Profiling the Word Reading Abilities of School-Age Children with Neurofibromatosis Type 1

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ABSTRACT

Objective: Reading difficulties are one of the most significant challenges for children with neurofibromatosis type 1 (NF1). The aims of this study were to identify and categorise the types of reading impairments experienced by children with NF1 and to establish predictors of poor reading in this population.

Method: Children aged 7-12 years with NF1 (n=60) were compared with typically developing children (n=36). Poor word readers with NF1 were classified according to impairment type (i.e. phonological, surface, mixed) and their reading subskills were compared. A hierarchical multiple regression was conducted to identify predictors of word reading.

Results: Compared to controls, children with NF1 demonstrated significantly poorer literacy abilities. Of the 49 children with NF1 classified as poor readers, 20 (41%) were classified with phonological dyslexia, 24 (49%) with mixed dyslexia, and five (10%) fell outside classification categories. Children with mixed dyslexia displayed the most severe reading impairments. Stronger working memory, better receptive language and fewer inattentive behaviours predicted better word reading skills.

Conclusions: The majority of children with NF1 experience deficits in key reading skills which are essential for them to become successful readers. Weaknesses in working memory, receptive language and attention are associated with reading difficulties in children with NF1.

Keywords: literacy, dyslexia, NF1, reading impairments, cognition, working memory, children

Word count for abstract: 200

Word count for manuscript: 5281

Neurofibromatosis type 1 (NF1) is a single gene disorder that affects approximately 1 in 2700 people (Evans et al., 2010). Learning difficulties are one of the most frequent complications in childhood (Lehtonen, Howie, Trump, & Huson, 2013), with poor reading being one of the most significant challenges for children with NF1 (Cutting, Clements, Lightman, Yerby-Hammack, & Denckla, 2004). Although impairments in basic word reading (Watt, Shores, & North, 2008) and reading comprehension (Cutting, Koth, & Denckla, 2000) are consistently reported in children with NF1, the specific nature of these impairments and contributing cognitive and literacy factors are not well understood.

Reading aloud is complex, with a number of cognitive processes involved (Coltheart, 2005). The dual route cascaded (DRC) model is a well-established framework that theorises the cognitive processes needed for accurate word reading (see Figure 1). According to the DRC model (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001), when a child initially sees a written word (e.g., SHIP), they must first correctly identify the letters, and their order in the word (*letter identification*). The output of this process triggers further processing in two routes. The sublexical route translates each grapheme (e.g., SH I P) into a phoneme ("sh" "i" "p") by applying the child's existing *grapheme-to-phoneme correspondence* (GPC) knowledge. At the same time, the lexical route carries out a "look-up" procedure whereby the visual form of the written word (e.g., SHIP) is searched for in their *orthographic lexicon* of all learned written words. If a match is found, this triggers the spoken version of the word (e.g., "ship") in the *phonological lexicon* - sometimes via the *semantic system* if it comprises the meaning of the written word (e.g., a big boat). Both the sublexical and lexical routes link again at the *phonological output* system that contains information that enables the word to be pronounced aloud.

Insert Figure 1 here

Children need to develop both the sublexical and lexical routes to become a skilled reader of the English language (Castles & Coltheart, 1993) since written English includes regular and irregular words. However not all children have fully-functioning reading routes. Some children have an impaired sublexical route or ‘phonological dyslexia’ (Castles & Coltheart, 1993) characterised by poor reading of nonwords (i.e. nonsense words that can be read using GPC knowledge e.g. gop). Other children have an impaired lexical route or 'surface dyslexia', characterised by impaired reading of irregular words (Castles & Coltheart, 1993). Children with both routes impaired have ‘mixed dyslexia’ which occurs most frequently in children with poor word reading skills (Castles & Coltheart, 1993; McArthur et al., 2013a).

To date, one study which used the DRC model to investigate subtypes of dyslexia (Watt et al., 2008) found that two thirds of children with NF1 (20/30) demonstrated a significant reading impairment (i.e. performance in the bottom 5% for nonword and/or irregular word reading), with 75% of these children having phonological dyslexia, 20% having mixed dyslexia and no children having surface dyslexia. This distribution of subtypes differs substantially to that of children in the general population, where using the same criteria, 17% of poor readers have surface dyslexia and 9% have phonological dyslexia (McArthur et al., 2013a).

Children with NF1 commonly experience a range of cognitive and behavioural difficulties (Lehtonen et al., 2013) and it is not clear how these difficulties impact on their reading abilities. Deficits in phonological awareness (i.e. detecting and manipulating sounds of language) and phonological memory (i.e. the ability to store and manipulate sounds in short-term memory) have been reported (Arnold, Payne, Lorenzo, North, & Barton, 2018; Chaix et al., 2017; Cutting et al., 2000; Mazzocco et al., 1995). In addition, the relationship between the Judgement of Line Orientation (JLO) (Benton, Sivan, Hamsher, Varney, & Spreen, 1983), which is frequently impaired in children with NF1 (Lehtonen et al., 2013), and reading is not clear. One study found that children with NF1 and reading difficulties display distinct visuospatial deficits on the JLO when compared to children with reading difficulties and controls. In addition, only for children with NF1 and reading difficulties did their single word reading skills correlate positively with JLO performance (Cutting & Levine, 2010). In the general population children with reading disabilities also experience visual spatial deficits which are age dependent (Giovagnoli, Vicari, Tomassetti, & Menghini, 2016) and are proposed to be associated with visual magnocellular pathway abnormalities (Stein, 2019). While Cutting et al. (2010) found no significant relationships between reading and cognitive factors (e.g. language, attention) in children with NF1, future studies are needed given the relatively small sample size (Cutting & Levine, 2010) and to examine other factors that may contribute to poor reading outcomes, such as working memory (Wang & Gathercole, 2013), sex (Quinn & Wagner, 2015), and socio-economic status (SES; Hecht, Burgess, Torgersen, Wagner, & Rashotte, 2000). Developing a better understanding of these impairments and related factors is vital for the design of effective reading interventions.

Therefore the aims of this study were to (1) identify the incidence of reading impairments in children with NF1 compared to an unaffected comparison group; (2) categorise the types of reading impairments in poor word readers with NF1 and compare the profile associated with each type (3) identify cognitive and demographic predictors of poor word reading in children with NF1. We predicted that: (1) as a group, children with NF1 are at a greater risk of being a poor reader than typically developing (TD) controls; (2) based on Watt et al. (2008) study findings, the majority of poor readers with NF1 would be classified with phonological dyslexia, with fewer cases demonstrating mixed dyslexia and no cases of surface dyslexia; and (3) reading would be associated with gender, SES, working memory, attention, language and visuospatial abilities.

METHOD

Sixty-two children, aged 7 to 12 years, who met clinical diagnostic criteria for NF1 (1988) were recruited from the Neurogenetics Clinic at The Children's Hospital at Westmead in Sydney, Australia. Families were offered the opportunity to participate during routine evaluation of their child's neuropsychological functioning. Participants were also recruited via an invitation letter mailed to families who attend the clinic with children within the study age range.

NF1 participants were excluded if they had: (1) diagnosed intracranial pathology (i.e. symptomatic optic gliomas), (2) vision or hearing loss that may impact the validity of assessment, (3) inadequate English to complete tasks, or (4) an extremely low full-scale intelligence quotient (FSIQ<70). Two children with NF1 were excluded following IQ assessment (FSIQ<70), resulting in 60 children with NF1 in the final analysis.

An unaffected peer comparison group of 36 TD children were recruited from a longitudinal study being conducted at the hospital (Lorenzo, Barton, Arnold, & North, 2015), advertisements placed within local primary schools, community newspapers, and the hospital. A structured parent interview regarding the child's development was conducted prior to the assessment. No TD child had a reported history of genetic, neurological or psychological disorders, intellectual impairment, learning difficulties or developmental delay.

Approval for this study was granted by the Sydney Children's Hospital Network (HREC/11/CHW/28) Human Research Ethics Committees and was conducted in accordance with Helsinki Declaration. Written informed consent was obtained from all participants. All participants were individually assessed at the hospital by a psychologist with short breaks provided as needed. Parents completed questionnaires regarding their child's development and behaviour.

Measures

For those tests with normative data, raw scores were converted to standard scores using the published test manual or the methods and normative tables contained within the citation for the test. Unless specified otherwise, all scores were normed according to age and higher scores indicate better performance.

Cognitive and Demographic Measures

IQ: General intellectual functioning was assessed with either the Wechsler Intelligence Scale for Children - Australian Adaptation (WISC-IV; Wechsler, 2003) or the Wechsler Abbreviated Scale of Intelligence - 2nd Edition (WASI-II; Wechsler, 1999). The WASI-II was used for control and NF1 participants (n=16) who had not undergone an IQ assessment in the preceding 12 months. As the correlation coefficient between these two measures is very high for FSIQ (r=0.86; Homack & Reynolds, 2007), scores were pooled across participants to provide an overall estimate of intellectual functioning (FSIQ), verbal IQ and performance IQ (standard score; M=100, SD=15).

Verbal working memory: Children assessed with the WASI-II completed the Working Memory subtests of the WISC-IV (standard score; M=100, SD=15) (Wechsler, 2003).

Attention: Children's ability to focus, sustain, switch and divide their attention was assessed by Sky Search, Score, Creature Counting and Sky SearchDT from the Test of Everyday Attention for Children (scaled score; M=10, SD=3) (TEA-Ch; Manly, Robertson, Anderson, & Nimmo-Smith, 1999). Parents also completed the Conners 3 (Conners, 2009), yielding T scores for the Inattention and Hyperactivity/Impulsivity scales (standard score M=50, SD=10). Higher T scores indicate more problem behaviours.

Visuospatial functioning: The Judgement of Line Orientation task (JLO; Benton et al., 1983) was used to assess visuospatial abilities as children with NF1 typically display impairments on this measure (Clements-Stephens, Rimrodt, Gaur, & Cutting, 2008). Raw scores were converted to z scores (M=0, SD=1) using published normative data.

SES: SES was estimated using the Index of Relative Socio-Economic Advantage and Disadvantage, which ranks geographic areas in terms of their socio-economic advantage and disadvantage ("Statistical Local Area, Table 2: Socio-Economic Indexes for Areas (SEIFA), data cube: Excel spreadsheet, cat. no. 2033.0.55.001," 2011). The lowest 10% of areas are ranked a decile of 1 and the highest 10% are ranked a decile of 10.

Reading measures

Single word reading: Single word reading abilities were assessed with the Castles and Coltheart Word/Nonword test – second edition (CC2; Castles et al., 2009), a revision of the original Word/Nonword test (Castles & Coltheart, 1993). The revised test has an expanded set of words to minimise ceiling effects, incorporation of a stopping rule, changes in the order of word presentation and updated norms. Raw scores for regular, irregular and nonword reading scores were converted to age adjusted normalized z scores (M=0, SD=1) using the normative tables reported by Castles et al. (2009) that were calculated from a sample of 1036 Australian children (6-12 years old).

Word reading fluency*:* The Test of Word Reading Efficiency – Form A (TOWRE; Torgesen, Wagner, & Rashotte, 1999) was administered to provide a measure of sight word and phonemic decoding efficiency (standard score; M=100, SD=15).

Reading comprehension: Reading comprehension was assessed by the Test of Everyday Reading Comprehension (TERC; McArthur et al., 2013b). Raw scores were converted to z scores (M=0, SD=1) based on the child's age using normative tables reported by McArthur et al. (2013b) that were calculated from a sample of 535 Australian children (6-12 years old).

Common Processes (Lexical and Sublexical)

Letter identification: The cross-case copying measure was used to assess children's basic letter knowledge (McArthur, Coltheart, Castles, & Kohnen, 2008) and consisted of 14 items. For the Letter Orientation Task (LOT), children were asked to identify whether letters were facing the correct way or "flipped backwards" (McArthur et al., 2008). For both measures one point was awarded per correct item, raw scores reported.

Phonological output*:* Children's phonological output was assessed by i) the Repetition of Nonsense Words subtest from A Developmental Neuropsychology Assessment, 2nd edition, (scaled score; M=10, SD=3) (NEPSY-II; Korkman, Kirk, & Kemp, 2007) and ii) the

Blending nonwords test (McArthur et al., 2008) which contains 28 items, with higher scores indicating better performance. One point per correct item, raw scores reported.

Lexical processes

Orthographic lexicon: The Test of Orthographic Choice (TOC; Kohnen, Anandakumar, McArthur, & Castles, 2012) assessed children's written word recognition. Raw scores were converted to z scores (M=0, SD=1) using grade-based normative tables that were calculated from a sample of 102 Australian children (Grades 1-6) (Kohnen et al. 2012).

Phonological Lexicon: The Rain/Hane task assessed children's phonological representation of 20 spoken words (McArthur et al., 2013a). One point per correct item, raw scores reported.

Semantic knowledge*:* To assess semantic knowledge the Peabody Picture Vocabulary Test – Fourth Edition (PPVT-4; Dunn & Dunn, 2007) was administered (standard score; M=100, SD=15).

Sublexical processes

GPC knowledge*:* To assess letter-sound knowledge the Letter-Sound Test comprising of 51 items (LeST; Larsen, Kohnen, Nickels, & McArthur, 2015) and the Grapheme-Phoneme Conversion (GPC) test (McArthur et al., 2015) consisting of 39 items was administered. For both measures one point awarded per correct item, raw scores reported.

Categorising word reading impairments

Children were categorised as poor readers if their z score for nonword and/or irregular word reading on the CC2 was at least 1 standard deviation below the mean (McArthur et al., 2013a). The type of reading impairment experienced by poor readers in the NF1 group were categorised using 'classification system 5'. Utilising the CC2, this classification system was evaluated by McArthur et al. (2013) to be the most appropriate of five different classification systems (including the Edwards and Hogben classification criteria used by Watt et al. 2008 which she applied to the original Castles Word/Nonword test) for poor readers in the general population since it produced similar percentages of each type of reading impairment compared to the other four classification systems; included a clear distinction (half a standard deviation) between lexical and sublexical reading abilities; ensured that a child's stronger word reading skill was in the average range and resulted in sufficient group numbers for each type of reading impairment for statistical comparisons (McArthur et al., 2013a). The criteria for classification system 5 used to categorise reading impairments in this study was:

1. Phonological dyslexia: a z score at or below -1.3 (the 10^{th} percentile or lower) for nonword reading and a z score higher than -1 for irregular word reading.
2. Surface dyslexia: a z score at or below -1.3 for irregular word reading and a z score higher than -1 for nonword reading.
3. Mixed dyslexia: a z score of -1.3 or lower for both nonword and irregular word reading.
4. Unclassified dyslexia; poor readers who were not classified by any of the above criteria. These children were removed from subtype analyses.

Statistical analysis

Data were analysed using SPSS version 23 (SPSS Inc., Chicago, Illinois). Descriptive statistics for continuous normally distributed variables are reported as means (M) and standard deviations (SD) or as medians (Mdn) and interquartile ranges (IQR) for non-normally distributed data. Tests of chi-squared was used to examine differences between groups for categorical variables. Independent-samples *t* tests (or Mann-Whitney *U* tests for non-normally distributed data) were used to compare the NF1 and control groups for cognitive and literacy measures. The risk of being a poor reader in each group (NF1, control) was calculated.

To minimise the number of comparisons made, a univariate analyses of variance (ANOVA) or Kruskal-Wallis (non-normally distributed data) was conducted to identify if there were any differences between all groups (i.e. dyslexic subtypes for NF1, NF1 non-poor readers and control non-poor readers), with effect sizes calculated (partial eta squared or epsilon squared). For ANOVAs, Welch's F was used when the homogeneity of variance assumption was violated. For significant group differences, pairwise planned comparisons between i) the NF1 dyslexic groups and ii) non-poor readers (NF1 vs controls) were conducted using independent-samples *t* tests or Mann-Whitney *U*. Effect sizes are reported as partial eta-squared with values of 0.01, 0.06 and over 0.14, and Cohen's *d* values of 0.2-0.4, 0.5-0.7 and ≥ 0.8, representing small, medium and large effect sizes respectively (Cohen, 1988). When scores were non-normally distributed, effect sizes were calculated (*r*) and converted to Cohen's *d* (Fritz, Morris, & Richler, 2012). All tests were two-tailed, with level of significance equal to 0.05 and the Holm procedure applied to control the familywise error rate.

In identifying predictors of word reading, to minimise the number of regression models and reduce the number of word reading variables (i.e. nonword, irregular and regular words), a principal component analysis (PCA) was conducted to generate a *combined word reading* variable. The Kaiser-Meyer-Olkin (KMO) and Bartlett's test of sphericity were also calculated to check the suitability of the data for PCA. The relationship between *combined word reading* and cognitive and demographic variables were examined using Pearson correlation coefficient (r), or Spearman rho (r^s) for asymmetrically distributed data. Only factors that significantly correlated with *combined word reading* were entered into the hierarchical multiple regression (stepwise) model according to the strength of their correlation. Because of a significant relationship between IQ and reading ability (Naglieri, 2001), we controlled for the potential influence of intelligence using an estimate of non-verbal ability (PRI from the WISC-V or PIQ from the WASI-II), which was entered at step 1.

RESULTS

Demographic and cognitive data for both groups are displayed in Table 1. There were no significant between group differences for sex, age or SES. Significant group differences were evident for most cognitive measures, with the NF1 group demonstrating significantly poorer performance (with large effect sizes) for IQ measures, visuospatial functioning, and switching attention (all $p<.001$). Medium effect sizes were observed on measures of divided and sustained attention with performance of the NF1 group falling significantly below controls. There were no significant between-group differences for selective attention. Behaviourally, there was a large effect size for inattentive Attention Deficit Hyperactivity Disorder (ADHD) symptoms with the NF1 group displaying significantly elevated inattentive behaviours.

Insert Table 1 here

The performance of the NF1 group was significantly poorer than controls on all literacy measures except the LOT, a measure of letter identification (Table 2). Large effect sizes were evident for all other literacy and language variables except for cross-case copying, which yielded a medium effect size.

Insert Table 2 here

Within the NF1 group, 49/60 (82%) were classified as poor readers and 11/60 (18%) children as typical readers. In the control group, 7/36 (19%) children were classified as poor readers. The relative risk of poor reading occurring was 4.20 times greater (95% CI 2.14, 8.25) in the NF1 group compared to the control group.

Within the NF1 group of poor readers, 20/49 (41%) met classification for phonological dyslexia, 24/49 (49%) for mixed dyslexia and 5/49 (10%) did not meet any classification criteria, despite being poor readers. Literacy measures by subgroup (control non-poor readers, NF1 non-poor readers, NF1 phonological dyslexics, NF1 mixed dyslexics) are displayed in Table 3. While there was no significant difference between the four groups for age, for those variables with raw scores only ANCOVAs were conducted to control for the potential effects of age (Supplementary table 2). The ANCOVAs resulted in the same pattern of statistical significance for all except one test, the Rain/Hane test, a measure of the phonological lexicon (Supplementary table 2), which was no longer significantly different between groups after controlling for age. Overall group comparisons indicated significant differences between groups for all literacy variables, except for phonological lexicon, with large effect sizes**.** Planned contrasts indicated the NF1 non-poor readers group performed significantly poorer on measures of nonword reading, nonword repetition, reading comprehension and semantics when compared to control non-poor readers. Planned contrasts between the NF1 dyslexic groups indicated that children with mixed dyslexia performed significantly poorer on measures of regular, irregular word and nonword reading, sight word and phonemic decoding efficiency, letter-sound knowledge, parsing and reading comprehension when compared to children with phonological dyslexia (Table 3).

Insert Table 3 here

The KMO value (KMO=0.73) indicated that the sampling adequacy of the data was suitable for PCA. Bartlett's test of sphericity also indicated that between-items correlations were appropriate for PCA ($\chi^2(3)$ =299.70, p<.001). Analysis of the eigenvalues indicated three components with only one having an eigenvalue over Kaiser's criterion of 1, explaining 90.45% of the variance. Hence this was the only component retained. This new variable, *combined word reading* was examined for normality and univariate outliers using a cut-off of three SDs outside the mean. Two participants had scores that fell outside this range. To reduce the influence of these outliers, the combined word reading variable was transformed (Field, 2009). However, after transformation the outliers still remained. Hence, as recommended by Field (p. 153, Field, 2009) the scores for these two participants were changed to one unit above the next highest score for combined word reading variable. There was no significant difference between males (Mean=-0.51, SD=0.66) and females (Mean=-0.50, SD=0.62) on the *combined word reading* variable (t (58) =-0.07, p=.95, d=0.02) or any of the individual measures of reading subskills (all p>.07; Supplementary Table 1).

Stronger *combined word reading* was moderately associated with better receptive language, working memory, and higher FSIQ and VIQ (Table 4). There was a significant moderate negative relationship between *combined word reading* and inattentive behaviours indicating that children with elevated inattentive ADHD symptoms had poorer *combined word reading*. There was no significant relationship between *combined word reading* and SES or visuospatial functioning.

Insert Table 4 here

In the final regression model, working memory, inattentive behaviours and receptive language were significant predictors of *combined word reading,* accounting for 31% of the variance (Table 5).

Insert Table 5 here

DISCUSSION

Consistent with our prediction, children with NF1 demonstrated poorer performance than controls on all literacy measures except letter orientation. Examination of the NF1 group revealed that 82% displayed poor word reading compared to 19% of controls. The relative risk of being a poor word reader was 4.20 times greater for children with NF1 compared to controls, providing support for previous findings that children with NF1 are at high risk of reading difficulties (Cutting et al., 2000; Watt et al., 2008).

This is the first time the DRC model has been used as a framework to examine the cognitive processes underlying word reading in children with NF1. Results indicated that nonword reading was the most severely impaired literacy skill in the NF1 group. Significant The NF1 group also demonstrated significant weaknesses in irregular word reading and lexical subskills (i.e. orthographic lexicon, phonological lexicon, semantics). Poor performance was also identified for subskills common to both reading routes (i.e. letter identification, blending, nonword repetition). These findings indicate that children with NF1 present with widespread difficulties across subskills that map onto lexical and sublexical reading routes.

Within the NF1 poor-reading group, there was a fairly comparable breakdown of children with phonological (41%) and mixed dyslexia (49%). Poor readers with NF1 were more likely to have phonological dyslexia than that observed in poor readers from the general population (McArthur et al., 2013a). Similar to Watt et al. (2008), we found no NF1 children with surface dyslexia. Poor readers with NF1 displayed a similar rate of mixed dyslexia to that observed in poor readers in the general population (McArthur et al., 2013a). Children with phonological dyslexia performed similarly to those with mixed dyslexia although the latter demonstrated more widespread difficulties in reading subskills, and overall, performed more poorly. Critically, children with mixed dyslexia displayed significant weaknesses in reading fluency and comprehension, indicating a greater functional impairment than children with phonological dyslexia.

Although we found an unusually high percentage of phonological dyslexics in our NF1 sample, the proportion was lower than anticipated and did not support our hypothesis that the majority of poor readers would present with phonological dyslexia. While it is not clear why our findings differed from a previous study (Watt et al., 2008), potential contributing factors include utilizing a revised version of the CC2 test and applying a different classification system for categorising dyslexia subtypes. Here, rather than the Edwards and Hogben (1999) criteria used by Watt et al. (2008) we used a modified criteria (classification 5) reported by McArthur et al. (2013a). Interestingly, when McArthur et al. (2013) compared classification system 5 to the Edwards and Hogben criteria using CC2 from the same group of children they found classification 5 returned a threefold increase in the percentage of poor readers identified as having phonological dyslexia compared to the Edwards and Hogben criteria. Therefore it seems unlikely that the use of a different classification system contributed to the lower percentage of phonological dyslexia we observed compared to Watt et al. (2008). It is also possible that our findings are more representative of the broader NF1 population as the sample size for the current study was twice the size of Watt et al.'s (2008).

The reason why children with NF1 experience such an unusually high incidence of phonological dyslexia is unclear. Evidence from the general population indicates a strong genetic basis to phonological dyslexia and that it may be related to an underlying impairment in processing spoken language (Castles, Datta, Gayan, & Olson, 1999). It has previously been suggested that a phonological impairment may be an inherent feature of NF1 (Chaix et al., 2017) which is supported by previous findings indicating that children with NF1 (5 to 6 years old) were 5.60 times more likely to display phonological deficits than unaffected children (Arnold et al., 2018). Abnormalities in brain structure (Payne, Moharir, Webster, & North, 2010) and abnormal cell signalling (Costa et al., 2002) in NF1 may contribute to phonological impairments. While there are no conclusive links between neurobiological abnormalities in NF1 and poor reading, one study reported greater symmetry in the planum temporale of boys with NF1 and that lack of typical asymmetry was related to poorer reading performance (Billingsley, Schrimsher, Jackson, Slopis, & Moore, 2002). However it should be noted that the participants in the Billingsley et al. (2002) study were not reading impaired and presented with intact phonological processing. Further research is needed to clarify possible relationships between the neurobiological and cognitive abnormalities reported in NF1.

As expected, verbal working memory skills were a significant predictor of reading ability of children with NF1. Impairments in working memory are a common feature in children with NF1 (Payne, Arnold, Pride, & North, 2012). Our findings suggest that children with reduced working memory capacity are at an increased risk of reading difficulties, which is consistent with findings in the general population (Wang & Gathercole, 2013). Stronger working memory abilities support complex, higher-level processing (Pham & Hasson, 2014) and are proposed to play an important role when several cognitive processes are concurrently involved (e.g. when decoding words, accessing semantic knowledge and retrieval of information previously read) (Sesma, Mahone, Levine, Eason, & Cutting, 2009). As a consequence, greater working memory capacity has been linked to better reading fluency and comprehension as well as basic reading abilities (Pham & Hasson, 2014; Sesma et al., 2009). There is also evidence to suggest that children with NF1 who have stronger working memory capacity experience greater benefits from reading intervention than those with poorer working memory (Arnold, Barton, McArthur, North, & Payne, 2016).

Comorbidity between ADHD symptoms and literacy problems has previously been reported in the general population (Peterson & Pennington, 2015) and in children with NF1 (Hyman, Shores, & North, 2006; Pride, Payne, & North, 2012). Consistent with this, we found elevated inattentive symptoms were significantly associated with poorer word reading in children with NF1. It may be beneficial to treat comorbid ADHD symptoms in conjunction with targeted literacy intervention. However in the general population there is mixed support for the transfer effects of stimulant medication upon children's literacy abilities (Kortekaas-Rijlaarsdam, Luman, Sonuga-Barke, & Oosterlaan, 2018). While there is some evidence that methylphenidate can improve ADHD symptoms in children with NF1 (Lion-François et al., 2014; Mautner, Kluwe, Thakker, & Leark, 2002), no studies have examined the effects of stimulant medication on reading outcomes in NF1.

We found that the word reading skills of children with NF1 were not significantly related to sex or SES. We found a weak association between SES and academic achievement ($r_s = 0.21$ converted $r = 0.22$ (Gilpin, 1993)), which is consistent with another Australian study that also used the SEIFA (Marks, 2017) and two meta-analysis indicating a SES-achievement correlation value ranging from 0.22 (White, 1982) to 0.25 (Harwell, Maeda, Bishop, & Xie, 2017). Our measure of SES (SEIFA) is area based (i.e. geographical location of the child's family home) which may potentially underestimate the SES-achievement correlation. An Australian study found that correlations of SEIFA indexes with achievement were approximately one-third less than the correlations between composite individual-levels of SES and achievement (Ainley & Long, 1995). It is possible that a measure of SES that assessed individual aspects of the family such as parental years of education, income and/or occupation may have produced different results (Diemer, Mistry, Wadsworth, López, & Reimers, 2013; Hauser, 1994; Marks, 2017). Also our SES findings might not generalize to areas outside of Australia, especially in other parts of the world that have greater wealth disparities. In addition, we found no evidence of a relationship between visuospatial skills (JLO) in children with NF1 and reading. The relationship observed by Cutting and Levine (2010) was for only a small group of children with NF1 and reading disabilities (n=12). While results from a study suggest that the visual magnocellular pathway is impaired in individuals with NF1 (Violante et al., 2012), their reading abilities were not assessed. Further research is needed to clarify the relationship between reading and visuospatial abilities of children with NF1.

This study is not without limitation. We acknowledge there are a number of other models of reading (i.e. Connectionist; Harm & Seidenberg, 1999; Seidenberg & McClelland, 1989). However the DRC was utilized in this study as it is a particularly useful theoretical basis for conceptualising links between particular reading impairments and the subskills that underlie them. Further it has been shown to be appropriate for detecting the high occurrence of phonological deficits in children with NF1 (Watt et al., 2008). Consequently, we feel the results of this study have important contributions to make regarding the nature of reading difficulties in school-aged children with NF1.

Study findings highlight the high incidence of phonological decoding difficulties occurring in children with NF1. Previous research from the general population (Galuschka, Ise, Krick, & Schulte-Korne, 2014) and in children with NF1 (Arnold et al., 2016) indicates that most poor readers will benefit from phonics training which explicitly teaches letter-sound knowledge. Our results highlight the importance of a thorough assessment of the reading abilities and underlying subskills in children with NF1 so that children can receive appropriate, targeted intervention. Finally the relationship identified between reading and other cognitive abilities (i.e. working memory, language, attention) emphasises the need for a combined assessment of literacy and broader cognitive skills.

Further investigation of the reading subskills of children with NF1 who are poor readers is needed to better understand the differences between children with predominately phonological impairments and those with mixed dyslexia. There is some evidence from the general population indicating that children with mixed dyslexia may be the most severely impaired (McArthur et al., 2013a). Case studies of children with mixed dyslexia in the general population indicate that although there may be some generalisation of specific training of sublexical skills to lexical skills (Brunsdon, Hannan, Nickels, & Coltheart, 2002), there is also independence between the two reading routes (Brunsdon et al., 2002). Hence children with mixed dyslexia in our NF1 sample may require more intensive intervention than those with phonological dyslexia.

In conclusion, we confirm an elevated risk of reading impairment in children with NF1; over 80% of children with NF1 in our sample displayed poor word reading and they exhibited a 4.20 times greater risk of experiencing a reading difficulty than unaffected controls. For the first time, we have shown that deficits occur throughout lexical and sublexical reading subskills and also in basic reading precursor skills, such as letter identification. Higher-level literacy processes such as reading fluency and comprehension are also commonly impaired. The high frequency of word reading impairments and study findings from others (Cutting et al., 2004; Mazzocco et al., 1995) indicate that the cognitive phenotype of NF1 cannot be adequately described as being consistent with a nonverbal learning disability profile as previously proposed (Denckla, 1996). Poor readers with NF1 appear to be at increased risk for a phonological dyslexia compared to peers in the general population (McArthur et al., 2013a).

ACKNOWLEDGEMENTS

We report no conflict of interests. The authors received no financial support for this research.

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Table 1. Demographics and means (SD) for general cognitive measures

	NF1 (*n* = 60)		Controls (*n* = 36)			
Measure	**n**	**M (SD)**	**n**	**M (SD)**	***p***	**Cohen's *d***
Sex Male	32 (53%)		18 (50%)		.80	
NF1 inheritance Familial	23 (38%)					
Age (Years)	60	8.75 (1.84)	36	8.78 (-1.64)	.79	0.05
SEIFA[a]	60	8.00[b] (4.00)[c]	36	10.00[b] (4.00)[c]	.07[d]	0.36
WISC-IV/WASI-II						
FSIQ (Standard score)	60	87.00[b] (12.00)[c]	36	109.00[b] (14.00)[c]	<.001[d]	1.66
VCI/VIQ (Standard score)	60	92.02 (9.33)	36	104.28 (11.22)	<.001	1.19
PRI/PIQ (Standard score)	60	89.95 (10.73)	36	105.67 (10.64)	<.001	1.47
WMI (Standard score)	60	88.37 (9.91)	36	101.08 (9.76)	<.001	1.30
JLO (Z score)[e]	58	-1.20 (1.17)	34	-0.17 (0.89)	<.001	1.00
TEA-CH						

Divided attention, Sky Search DT (Scaled score)[f]	56	1.50[b] (6.00)[c]	34	7.00[b] (6.00)[c]	.001[d]	0.69
Selective attention, Sky Search (Scaled score)[g]	58	8.00[b] (4.00)[c]	34	8.00[b] (3.00)[c]	.83[d]	0.04
Sustained attention, Score (Scaled score)	60	6.00[b] (5.00)[c]	35	9.00[b] (7.00)[c]	.001[d]	0.74
Switching attention, Creature counting (Scaled score)[h]	55	8.00[b](5.00)[c]	34	10.00[b] (5.00)[c]	<.001[d]	0.89
CONNERS-3						
Inattentive (T score)[i]	57	66.40 (13.92)	36	(53.28) (9.57)	<.001	1.10
Hyperactive/Impulsive (T score)[i]	57	57.00[b] (19.00)[c]	36	49.00[b] (17.00)[c]	.03[d]	0.46

Note. Conners-3 = Conners' Rating Scales, Third Edition – Parent Rating Forms; FSIQ = Full-Scale IQ; JLO = Judgment of Line Orientation; PRI/PIQ = Performance IQ; SEIFA = Socio-Economic Indexes for Areas; TEA-Ch = Test of Everyday Attention for Children; VCI/VIQ = Verbal IQ; WASI-II = Wechsler Abbreviated Scale of Intelligence-Second Edition; WISC-

IV = Wechsler Intelligence Scale for Children Scale of Intelligence-Fourth Edition, Australian Adaptation; WMI = Working Memory Index.

[a] Decile ranking of areas in Australia according to relative socio-economic advantage and disadvantage; 1 is lowest and 10 is highest SES, [b]Median, [c]Interquartile range, [d]Mann Whitney-U test, [e] Missing data for JLO (n=2) as test not administered, [f] Missing data for TEA-Ch Divided attention subtest (n=4) as test not administered, [g] Missing data for TEA-Ch Selective attention subtest (n=2) as test not administered, [h] Missing data for TEA-Ch Switching attention subtest (n=5) as test not administered, [i] Missing data for Conners 3 (n=3) as questionnaire not completed.

Holm's procedure applied to all analyses; Higher scores indicate better performance except for Conners 3 where higher scores represent higher levels of ADHD behaviours

Table 2. Means (SD) for Literacy Measures for the NF1 and Control groups

	NF1 (n = 60)		Controls (n = 36)			
Measure	**n**	**M (SD)**	**n**	**M (SD)**	***p***	**Cohen's *d***
General Reading						
Regular word reading - CC2 (Z score)	60	-1.45[a] (0.81)[b]	36	0.34[a] (1.95)[b]	<.001[c]	1.50
Sight word reading fluency - TOWRE (Standard score)	60	90.00[a] (15.00)[b]	36	105.00[a] (16.00)[b]	<.001[c]	1.29
Nonword reading fluency - TOWRE (Standard score)	60	85.00[a] (14.00)[b]	36	103.00[a] (23.00)[b]	<.001[c]	1.36
Reading comprehension - TERC (Z score)	60	-0.81 (0.85)	34	0.65 (0.95)	<.001	1.62
Sublexical route						
Nonword reading - CC2 (Z score)	60	-1.64[a] (0.52)[b]	36	-0.08[a] (1.55)[b]	<.001[c]	1.78
Lexical route						
Irregular word reading - CC2 (Z score)	60	-0.94[a] (0.94)[b]	36	0.19[a] (1.40)[b]	<.001[c]	1.26
Sublexical subskills						
GPC knowledge - LeST (Raw score, /51)	60	34.83 (6.29)	36	42.00 (6.00)	<.001	1.17

GPC knowledge - GPC test (Raw score, /39)	60	7.00[a] (11.00)[b]	34	28.00[a] (13.00)[b]	<.001[c]	1.65
Lexical subskills						
Orthographic lexicon - TOC (Z score)[d]	59	-0.92[a] (1.29)[b]	34	0.05[a] (1.84)[b]	<.001[c]	1.06
Phonological lexicon - Rain/Hane test (Raw score, /20)	60	16.00[a] (4.00)[b]	34	19.00[a] (2.00)[b]	<.001[c]	1.04
Semantics - PPVT-4 (Standard score)[e]	58	93.84 (10.45)	35	111.37 (11.91)	<.001	1.56
Common subskills (lexical and sublexical)						
Letter identification - Cross-case (Raw score, /14)	60	14.00[a] (2.00)[b]	36	14.00[a] (0.00)[b]	.001[c]	0.61
Letter identification - LOT (Raw score, /54)	60	51.00[a] (6.00)[b]	33	53.00[a] (4.00)[b]	.06[c]	0.40
Phonological output - NEPSY nonword repetition (Scaled score)	60	7.00[a] (3.00)[b]	34	11.00[a] (3.00)[b]	<.001[c]	1.58
Phonological output - Blending nonwords (Raw score, /28)	60	9.00[a] (14.00)[b]	34	18.00[a] (11.00)[b]	<.001[c]	0.86

Note. CC2 = Castles and Coltheart 2; GPC = Grapheme-phoneme conversion; LeST = Letter-sound test; LOT = Letter orientation test; NEPSY = A Developmental Neuropsychology Assessment; PPVT-4 = Peabody Picture Vocabulary Test - Fourth Edition; TERC = Test of Everyday Reading Comprehension; TOC = Test of Orthographic Choice; TOWRE = Test of Word Reading Efficiency

[a]Median, [b] Interquartile range, [c] Mann-Whitney U Test.

Holm's procedure applied to all analyses; Higher scores indicate better performance for all measures

Table 3. Means (SD) Literacy scores by reading subtypes

Variable	Controls non-poor readers (n = 29)	NF1 non-poor readers (n = 11)	NF1 phonological dyslexics (n = 20)	NF1 mixed dyslexics (n = 24)	All groups ANOVA	ηp²	Controls vs NF1 non poor readers	Controls vs NF1 non poor readers	Phonological vs. Mixed	Phonological vs. Mixed
			n (%)	n (%)	*p*		*p*	Cohen's *d*	*p*	Cohen's *d*
Sex Male	14 (48)	5 (45)	12 (60)	12 (50)	0.83[a]	-				
NF1 inheritance Familial		4 (36)	7 (35)	12 (50)	0.36[a]	-				
SEIFA	10.00[b] (4.00)[c]	9.00[b] (5.00)[c]	9.00[b] (4.00)[c]	8.00[b] (6.00)[c]	0.31[d]	0.17[e]				
	M (SD)	**M (SD)**	**M (SD)**	**M (SD)**						
Age (Years)	8.83 (1.73)	9.09 (2.02)	9.10 (2.02)	8.13 (1.36)	0.24	0.05				
FSIQ (SS)	110.00[b] (14.00)[c]	96.55 (11.15)	89.50 (8.69)	84.00[b](8.00)[c]	<.001**	0.51	0.017*	0.81	0.037*	0.66
General reading										
Regular word reading CC2 (z score)	0.63 (0.98)	-0.14 (1.10)	-1.34 (0.34)	-1.83 (0.44)	<.001**[f]	0.67	0.04	0.76	<.001**	1.23
Sight word fluency TOWRE (SS)	111.55 (13.66)	101.91 (14.04)	97.20 (8.70)	83.42 (8.59)	<.001**	0.51	0.06	0.70	<.001**	1.60

Nonword fluency TOWRE (SS)	108.86 (12.96)	103.09 (13.54)	85.50 (8.07)	78.88 (6.10)	<.001**[f]	0.62	0.22	0.44	.003**	0.94
Reading comprehension TERC (z score)	0.79 (0.93)	-0.11 (0.82)	-0.67[b] (0.80)[c]	-1.61[b] (0.87)[c]	<.001**[d]	2.25[e]	.008**	1.00	<.001**[g]	1.45
Sublexical reading										
Nonword reading CC2 (z score)	0.27[b] (1.31)[c]	-0.74[b] (0.72)[c]	-1.64[b] (0.30)[c]	-1.69[b] (0.40)[c]	<.001**[d]	3.71[e]	<.009**[e]	0.90	.032*[g]	0.68
Sublexical subskills										
GPC knowledge LeST (Raw score, /51)	45.00[b] (6.00)[c]	41.00[b] (11.00)[c]	36.10 (5.11)	30.71 (4.53)	<.001**[d]	2.06[e]	0.35[g]	0.30	.001**	1.12
GPC knowledge GPC test (Raw score, /39)	31.00[b] (10.00)[c]	22.00[b] (20.00)[c]	8.50[b] (10.00)[c]	1.50[b] (6.00)[c]	<.001**[d]	3.13[e]	.030[g]	0.73	<.001**[g]	1.30
Lexical reading										
Irregular word reading CC2 (z score)	0.46 (0.77)	0.42 (1.07)	-0.80[b] (0.41)[c]	-1.73[b] (0.57)[c]	<.001**[d]	3.56[e]	0.90	0.05	<.001**[g]	3.27
Lexical subskills										

Orthographic lexicon TOC (z score)	0.36 (1.12)	0.03 (1.02)	-0.86[b] (1.11)[c]	-1.72[b] (1.11)[c]	<.001**[d]	1.52[e]	0.41	0.30	0.024[g]	0.73
Phonological lexicon Rain/Hane (Raw score, /30)	19.00[b] (2.00)[c]	17.30 (2.98)[h]	15.95 (2.86)	14.88 (2.56)	.09[i]					
Semantics PPVT - 4 receptive vocab (SS)	112.76 (11.22)	100.10 (9.01)[e]	95.85 (11.28)	89.26 (9.36)	<.001**	0.47	<.003**	1.18	0.04	0.64
Common processes										
Letter identification - Cross case (Raw score, /14)	14.00[b] (0.00)[c]	14.00[b] (0.00)[c]	14.00[b](2.00)[c]	13.00[b] (4.00)[c]	<.001**[d]	1.05[e]	0.74[g]	0.11	0.17[g]	0.40
Letter identification - LOT (Raw score, /54)	52.00[b] (4.00)[c]	53.00[b] (2.00)[c]	51.00[b] (4.00)[c]	48.00[b] (7.00)[c]	<.001**[d]	0.99[e]	0.19[g]	0.44	0.023[g]	0.73
Phonological output - Blending (Raw score, /28)	18.00[b] (10.00)[c]	16.00[b] (20.00)[c]	9.50[b] (8.00)[c]	6.00[b] (10.00)[c]	<.001**[d]	1.21[e]	0.21[g]	0.41	0.10[g]	0.51
Phonological output - NEPSY-II (scaled score)	10.86 (2.01)	8.91 (1.04)	6.80 (2.02)	7.17 (1.93)	<.001**	0.48	<.001**	1.08	0.54	0.19

ηp^2 = partial eta-squared; CC2, Castles and Coltheart 2; GPC, Grapheme-Phoneme conversion; LEST, Letter-sound test; NEPSY, A Developmental Neuropsychology Assessment; PPVT-4, Peabody Picture Vocabulary Test - Fourth edition; TERC, Test of Everyday Reading Comprehension; TOC, Test of Orthographic choice; TOWRE, Test of Word Reading Efficiency; SS, Standard score.

*p≤.05, **p≤.01

[a]Chi square test of independence, [b]Median, [c]Interquartile range, [d]Kruskal-Wallis H Test, [e]Cohen's *d*, [f]Welch's F, [g]Mann-Whitney U Test, [h] Missing data (n=1) as test not administered, [i]ANCOVA results controlling for age (see Supplementary Table 2)

Table 4. Correlations between word reading and cognitive, demographic and behavioural variables for the NF1 group

Measure	1	2	3	4	5	6	7	8	9
1. Combined word reading	-								
2. SEIFA[a,b]	.215	-							
3. FSIQ[a]	.460**	.345**	-						
4. VCI/VIQ	.359**	.055	.544**	-					
5. PRI/PIQ	.282*	.374**	.744**	.221	-				
6. WMI	.419**	.202	.618**	.222	.522**	-			
7. JLO[c]	.068	.209	.457**	.063	.499**	.291*	-		
8. PPVT-4[c]	.338**	.177	.296*	.345**	.374**	.134	.189	-	
9. Conners 3 - Inattention[d]	-.357**	-.240	-.171	-.082	-.152	-.171	-.081	.002	-

Note. FSIQ = Full-scale IQ; JLO = Judgement of Line Orientation; PPVT-4 = Peabody Picture Vocabulary Test – Fourth edition; PRI/PIQ = Performance IQ; SEIFA = Socio-Economic Indexes for Areas; VCI/VIQ = Verbal IQ; WMI = Working Memory Index

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

[a] Spearman's rho, [b]Decile ranking of areas in Australia according to relative socio-economic advantage and disadvantage; 1 is lowest and 10 is highest SES, [c]n=58, [d] n=57

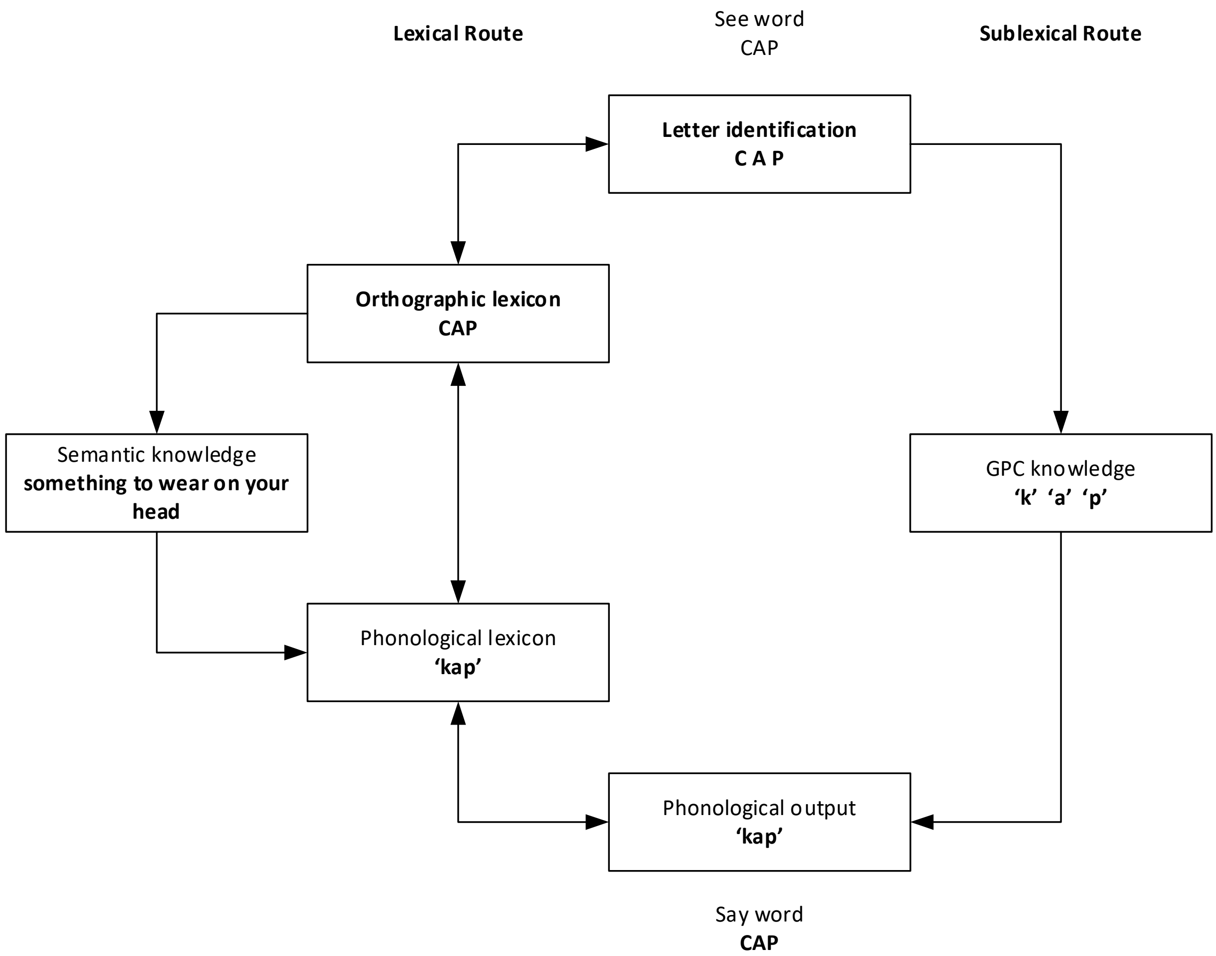
Table 5. Hierarchical regression analysis predicting word reading in the NF1 group

Variable	B	SE B	β	Adjusted R^2	ΔR^2
Step 1				.11	.12
Constant	-2.41	.70			
PIQ	.02	.01	.35**		
Step 2				.20	.11
Constant	-3.63	.80			
PIQ	.01	.01	.21		
Working Memory Index	.02	.01	.36**		
Step 3				.25	.07
Constant	-2.47	.94			
PIQ	.01	.01	.17		
Working Memory Index	.02	.01	.32*		
Conners Inattention	-.01	.01	-.27*		
Step 4				.31	.07
Constant	-3.31	.97			
PIQ	.00	.01	.05		
Working Memory	.02	.01	.33**		
Conners Inattention	-.01	.01	-.29*		
Receptive language	.02	.01	.28*		

Note. PIQ = Performance IQ; B = Unstandardized beta; SE B = Standard error of B; β = Standardized beta

**$p \leq .01$, *$p \leq .05$

Figure 1: Dual-route model of reading (Coltheart et al., 2001) Adapted from Figure 1 (McArthur et al., 2013a)



Supplementary Table 1. Males compared to females on literacy measures for the NF1 group

		Males (n = 32)		Females (n= 28)		Males vs. females	
Variable	**Measure**	**n**	**M (SD)**	**n**	**M (SD)**	***p***	**Cohen's *d***
General reading							
Regular word reading	CC2 Regular word reading (Z score)	32	-1.45[a] (0.84)[b]	28	-1.43[a] (0.77)[b]	.790[c]	.069
Sight word reading fluency	TOWRE Sight word (Standard score)	32	90.59 (13.51)	28	93.18 (12.52)	.447	.198
Nonword reading fluency	TOWRE Phonemic decoding (Standard score)	32	85.50[a] (13.00)[b]	28	84.50[a] (16.00)[b]	.609[c]	.132
Reading comprehension	TERC (Z score)	32	-0.82 (0.87)	28	-0.81 (0.85)	.943	.019
Word reading ability	*Combined word reading* variable	32	-0.51 (0.66)	28	-0.50 (0.62)	.947	.018
Sublexical reading							
Nonword reading	CC2 Nonword reading (Z score)	32	-1.64[a] (0.41)[b]	28	-1.65[a] (0.82)[b]	.651[c]	.117
Sublexical subskills							
GPC knowledge	LeST (Raw score, /51)	32	35.22 (6.10)	28	34.39 (9.00)	.616	.131
GPC knowledge	GPC test (Raw score, /39)	32	6.50[a] (10.00)[b]	28	8.00[a] (14.00)[b]	.661[c]	.113
Lexical reading							
Irregular word reading	CC2 Irregular word reading (Z score)	32	-0.89[a] (1.07)[b]	28	-0.95[a] (0.96)[b]	.573[c]	.146
Lexical subskills							
Orthographic lexicon	TOC (Z score)	31[d]	-0.83[a] (1.29)[b]	28	-1.01[a] (1.48)[b]	.808[c]	.063
Phonological lexicon	Rain/Hane test (Raw score)	32	16.34 (2.55)	27[d]	15.22 (3.03)	.128	.403
Semantics	PPVT-4 receptive vocabulary (Standard score)	32	96.03 (9.97)	26[e]	91.15 (10.60)	.077	.476

Common subskills (lexical and sublexical)							
Letter identification	Cross case copying (Raw score, /14)	32	13.00[a] (1.00)[b]	28	14.00[a] (3.00)[b]	.917[c]	.025
Letter identification	Letter orientation (Raw score, /54)	32	51.00[a] (3.00)[b]	28	51.00[a] (9.00)[b]	.612[c]	.130
Phonological output	Blending nonwords (Raw score, /28)	32	9.50[a] (10.00)[b]	28	7.00[a] (15.00)[b]	.443[c]	.198
Phonological output	NEPSY-II nonword repetition (Scaled score)	32	7.00[a] (3.00)[b]	28	7.50[a] (3.00)[b]	.958[c]	.013

Note. Higher scores indicate better performance for all measures

Supplementary Table 2. ANCOVA results controlling for age

Variable	Measure	p	ηp^2
Sublexical subskills			
GPC knowledge	LeST (Raw score, /51)	<.001[a]	.52
GPC knowledge	GPC test (Raw score, /39)	<.001[a]	.76
Lexical subskills			
Phonological lexicon	Rain/Hane test (Raw score)	.09[a]	.08
Common subskills (lexical and sublexical)			
Blending nonwords		.001[a]	.20

ηp^2 = partial eta-squared

[a]Data were transformed to a normal distribution using a square root transformation and ANCOVAs were conducted.

Note. Ceiling effects were present for letter identification (cross case and LOT) and could not be transformed to a normal distribution.