Visual-processing deficits in children with neurofibromatosis type 1
Marie Vernet, Marianne Jover, Stéphanie Bellocchi, Stéphanie Maziero, Mélanie Jucla, Jessica Tallet, Jérémy Danna, Yves Chaix, Stéphanie Ducrot

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Visual-processing deficits in children with neurofibromatosis type 1: A clinical marker of reading difficulties

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Today’s estimates indicate that nearly 50% of children with Neurofibromatosis type 1 (NF1) suffer from reading disabilities, with a high impact on their academic achievement. In addition to the well-documented importance of phonological skills in reading acquisition and neurodevelopmental disorders, visual-attention processes also appear as important factors in learning to read. The present study aimed at assessing the role of visual-processing dysfunction in the high prevalence of reading disabilities in NF1 children and providing a useful tool for clinician in the early detection of reading impairment in this neurogenetic disorder. Forty-two children with NF1 and 42 typically developing children (TD) participated in the study. All were right-handed and did not present intellectual disability or attention deficit hyperactivity disorder. Visual-attention processes were assessed with the Developmental Eye Movement (DEM) test, together with the NF1 children’s reading level. NF1 children with and without reading disabilities were then compared. The results showed that visual-processing deficits were highly present among the NF1 children included in our study. Furthermore, poor readers with NF1 presented an increased risk of visual-processing deficits compared to peers. This finding supports the role of visual-processing deficits in the reading difficulties encountered in nearly half of children with NF1. Finally, in NF1 children without intellectual or attention disability, visual-processing deficits emerge as one of the clinical markers of reading disabilities. The study holds important clinical implications both for the identification, by providing a useful screening tool, and the management of reading disabilities in NF1 children.

KEYWORDS. Neurofibromatosis type 1; Reading; Visual information processing; DEM-test; Screening tool
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<td>53</td>
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<td>HTaj Adjusted Horizontal Time</td>
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<td>55</td>
<td>JLO Judgment of Line Orientation</td>
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<td>56</td>
<td>NF1 Neurofibromatosis type 1</td>
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<td>NF1RD Children with neurofibromatosis type 1 with reading disabilities</td>
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<td>58</td>
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<td>RAN Rapid Automatic Naming</td>
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<td>TD Typically developing children</td>
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1. INTRODUCTION

Neurofibromatosis type 1 (NF1) is a neurogenetic disorder, affecting approximately 1 in 2500 to 3000 births (Evans et al., 2010). The diagnosis of NF1 is based on the clinical criteria stated in the recently revised NIH Consensus Conference Statement (Legius et al., 2021; NIH National Institutes of Health, 1988), including cutaneous, ophthalmologic, orthopedic and neurologic manifestations (Baudou & Chaix, 2020). In addition to physical manifestations, children with NF1 frequently experience deficits in a range of cognitive domains including visual-perception, executive functioning, motor skills, attention, and language (Hyman et al., 2005). Academic underachievement is also common in NF1 (Coudé et al., 2006), and reading disabilities are highly prevalent (between 30% to 80%; Arnold et al., 2020; Chaix et al., 2017; Hyman et al., 2005; Orraca-Castillo et al., 2014; Watt et al., 2008). Up to 67% of school-aged children with NF1 demonstrate single-word reading impairments (Watt et al., 2008) and rate of reading comprehension difficulties is also high (Cutting & Levine, 2010). Despite a wide variability, the frequency of reading difficulties in NF1 appears to be considerably higher than in the general population, where 5 to 10% of children suffer from developmental dyslexia (Inserm, 2007). Owing to this high incidence and the lifelong negative implications of reading problems (Sanagoo et al., 2019), it is crucial to clarify their causes in NF1.

First of all, several studies have shown that phonological impairments are an integrant feature of the neurocognitive profile of the NF1 child (Arnold et al., 2018; Chaix et al., 2017; Cutting & Levine, 2010). Other linguistic processes appear to be deficient in NF1 such as phonological memory, rapid automatic naming (RAN) and letter-sound knowledge (Arnold et al., 2018; Cutting & Levine, 2010). Interestingly, all of these linguistic skills are known to be fundamental prerequisites for learning to read, and children with difficulties in these prerequisite skills are at serious risk of later reading difficulties and developmental reading disabilities (Carroll et al., 2016).
Although linguistic deficits probably constitute the most common cause of reading difficulties in NF1, there is evidence suggesting that the visual processing is also impaired in NF1. Some studies have suggested a delay in the maturation of low-level vision processes, with significant alterations of the visual magnocellular pathway (Ribeiro et al., 2012; Violante et al., 2012), visual spatial dysfunction (Baudou et al., 2020; Hyman et al., 2005; Schrimsher et al., 2003), and abnormalities in saccadic programming (Lasker et al., 2003, but see Krab et al., 2011).

Reading is a visual task, highly constrained by the anatomical and functional limits of our visual system (for a review, see Leibnitz et al., 2017). The high visual acuity that is needed to rapidly identify words is spatially limited and the anatomo-functional constraints of the eye require saccades and fixations to shift the foveal area to the optimal fixation location of the word in order to extract the relevant information (Ducrot et al., 2013). Visual attention is also needed to optimize the information extraction through foveal and parafoveal vision, and to initiate saccadic programming (Leibnitz et al., 2017). As a result, basic aspects of oculomotor control, the ability to orient the focus of attention as well as the ability to control its size are assumed to play a crucial role in the development of reading skills. Their inadequate development might also cause reading disabilities. In that sense, several studies with typically developing readers and dyslexics demonstrated a strong relationship between reading ability and visual processing (for a review, see Grainger et al., 2016). An increasing number of studies shows today that visual-attention deficits may predict future reading difficulties in kindergarteners (Bellocchi et al., 2017; Franceschini et al., 2012; Vernet et al., 2021) and are present in several neurodevelopmental disorders (e.g., Bellocchi et al., 2019). Interestingly, at the biological level, such deficits have been related to the distinction between two different visual pathways, the magnocellular (10% of retinal ganglion cells) and parvocellular pathways (90% of retinal ganglion cells) (see, for example, Chase, 1996; Stein, 2019). The magnocellular
system (M-system) is assumed to be involved in low-spatial- and high-temporal-frequency processing, whereas the parvocellular system (P-system) is most sensitive to high-spatial and low-temporal frequencies. Slaghuis et al. (1996) have referred to the P-sustained-system as the determinant of what a visual stimulus is, and the M-transient-system of where a visual stimulus is. P-system has also been associated with foveal vision, and M-system with parafoveal and peripheral vision. Note that the M-system has been shown to play an important role in the reading process. Stein (2003, 2019) considered that this visual system plays a dominant role in the bottom-up direction of attention. Because the M-system of poor readers is weaker, the speed with which they can disengage and reengage attention on words is reduced compared with good readers. Stein (2003) also considered that the M-system stabilises eye movements. In the case of a deficient system, the retinal images of letters and words are not stationary, and they move on the retina. As a result, disruption of the M-system would impact visuo-perceptual processes (i.e., global processing strategy), visuo-attentional mechanisms (i.e., atypical attentional deployment), and oculomotor control, which are all implied in reading (Franceschini et al., 2012, 2017).

Whereas both phonology and visual processes contribute to reading, very few studies have been conducted to examine visual-processing skills related to word recognition in NF1 children. This paper is therefore focused upon those processes and on their contribution to reading behaviour and reading problems in the context of this neurogenetic disorder. Using the Judgment of Line Orientation test (JLO), Cutting and Levine (2010) showed a significant association between word reading outcomes and the visuo-spatial processes assessed in NF1 children with reading disabilities only. Moreover, compared to the two control groups (without NF1), NF1 children with a reading disorder showed significantly lower visuo-spatial performance. These results provide the first support for the implication of visual-perceptual processes in the reading difficulties frequently observed in this genetic disease (but see Arnold
et al., 2020). Note that there is some evidence suggesting that the visuo-spatial deficits observed in the JLO test might be linked to executive functions, making this test unsuitable for assessing the role of visual skills in reading failure (Van Eylen et al., 2017).

To sum up, in addition to the well-documented importance of phonological skills in reading acquisition and neurodevelopmental disorders, visual-processing skills also appear as important factors in learning to read. Despite the high incidence of reading impairment in school-aged children with NF1, the data showing alterations in low-level visual processes, and their significant impact on children’s quality of life, little is known about the contribution of visual-processing impairments in the explanation of the reading difficulties of the NF1 children. We assume that it is crucial to be able to assess visual-processing skills, in view of establishing thorough and accurate assessment procedures and proposing remediation methods that take into account the particular processes affected.

Considering this clinical perspective, it is important to use a reliable and convenient test to assess visuo-processing skills in NF1 children. Today, most psychometric tools used to identify visual-processing difficulties are based on visuo-spatial skills, which is not ecological with respect to reading. However, complex technical equipment such as eye-tracking can hardly be used in clinical and school situations (e.g., expensive material, hard to use and long time required). In that context, we have examined the usefulness of the Developmental Eye Movement (DEM) test (Garzia et al., 1990) that provides an indirect measure of the efficiency of visual-attention processes in a simulated reading task (horizontal and vertical digit naming task). Our preference went to the DEM-test to clinically assess the reading performance of children with NF1, because all studies using it agreed that visuo-perceptual and visuo-attentional processes play a major role in this task (Ayton et al., 2009; Facchin et al., 2014; Hopkins et al., 2019; Larter et al., 2004; Moiroud et al., 2018; Portnoy & Gilaie-Dotan, 2020;
Raghuram et al., 2018). Moreover, there is a large consensus on the relationship between the DEM-test and reading abilities, both in school-age children (Ayton et al., 2009; Larter et al., 2004) and in children with learning difficulties (Bellocchi et al., 2021; Moiroud et al., 2018; Raghuram et al., 2018).

In the present study, we examined the role of visual-processing dysfunctions in the high prevalence of reading disabilities in children with NF1. Specifically, we were interested in the prevalence of visual-processing deficits as assessed with the DEM-test in NF1 children compared to typically developing children. To better understand the contribution of visual-processing deficits in the explanation of the reading disabilities of the NF1 children, we investigated the relationship between DEM-test outcomes and reading performance. Finally, we aimed at discussing the usefulness of the DEM-test as a clinical tool to understand and screen as early as possible reading disabilities in children with NF1. This could constitute an important asset for practitioners to identify children at risk of reading difficulties, based upon their visual processing performance.

2. METHOD

2.1. Participants

Forty-two children with NF1 took part in the present study. The participants were enrolled in the DYSTAC-MAP cohort (ANR-13-APPR-0010). Participation in this research was proposed to all children who met the clinical criteria for the diagnosis of NF1 in accordance with the Neurofibromatosis Conference statement (National Institutes of Health, 1988). NF1 children were compared with forty-two typically developing children (TD). The demographic characteristics of the two groups are summarized in Table 1. Children were 8–12 years old and attended school from 2nd to 6th grade. They were all right-handed and French native speakers, with normal or corrected-to-normal vision. There were no significant differences between the
groups for age and sex ratio. As part of this research, all children underwent a complete medical and neuropsychological assessment. Children with Attention Deficit Hyperactivity Disorder (i.e., more than 6 symptoms of Hyperactivity and/or Inattention in a parent rating on the DSM-5 diagnosis criteria), intellectual disability (i.e., WISC total IQ at least below to 70 or/and standard score below to 7 at the Similarities and/or Picture Concepts subtests), neurological or psychiatric disorder (e.g., epilepsy, brain tumor, or autism) or hearing deficits were not included. Note that although Attention Deficit Hyperactivity Disorder is common in NF1, we wanted to make sure that the difficulties we could observe were really due to a deficit in the domain of interest and not the consequence of attentional biases during the tasks. For the control group, the reading level was controlled to include only children with typical reading development, i.e. scores at least superior to -0.5 SDs on the Alouette-test (Lefavrais, 2005) and the ODEDYS-2 test ("Outil de dépistage des dyslexies"; Jacquier-Roux et al., 2002).

This research was conducted in accordance with the Declaration of Helsinki (World Health Organisation, 2008) and approved by the French Ethics Committee Review Board (2014-A01239-38 and 2014-A01960-47). Written parental and child consent was obtained for each participation in the study.

2.2. Material

2.2.1. DEM-test

The DEM-test (Garzia et al., 1990) consists in horizontal and vertical digit naming tasks, printed on four different sheets of paper: (1) a pre-test (a horizontal line of ten digits) to ensure that the child is familiar with all the digits presented in the following tasks, (2) two vertical tests (Test A and B; each composed of two vertical columns of twenty digits), and (3) one horizontal test that simulates a reading situation (Test C; sixteen lines of five irregularly separated digits). Children were asked to read aloud the digits, as quickly and as accurately as possible. The DEM-test provides four main indices: (1) the vertical time in seconds (i.e., VT) corresponding
to the sum of the times spent on naming the vertically organized digits of Test A and B; (2) the 
adjusted horizontal time in seconds (i.e., HTaj), which corresponds to the time spent on naming 
the horizontally organized digits of test C, adjusted according to the number of omission and 
addition errors (Test C time x [80 / (80 – number of omission errors + number of addition 
errors)]); (3) the total number of errors (i.e., HE) made on test C corresponding to the sum of 
the 4 possible types of errors: addition errors, omission errors, substitution errors and 
transposition errors; and finally (4) the ratio between the VT and HTaj indices (i.e., Ratio) 
calculated from the following formula: R = HT/VT. Note that the validity of the ratio index has 
been strongly questioned in the literature (Ayton et al., 2009; Webber et al., 2011), so we chose 
to exclude this index from our analyses. Furthermore, as the total number of errors was almost 
zero in the vertical organization test and in accordance with the test manual, it was not used for 
scoring purpose.

2.2.2. Alouette test

The Alouette test (Lefavrais, 2005) is commonly used in France to assess reading 
proficiency. It consists of reading aloud a text composed by 265 words included in syntactically 
correct but semantically poor sentences. Children were instructed to read aloud the text as fast 
and as accurately as possible, within 3 minutes. The Alouette test provides two main indices: 
the reading-accuracy index and the reading-fluency index.

2.3. Procedure

Participants were recruited at the Timone University Hospital in Marseille, at the 
Hospital of Aix-en-Provence, and at the Purpan University Hospital in Toulouse. Each child 
was seen individually at the hospital and at the university laboratories. An assessment session, 
lasting approximately 1 hour and a half was conducted at the hospital to check for the inclusion 
criteria, including the assessment of reading level (5 min). The DEM-test was also proposed
during this session and lasted approximately 10 minutes per child. Children were in a quiet room in which the brightness was adapted according to the different tasks.

2.4. Data analysis

Due to the age differences of the children included within each group, all statistical analyses were performed using Z-scores, which have been modified so that a negative value represents a poor performance. The statistical analyses were conducted using R and GraphPad statistical computer softwares. Shapiro-Wilk normality tests showed non-normal distributions for several variables. Therefore, the statistical tests performed were non-parametric. The statistically significant threshold for all the analyses was set at \( p = .05 \).

Descriptive analyses were conducted for the demographic characteristics and the DEM-test performances between NF1 and TD groups. Chi-square analyses were completed for categorical variables, while Mann-Whitney U test analyses were performed for continuous variables and effect sizes are reported with the rank-biserial correlation (rb). Chi-square analyses were also carried out to investigate the proportion of children with deficits at the different indices of the DEM-test in each group. For all the analyses relating to the proportion of children with deficit, it was considered that a score may reflect a deficit when it was equal or below -1.5 SD.

3. RESULTS

3.1. Impact of NF1 on DEM-test performances

3.1.1. DEM-test performances

Mean scores on the DEM-test for both groups of children are provided in Table 1. The NF1 group had significantly poorer performances than the control group for HTaj and HE with
moderate effect sizes for these two indices, whereas no group differences were found for the VT index.

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[Insert Table 1 about here]
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3.1.2. Prevalence of visual-processing deficits in NF1 children

Regarding the prevalence of visual-processing deficits at the DEM-test, a total of 28 NF1 children had at least one score below -1.5 SD compared to the control group (with 13 children). Ten NF1 children and seven TD children were below -1.5 SD on the VT index, 20 NF1 children and 3 TD children on the HTaj index, and finally, 13 NF1 children and 6 TD children on the HE index. The difference between the groups in the proportion of children with deficit was significant for HTaj ($\chi^2 = 17.3, p < .001$) with more NF1 children exhibiting deficit on this index than those in the control group. There were no significant group differences for VT and HE indices (all $p$s > .05).

3.2. NF1 children’s reading level and visual processing performance

In order to better understand the poor performance of children with NF1, all the following analyses were focused on the NF1 children group, considering performance in both the DEM-test and the reading test.

3.2.1. Relationship between visual processing and reading outcomes in NF1 children

The reading level of children with NF1 was included in the analyses and Spearman’s correlations were performed to examine the relationship between the reading level (i.e., fluency and accuracy) and performance at the DEM-test. The correlation analyses between the indices of the DEM-test and the Alouette test showed a significant relationship between reading
accuracy and HTaj (r(40) = .37, p = .016) and HE (r(40) = .37, p = .016). The reading fluency was also correlated with the same DEM-test indices: HTaj (r(40) = .58, p < .001), and HE (r(40) = .32, p = .041). Thus, the longer the adjusted horizontal time is and the more errors there are at the DEM-test, the worst the reading is.

3.2.2. DEM-test performance and visual-processing deficit prevalence between NF1RD and NF1noRD

For subsequent analyses, the NF1 group of children was divided into two groups to dissociate children with reading disabilities (i.e., NF1RD) and normo-readers (i.e, NF1noRD) and determine whether the deficits on the DEM-test are specific to NF1 children with RD. A child was included in the NF1RD group if he/she had at least one of the two reading indices (i.e., accuracy and/or fluency) below -1.5 SD. Mann-Whitney U Test and Chi-square analyses were conducted to compare the performance between these groups. The kurtosis index was also calculated to study the performance distributions.

The performance of NF1 children in the Alouette and in the DEM tests according to reading group are detailed in Table 2. The NF1RD group included 17 children (40.5%) with at least one of the two indices of the Alouette test below than -1.5 SD.

The data distributions of the HT and HE indices confirmed the amplitude of the difficulties encountered by the NF1 children with reading deficit in this task. Except for the VT index, the distributions of the DEM-test indices, shown in Figure 1, behaved differently between NF1RD and NF1noRD children, with a deviant density peak for the first ones. More specifically, the density peak was flatter and left lateralized towards negative values in the NF1RD group (HTaj: kurtosis = 1.30; HE: kurtosis = -0.95) compared to NF1noRD children (HTaj: kurtosis = 10.55; HE: kurtosis = 6.00). Note that for the HTaj (and the HE to a lesser extent), the NF1noRD children performance distribution mirrored that of the control group (TD). The statistical analyses confirmed that HTaj performances were significantly different.
between the two groups (U(40) = 106.00, p = .007) with poorer performances for NF1RD children. The VT and HE indices were not significantly different between the groups.

Of the total NF1 sample, 31% suffered from both visual-processing deficits on the DEM-test and reading deficits. When we focus on children with a reading deficit only, 76.5% also reported visual-processing difficulties on the DEM-test. More precisely, among these 13 children with both reading- and visual-processing deficits, 5 were below average on the VT index, 13 on the HTaj index and 8 on the HE index. Regarding the nature of the errors made in the NF1RD group, 68.5 % were omission, 17.4 % were addition, 10.0 % were substitution, and only 4.1 % were transposition errors. Similarly, for NF1noRD, 59.9 % were omission, 21.3 % were addition, 10.4 % were substitution, and only 8.4 % were transposition errors.

3.2.3. Sensitivity and specificity of the DEM-test in NF1

In this section, ROC curve analyses were conducted on the DEM-test indices to determine whether this tool was able to differentiate NF1 children with and without reading disabilities. The area under the ROC curve (AUC) provides an index of the test's usefulness. An AUC greater than 0.9 is considered excellent, between 0.8 - 0.9 is very good, between 0.7 - 0.8 is good, between 0.6 - 0.7 is average, and an AUC less than 0.6 is poor (Choi, 1998). Note
that the ROC curve analyses were not used for the NF1 diagnosis purposes, but for the screening of reading deficit in NF1 children.

The ROC curve analyses, provided Figure 2, showed that the HTaj index was the only variable of the DEM-test that significantly dissociated NF1 children with and without reading deficits \([\text{AUC} = .7506 \pm .0803 \ (p < .01), \ 95\% \ CI \ [0.5933 \ – \ 0.9079]]\). The AUC for HTaj is very similar than those obtained by Hopkins et al. (2019) and Larter et al. (2004), with AUCs of .72 and .83 respectively. The AUCs for the VT and HE indices were not statistically significant (all \(p > .10\)).

4. DISCUSSION

One of the main objectives of the present study was to examine NF1 children’s visual-processing skills, to assess the occurrence of visual-processing difficulties in this neurogenetic disorder and to study beyond the linguistic ones, the visuo-attentional mechanisms impacted in the learning-to-read process in this population.

Although data is already available for the DEM-test in several neurodevelopmental disorders (Bellocchi et al., 2021; Bilbao & Piñero, 2020; Moiroud et al., 2018; Raghuram et al., 2018), no research, to the best of our knowledge, has specifically questioned its usefulness in the assessment of visual-processing skills in NF1 children. The results of the present study corroborated our predictions: visual-processing difficulties are highly present among NF1 children, with nearly 70% of NF1 children in our study presenting difficulties on this test. NF1 children exhibited poorer performance on DEM-test parameters and had more frequent visual-
processing deficits than TD children, especially on the HTaj index. In addition to deviant performance on the HTaj index, NF1 children also made many errors, whatever they present RD or not. The nature of these errors is very relevant since most of them are errors of omission resulting mainly from skipping lines and characters, suggesting immature and/or inaccurate eye-movement control, or visuo-attentional difficulties (Coulter & Shallo-Hoffman, 2001). These results are in line with previous studies which showed delayed maturation of low-level vision processes in children with NF1 (Lasker et al., 2003; Ribeiro et al., 2012; Violante et al., 2012).

Examination of the NF1 group also revealed that 41% of the children displayed poor word reading, providing support for previous findings showing that children with NF1 are at high risk of reading difficulties (Arnold et al., 2018; Watt et al., 2008). Significant weaknesses were evident on reading fluency and accuracy measures. Furthermore, 31% of the NF1 children presented difficulties on both the DEM-test and the reading assessment and it clearly appeared that the HTaj performance distribution at the DEM-test differed between NF1 good and poor readers. The results of this study are in line with previous findings indicating that children with reading problems have a higher prevalence of associated visual-processing deficits, such as visuo-attentional deficits, than children who are proficient readers (Franceschini et al., 2012; Portnoy & Gilaie-Dotan, 2020; Vernet et al., 2021).

Visual-processing deficits detected here with the DEM-test in our sample of NF1 children can have different causes such as orthoptic disorders, poor eye-movement control, visual-attentional impairments, or simply insufficient exposure to written language. But whatever their causes, visual-processing impairments can have major consequences on the likelihood of academic difficulties and more generally on the quality of life for children with NF1 (Coudé et al., 2006), highlighting the need for systematic screening the visual-processing abilities of all NF1 children.
As demonstrated above, visual information processing ability, based on measures of the DEM-test in NF1 children, was significantly associated with their reading scores. In this context, the second objective of the study was to determine whether the high prevalence of reading difficulties reported in NF1 could be partly explained by a visual processing deficit. For this purpose, we distinguished, from the reading performance, two subgroups within our sample of NF1 children: NF1 children with (NF1RD) and without (NF1noRD) a reading deficit. The results showed that NF1RD children presented lower performance and a higher proportion of children with performance below -1.5 SD on the HTaj index compared to NF1noRD children. These results were reflected in the atypical distribution of performance in NF1RD children in contrast to NF1noRD children who mirrored the performance of TD children. The differences between the two groups on the HTaj index were consistent with previous studies comparing children with and without reading difficulties (Bellocchi et al., 2021; Larter et al., 2004; Moiroud et al., 2018; Raghuram et al., 2018). Furthermore, our finding that the HTaj index was most strongly associated with the NF1 reading performance was in line with the results of Ayton et al. (2009) who reported the strongest correlations between the DEM horizontal subtest and reading test scores. Note that in our study, VT and HE indices did not differentiate the 2 groups, neither in average performance nor in deficit frequency (see Vernet et al., 2021 for different results with pre-readers). A possible explanation for this finding is that the processes specifically involved in the VT index are not impaired to a greater extent in NF1 children. In this sense, Arnold et al. (2018) demonstrated that the RAN abilities of children with NF1 were not significantly different from controls. In addition, the implication of the visuo-attentional mechanisms involved in the DEM horizontal vs. vertical subtests change during reading development. According to the perceptual learning account, the visual training associated with the regularity of reading eye movements improves word recognition within a restricted horizontal region close to the fovea, and mostly within the regions of the retina that fall on the
side of the reading direction (Dehaene et al., 2005). It is therefore likely that the HT index becomes more strongly associated with the reading performance as children learn to read and take the left-to-right directionality of visual scanning into account (Vernet et al., 2021). We argue that the greater prevalence of failure on the HTaj index in the NF1RD group would be related to a deficit in the visual-attention processes specifically involved in reading and more precisely to the left-to-right directionality of visual scanning.

For the first time, we have shown that the reading deficits encountered by NF1 children (without ADHD or intellectual disability) occurred together with visual-processing deficits and that poor NF1 readers in our sample appeared to be at increased risk for visual-processing impairments compared to peers. This suggests that visuo-attentional weaknesses contribute to NF1 reading disabilities. These results corroborated previous studies demonstrating the involvement of visual and/or visu-motor skills and their potential underlying causes of learning difficulties in some children (Bellocchi et al., 2017; Franceschini et al., 2012). Although it has been suggested that a phonological impairment may be an inherent feature of NF1 (Chaix et al., 2017), our data demonstrated that visual-processing deficits emerge as another clinical marker of reading impairment.

Given the high prevalence of reading impairments in NF1 and the associated academic difficulties (Coudé et al., 2006), it is crucial to be able to intervene as early as possible in the children developmental trajectory. Currently, neuropsychological assessments are not systematic in NF1, visual-processing deficits are not always explored and reading difficulties can be detected with a significant delay. Another goal of the present study was thus to evaluate the effectiveness of the DEM-test in the understanding and screening for reading disabilities in this population. A test’s precision of classification can be evaluated based on the ROC curve, considering the AUC (Choi, 1998). Our results showed that the HT index was able to dissociate NF1 children with and without RD, with an AUC considered as good (comprised between 0.70
and 0.80). These results extended previous works showing that HT is a good indicator discriminating school-aged children with and without RD (Hopkins et al., 2019; Larter et al., 2004; Vernet et al., 2021). This index can also be a reliable indicator in clinical practice for the screening of reading disabilities in NF1 children. We want to draw attention to the fact that the DEM-test is not intended to be used for diagnostic purposes (Facchin, 2021), but rather considered as a first-line tool requiring only 5 minutes. For clinicians, this tool could improve the diagnostic assessment to better understand the difficulties observed in NF1 and thus improve the management of children. The systematic implementation of visual-processing skills screening for all children with NF1 and early intervention (if appropriate), may result in a greater success rate of remediation, and decrease the likelihood of later literacy difficulties. Moreover, this test has been shown to be effective, in kindergarteners without specific genetic disease, for early identification of children at risk of reading deficits later in their education (Vernet et al., 2021), thus suggesting that the DEM-test can as well be useful at a time when tests directly involving reading cannot be used.

The main limitation of the present study was the small sample size of the two NF1 groups, due to both the rare occurrence of this disease and the strict inclusion criteria necessary to limit potential biases that could influence our results. For instance, although nearly 40% of children with NF1 satisfied the diagnostic criteria for ADHD (Hyman et al., 2005), children with NF1+ADHD were not included in our study. The aim was to ensure that the mechanism studied accurately reflects visual difficulties associated with a reading disorder without a possible influence of inattentive and/or impulsive behaviour. From a clinical point of view, the use of the DEM-test must be conducted keeping in mind that attentional disorders such as those observed in ADHD may interfere with this task (Coulter & Shallo-Hoffman, 2001). Notwithstanding, given the large proportion of ADHD in this population, further investigations are needed to evaluate how ADHD in NF1 children would influence the use of the DEM-test.
One way could be to examine this question from a comorbidity perspective, by comparing groups of children with NF1 only vs. NF1+ADHD. Nevertheless, we feel the results of this study have important contributions to make regarding the nature of reading disabilities in school-age children with NF1. Another limitation concerns the choice of the DEM-test to assess visual-processing skills in NF1 children. Regarding this issue, two important points should be noted: (1) even though the DEM-test does not assess basic components of eye-movement control, studies on the DEM-test all agreed that visuo-perceptual and visuo-attentional processes play a major role in this task (Ayton et al., 2009; Facchin, 2021; Hopkins et al., 2019; Moiroud et al., 2018; Raghuram et al., 2018; Tanke et al., 2021), and (2) the ultimate aim of our study was to provide an easy and quick first-line tool for clinicians to screen for reading disabilities in neurodevelopmental disorders. Future longitudinal research is needed, following NF1 children from a young age through their school years, to assess the potential of these processes in predicting NF1 reading acquisition proficiency as early as possible and be able to identify NF1 pre-schoolers at risk of reading difficulties. The underlying idea is to provide NF1 children with the best possible support in their learning and thus limit school failure and its psychological and emotional repercussions.

5. CONCLUSION

In conclusion, the study highlights the high incidence of visual-processing difficulties occurring in NF1 children without ADHD or intellectual disability. The results also support the role of these visual-processing deficits in contributing to reading disabilities encountered in nearly half of the children with NF1. The relationship identified between reading- and visual-processing abilities emphasizes the need for a thorough assessment of the skills underlying reading in NF1 children (including visuo-attentional abilities), so that children can receive
appropriate, targeted intervention. In that respect, our study demonstrated the usefulness of a rapid and easy clinical tool, in addition to the classical tests assessing linguistic processes: poor NF1 readers in our study having more severe visual-processing impairments compared to peers. As we have excluded from this study, a large subgroup of children with NF1 (NF1 with ADHD), future studies should replicate our results with this population, before to extend the conclusions to the entire NF1 population. There is a real challenge to raise awareness among professionals regarding the importance of visual-processing skills in NF1 children.

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The authors have no conflicts of interest to disclose.
REFERENCES


620  Neuroscience, 8(August). https://doi.org/10.3389/fnhum.2014.00386

621  Portnoy, A., & Gilaie-Dotan, S. (2020). Oculomotor-related measures but not distance visual
622  acuity are predictive of reading ability in first graders.
623  https://doi.org/https://doi.org/10.1101/2020.03.09.983197

625  https://doi.org/10.1001/jamaophthalmol.2018.2797


Table 1. Characteristics and DEM-test performances of NF1 and control groups.

<table>
<thead>
<tr>
<th>Measures</th>
<th>NF1</th>
<th>TD</th>
<th>p</th>
<th>Effect size (r_b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>42</td>
<td>42</td>
<td>1.000</td>
<td>-</td>
</tr>
<tr>
<td>Age (years; months)</td>
<td>9;9</td>
<td>10;0</td>
<td>0.354</td>
<td>0.118</td>
</tr>
<tr>
<td>Sex ratio (F/M)</td>
<td>20/22</td>
<td>26/16</td>
<td>0.188</td>
<td>-</td>
</tr>
<tr>
<td>Handedness (R/L)</td>
<td>42/0</td>
<td>42/0</td>
<td>1.000</td>
<td>-</td>
</tr>
<tr>
<td>DEM-test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT (Z-score)</td>
<td>-0.850</td>
<td>-0.306</td>
<td>0.108</td>
<td>0.204</td>
</tr>
<tr>
<td>HTaj (Z-score)</td>
<td>-2.092</td>
<td>-0.431</td>
<td>&lt;.001</td>
<td>0.447</td>
</tr>
<tr>
<td>HE (Z-score)</td>
<td>-1.275</td>
<td>-0.080</td>
<td>0.003</td>
<td>0.373</td>
</tr>
</tbody>
</table>

Notes. NF1: neurofibromatosis type 1; TD: typically developing children; M: male; F: female; R: right-handed; L: left-handed; VT: Vertical Time; HTaj: adjusted Horizontal Time; HE: Horizontal Errors; Significant effects appear in bold.
Table 2. DEM-test and reading performance between NF1RD and NF1noRD children.

<table>
<thead>
<tr>
<th>Measures</th>
<th>NF1RD</th>
<th></th>
<th>NF1noRD</th>
<th></th>
<th>p</th>
<th>Effect size (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alouette test</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading accuracy (Z-score)</td>
<td>-3.47</td>
<td>2.07</td>
<td>-0.31</td>
<td>0.66</td>
<td>&lt; .001</td>
<td>-0.892</td>
</tr>
<tr>
<td>Reading fluency (Z-score)</td>
<td>-1.52</td>
<td>0.56</td>
<td>-0.16</td>
<td>0.90</td>
<td>&lt; .001</td>
<td>-0.866</td>
</tr>
<tr>
<td><strong>DEM-test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT (Z-score)</td>
<td>-1.25</td>
<td>1.62</td>
<td>-0.58</td>
<td>1.24</td>
<td>.228</td>
<td>-0.224</td>
</tr>
<tr>
<td>HTaj (Z-score)</td>
<td>-3.13</td>
<td>2.64</td>
<td>-1.39</td>
<td>2.42</td>
<td>.007</td>
<td>-0.501</td>
</tr>
<tr>
<td>HE (Z-score)</td>
<td>-1.95</td>
<td>2.32</td>
<td>-0.81</td>
<td>1.65</td>
<td>.159</td>
<td>-0.261</td>
</tr>
</tbody>
</table>

Notes. NF1RD: Children with neurofibromatosis type 1 with reading disorders; NF1noRD: Children with neurofibromatosis type 1 without reading disorders; VT: Vertical Time; HTaj: adjusted Horizontal Time; HE: Horizontal Errors; Significant effects appear in bold.
Figure 1. Data distribution for all the DEM-test indices across NF1 children with or without a reading deficit and TD children.

Notes. NF1RD: NF1 children with reading disorders; NF1noRD: NF1 children without reading disorders; TD: Typically developing children; VT: Vertical Time; HTaj: adjusted Horizontal Time; HE: Horizontal Errors.
Figure 2. ROC curve analysis for each DEM-test index between NF1 children with and without reading deficits.

Notes. AUC: Area Under the Curve; VT: Vertical Time; HTaj: adjusted Horizontal Time; HE: Horizontal Errors.

* p<.05; ** p<.01; *** p<.001