1093/jpepsy/jsw042


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Appendix A

Collaborative Programs of Excellence in Autism (CPEA) Diagnosis

CPEA Diagnoses of Autism, Asperger Disorder, or ASD are determined hierarchically and based upon scores from the ADI-R, ADOS, and the Best Estimate Clinical (BEC) diagnosis made by the supervising clinicians; criteria for Asperger’s also include consideration of child age, IQ, and language milestones. These criteria were established by the CPEA to ensure standardized diagnostic classification across sites and adopted by the SSC under the same rationale. The criteria used in the SSC were slightly modified from those described by Lainhart et al. (2006):

1. For a CPEA diagnosis of “Autism” an individual must meet the following:
   a. ADI-R classification of “Autism.” This is based on meeting published cut-offs on the ADI-R diagnostic algorithm (LeCouteur et al., 2003) in the domains of Reciprocal Social Interaction (SOC), Communication, Restricted, Repetitive & Stereotyped Patterns (RRB) of Behaviors, and Age of Onset.
   b. ADOS classification of “Autism” or “Autism Spectrum.” This is based on meeting published cut-offs on the revised diagnostic algorithms for Modules 1-3 (Gotham et al., 2009) and cut-offs on the originally published diagnostic algorithms for Module 4 (Lord et al., 2000).
   c. BEC Diagnosis of “Autism,” “Autism Spectrum” or “Asperger’s.”

2. For a CPEA diagnosis of “Asperger’s” an individual must not meet criteria for “Autism” and must also meet the following:
   a. Chronological age of 5 years or older
   b. Verbal IQ of 80 or above
c. Age of First Words (from the ADI-R) is 24 months or younger

d. Age of First Phrases (from the ADI-R) is 33 months or younger

e. ADI-R classification is not “Autism”

f. ADI-R SOC domain score is 10 or higher

g. ADI-R RRB domain score is 2 or higher

h. ADOS classification of “Autism” or “Autism Spectrum” or ADOS

   Social+Communication Total (based on originally published algorithms) is 4 or higher

i. BEC Diagnosis of “Autism,” “Autism Spectrum” or “Asperger’s.”

3. For a CPEA diagnosis of “Autism Spectrum Disorder” an individual must not previous criteria for “Autism” or “Asperger’s” and must also meet the following:

a. ADI-R classification of “Autism Spectrum.” This is based on CPEA criteria (Lainhart et al., 2006; Risi et al., 2006), which requires one of the following:

   i. Meeting cut-offs on the SOC and Communication domains

   ii. Meeting cut-offs on either the SOC or Communication domain and score within 2 points of the cut-off on the other

   iii. Score within 1 point on both the SOC and Communication domains.

b. ADOS classification of “Autism Spectrum.” This is based on revised diagnostic algorithms for Modules 1-3 and originally published diagnostic algorithms for Module 4.

c. BEC Diagnosis of “Autism,” “Autism Spectrum” or “Asperger’s.”

4. If none of the above criteria is met, the participant receives a CPEA diagnosis of “Nonspectrum”.
Appendix B

ASI Total Score Correlations to Related Variables

In order better understand what variables could help explain social difficulties reported by parents of children with NF1, the relationship between the ASI Total Score and the variables described above were investigated using Pearson product-moment correlation coefficients.

Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity, and homoscedasticity. There were medium, negative correlations between ASI Total Score and GCA ($r = -.45, n = 25, p = .02$), SECT ($r = -.39, n = 25, p = .05$), and MPLI ($r = -.49, n = 25, p = .01$). Given the significant correlation found between the ASI Total score and GCA, additional correlational analyses were conducted to examine if a specific domain score was responsible for driving the correlation. Given the significant correlation between the ASI Total score and MPLI, additional correlational analyses were investigated. Results highlighted a large, negative correlation between the ASI Total score and MI ($r = -.65, n = 25, p < .001$). There was no significant correlation between the ASI Total score and CS ($r = -.21, n = 25, p = .32$).

<table>
<thead>
<tr>
<th>Measures/Subtests</th>
<th>Score</th>
<th>M</th>
<th>SD</th>
<th>Range</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRS-2 Total Score</td>
<td>T-score</td>
<td>55.76</td>
<td>10.65</td>
<td>40-75</td>
<td>.836</td>
<td>&lt;.001***</td>
</tr>
<tr>
<td>GCA</td>
<td>Standard</td>
<td>90.84</td>
<td>11.63</td>
<td>67-109</td>
<td>-.450</td>
<td>.024*</td>
</tr>
<tr>
<td>Identification Task</td>
<td>Accuracy</td>
<td>1.31</td>
<td>0.22</td>
<td>0.60-1.57</td>
<td>-.233</td>
<td>.263</td>
</tr>
<tr>
<td>Identification Task</td>
<td>Accuracy</td>
<td>1.31</td>
<td>0.22</td>
<td>0.60-1.57</td>
<td>-.233</td>
<td>.263</td>
</tr>
<tr>
<td>AA/RS Combined</td>
<td>Scaled</td>
<td>8.16</td>
<td>3.39</td>
<td>1-13</td>
<td>-.092</td>
<td>.661</td>
</tr>
<tr>
<td>One Back Task</td>
<td>Accuracy</td>
<td>1.15</td>
<td>0.25</td>
<td>0.57-1.57</td>
<td>-.266</td>
<td>.199</td>
</tr>
<tr>
<td>Two Back Task</td>
<td>Accuracy</td>
<td>0.99</td>
<td>0.25</td>
<td>0.40-1.27</td>
<td>-.126</td>
<td>.548</td>
</tr>
<tr>
<td>Cogstate SECT</td>
<td>Accuracy</td>
<td>0.94</td>
<td>0.20</td>
<td>0.55-1.28</td>
<td>-.391</td>
<td>.054*</td>
</tr>
<tr>
<td>Pragmatic Language</td>
<td>Standard</td>
<td>98.76</td>
<td>17.01</td>
<td>70-132</td>
<td>-.485</td>
<td>.014*</td>
</tr>
<tr>
<td>Making Inferences</td>
<td>Scaled</td>
<td>8.60</td>
<td>3.39</td>
<td>3-16</td>
<td>-.645</td>
<td>.001**</td>
</tr>
<tr>
<td>Conversation Skills</td>
<td>Scaled</td>
<td>10.92</td>
<td>3.34</td>
<td>4-16</td>
<td>-.208</td>
<td>.318</td>
</tr>
</tbody>
</table>

Significantly higher than normative mean: + $p < .05$
Significant correlation: * $p < .05$, ** $p < .01$
CHRISTINA CASNAR

EDUCATION

Doctor of Philosophy in Clinical Psychology (Expected 2017)
University of Wisconsin – Milwaukee / Milwaukee, Wisconsin / 2013 – Present
Dissertation: Autism spectrum disorder symptomatology in children with neurofibromatosis type 1
Minor: Cognition and Perception

Master of Science in Clinical Psychology
University of Wisconsin – Milwaukee / Milwaukee, Wisconsin / 2010 – 2013
Masters: Relations between fine motor skill and parental report of attention in young children with neurofibromatosis type 1

Bachelors of Arts in Psychology and Sociology
University of Missouri – St. Louis / Missouri, St. Louis / 2002 - 2006
Minor: Political Science

HONORS AND AWARDS

Advanced Opportunity Program Fellowship Travel Award / 2014 – 2016
Department of Psychology Summer Research Fellowship / 2015
WI LEND Graduate Fellowship / 2014
WI LEND Trainee Fellowship / 2013 – 2014
Graduate School Travel Award / 2013 – 2014
Sociology Department Honors / 2006
Cum Laude Graduation Honors / 2006
Deans List, University of Missouri-St. Louis / 2002 – 2006
University Scholarship / 2002 – 2006

TRAINING

Leadership Education in Neurodevelopmental and Related Disabilities
University of Wisconsin – Milwaukee / Milwaukee, Wisconsin / 2013 – 2014
Track: Psychology Fellow

The LEND program provides graduate level interdisciplinary training to improve the health and quality of life for individuals with disabilities. Participation in leadership trainings, learning modules focused on increasing knowledge of neurodevelopmental disabilities, interdisciplinary research
teams, education, and advocacy of relevant public policy, and participation in a weekly, interdisciplinary clinic specializing in the diagnosis of autism spectrum disorders.

**Clinical and Research Reliability Certification: ADI-R and ADOS-2 (Modules 1 - 4)**

University of Wisconsin – Milwaukee / Milwaukee, Wisconsin / 2013

Advanced training and completed research reliability certification in Autism Diagnostic Interview – Revised (ADI-R) and Autism Diagnostic Observation Schedule – Second Edition (ADOS-2) for modules 1 – 4. Established at least 80% agreement on the ADOS-2 for both protocol and algorithm and at least 90% agreement on the ADI-R for both protocol and algorithm on at least three consecutive administrations.

---

**CLINICAL EXPERIENCE**

**Doctoral Internship in Clinical Psychology**

University of Chicago Medicine / Chicago, Illinois / 2016 – Present  
Track: Pediatric Neuropsychology  
Supervisors: Scott Hunter, Ph.D.; Megan Scott, Ph.D.; Matthew Young, Ph.D.; Tina Drossos, Ph.D.

Outpatient neuropsychological evaluation with children and adolescents with complex medical, neurological, neurodevelopmental, and genetic disorders through the Pediatric Neuropsychology Clinic and Neurodevelopmental Disorder Clinic. Outpatient diagnostic evaluation and intervention with children and families with a variety of sleep disorders through the Pediatric Sleep Clinic. Individual and family outpatient psychotherapy with community children, with and without medical conditions, through the Child Psychology Clinic. Assessment and intervention for a variety of psychological concerns related to medical illness/treatments as part of an inpatient, multidisciplinary environment through the Pediatric Psychiatry Consultation & Liaison Service. Consultation regarding cognitive, behavioral, and adaptive needs and brief outpatient neuropsychology evaluations with children and adolescents seen through the Pediatric Neurology Clinic.

**Advanced Student Therapist: UWM Child Anxiety Clinic**

University of Milwaukee - Wisconsin / Milwaukee, Wisconsin / 2014 – 2016  
Supervisor: Bonnie Klein-Tasman, Ph.D.

Provided interventions with children and adolescents with Social Anxiety Disorder and Generalized Anxiety Disorder as part of a community, no-fee clinic. Supervision in cognitive-behavioral and family systems approaches.

**Advanced LEND Trainee: WI LEND – Milwaukee Link ASD Diagnostic Clinic**

University of Milwaukee - Wisconsin / Milwaukee, Wisconsin / 2013 – 2016  
Supervisor: Bonnie Klein-Tasman, Ph.D.
Administered, scored, and interpreted developmental testing and gold standard diagnostic measures (ADOS-2; ADI-R) to young children referred for concerns of a possible autism spectrum disorder as part of a community, no-fee clinic. Worked as part of an interdisciplinary team with speech therapists, occupational therapists, and nurse practitioners to provide comprehensive diagnostic evaluations.

**Graduate Assistant: UWM Child Neuropsychology Clinic**  
University of Milwaukee - Wisconsin / Milwaukee, Wisconsin / 2010 – 2016  
Supervisor: Bonnie Klein-Tasman, Ph.D.

Completed neuropsychological evaluations, report writing, and feedback for children and adolescents with learning disabilities, ADHD, autism spectrum disorders, and other genetic and neurodevelopmental disorders.

**Teen & Young Adult Lead Therapist: Marquette University PEERS Project**  
Marquette University / Milwaukee, Wisconsin / 2013 – 2015  
Supervisor: Amy Van Hecke, Ph.D.

Provided evidence-based, manualized, 14/16-week, relationship-development therapy for a group of teens/young adults, with autism spectrum disorders utilizing the Program for the Education and Enrichment of Relational Skills (PEERS) intervention program.

**Advanced Practicum Student: Pediatric Neuropsychology Clinic**  
Medical College of Wisconsin / Milwaukee, Wisconsin / 2013 – 2015  
Supervisor: Amy Heffelfinger, Ph.D., ABPP; Jennifer Koop, Ph.D., ABPP; Michelle Loman, Ph.D.

Provided neuropsychological evaluations, observation of parent-child interactions, report writing, attending feedback for children and adolescents in a hospital outpatient setting. Experience in working with children of all ages, including preschool and infant evaluations in the Preschool and Infant Neuropsychological Testing clinic.

**Project Assistant: UWM Adult Neuropsychology Learning Disabilities Clinic**  
University of Milwaukee - Wisconsin / Milwaukee, Wisconsin / 2012 – 2013  
Supervisor: David Osmon, Ph.D., ABPP

Comprehensive neuropsychological evaluations and scoring for adults with learning disabilities, ADHD, and a variety of mood disorders. Measures administered included intellectual functioning, academic, executive functions, memory, effort, personality, learning styles, and career measures.

**Student Therapist: UWM Tic Disorders Clinic**  
University of Milwaukee - Wisconsin / Milwaukee, Wisconsin / 2012 – 2013  
Supervisor: Doug Woods, Ph.D.

Provided outpatient therapy for children and adolescents with concerns related to mood disorders, behavioral difficulties, anxiety, and repetitive behavior disorders such as Obsessive Compulsive
Disorder, tic disorders, and Trichotillomania. Interventions included behavioral activation, habit reversal training, cognitive-behavioral therapy, and parent training.

**Student Therapist: Pediatric Constipation and Incontinence Clinic**  
Children’s Hospital of Wisconsin / Milwaukee, Wisconsin / 2012 – 2013  
Supervisor: W. Hobey Davies, Ph.D.; Alan Silverman, Ph.D.; Andrea Begotka, Ph.D.

Provided outpatient therapy with families and young children with encopresis and enuresis in an outpatient hospital setting. Conducted initial evaluation and weekly treatment utilizing behavior and family therapy techniques.

**Clinical Psychology Practicum Student: UWM Psychology Clinic**  
University of Milwaukee - Wisconsin / Milwaukee, Wisconsin / 2010 – 2012  
Supervisor: David Osmon, Ph.D., ABPP; Bonnie Klein-Tasman, Ph.D.; Han Joo Lee, Ph.D.

Provided diagnostic and psychoeducational assessments for college students and children referred from the community. Participated in school Individualized Education Program meetings as part of practicum experience.

**Pediatric Neuropsychology Psychometrist: University of Chicago**  
Pediatric Neuropsychology Service & Pediatric Forensic Psychiatry Program  
University of Chicago / Chicago, Illinois / 2008 – 2010  
Supervisor: Scott Hunter, Ph.D.

Conducted neuropsychological assessments for children and adolescents with a wide range of psychological and medical concerns. Assisted in pre- and post- brain surgery testing and WADA testing for the pediatric epilepsy team. Scored and checked accuracy of test data; supervised testing by trainees; attended weekly didactics focused on pediatric and adult neurological and neuropsychological concerns.

**Lead ABA Therapist: St. Louis Special School District**  
Supervisor: Julie Snider, M.A.

Provided applied behavioral analysis (ABA) therapy with young children diagnosed with an autism spectrum disorder. Collected detailed data on core curriculum. Managed team of therapists on specific skill development and new procedures. Met and reported weekly with school personal on progress and areas of concern.

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**PUBLICATIONS**


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**INTERNATIONAL / NATIONAL PRESENTATIONS**


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**REGIONAL PRESENTATIONS**


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**RESEARCH EXPERIENCE**

**Doctoral Internship in Clinical Psychology**
University of Chicago Medicine / Chicago, Illinois / 2016 – Present
Track: Pediatric Neuropsychology
Supervisor: Scott Hunter, Ph.D.

*Neurocognitive and Psychiatric Functioning of Homeless Youth in Chicago and LA*: A study aimed to examine the family, academic, and interpersonal factors that may contribute to homelessness, as well as, examine the relations among neuropsychological factors, psychosocial factors, and risky behavior in homeless youth. Participants include English-speaking youth, aged 12-24, who lacked a fixed, regular, and adequate nighttime residence in the Chicago or LA area. Role: Support Staff
Graduate Assistant: UWM Child Neuropsychology Clinic  
University of Milwaukee - Wisconsin / Milwaukee, Wisconsin / 2010 – 2016  
Supervisor: Bonnie Klein-Tasman, Ph.D.

**School-Aged Outcomes in Neurofibromatosis Type 1: Attention, Social, and Academic Functioning:**  
As a continuation of a longitudinal research study, this study aims to assess functioning at ages 9-13 to enable examination of preschool-age predictors of functioning in the school-age years. Additionally, this study aims to characterize social difficulties in children with NF1 and identify possible contributing factors to those social difficulties. Role: Co-Investigator

**Response Inhibition Training for Children with Williams Syndrome:** A pilot study aimed to examine the effects of Response Inhibition Training for individuals with Williams syndrome on improving impulsivity and general functioning levels. Responsibilities include administration of MINI and neuropsychological measures at baseline, pre-intervention, post-intervention, and follow-up. Role: Graduate Research Assistant

**Early Indicators of Emotional, Cognitive, and Learning Difficulties in Neurofibromatosis Type 1:** 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. Role: Graduate Research Assistant

**Patience and Planning in Typically Developing Children:** 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. Role: Graduate Research Assistant

Pediatric Neuropsychology Psychometrist: University of Chicago  
University of Chicago / Chicago, Illinois / 2008 – 2010  
Supervisor: Scott Hunter, Ph.D.

**Neurofibromatosis Type 1 (NF1) Clinical Trials Consortium: Phase II Study:** A prospective randomized placebo-controlled study of Lovastatin to improve neurocognitive outcome in children between 10 and 17 years of age with NF1 and learning disabilities. Aim of study was to determine whether Lovastatin significantly improves visual spatial learning and/or sustained attention in children, ages 10 to 16, with NF1. Explored effect of Lovastatin on executive function, behavior and quality of life. Role: Support Staff

**Pediatric HIV/AIDS Cohort Study (PHACS): Adolescent Master Protocol (AMP):** Examined cognitive, behavioral, and risk factors in adolescents prenatally exposed to HIV-infected mothers. Study looked at adolescents who are HIV-uninfected and those who are HIV-infected and taking ART. Study also explored medical adherence in those children taking ART. Role: Support Staff
**Pediatric HIV/AIDS Cohort Study (PHACS): SMARTT (PH100) Protocol.** Research investigates potential toxicities and long term effects among HIV-uninfected children born to mothers with HIV infection, with or without exposure to ART in utero and/or in the child’s first 2 months. Assessments conducted on children (starting at 1 year old) and their caregiver. Role: Support Staff

**Children’s Oncology Group Protocol ACNS0232: Radiotherapy alone vs. chemotherapy followed by response-based radiotherapy for newly diagnosed primary CNS Germinoma: A phase-III group wide study.** Study compared survival, patterns of recurrence, health-related quality of life and neuropsychological function in a prospective, randomized clinical trial of conventional radiotherapy versus pre-radiotherapy chemotherapy followed by response-based reduced radiotherapy in patients diagnosed with CNS Germinoma, between the ages of 3 and 25. Role: Support Staff

**Children’s Oncology Group Protocol ALTE07C1: Neuropsychological, social, emotional, and behavioral outcomes in children with cancer.** Research aimed to streamline administration of neuropsychological and behavioral test to patients with cancer. A streamlined, efficient battery will help monitor the late effects in patients being treated for cancer. Neuropsychological batteries designed for children as young as 2 years old to adults. Role: Support Staff

**Neurological and behavioral change in the pediatric epilepsies.** Study focused on examining neuropsychological and behavioral changes in patients with intractable epilepsy, post resection surgery. Patients assessed between 6 and 1 month pre-surgery and then again 6 months post surgery. Role: Support Staff

**Research Assistant: Human Behavior and Pharmacological Laboratory**  
Supervisor: Harriet de Wit, Ph.D.

Conducted clinical interviews, EKG, and administered questionnaires during participant screening process. Managed all aspects of participant recruitment such as advertisement, screening and tracking.

**Research Assistant: Memory and Development Laboratory**  
Washington University / St. Louis, Missouri / 2006 – 2007  
Supervisor: Pascal Boyer, Ph.D.

Assisted in recording and analyzing data and developed and submitted required documents for Institutional Review Board process. Conducted interviews with child participants and administered research measures in study protocol. Research studies conducted in natural and lab settings with adults and children.
SUPERVISION EXPERIENCE

Doctoral Internship in Clinical Psychology
University of Chicago Medicine / Chicago, Illinois / 2016 – Present
Track: Pediatric Neuropsychology
Supervisor: Scott Hunter, Ph.D.

Supervised advanced graduate students in research and clinical experiences. Provided clinical research supervision with pediatric neuropsychology externs with administration, scoring, interpretation, and report writing as part of Homeless Youth Study. Provided clinical supervision in Neurodevelopmental Disorders Clinic. Supervised advanced graduate students and psychiatry fellow in the administration of neuropsychological evaluations, including administration and scoring on the ADOS-2 (all modules).

Advanced Student Therapist: UWM Child Anxiety Clinic
University of Milwaukee - Wisconsin / Milwaukee, Wisconsin / 2014 – 2016
Supervisor: Bonnie Klein-Tasman, Ph.D.

Supervised third-year graduate students and provided individual cognitive-behavioral therapy to community clients in a low-cost clinic that specialized in treating children with anxiety disorders.

Clinical Psychology Practicum Supervisor: UWM Psychology Clinic
University of Milwaukee - Wisconsin / Milwaukee, Wisconsin / 2013 – 2014
Supervisor: Bonnie Klein-Tasman, Ph.D.; Han Joo Lee, Ph.D.

Supervised second-year graduate students in administration of neuropsychological and clinical assessments with patients from the child neuropsychology and general psychology clinic. Provided individual student feedback and supervision following assessment sessions. Facilitated course meetings and participation in weekly group supervision of supervision to review progress of the students and approaches to supervision.

Clinical Psychology Practicum Supervisor: UWM Psychology Clinic
University of Milwaukee - Wisconsin / Milwaukee, Wisconsin / 2011 – 2012
Supervisor: Bonnie Klein-Tasman, Ph.D.; Han Joo Lee, Ph.D.

Supervised first-year graduate students completing psychodiagnostic and neuropsychological assessments, including nonspecific/general factors in client interactions. Participation in weekly group supervision of supervision to review progress of the students and approaches to supervision.

TEACHING EXPERIENCE

Associate Lecturer: Online Child Psychology
University of Wisconsin - Milwaukee, Milwaukee, Wisconsin
Spring 2015
Teaching Assistant: Online Child Psychology
University of Wisconsin - Milwaukee, Milwaukee, Wisconsin
Spring 2011

Teaching Assistant: Child Psychology
University of Wisconsin - Milwaukee, Milwaukee, Wisconsin
Fall 2010

PROFESSIONAL SERVICE

Member of American Psychological Association 2012 – Present
Member of International Neuropsychology Society 2012 – Present
Member of National Academy of Neuropsychology 2012 – Present
Division 40 Association of Neuropsychology Students in Training 2012 – Present
Health Psychology Graduate Student Club: UWM Chapter Secretary 2012 – 2016
Clinical Training Committee Student Representative 2010 – 2013