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ORIGINAL PAPER

Sex- and age-related differences in autistic behaviours in children with neurofibromatosis type 1

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Abstract

This study investigated sex and age differences in autistic behaviours in children with neurofibromatosis type 1 (NF1) who scored within the clinical range on the Social Responsiveness Scale - Second Edition (T score ≥ 60). Thirty-four males and 28 females (3–16 years) were assessed with the Autism Diagnostic Observation Schedule - Second Edition and Autism Diagnostic Interview - Revised. Across both measures, males exhibited greater social communication deficits relative to females. Age-related abatement of social communication difficulties was observed for males but not females. Conversely, no sex differences were found for restricted/repetitive behaviours, which were stable over time for both males and females. The findings are discussed within the context of broader neurodevelopmental considerations that are common in NF1.

Keywords Neurofibromatosis type 1 · Autism · Autistic · Sex differences · Age-related differences · Children

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic syndrome with a birth incidence of 1 in 2700 (Evans, Howard, Giblin, Clancy, Spencer, Huson et al., 2010). While NF1 is characterised by a heterogeneous range of cutaneous, neurological, neoplastic, and skeletal manifestations (Ferner, 2007; Korf, 2013; Viskochil, 2021), cognitive, language, and behavioural deficits are the most frequent complications in childhood (Hyman et al., 2005; Lehtonen et al., 2013). Indeed, comorbidities including attention deficit hyperactivity disorder (ADHD), language disorder, anxiety, and depression are all diagnosed with substantially higher frequency in children with NF1 than in the general population (Noll, Reiter-Purtill, Moore, Schorry, Lovell, Vannatta et al., 2007; Payne, Haebich, MacKenzie, Walsh, Hearps, Coghill et al., 2021; Payne et al., 2013). A more recently recognised behavioural phenotype in NF1 is that of autism spectrum disorder (henceforth referred to as autism), a neurodevelopmental disorder behaviourally defined by social communication difficulties and restricted, repetitive behaviours and interests (American Psychiatric Association, 2013). A meta-analysis reported evidence of significantly elevated autistic traits in NF1, with a large effect size (g = 0.91; Chisholm et al., 2018), and studies using gold standard measures to determine autism diagnosis have yielded prevalence estimates ranging between 11% and 26% in NF1 cohorts (Eijk, Mous, Dieleman, Dierckx, Rietman, de Nijs et al., 2018; Garg, Green, Leadbitter, Emsley, Lehtonen, Evans et al., 2013; Plasschaert et al., 2015), compared with 1–4% prevalence reported in the general population (Lai et al., 2014; May et al., 2020).

While examination of the phenotypic profile of autism in NF1 is a growing area of research (Chisholm, Haebich, Pride, Walsh, Lami, Ure et al., 2022; Garg, Plasschaert, Descheemaeker, Huson, Borghgraef, Vogels et al., 2015; Geoffray, Falissard, Green, Kerr, Evans, Huson et al., 2021), the presentation of autistic behaviours in children with NF1 remains to be definitively characterised. A necessary step for advancing our knowledge in this area is the investigation of sex dependent differences in the manifestation of both core autistic behaviours and comorbid symptoms. Appreciation of potential disparities in the male and female phenotypes of autism in NF1 not only has meaningful clinical implications, but may contribute to our understanding of sex differences in autism more generally, due to the relatively straightforward correspondence between genes and

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behaviour in NF1 (Garg & Green, 2018). The few studies that have explored the sex ratio in children with NF1 and autism have detected a male predominance, with ratios ranging from 1.7:1 to 3:1 (Eijk et al., 2018; Garg, Green, et al., 2013; Garg et al., 2016; Plasschaert et al., 2015). While consistent with the well-established male bias for autism, this ratio appears somewhat attenuated compared with estimates of a 3:1 to 4:1 male-to-female ratio in the idiopathic population (Christensen, Braun, Baio, Bilder, Charles, Constantino et al., 2018; Loomes et al., 2017). Over the past decade, research in the idiopathic autism population suggests that autistic behaviours may present differently in males versus females. For example, there is evidence that female 'camouflaging' behaviours (i.e., masking or compensating for autistic behaviours) contribute to delayed or missed recognition of autism in females Hull et al., 2017; Lai et al., 2015; Loomes et al., 2017; Ratto, Kenworthy, Yerys, Bascom, Wieckowski, White et al., 2018). As in idiopathic autism, it is important to carefully examine possible sex-based phenotypic disparities in NF1 that may influence diagnostic decision making and the estimation of autism prevalence in males versus females with NF1.

Only one study has explored sex differences in autistic behaviours using gold standard measures in children with NF1. Garg and colleagues (2016) reported on phenotypic sex differences using the Autism Diagnostic Interview - Revised (ADI-R; Le Couteur et al., 2003) and the Autism Diagnostic Observation Schedule - Second Edition (ADOS-2; Lord et al., 2012) in a sample of children with NF1 who scored in the clinical range on the Social Responsiveness Scale - Second Edition (SRS-2; Constantino & Gruber 2012). Across both measures, males demonstrated greater social communication deficits relative to females, however, there was less consistent evidence for sex differences in restricted and repetitive behaviours (RRB). Verbal IQ and ADHD symptoms were comparable across males and females, suggesting these factors did not account for the observed sex discrepancy in social communication skills. However, the potentially confounding effects of sex differences in other neurodevelopmental and mental health comorbidities on the expression of autistic behaviours in NF1 are yet to be examined. Certainly, child characteristics such as language impairment and internalising symptoms, which commonly co-occur with NF1, and have an overlap in clinical presentation with autism, also warrant investigation to enhance our understanding of sex differences in NF1-related autistic behaviours (Cholemkery et al., 2014; May, Brignell, Hawi, Brereton, Tonge, Bellgrove et al., 2018).

The degree to which chronological age influences the symptom presentation or diagnosis of autism in children with NF1 is not well understood, and existing evidence is limited to cross-sectional retrospective cohort designs. Several studies report no association between age and autistic behaviours in children with NF1 (Garg, Green, et al., 2013; Garg, Lehtonen, Huson, Emsley, Trump, Evans et al., 2013; Morotti, Mastel, Keller, Barnard, Hall, O'Roak et al., 2019). In contrast, one study reported higher levels of parent-rated social communication deficits with increasing age (Plasschaert et al., 2015), and another reported increased severity of autistic behaviours in NF1 participants aged 8–17 years, compared with those aged 2–7 years in a large multisite cohort (N = 531; Morris, Acosta, Garg, Green, Huson, Legius et al., 2016). Although not directly comparable to studies reporting age at first diagnosis in the idiopathic literature, these findings suggest that recognition of autism in children with NF1 may occur later than in the idiopathic autism population (Baio, Wiggins, Christensen, Maenner, Daniels, Warren et al., 2018; Bent et al., 2015). The mechanisms underlying this disparity are unclear. It is possible that the severity of NF1-related autistic behaviours increases over time, with some children exceeding thresholds on autism-specific instruments or meeting clinical criteria at older but not younger ages. This is consistent with Eijk et al., (2018) who found that the mean age of clinical diagnosis of autism in children with NF1 was significantly higher than the age of those not meeting criteria. Medical, emotional, and behavioural problems commonly associated with NF1 may also complicate recognition of autistic behaviours in the syndrome (Levy, Giarelli, Lee, Schieve, Kirby, Cunniff et al., 2010; Miodovnik et al., 2015). Irrespective of the drivers of late detection, affected individuals may not receive timely intervention (Zwaigenbaum, Bauman, Choueiri, Kasari, Carter, Granpeesheh et al., 2015), highlighting the importance of improving our understanding of age-related variations in the manifestation of autistic behaviours in NF1.

Longitudinal investigations in the idiopathic autism literature have identified heterogeneity in the developmental trajectories of core autistic behaviours, with variability between and within individuals across development Barbaro & Dissanayake, 2017; Lord et al., 2015; Richler et al., 2010; Venker, Ray-Subramanian, Bolt, & Ellis Weismer, 2014). There is also growing evidence of complex relationships between change in autism severity over time and developmental characteristics of IQ and language (Gotham et al., 2012; Richler et al., 2010; Visser et al., 2017). Emerging data have further indicated sex-by-age interactions (Mahendiran, Dupuis, Crosbie, Georgiades, Kelley, Liu et al., 2019; Rynkiewicz, Schuller, Marchi, Piana, Camurri, Lassalle et al., 2016; Szatmari, Georgiades, Duku, Bennett, Bryson, Fombonne et al., 2015); for example, males have been shown to exhibit higher levels of repetitive and stereotyped behaviours from six years of age, but not below the age of six (Van Wijngaarden-Cremers et al., 2014). These

observations suggest that autistic behaviours can present differentially across development and be modified by sex, IQ, and language level, underscoring the importance of accounting for these factors when examining the autistic phenotype in NF1.

The current study, which used the same sample described by Chisholm and colleagues (2022), aimed to improve our understanding of sex- and age-related differences in the autistic behaviours of children with NF1. Similar to a previous study (Garg et al., 2016), our first aim was to compare the autistic phenotype in males and females using the ADI-R parent interview and the clinician administered ADOS-2. As part of this aim, we also explored the potential contributions of characteristics not specific to autism (e.g., IQ, early language delay, and ADHD) to sex differences in autistic behaviours. Our second aim extends this by investigating age-related differences in autistic behaviours. We approached this in two ways: (i) we examined associations between the severity of current autistic behaviours, as measured by current SRS-2, ADI-R, and ADOS-2 ratings, and chronological age, and (ii) we investigated age-related change in autistic behaviours by comparing current and past or 'lifetime' ratings on the ADI-R. Our third aim was to examine whether developmental change in autistic behaviours differed for males and females over time. Since autistic behaviours in the general population vary along a continuum of severity (Constantino & Charman, 2016) and are heterogeneous (i.e., not all behaviours are required for an autism diagnosis), we investigated sex- and age-related differences in a broader 'screen positive' NF1 sample identified by scores in the clinical range on the SRS-2 autism trait questionnaire (T-score ≥ 60). Not restricting our examination to individuals with a 'diagnosis' of autism was also believed to be important given the under identification of autistic females suggested by the idiopathic literature (Loomes et al., 2017).

Methods

Participants

Participants were drawn from a larger and ongoing prospective cross-sectional study characterising the social and autism phenotype in children with NF1 (Haebich, Pride, Walsh, Chisholm, Rouel, Maier et al., 2019). Children were aged between 3 and 16 years at the time of sequential recruitment from NF1 clinics at three centres: (1) The Royal Children's Hospital, Melbourne, Australia; (2) the Children's Hospital at Westmead, Sydney, Australia; and (3) the Children's National Hospital, Washington DC, USA. All participants were diagnosed with NF1 by an expert neurologist or clinical geneticist using clinical diagnostic criteria (Neurofibromatosis, 1988). Children were eligible for the current study if they scored in the clinical range on the parent rated SRS-2 (T score ≥ 60), and were assessed with the ADOS-2 (Lord et al., 2012) and ADI-R (Rutter et al., 2003). Children were excluded from the study if: (i) they and at least one parent were not fluent in English; (ii) there was evidence of diagnosed, symptomatic intracranial pathology such as an acquired brain injury or hydrocephalus (asymptomatic lesions such as optic gliomas were allowed), and (iii) they exhibited visual or auditory impairment that would compromise the validity of psychometric testing. To avoid 'artificial' inflation of performance on measures of cognitive function, children prescribed behavioural medication for ADHD were asked to refrain from taking this at least 24 h prior to assessment. The final study sample consisted of 34 male and 28 female participants (see Fig. 1).

Procedure

This study was performed in line with the principles of the Declaration of Helsinki. All procedures were approved by the Human Research Ethics Committee of The Royal Children's Hospital (HREC/16/RCHM/137), Sydney Children's Hospitals Network (HREC/16/SCHN/42), and Children's National Hospital (Pro00007045). Prior to participation in the study, informed written consent was obtained from parents of children with NF1. All children underwent cognitive evaluations conducted by clinical neuropsychologists, and parents were asked to complete a range of questionnaires evaluating their child's emotional and behavioural functioning. Eligible participants were administered the ADOS-2 and ADI-R by clinicians who completed relevant certified training and met requirements for research reliability.

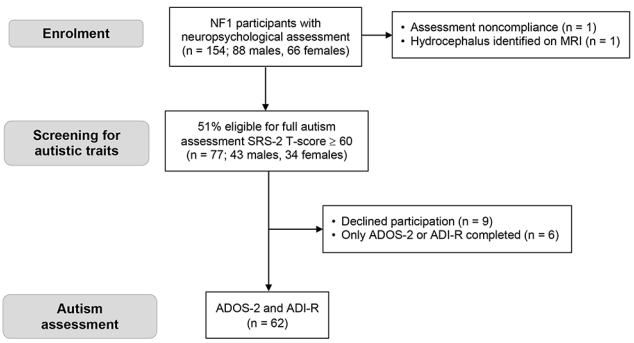

Fig. 1 Flow diagram depicting enrolment and assessment process of participants with NF1

Measures

Autistic behaviours

The ADOS-2 is a standardised, observational assessment of a child's communication, social interaction, and RRBs (ADOS-2: Lord et al., 2012). Participants in the current study received ADOS-2 modules 2 or 3 depending on their age and expressive language level. Individual items are coded 0 to 3, with 0 indicating that the specified behaviour is not abnormal and 3 indicating marked abnormality. Scores of 3 are converted to 2 for selected algorithm items, which are summed to form the Social Affect (SA-ADOS; 0–20) and RRB (RRB-ADOS; 0–8) domain scores, and an overall algorithm score (Overall-ADOS; 0–28). We preferentially employed raw total scores to examine sex differences and age-related associations due to the restricted range (1–10) of the calibrated severity scores (CSS) that are also available for the ADOS-2 (Hus et al., 2014) and to facilitate comparisons with the current NF1 literature (Garg et al., 2016). However, since the ADOS-2 CSS are standardised according to age and language level, thereby reducing the potentially confounding effects of these non-autism-specific child characteristics and facilitating comparisons across different modules, we also calculated CSS and re-ran analyses using these scores to determine comparability of findings. The ADOS-2 provides cut-off scores for 'autism' and the broader diagnostic category of 'autism spectrum'. We used the 'autism spectrum' cut-off (7 or 8 depending on the age of the child and the module used), as this corresponds to the current Diagnostic and Statistical Manual of Mental Disorders (DSM-5) conceptualisation of autism (American Psychiatric Association, 2013).

The ADI-R is a standardised, semi-structured parent interview designed to identify typical features of autism that are categorised into three functional domains: (i) Reciprocal Social Interactions (Social-ADI); (ii) Communication (Communication-ADI); and (iii) Restricted, Repetitive, and Stereotyped Patterns of Behavior (RRB-ADI) (Le Couteur et al., 2003). All participants in the current study were 'verbal' (i.e., using at least 3-word phrases), and were administered the verbal communication items from the ADI-R Communication domain. Individual items are coded 0 to 3 according to the clinician's judgement of parent-reported information, with a score of 0 indicating no abnormality and a score of 3 signifying abnormal behaviour that is marked in severity. All items used for calculation of diagnostic algorithms have two ratings, (i) 'current ratings,' which reflect behaviours around the time of the interview, and (ii) 'lifetime ratings,' which are composed of either the 'most abnormal' behaviours evident while the child was aged 4:0 to 5:0 years of age, or a worst 'ever' rating indicating highest level of severity in the specified behaviour across the individual's lifetime. For participants aged < 4 years, only current/ever ratings are used. Selected lifetime items are summed into three diagnostic algorithm scores: Social-ADI (range 0–30); Communication-ADI (range 0–26); and RRB-ADI (range 0–12). Following ADI-R scoring conventions, scores of 3 are recoded to 2 for calculation of these algorithm scores. The ADI-R provides cut-offs for autism, as defined by DSM-IV Text Revision (TR) criteria (American Psychiatric Association, 2000), for each of the three domains: Social-ADI = 10; Communication-ADI = 8; and RRB-ADI = 3.

The comparison of lifetime with current ADI-R ratings also provides a within-subject index of age-related change in autistic behaviours. Although this methodology is cross-sectional and subject to retrospective bias, findings in the idiopathic autism literature have supported use of this method as a valid measure of developmental change (McGovern & Sigman, 2005; Shattuck, Seltzer, Greenberg, Orsmond, Bolt, Kring et al., 2007). Since some items only apply to a restricted age range, they cannot be used for this analysis (e.g., friendships, direct gaze). However, 28 items are available irrespective of participant age: 10 each in the Social and Communication domains (Social-ADI_{10} and Communication-ADI_{10}) and 8 in the RRB domain (RRB-ADI_8). To maximise the variability of scores and sensitivity to age-related change, item ratings of 3s were maintained for these analyses, hence the possible range of scores were: Social-ADI_{10} (range 0–28); Communication-ADI_{10} (range 0–24); and RRB-ADI_8 (range 0–23). There is a caveat to note for ADI-R items that rate the worst 'ever' behaviours. It is a function of the protocol that an 'ever' rating cannot be scored as more impaired than a 'current' rating. Therefore, these 'ever' items can only gauge behavioural improvement, not deterioration over time. This limiting factor applies to all RRB items, but also to two Social-ADI_{10} and six Communication-ADI_{10} items.

Parent rated questionnaires

For all questionnaires, separate sex norms were used for the calculation of standardised scores.

The SRS-2 is a quantitative measure of autistic traits extensively used as a screening instrument in the general population (Constantino & Gruber, 2012). Items are organised into two symptom domains of (i) Social Communication and Interaction and (ii) Restricted Interests and Repetitive Behavior, which correspond to the contemporary DSM-5 criteria for autism (American Psychiatric Association, 2013). Raw scores were converted to T-scores with a mean (M) of 50 and a standard deviation (SD) of 10. Total T-scores ≥ 60 represent clinically significant autistic traits.

The Child Behavior Checklist (CBCL/1½-5; Achenbach & Rescorla 2000) and CBCL/6–18 (Achenbach & Rescorla, 2001) were administered to determine the emotional and behavioural functioning of children aged 3–5 and 6–16 years, respectively. These two questionnaires yield similar subscales, although some items vary to ensure age appropriateness (Achenbach et al., 2017). We reported the DSM-oriented subscales of Anxiety Problems, Affective Problems, and Oppositional Defiant Problems for both versions of the CBCL (Achenbach et al., 2003). We considered these to be a purer estimate of anxiety and depression in our cohort since the syndrome scales contain a combination of commonly comorbid yet distinct problems, and the broad-band Internalizing scale includes somatic complaints, which may be endorsed due to the wide ranging somatic symptoms associated with NF1, rather than internalising problems per se (Gutmann et al., 2017; Naar-King et al., 2003). Subscales were translated into T-scores (M = 50, SD = 10), with higher scores indicating greater psychopathology.

The Conners ADHD DSM-IV Rating Scale (CADS; Conners, 1997) and Conners - Third Edition (Conners-3; Conners 2009) were administered to evaluate ADHD symptoms of participants aged 3–5 and 6–16 years, respectively. Both scales yielded T-scores for Inattentive and Hyperactive/Impulsive content scales (M = 50, SD = 10), with higher scores reflecting more severe ADHD symptoms. Correlation coefficients between the Conners-3 and CADS demonstrate moderate to strong associations between the two questionnaires for the Inattention ($r = .66$) and Hyperactivity-Impulsivity scales ($r = .72$) (Conners, 2009).

Intellectual functioning

The Wechsler Preschool and Primary Scale for Children - Fourth Edition (WPPSI-IV) (Wechsler, 2012) and Wechsler Intelligence Scale for Children - Fifth Edition (WISC-5) (Wechsler, 2014) were employed to estimate the general intelligence of participants aged 3–5 years and 6–16 years, respectively. All subtests required for calculation of Full-Scale IQ (FSIQ) and primary index scales were administered. FSIQ and Verbal Comprehension Index (VCI) scores are reported in this study, with higher scores reflecting better performance (M = 100, SD = 15). Corrected correlation coefficients between the WPPSI-IV and WISC-5 for FSIQ ($r = .83$) and VCI ($r = .71$) show strong associations between the two measures (Wechsler, 2014).

Early language milestones and language abilities

Early language milestones were evaluated via the ADI-R and classified as a categorical variable (delayed/not delayed). As prescribed by the ADI-R manual (Le Couteur et al., 2003), delay in age of first words was defined as first words spoken after 24 months of age (Word Delay). Delay in age of first phrases was defined as first 2–3 word phrases spoken after 33 months of age (Phrase Delay).

Receptive and expressive language abilities of participants aged 3–5 years were assessed with three subtests from the Clinical Evaluation of Language Fundamentals - Preschool - Second Edition (CELF-Preschool-2; Wiig et al., 2006). The Sentence Structure subtest was used to estimate receptive language and scaled scores from the Word Structure and Expressive Vocabulary subtests were averaged to measure expressive language. For participants aged 6–16 years, receptive language was measured with the Comprehension of Instructions subtest from A Developmental Neuropsychological Assessment - Second Edition (NEPSY-II; Korkman et al., 2007), and expressive language was assessed with Formulated Sentences from the Clinical Evaluation of Language Fundamentals - Fourth Edition (CELF-4; Semel et al., 2003). Higher scores for all subtests indicate better performance (M = 10, SD = 3).

Social risk

Children's social risk was assessed via maternal education level (high risk < 12 years of schooling; low risk ≥ 12 years of schooling), which has been found to predominantly explain socioeconomic effects on child behavioural outcomes (Bornstein et al., 2003).

Data Analysis

All data were analysed with SPSS Statistics (version 27) and plotted using Microsoft Excel and *R* (R Core Team, 2020). We performed descriptive analyses to present the demographic and clinical characteristics of our male and female groups. Clinical characteristics for the two groups were compared to population norms with one sample *t* tests. For sex comparisons, we used independent *t* tests for normally distributed continuous variables. Where data did not meet the assumptions of normality (i.e., z-statistics for skewness and/or kurtosis fell outside ± 3), Mann-Whitney *U* (M-W) tests were used instead. While M-W tests do not statistically compare mean scores, we report means and 95% confidence intervals (CIs) to provide comparability to other relevant NF1 publications (e.g., Garg et al., 2016; Garg et al., 2015; Geoffray et al., 2021). Chi-square tests were employed to examine sex differences for categorical variables. Analysis of covariance (ANCOVA) was used to assess the influence of child characteristics on autistic behaviours. Non-normally distributed scores were transformed using a square root transformation (McDonald, 2014) to permit ANCOVA analyses.

Bivariate correlational analyses investigated associations between chronological age and autistic behaviours, and paired samples *t* tests were used to compare lifetime to current ADI-R scores. To assess for sex differences in change over time for the ADI-R domain scores, we conducted repeated measures analysis of variance (ANOVA) with timepoint (lifetime vs. current) as the within-subject factor and sex as the between-subject factor. To provide a clear demarcation between the two timepoints, only participants aged > 5 years; 6 months were included in these analyses. To examine the robustness of our results when individual differences in participant characteristics were accounted for in the analysis, we reran them using linear mixed models. Group differences were considered statistically significant at $p < .05$ (two-sided), and we applied the false discovery rate (FDR) procedure to correct for multiple comparisons (Benjamini & Hochberg, 1995). To illustrate the heterogeneity of age-related change in social communication behaviours across individual participants, we plotted the change from lifetime to current ratings for each participant on a combined social communication score ($SC\text{-}ADI_{20}$). This variable was computed by summing $Social\text{-}ADI_{10}$ and $Communication\text{-}ADI_{10}$.

Effect sizes were reported as Cohen's *d* for differences derived from *t* tests, M-W tests, and Wilcoxon tests (*d*, small: 0.2, medium: 0.5, large: 0.8). Partial η^2 was reported for differences derived from ANCOVAs (η^2_p, small: 0.01, medium: 0.06, large = 0.14) (Cohen, 1988). To denote effect sizes for chi-square analyses, *Phi (φ)* was interpreted as 0.1: small, 0.3: medium, 0.5: large (Cohen, 1988), and Pearson's *r* and Spearman's *rho* coefficients were interpreted as 0.3: weak, 0.5: moderate, 0.7: strong (Hinkle et al., 2003).

Results

Participant characteristics by sex are described in Table 1. Males and females did not differ in chronological age, NF1

Table 1 Demographic and clinical characteristics of the NF1 sample by sex

	Male (N = 34)	Female (N = 28)	Sex comparisons		
			t/χ^2	*p*	*d*/φ
Age in years	9.3 (3.3)	10.0 (3.8)	-0.79	0.432	0.20
Familial inheritance N (%)[a]	10 (30.3)	15 (53.6)	0.08	0.075	0.24
Social risk, low-risk N (%)[a]	24 (73%)	23 (85%)	1.36	0.348	0.15
Wechsler Full Scale IQ SS	83.4 (11.4)	87.6 (12.7)	-1.37	0.109	0.40
Wechsler Verbal Comprehension Index SS	84.5 (15.0)	92.9 (13.9)	-2.26	0.027	0.58
ADI-R Word Delay N (%)	12 (33.3)	4 (13.8)	3.31	0.139	0.21
ADI-R Phrase Delay N (%)[a]	19 (52.8)	6 (21.4)	6.50	0.035	0.29
CELF/NEPSY-II Receptive language ScS[b]	7.70 (3.4)	8.6 (3.0)	-1.04	0.304	0.28
CELF Expressive language ScS[c]	7.27 (3.5)	8.6 (3.3)	-1.38	0.174	0.38
SRS-2 Total raw score	92.6 (21.8)	91.5 (28.6)	0.16	0.873	0.04
SRS-2 Social Communication/Interaction raw score[a]	74.1 (19.1)	73.9 (22.4)	0.04	0.970	0.01
SRS-2 Restricted/Repetitive Behaviour raw score	16.9 (6.6)	17.6 (7.7)	-0.39	0.696	−0.10
SRS-2 Total T-score	72.9 (8.7)	76.6 (11.5)	-1.42	0.163	−0.37
SRS-2 Social Communication/Interaction T-score[a]	72.7 (8.0)	74.9 (10.9)	−0.88	0.382	−0.24
SRS-2 Restricted/Repetitive Behaviour T-score	71.4 (11.9)	78.1 (15.2)	-1.96	0.054	−0.51
Conners Inattention T-score	77.9 (11.7)	77.0 (13.8)	0.25	0.801	0.07
Conners Hyperactivity-Impulsivity T-score	76.9 (12.1)	77.1 (15.8)	0.07	0.942	0.02
CBCL Anxiety Problems T-score	60.9 (9.1)	66.2 (10.8)	-2.09	0.040	−0.53
CBCL Affective Problems T-score	64.8 (8.5)	68.3 (9.3)	-1.56	0.124	−0.40
CBCL Oppositional Defiant Problems T-score	60.4 (9.8)	62.2 (10.5)	−0.70	0.488	−0.18

ADI-R Autism Diagnostic Interview-Revised, *CELF* Clinical Evaluation of Language Fundamentals-Fourth Edition or Preschool-Second Edition, *Conners* Conners-Third Edition or Conners ADHD DSM-IV Rating Scale, *IQ* intelligence quotient, *NEPSY-II* A Developmental Neuropsychological Assessment-Second Edition, *SRS-2* Social Responsiveness Scale-Second Edition, *SS* Standard score, *ScS* Scaled score

Data reported as mean (M) and standard deviation (SD) unless otherwise specified. [a] female n = 27, male n = 34, [b] female n = 24, male = 30, [c] female n = 26, male n = 26

Positive effect sizes (Cohen's *d or φ)* express greater impairment in males compared with females for cognitive/language and parent questionnaire comparisons

inheritance type (familial vs. sporadic), or social risk. As per the selection criteria, all participants scored in the clinical range on the SRS-2 (Total T-score ≥ 60). Males and females exhibited equivalent raw and sex-normed scores on the SRS-2. Males and females were also comparable for severity of ADHD, affective, and oppositional defiant symptoms, FSIQ, frequency of Word Delay, and receptive and expressive language. While there were trends for female participants to demonstrate higher anxiety symptoms, higher VCI, and a lower incidence of Phrase Delay, none of these were statistically significant after correcting for multiple comparisons (all, medium effect size). All cognitive, language, and emotional/behavioural outcomes, in both males and females with NF1, were impaired relative to normative data (all, $p < .05$).

Sex differences in autistic behaviours

Males exhibited significantly higher lifetime social communication deficits relative to females on the ADI-R Social and Communication domains with medium-to-large effect sizes ($d = 0.73$ and 0.74, respectively). Inspection of the subscale scores revealed that the sex difference in the Social domain was driven by the 'Failure to use nonverbal behaviours to regulate social interaction,' 'Lack of socioemotional reciprocity,' and 'Lack of shared enjoyment' subscales. The Communication domain sex difference was driven by the 'Lack of varied spontaneous make-believe or social imitative play' and 'Stereotyped, repetitive or idiosyncratic speech' subscales. Consistent with parent-reported behaviours, the ADOS-2 Social Affect score also indicated greater impairment of social communication behaviours in

Table 2 Sex differences in ADI-R and ADOS-2 diagnostic algorithms and subscales

ADI-R	Male N = 34	Female N = 28	*t* / *U*	*p*	*d*
	Mean (95% CI)				
Reciprocal Social Interaction (Cut-off = 10)	**14.1 (11.4–16.8)**	**8.8 (6.2–11.4)**	**2.85**	**0.006***	**0.73**
Failure to use nonverbal behaviours to regulate social interaction	3.0 (2.3–3.6)	1.5 (0.9–2.2)	274.0	0.004*	0.78
Failure to develop peer relationships	4.1 (3.3–4.9)	3.0 (2.1–3.9)	353.0	0.079	0.45
Lack of shared enjoyment	2.8 (2.1–3.5)	1.7 (0.9–2.4)	317.5	0.022*	0.59
Lack of socioemotional reciprocity	4.3 (3.3–5.2)	2.6 (1.6–3.5)	304.0	0.014*	0.65
Communication (Cut-off = 8)	**11.3 (9.4–13.2)**	**7.1 (5.0-9.3)**	**2.91**	**0.005***	**0.74**
Lack/delay in spoken language and failure to compensate through gesture	2.2 (1.4-3.0)	1.4 (0.7–2.2)	373.0	0.131	0.38
Lack of varied spontaneous make-believe or social imitative play	3.7 (2.9–4.4)	2.3 (1.6–2.9)	287.5	0.007*	0.72
Relative failure to initiate or sustain conversational interchange	2.7 (2.1–3.2)	2.3 (1.7–2.8)	382.0	0.168	0.34
Stereotyped, repetitive or idiosyncratic speech	2.7 (2.2–3.2)	1.4 (0.7-2.0)	227.5	< 0.001*	1.00
Restricted/Repetitive Behaviour (Cut-off = 3)	**3.2 (2.5-4.0)**	**2.6 (1.7–3.5)**	**1.10**	**0.276**	**0.28**
Encompassing preoccupation or circumscribed interest	1.3 (0.9–1.7)	1.0 (0.6–1.3)	413.0	0.349	0.23
Apparently compulsive adherence to non-functional routines or rituals	0.4 (0.1–0.7)	0.4 (0.03–0.8)	456.0	0.691	−0.07
Stereotyped and repetitive motor mannerisms[a]	0.5 (0.2–0.8)	0.5 (0.2–0.8)	467.5	0.886	−0.03
Preoccupation with parts of objects or non-functional elements of material[a]	1.2 (0.9–1.4)	0.7 (0.4-1.0)	341.0	0.043	0.50
ADOS-2 Overall (Autism Spectrum Cut-off = 7/8)	**10.1 (8.4–11.9)**	**7.1 (5.8–8.5)**	**304.0**	**0.015***	**0.65**
Social Affect	8.9 (7.5–10.3)	5.8 (4.5-7.0)	260.0	0.002*	0.84
Restricted/Repetitive Behaviour	1.2 (0.6–1.9)	1.4 (0.9–1.8)	388.5	0.195	−0.32

ADI-R Autism Diagnostic Interview-Revised, *ADOS-2* Autism Diagnostic Observation Schedule-Second Edition, *CI* Confidence interval,

d Cohen's *d*, [a] subscale score derived from higher item of two items

* indicates statistical significance after FDR corrections, positive effect sizes express greater impairment in males compared with females

males relative to females, with a large effect size ($d = 0.84$). Additional analysis using the ADOS-2 Social Affect CSS confirmed this pattern of sex discrepancy ($p = .001$; $d = 0.87$; see supplemental Table 1s). These sex differences translated into a significantly greater proportion of males, as compared with females, exceeding ADI-R Social (64.7% vs. 32.1%; $p = .021$) and Communication (67.6% versus 39.3%; $p = .040$) cut-off scores as well as the ADOS-2 'autism spectrum' cut-off (74% versus 46%; $p = .038$).

In contrast, there were no significant sex differences in the severity of the overall RRB domain on the ADOS-2 (raw scores and CSS) and ADI-R, nor the ADI-R subscale scores (see Table 2 and supplemental Table 1s). Although we found a trend for males to be more severely rated on the ADI-R 'Preoccupation with parts of objects or non-functional elements of material' subscale, this between-sex discrepancy did not withstand FDR correction. Equivalent proportions of males and females met the ADI-R RRB cut-off (59% versus 57%; $p = 1.00$). While more than twice as many males as females exceeded all three cut-offs on the ADI-R, this was not significantly different (44% versus 21%; $p = .105$).

Given the trend for lower incidence of Phrase Delay and higher VCI in females, we conducted ANCOVAs adjusting for these factors to better understand their effects on social communication scores. We examined these covariates separately due to a moderate degree of multicollinearity between Phrase Delay and VCI ($r = .53$, $p < .001$). First considering the ADI-R, Phrase Delay significantly contributed to the model for both Social-ADI ($p = .015$, $\eta^2_p = 0.10$) and Communication-ADI ($p = .003$, $\eta^2_p = 0.15$). Despite this, males continued to exhibit greater impairment for both Social-ADI ($p = .035$, $\eta^2_p = 0.07$) and Communication-ADI ($p = .047$, $\eta^2_p = 0.07$). In contrast, VCI did not significantly contribute to either Social-ADI or Communication-ADI (both, $p > .327$), and the robust sex effects remained: Social-ADI ($p = .012$, $\eta^2_p = 0.10$), Communication-ADI ($p = .015$, $\eta^2_p = 0.10$).

ANCOVAs were conducted on square root transformed ADOS-2 Social Affect raw scores covarying for Phrase Delay and VCI (McDonald, 2014). While Phrase Delay significantly contributed to the model ($p = .029$, $\eta^2_p = 0.08$), a robust sex effect for SA-ADOS remained ($p = .015$, $\eta^2_p = 0.10$). VCI also significantly contributed to the model ($p = .032$, $\eta^2_p = 0.08$), and again, the sex effect for SA-ADOS remained significant after covarying for VCI ($p = .011$, $\eta^2_p = 0.11$).

Age-related differences in autistic behaviours

All correlations between age and current domain-level scores on the SRS-2 (raw scores), ADOS-2 (raw scores and CSS), and ADI-R were negligible (all, $r/rho < 0.16$ and $p > .2$).

Next, we compared lifetime and current scores for Social-ADI_{10}, Communication-ADI_{10}, and RRB-ADI_8 in participants aged > 5 years; 6 months (29 males, 25 females). Figure 2 depicts the mean age-related changes in the three ADI-R domains for the total subsample as well as for males and females. For both sexes, there was evidence of significant abatement of autistic behaviours in all domains, accompanied by medium-to-large effect sizes: Social-ADI_{10} ($p < .001$, $d = 0.68$); Communication-ADI_{10} ($p < .001$, $d = 0.67$); and RRB-ADI_8 ($p < .001$, $d = 0.73$). To investigate the potential confounding effect of lifetime items that were derived from 'ever' ratings on estimation of age-related change, we reran the analyses using only the 12 items derived from 'most abnormal' ratings (i.e., exhibited at 4:0 to 5:0 years of age) across the Social and Communication domains. This analysis indicated a similar pattern of age-related improvement in social communication behaviours ($p < .001$, $d = 0.56$).

Sex differences in age-related changes in autistic behaviours

Analyses confirmed that the age of males and females were comparable in this subsample (t = -0.57, $p = .570$; see supplemental Table 2s). Significant interactions were observed between age-related change in autistic behaviours and sex for Social-ADI_{10} ($p = .014$, $\eta^2_p = 0.11$) and Communication-ADI_{10} ($p = .025$, $\eta^2_p = 0.09$). A large and significant improvement in Social-ADI_{10} ($p < .001$, $d = 0.98$) and Communication-ADI_{10} ($p < .001$, $d = 1.00$) scores was evident in males, while the scores for females remained relatively stable for Social-ADI_{10} ($p = .080$, $d = 0.37$) and Communication-ADI_{10} ($p = .084$, $d = 0.36$; see Fig. 2a and b). Rerunning these analyses using linear mixed models suggested that the general interpretation of findings remained unchanged when individual differences in participant characteristics were accounted for in our analyses.

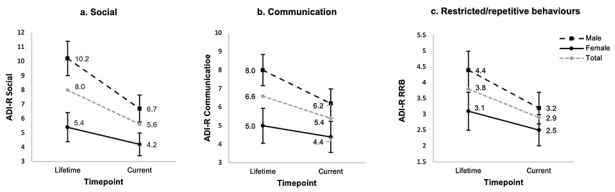

Fig. 2 Mean lifetime and current scores on the ADI-R domains for males, females, and total cohort (n = 54), **(a)** Social **(b)** Communication **(c)** Restricted/repetitive behaviours. Note: Error bars for males and females represent one standard error. Maximum scores: Social = 28; Communication = 24; RRB = 23

Further information regarding these analyses is available in the online supplement.

A different pattern of age-related change was observed in the RRB domain. As shown in Fig. 2c, there were significant improvements in RRB-ADI_8 scores for males ($p < .001$, $d = 1.43$) and females ($p = .008$, $d = 1.04$) over time, with no interaction between age and sex ($p > .05$). Mean scores and 95% CIs for lifetime and current ratings in the three ADI-R domains are presented in supplemental Table 2s.

Age-related change in social communication behaviours for individual participants

We plotted the change from lifetime to current ratings for each participant on a combined social communication score (SC-ADI_{20}). Figure 3 depicts lifetime SC-ADI_{20} scores plotted from mid-point of lifetime ratings (4.5 years of age) to current ratings obtained at the time of assessment, illustrating the variability among participants in terms of their degree and direction of change in SC-ADI_{20} scores (a colour version of this figure that additionally illustrates mean regression lines and 95% CIs is available as supplementary Fig. 1s).

Discussion

In this study, we investigated sex- and age-related differences in core autistic behaviours of a cohort of children with NF1 that scored in the clinical range on the SRS-2, a questionnaire assessing autistic behaviours. Our study yielded several novel and interesting findings. Compared with females, males in our cohort displayed more severely impaired social communication behaviours across two gold standard measures: parent reported ADI-R and clinician rated ADOS-2. In contrast, we observed minimal sex differences in restricted and repetitive behaviours across both instruments. These findings are broadly consistent with a previous study that evaluated sex-based discrepancies with the ADI-R and ADOS-2 in a similar screen positive paediatric NF1 sample (Garg et al., 2016). While our study confirms observations of overall female superiority for social communication skills across both autism-specific measures (Garg et al., 2016), the sex differences in our cohort appear to be less pronounced. Furthermore, our findings of equivalent scores for the two sexes on the 'Encompassing preoccupation or circumscribed pattern of interest' ADI-R subscale contrast with their earlier results of greater atypicality for males on this subscale. As the two items comprising this subscale (i.e., circumscribed interests and unusual preoccupations) were not separately reported by Garg et al., it is unclear whether both or just one of these behaviours drove the sex difference in their study. It is worth noting that our cohort demonstrated comparable scores for males and females across both these distinct RRBs. One potential explanation for the less pronounced sex differences in our study is the increased severity of autistic behaviours in females in our cohort (SRS-2 total T score: females = 76.6, males = 72.9), compared with the Garg et al. sample (females = 67.0, males = 72.2). Future studies performing more fine-grained analyses of autistic behaviours are required to help clarify the extent and manner of sex differences in social communication skills and RRBs in children with NF1.

As expected, the higher social communication scores of males in our NF1 cohort translated into their significantly greater likelihood of exceeding ADI-R and ADOS-2 diagnostic cut-offs. Although sex differences in social communication skills remained after accounting for females' higher verbal intellect and lower incidence of early language delay, these characteristics were nevertheless related to social communication scores on both the ADI-R and ADOS-2. Regardless of their sex, children with early phrase delay demonstrated greater parent reported social communication deficits in early childhood, and children with early phrase delay or lower verbal intellect exhibited greater clinician rated social communication difficulties. Our findings raise several plausible explanations. One possible account is that children who score highly on autism diagnostic measures are more likely to have broader verbal difficulties such as delayed language or a reduced verbal IQ. Although these impairments are not specific to autism, they are frequent comorbidities of autism (Levy et al., 2010; Reindal et al., 2021). It is also possible, however, that the broader verbal difficulties of males with NF1 may inflate their social

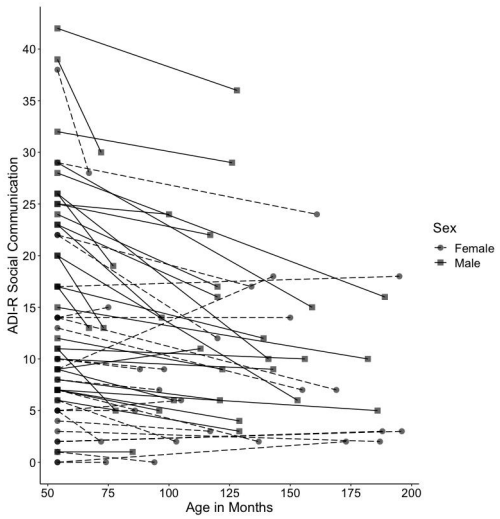

Fig. 3 Lifetime and current scores on the ADI-R combined Social and Communication domains for 54 participants. Note: Lifetime scores are plotted at 4.5 years of age, and age in months depicts chronological age

communication scores on the ADI-R and ADOS-2. This hypothesis is consistent with a recent finding that lower IQ was associated with higher ADI-R scores (although not ADOS scores) in children with non-autistic neurodevelopmental disorders (Havdahl, Bal, Huerta, Pickles, Øyen, Stoltenberg et al., 2016).

Another important issue to highlight here is the precariousness of interpreting sex differences in autistic behaviours via measures that do not provide sex-specific normative data or algorithmic cut-off scores. Given the well documented superiority of typically developing (TD) females' social communication skills (Leman & Tenenbaum, 2011), it is plausible that the 'true' extent of social communication impairments in our female NF1 cohort was underestimated by the ADI-R and ADOS-2. This possibility is supported by a meta-analytic study examining sex disparities in idiopathic autistic and TD groups, which suggested that sex effects for some core features of autism were not disorder-specific but reflected typical sex differences (Hull et al., 2017). Taken together, our findings and these considerations emphasise that it is critical to place scores from autism measures into a clinical context to reduce the likelihood of erroneous or missed autism diagnoses. These issues also have implications for NF1 research, since categorising females as autistic on the basis of cut-off scores from instruments that are sex-blind, if not male-centric (Loomes et al., 2017), can lead to a false impression regarding the female autism phenotype as well as biased sex ratio estimates of autism in NF1.

It is also important to note here that, despite the marked sex disparity in social communication scores on the ADI-R and ADOS-2, all SRS-2 raw scores (unadjusted for sex) were equivalent for males and females in our cohort. This measure-specific discrepancy is consistent with the NF1 literature, where studies using the ADOS-2 or ADI-R to determine sex differences have indicated more severe social communication deficits in males (Eijk et al., 2018; Garg, Green, et al., 2013; Garg et al., 2016; Plasschaert et al., 2015; Plasschaert et al., 2016), while SRS scores in larger NF1 samples have not revealed a sex difference in the severity of autistic traits (Morris et al., 2016; Payne, Walsh, Pride, Haebich, Maier, Chisholm et al., 2020). Interestingly, these findings also mirror results from two large scale studies in idiopathic autistic cohorts that observed higher severity scores in males relative to females on the ADI-R and ADOS but not on the SRS-2 (Charman, Loth, Tillmann, Crawley, Wooldridge, Goyard et al., 2017; Kaat, Shui, Ghods, Farmer, Esler, Thurm et al., 2021). While we could speculate that as clinician rated tools, the ADI-R and ADOS-2 may have higher specificity for autistic behaviours and, therefore a higher sensitivity to sex differences in NF1 than the parent rated SRS-2, this hypothesis in NF1 is yet to be investigated. It is, however, essential for future studies to examine the factors underpinning these distinct sex effects across autism measures, given the implications for determining whether there is a female protective effect operating in NF1, as has been indicated in idiopathic autism (Werling & Geschwind, 2013). These questions will need to be addressed by future studies comparing sex differences in *clinical* autism diagnoses with sex differences in autistic behaviours, as indexed by these commonly used autism measures.

An additional observation with clinical and research implications is that despite all participants in our screen positive cohort scoring above a threshold of 60 on the SRS-2, considerably smaller proportions of males and females met all three cut-offs on the ADI-R (44% and 21%, respectively) and the overall 'autism spectrum' cut-off on the ADOS-2 (74% and 46%%, respectively). These findings accord with prior concerns regarding the reduced specificity of the SRS-2 in child cohorts with non-autism specific neurodevelopmental disorders such as ADHD and anxiety (Cholemkery et al., 2014; Griffiths et al., 2017; Hus et al., 2013). Given the elevated frequency of behavioural and affective disorders in NF1, our findings underscore the importance of using autism-specific diagnostic tools in conjunction with clinical judgement in this population.

Retrospective parent ratings also indicated that social communication and RRB behaviours were evident in early childhood (i.e., 4:0 to 5:0 years) for a substantial proportion of our screen positive NF1 cohort, with 44% of males and 21% of females meeting all three cut-offs on the ADI-R. While it must be emphasised that the ADI-R classification of 'autistic disorder' does not equate to a clinical diagnosis (Vivanti & Volkmar, 2020), these findings suggest that autistic behaviours in NF1 are detectable at an earlier age than previously suggested by data from parent rating scales (Morris et al., 2016; Plasschaert et al., 2015). This result underscores the importance of early surveillance of neurodevelopmental difficulties in children with NF1 to facilitate the timely identification of autism, which can be a crucial step for accessing appropriate early intervention (e.g., applied behaviour analysis; Linstead, Dixon, Hong, Burns, French, Novack et al., 2017).

The current study's comparison of historical and current scores on the ADI-R suggested age-related improvement in social communication behaviours in males but not females. In contrast, comparable abatement of RRBs were evident in the two groups. Longitudinal investigations using the ADI-R have detected abatement of social communication deficits and RRBs in autistic cohorts from early childhood to late adolescence (McGovern & Sigman, 2005; Taylor & Seltzer, 2010), however none to the best of our knowledge have examined whether patterns of age-related change differ by sex. While our data are unable to determine the reasons

for sex differentially impacting age-related change in social communication behaviours, they raise several hypotheses which will be important to examine in future longitudinal research. Over time, males with NF1 may 'catch-up' with respect to their language development to an extent that poses less constraints on their 'current' social communication skills. This proposition is supported by the equivalent 'current' receptive and expressive language skills of males and females in our cohort, which contrast with the significantly larger proportion of males than females with parent reported early language delay. Another explanation may be that, over time, females with NF1 experience increasing social challenges relative to males with NF1 (e.g., absence of friendships), due to different gender-based expectations. Both the TD and idiopathic autism literature indicate that successful interpersonal relationships from late childhood and adolescence are increasingly dependent on social communication abilities in females, while males' social interactions are generally less complex and demanding (e.g., watching or playing sport) (Dean, Kasari, Shih, Frankel, Whitney, Landa et al., 2014; Hall, 2011; McLennan et al., 1993; Tierney et al., 2016). Hence, as gender expectations evolve with age, the gap between parental perceptions of the social communication deficits of males and females with NF1 may narrow. Supportive of this hypothesis are findings in idiopathic autism that females display more sex-typical behaviours than males as young children, but less sex-typical behaviours than males between childhood and early adolescence (Hull et al., 2017).

A further possible explanation for our results is that the higher anxiety of females in our NF1 cohort may have amplified their 'current' social communication scores on the ADI-R, due to the known overlap in phenotypic expression between internalising disorders and autism (e.g., social withdrawal; Cholemkery, Mojica, et al., 2014). Consistent with this hypothesis is evidence in idiopathic autism that ADI-R scores can be affected by emotional and behavioural difficulties (Havdahl et al., 2016). Of course, this relationship may be bidirectional, since social challenges or isolation in females with NF1 may place them at greater risk of developing mental health difficulties, as has been shown in autistic and TD females (Rose & Rudolph, 2006; Solomon et al., 2012). At present, it is unknown which hypotheses offer the best explanation for our findings, highlighting the need for longitudinal research employing TD comparison groups to examine the underlying factors accounting for the distinct developmental course of autistic behaviours in males and females with NF1.

Finally, while our study revealed informative sex- and age-differences in core autistic behaviours of children with NF1 at a group level, it is important to consider that the presence and developmental course of social communication impairments were highly variable across individuals. Despite the group difference of males being rated with more severe social communication deficits than females in early childhood (as reflected by lifetime ADI-R ratings), at an individual level, some males showed no social communication deficits while some females demonstrated marked difficulties in this domain. Similarly, while age-related abatement of social communication deficits was more evident in males than females at a group level, this was not a universal finding for males, some of whom displayed decline in social communication skills over time. This observed diversity in autistic behaviours and temporal change is perhaps not unexpected but requires longitudinal research to elucidate potential factors that may predict or moderate autistic behaviours in children with NF1.

Limitations

This study had several limitations. Our NF1 sample comprised a subgroup of children from a larger NF1 cohort whose selection was based on scoring in the clinical range on the SRS-2 screening questionnaire. As such, this cohort is not representative of all children with NF1. Nonetheless, as the SRS-2 has high sensitivity for detecting autism (Aldridge et al., 2012) and many participants with elevated SRS-2 scores showed minimal autistic symptoms on the ADI-R and ADOS-2, it is doubtful our selection process missed children with significant autistic behaviours. Another limitation was our use of different measures to evaluate intellectual function, language, and behaviour in the two age cohorts, some of which do not have published data relating to convergent validity between the different age versions or tests.

An additional limitation involves the metric properties of the ADI-R and ADOS-2 which were not specifically developed as dimensional measures and do not yield severity scores according to true interval scales (Lord & Jones, 2012). Hence, these tools are potentially limited in their capacity to capture severity of autistic behaviours and may lack sensitivity for determining subtle and extreme differences in autistic behaviours. Further, the ADI-R does not standardise scores for developmental level, and it is unclear whether the same score at different ages reflects an equivalent degree of severity. Although our measurement of age-related change in the autistic behaviours of children with NF1 with the ADI-R makes a novel contribution to the current literature, it is important to acknowledge that retrospective data can be problematic for inferring change over time (Jones, Risi, Wexler, Anderson, Corsello, Pickles et al., 2015). While the ADI-R is designed to minimise recall bias with the requirement for parents to provide concrete examples of behaviours that are then clinician coded, we cannot

rule out the occurrence of retrospective bias. Further, the accuracy of measurement of age-related change was compromised by the fact that comparison of 'ever' with current ADI-R items are unable to index deterioration in behaviour over time. Although analysis using only the 'most abnormal' social communication items confirmed significant age-related gains in social communication behaviours, we recognise that the degree of age-related improvement may have been over-estimated, especially in the RRB domain in which all lifetime items are 'ever' items. It is also important to note that this methodology only compares autistic behaviours at two time points, with the period of change varying across participants. Consequently, it is unclear what the developmental trajectories might look like between these time points of assessment and whether trends for either improvement or deterioration in autistic behaviours are maintained over the longer term. Additionally, while our mixed models suggested that the general interpretation of findings remained unchanged when individual differences in participant characteristics were accounted for in our analyses, our analyses of sex-specific developmental change did not explicitly account for possible regression to the mean.

While our data suggest that early language development and verbal intellect were related to autistic behaviours in children with NF1, the causal nature of these associations were unable to be ascertained by our cross-sectional design. We also acknowledge that our ADI-R measures of early language delay are retrospective and may have underestimated the proportion of the sample classified with language delay, as the TD literature indicates that first words and phrases in the general population typically emerge well before the 24 and 33 months ADI-R cut-offs, respectively (Conti-Ramsden & Durkin, 2012). While our consideration of the potential associations between non-autistic characteristics and autistic behaviours in NF1 is a strength of our study, longitudinal investigations will be required to clarify causal relationships.

Summary and conclusions

The current study examines sex- and age-related differences in autistic behaviours in a 'screen positive' sample of children with NF1 (SRS-2 T score $\geq$ 60). Study findings indicate that core social communication deficits are more pronounced in males than females, while the severity of restricted and repetitive behaviours are broadly similar across both sexes. Neurodevelopmental factors not specific to autism (i.e., language and verbal intellect) significantly influence the presentation of social communication behaviours in children with NF1. This emphasises the importance of considering common NF1 comorbidities in diagnostic decision-making for autism, since co-occurring difficulties may influence scores derived from diagnostic tools such as the ADOS-2 and ADI-R. Subsequent research that incorporates clinical judgement in the establishment of autism diagnoses will be essential to advance our understanding of sex disparities in NF1-related autistic behaviours, as well as the 'true' extent of male predominance for autism in the syndrome.

Results of the current study also indicate that core features of autism are detectable by early childhood, underscoring the importance of early surveillance for autism in this population. While our data indicate male-specific improvement in social communication behaviours over time, they also highlight substantial heterogeneity in both the severity and temporal change of autistic behaviours in males and females with NF1. A goal of future research should be to explore the specific child characteristics that moderate this variability, as a better appreciation of these factors is likely to promote earlier identification of autism and accuracy of clinical prognoses in children with NF1.

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