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

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1 **Visual-processing deficits in children with Neurofibromatosis type 1:**

2 **A clinical marker of reading difficulties**

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ABSTRACT

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

47

48 **KEYWORDS.** Neurofibromatosis type 1; Reading; Visual information processing; DEM-test;
49 Screening tool

50

51 **ABBREVIATIONS.**

| | | |
|----|---------|---|
| 52 | DEM | Developmental Eye Movement |
| 53 | HE | Horizontal Errors |
| 54 | HTaj | Adjusted Horizontal Time |
| 55 | JLO | Judgment of Line Orientation |
| 56 | NF1 | Neurofibromatosis type 1 |
| 57 | NF1RD | Children with neurofibromatosis type 1 with reading disabilities |
| 58 | NF1noRD | Children with neurofibromatosis type 1 without reading disabilities |
| 59 | RAN | Rapid Automatic Naming |
| 60 | TD | Typically developing children |
| 61 | VT | Vertical Time |

62 1. INTRODUCTION

63 Neurofibromatosis type 1 (NF1) is a neurogenetic disorder, affecting approximately 1
64 in 2500 to 3000 births (Evans et al., 2010). The diagnosis of NF1 is based on the clinical criteria
65 stated in the recently revised NIH Consensus Conference Statement (Legius et al., 2021; NIH
66 National Institutes of Health, 1988), including cutaneous, ophthalmologic, orthopedic and
67 neurologic manifestations (Baudou & Chaix, 2020). In addition to physical manifestations,
68 children with NF1 frequently experience deficits in a range of cognitive domains including
69 visual-perception, executive functioning, motor skills, attention, and language (Hyman et al.,
70 2005). Academic underachievement is also common in NF1 (Coudé et al., 2006), and reading
71 disabilities are highly prevalent (between 30 % to 80 %; Arnold et al., 2020; Chaix et al., 2017;
72 Hyman et al., 2005; Orraca-Castillo et al., 2014; Watt et al., 2008). Up to 67% of school-aged
73 children with NF1 demonstrate single-word reading impairments (Watt et al., 2008) and rate of
74 reading comprehension difficulties is also high (Cutting & Levine, 2010). Despite a wide
75 variability, the frequency of reading difficulties in NF1 appears to be considerably higher than
76 in the general population, where 5 to 10% of children suffer from developmental dyslexia
77 (Inserm, 2007). Owing to this high incidence and the lifelong negative implications of reading
78 problems (Sanagoo et al., 2019), it is crucial to clarify their causes in NF1.

79 First of all, several studies have shown that phonological impairments are an integrant
80 feature of the neurocognitive profile of the NF1 child (Arnold et al., 2018; Chaix et al., 2017;
81 Cutting & Levine, 2010). Other linguistic processes appear to be deficient in NF1 such as
82 phonological memory, rapid automatic naming (RAN) and letter-sound knowledge (Arnold et
83 al., 2018; Cutting & Levine, 2010). Interestingly, all of these linguistic skills are known to be
84 fundamental prerequisites for learning to read, and children with difficulties in these
85 prerequisite skills are at serious risk of later reading difficulties and developmental reading
86 disabilities (Carroll et al., 2016).

87 Although linguistic deficits probably constitute the most common cause of reading
88 difficulties in NF1, there is evidence suggesting that the visual processing is also impaired in
89 NF1. Some studies have suggested a delay in the maturation of low-level vision processes, with
90 significant alterations of the visual magnocellular pathway (Ribeiro et al., 2012; Violante et al.,
91 2012), visual spatial dysfunction (Baudou et al., 2020; Hyman et al., 2005; Schrimsher et al.,
92 2003), and abnormalities in saccadic programming (Lasker et al., 2003, but see Krab et al.,
93 2011).

94 Reading is a visual task, highly constrained by the anatomical and functional limits of
95 our visual system (for a review, see Leibnitz et al., 2017). The high visual acuity that is needed
96 to rapidly identify words is spatially limited and the anatomo-functional constraints of the eye
97 requires saccades and fixations to shift the foveal area to the optimal fixation location of the
98 word in order to extract the relevant information (Ducrot et al., 2013). Visual attention is also
99 needed to optimize the information extraction through foveal and parafoveal vision, and to
100 initiate saccadic programming (Leibnitz et al., 2017). As a result, basic aspects of oculomotor
101 control, the ability to orient the focus of attention as well as the ability to control its size are
102 assumed to play a crucial role in the development of reading skills. Their inadequate
103 development might also cause reading disabilities. In that sense, several studies with typically
104 developing readers and dyslexics demonstrated a strong relationship between reading ability
105 and visual processing (for a review, see Grainger et al., 2016). An increasing number of studies
106 shows today that visual-attention deficits may predict future reading difficulties in
107 kindergarteners (Bellocchi et al., 2017; Franceschini et al., 2012; Vernet et al., 2021) and are
108 present in several neurodevelopmental disorders (e.g., Bellocchi et al., 2019). Interestingly, at
109 the biological level, such deficits have been related to the distinction between two different
110 visual pathways, the magnocellular (10% of retinal ganglion cells) and parvocellular pathways
111 (90% of retinal ganglion cells) (see, for example, Chase, 1996; Stein, 2019). The magnocellular

112 system (M-system) is assumed to be involved in low-spatial- and high-temporal-frequency
113 processing, whereas the parvocellular system (P-system) is most sensitive to high-spatial and
114 low-temporal frequencies. Slaghuis et al. (1996) have referred to the P-sustained-system as the
115 determinant of *what* a visual stimulus is, and the M-transient-system of *where* a visual stimulus
116 is. P-system has also been associated with foveal vision, and M-system with parafoveal and
117 peripheral vision. Note that the M-system has been shown to play an important role in the
118 reading process. Stein (2003, 2019) considered that this visual system plays a dominant role in
119 the bottom-up direction of attention. Because the M-system of poor readers is weaker, the speed
120 with which they can disengage and reengage attention on words is reduced compared with good
121 readers. Stein (2003) also considered that the M-system stabilises eye movements. In the case
122 of a deficient system, the retinal images of letters and words are not stationary, and they move
123 on the retina. As a result, disruption of the M-system would impact visuo-perceptual processes
124 (i.e., global processing strategy), visuo-attentional mechanisms (i.e., atypical attentional
125 deployment), and oculomotor control, which are all implied in reading (Franceschini et al.,
126 2012, 2017).

127 Whereas both phonology and visual processes contribute to reading, very few studies
128 have been conducted to examine visual-processing skills related to word recognition in NF1
129 children. This paper is therefore focused upon those processes and on their contribution to
130 reading behaviour and reading problems in the context of this neurogenetic disorder. Using the
131 Judgment of Line Orientation test (JLO), Cutting and Levine (2010) showed a significant
132 association between word reading outcomes and the visuo-spatial processes assessed in NF1
133 children with reading disabilities only. Moreover, compared to the two control groups (without
134 NF1), NF1 children with a reading disorder showed significantly lower visuo-spatial
135 performance. These results provide the first support for the implication of visual-perceptual
136 processes in the reading difficulties frequently observed in this genetic disease (but see Arnold

137 et al., 2020). Note that there is some evidence suggesting that the visuo-spatial deficits observed
138 in the JLO test might be linked to executive functions, making this test unsuitable for assessing
139 the role of visual skills in reading failure (Van Eylen et al., 2017).

140

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

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

162 Raghuram et al., 2018). Moreover, there is a large consensus on the relationship between the
163 DEM-test and reading abilities, both in school-age children (Ayton et al., 2009; Larter et al.,
164 2004) and in children with learning difficulties (Bellocchi et al., 2021; Moiroud et al., 2018;
165 Raghuram et al., 2018).

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

176

177 **2. METHOD**

178 **2.1. Participants**

179 Forty-two children with NF1 took part in the present study. The participants were
180 enrolled in the DYSTAC-MAP cohort (ANR-13-APPR-0010). Participation in this research
181 was proposed to all children who met the clinical criteria for the diagnosis of NF1 in accordance
182 with the Neurofibromatosis Conference statement (National Institutes of Health, 1988). NF1
183 children were compared with forty-two typically developing children (TD). The demographic
184 characteristics of the two groups are summarized in Table 1. Children were 8–12 years old and
185 attended school from 2nd to 6th grade. They were all right-handed and French native speakers,
186 with normal or corrected-to-normal vision. There were no significant differences between the

187 groups for age and sex ratio. As part of this research, all children underwent a complete medical
188 and neuropsychological assessment. Children with Attention Deficit Hyperactivity Disorder
189 (i.e., more than 6 symptoms of Hyperactivity and/or Inattention in a parent rating on the DSM-
190 5 diagnosis criteria), intellectual disability (i.e., WISC total IQ at least below to 70 or/and
191 standard score below to 7 at the Similarities and/or Picture Concepts subtests), neurological or
192 psychiatric disorder (e.g., epilepsy, brain tumor, or autism) or hearing deficits were not
193 included. Note that although Attention Deficit Hyperactivity Disorder is common in NF1, we
194 wanted to make sure that the difficulties we could observe were really due to a deficit in the
195 domain of interest and not the consequence of attentional biases during the tasks. For the control
196 group, the reading level was controlled to include only children with typical reading
197 development, i.e. scores at least superior to -0.5 SDs on the Alouette-test (Lefavrais, 2005) and
198 the ODEDYS-2 test ("*Outil de dépistage des dyslexies*"; Jacquier-Roux et al., 2002).

199 This research was conducted in accordance with the Declaration of Helsinki (World
200 Health Organisation, 2008) and approved by the French Ethics Committee Review Board
201 (2014-A01239-38 and 2014-A01960-47). Written parental and child consent was obtained for
202 each participation in the study.

203 **2.2. Material**

204 *2.2.1. DEM-test*

205 The DEM-test (Garzia et al., 1990) consists in horizontal and vertical digit naming tasks,
206 printed on four different sheets of paper: (1) a pre-test (a horizontal line of ten digits) to ensure
207 that the child is familiar with all the digits presented in the following tasks, (2) two vertical tests
208 (Test A and B; each composed of two vertical columns of twenty digits), and (3) one horizontal
209 test that simulates a reading situation (Test C; sixteen lines of five irregularly separated digits).
210 Children were asked to read aloud the digits, as quickly and as accurately as possible. The
211 DEM-test provides four main indices: (1) the vertical time in seconds (i.e., VT) corresponding

212 to the sum of the times spent on naming the vertically organized digits of Test A and B; (2) the
213 adjusted horizontal time in seconds (i.e., HTaj), which corresponds to the time spent on naming
214 the horizontally organized digits of test C, adjusted according to the number of omission and
215 addition errors (Test C time x [80 / (80 – number of omission errors + number of addition
216 errors)]); (3) the total number of errors (i.e., HE) made on test C corresponding to the sum of
217 the 4 possible types of errors: addition errors, omission errors, substitution errors and
218 transposition errors; and finally (4) the ratio between the VT and HTaj indices (i.e., Ratio)
219 calculated from the following formula: $R = HT/VT$. Note that the validity of the ratio index has
220 been strongly questioned in the literature (Ayton et al., 2009; Webber et al., 2011), so we chose
221 to exclude this index from our analyses. Furthermore, as the total number of errors was almost
222 zero in the vertical organization test and in accordance with the test manual, it was not used for
223 scoring purpose.

224 2.2.2. *Alouette test*

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

230 2.3. Procedure

231 Participants were recruited at the Timone University Hospital in Marseille, at the
232 Hospital of Aix-en-Provence, and at the Purpan University Hospital in Toulouse. Each child
233 was seen individually at the hospital and at the university laboratories. An assessment session,
234 lasting approximately 1 hour and a half was conducted at the hospital to check for the inclusion
235 criteria, including the assessment of reading level (5 min). The DEM-test was also proposed

236 during this session and lasted approximately 10 minutes per child. Children were in a quiet
237 room in which the brightness was adapted according to the different tasks.

238 **2.4. Data analysis**

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

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

253

254 **3. RESULTS**

255 **3.1. Impact of NF1 on DEM-test performances**

256 *3.1.1. DEM-test performances*

257 Mean scores on the DEM-test for both groups of children are provided in Table 1. The
258 NF1 group had significantly poorer performances than the control group for HTaj and HE with

259 moderate effect sizes for these two indices, whereas no group differences were found for the
260 VT index.

261

262

[Insert Table 1 about here]

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3.1.2. Prevalence of visual-processing deficits in NF1 children

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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 $ps > .05$).

273

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

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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.

277

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

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281

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

282 accuracy and HTaj ($r(40) = .37, p = .016$) and HE ($r(40) = .37, p = .016$). The reading fluency
283 was also correlated with the same DEM-test indices: HTaj ($r(40) = .58, p < .001$), and HE ($r(40)$
284 $= .32, p = .041$). Thus, the longer the adjusted horizontal time is and the more errors there are
285 at the DEM-test, the worst the reading is.

286 3.2.2. DEM-test performance and visual-processing deficit prevalence between 287 NF1RD and NF1noRD

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

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

298 The data distributions of the HT and HE indices confirmed the amplitude of the
299 difficulties encountered by the NF1 children with reading deficit in this task. Except for the VT
300 index, the distributions of the DEM-test indices, shown in Figure 1, behaved differently
301 between NF1RD and NF1noRD children, with a deviant density peak for the first ones. More
302 specifically, the density peak was flatter and left lateralized towards negative values in the
303 NF1RD group (HTaj: kurtosis = 1.30; HE: kurtosis = -0.95) compared to NF1noRD children
304 (HTaj: kurtosis = 10.55; HE: kurtosis = 6.00). Note that for the HTaj (and the HE to a lesser
305 extent), the NF1noRD children performance distribution mirrored that of the control group
306 (TD). The statistical analyses confirmed that HTaj performances were significantly different

307 between the two groups ($U(40) = 106.00, p = .007$) with poorer performances for NF1RD
308 children. The VT and HE indices were not significantly different between the groups.

309

310

[Insert Figure 1 about here]

311

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

320

321

[Insert Table 2 about here]

322

323 3.2.3. Sensitivity and specificity of the DEM-test in NF1

324 In this section, ROC curve analyses were conducted on the DEM-test indices to
325 determine whether this tool was able to differentiate NF1 children with and without reading
326 disabilities. The area under the ROC curve (AUC) provides an index of the test's usefulness.
327 An AUC greater than 0.9 is considered excellent, between 0.8 - 0.9 is very good, between 0.7 -
328 0.8 is good, between 0.6 - 0.7 is average, and an AUC less than 0.6 is poor (Choi, 1998). Note

329 that the ROC curve analyses were not used for the NF1 diagnosis purposes, but for the screening
330 of reading deficit in NF1 children.

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

337 -----
338 [Insert Figure 2 about here]
339 -----

340

341 **4. DISCUSSION**

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

346 Although data is already available for the DEM-test in several neurodevelopmental
347 disorders (Bellocchi et al., 2021; Bilbao & Piñero, 2020; Moiroud et al., 2018; Raghuram et al.,
348 2018), no research, to the best of our knowledge, has specifically questioned its usefulness in
349 the assessment of visual-processing skills in NF1 children. The results of the present study
350 corroborated our predictions: visual-processing difficulties are highly present among NF1
351 children, with nearly 70% of NF1 children in our study presenting difficulties on this test. NF1
352 children exhibited poorer performance on DEM-test parameters and had more frequent visual-

353 processing deficits than TD children, especially on the HTaj index. In addition to deviant
354 performance on the HTaj index, NF1 children also made many errors, whatever they present
355 RD or not. The nature of these errors is very relevant since most of them are errors of omission
356 resulting mainly from skipping lines and characters, suggesting immature and/or inaccurate
357 eye-movement control, or visuo-attentional difficulties (Coulter & Shallo-Hoffman, 2001).
358 These results are in line with previous studies which showed delayed maturation of low-level
359 vision processes in children with NF1 (Lasker et al., 2003; Ribeiro et al., 2012; Violante et al.,
360 2012).

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

371 Visual-processing deficits detected here with the DEM-test in our sample of NF1
372 children can have different causes such as orthoptic disorders, poor eye-movement control,
373 visual-attentional impairments, or simply insufficient exposure to written language. But
374 whatever their causes, visual-processing impairments can have major consequences on the
375 likelihood of academic difficulties and more generally on the quality of life for children with
376 NF1 (Coudé et al., 2006), highlighting the need for systematic screening the visual-processing
377 abilities of all NF1 children.

378 As demonstrated above, visual information processing ability, based on measures of the
379 DEM-test in NF1 children, was significantly associated with their reading scores. In this
380 context, the second objective of the study was to determine whether the high prevalence of
381 reading difficulties reported in NF1 could be partly explained by a visual processing deficit.
382 For this purpose, we distinguished, from the reading performance, two subgroups within our
383 sample of NF1 children: NF1 children with (NF1RD) and without (NF1noRD) a reading deficit.
384 The results showed that NF1RD children presented lower performance and a higher proportion
385 of children with performance below -1.5 SD on the HTaj index compared to NF1noRD children.
386 These results were reflected in the atypical distribution of performance in NF1RD children in
387 contrast to NF1noRD children who mirrored the performance of TD children. The differences
388 between the two groups on the HTaj index were consistent with previous studies comparing
389 children with and without reading difficulties (Bellocchi et al., 2021; Larter et al., 2004;
390 Moiroud et al., 2018; Raghuram et al., 2018). Furthermore, our finding that the HTaj index was
391 most strongly associated with the NF1 reading performance was in line with the results of Ayton
392 et al. (2009) who reported the strongest correlations between the DEM horizontal subtest and
393 reading test scores. Note that in our study, VT and HE indices did not differentiate the 2 groups,
394 neither in average performance nor in deficit frequency (see Vernet et al., 2021 for different
395 results with pre-readers). A possible explanation for this finding is that the processes
396 specifically involved in the VT index are not impaired to a greater extent in NF1 children. In
397 this sense, Arnold et al. (2018) demonstrated that the RAN abilities of children with NF1 were
398 not significantly different from controls. In addition, the implication of the visuo-attentional
399 mechanisms involved in the DEM horizontal vs. vertical subtests change during reading
400 development. According to the perceptual learning account, the visual training associated with
401 the regularity of reading eye movements improves word recognition within a restricted
402 horizontal region close to the fovea, and mostly within the regions of the retina that fall on the

403 side of the reading direction (Dehaene et al., 2005). It is therefore likely that the HT index
404 becomes more strongly associated with the reading performance as children learn to read and
405 take the left-to-right directionality of visual scanning into account (Vernet et al., 2021). We
406 argue that the greater prevalence of failure on the HTaj index in the NF1RD group would be
407 related to a deficit in the visual-attention processes specifically involved in reading and more
408 precisely to the left-to-right directionality of visual scanning.

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

419 Given the high prevalence of reading impairments in NF1 and the associated academic
420 difficulties (Coudé et al., 2006), it is crucial to be able to intervene as early as possible in the
421 children developmental trajectory. Currently, neuropsychological assessments are not
422 systematic in NF1, visual-processing deficits are not always explored and reading difficulties
423 can be detected with a significant delay. Another goal of the present study was thus to evaluate
424 the effectiveness of the DEM-test in the understanding and screening for reading disabilities in
425 this population. A test's precision of classification can be evaluated based on the ROC curve,
426 considering the AUC (Choi, 1998). Our results showed that the HT index was able to dissociate
427 NF1 children with and without RD, with an AUC considered as good (comprised between 0.70

428 and 0.80). These results extended previous works showing that HT is a good indicator
429 discriminating school-aged children with and without RD (Hopkins et al., 2019; Larter et al.,
430 2004; Vernet et al., 2021). This index can also be a reliable indicator in clinical practice for the
431 screening of reading disabilities in NF1 children. We want to draw attention to the fact that the
432 DEM-test is not intended to be used for diagnostic purposes (Facchin, 2021), but rather
433 considered as a first-line tool requiring only 5 minutes. For clinicians, this tool could improve
434 the diagnostic assessment to better understand the difficulties observed in NF1 and thus
435 improve the management of children. The systematic implementation of visual-processing
436 skills screening for all children with NF1 and early intervention (if appropriate), may result in
437 a greater success rate of remediation, and decrease the likelihood of later literacy difficulties.
438 Moreover, this test has been shown to be effective, in kindergarteners without specific genetic
439 disease, for early identification of children at risk of reading deficits later in their education
440 (Vernet et al., 2021), thus suggesting that the DEM-test can as well be useful at a time when
441 tests directly involving reading cannot be used.

442 The main limitation of the present study was the small sample size of the two NF1
443 groups, due to both the rare occurrence of this disease and the strict inclusion criteria necessary
444 to limit potential biases that could influence our results. For instance, although nearly 40% of
445 children with NF1 satisfied the diagnostic criteria for ADHD (Hyman et al., 2005), children
446 with NF1+ADHD were not included in our study. The aim was to ensure that the mechanism
447 studied accurately reflects visual difficulties associated with a reading disorder without a
448 possible influence of inattentive and/or impulsive behaviour. From a clinical point of view, the
449 use of the DEM-test must be conducted keeping in mind that attentional disorders such as those
450 observed in ADHD may interfere with this task (Coulter & Shallo-Hoffman, 2001).
451 Notwithstanding, given the large proportion of ADHD in this population, further investigations
452 are needed to evaluate how ADHD in NF1 children would influence the use of the DEM-test.

453 One way could be to examine this question from a comorbidity perspective, by comparing
454 groups of children with NF1 only vs. NF1+ADHD. Nevertheless, we feel the results of this
455 study have important contributions to make regarding the nature of reading disabilities in
456 school-age children with NF1. Another limitation concerns the choice of the DEM-test to assess
457 visual-processing skills in NF1 children. Regarding this issue, two important points should be
458 noted: (1) even though the DEM-test does not assess basic components of eye-movement
459 control, studies on the DEM-test all agreed that visuo-perceptual and visuo-attentional
460 processes play a major role in this task (Ayton et al., 2009; Facchin, 2021; Hopkins et al., 2019;
461 Moiroud et al., 2018; Raghuram et al., 2018; Tanke et al., 2021), and (2) the ultimate aim of
462 our study was to provide an easy and quick first-line tool for clinicians to screen for reading
463 disabilities in neurodevelopmental disorders. Future longitudinal research is needed, following
464 NF1 children from a young age through their school years, to assess the potential of these
465 processes in predicting NF1 reading acquisition proficiency as early as possible and be able to
466 identify NF1 pre-schoolers at risk of reading difficulties. The underlying idea is to provide NF1
467 children with the best possible support in their learning and thus limit school failure and its
468 psychological and emotional repercussions.

469

470 **5. CONCLUSION**

471 In conclusion, the study highlights the high incidence of visual-processing difficulties
472 occurring in NF1 children without ADHD or intellectual disability. The results also support the
473 role of these visual-processing deficits in contributing to reading disabilities encountered in
474 nearly half of the children with NF1. The relationship identified between reading- and visual-
475 processing abilities emphasizes the need for a thorough assessment of the skills underlying
476 reading in NF1 children (including visuo-attentional abilities), so that children can receive

477 appropriate, targeted intervention. In that respect, our study demonstrated the usefulness of a
478 rapid and easy clinical tool, in addition to the classical tests assessing linguistic processes: poor
479 NF1 readers in our study having more severe visual-processing impairments compared to peers.
480 As we have excluded from this study, a large subgroup of children with NF1 (NF1 with ADHD),
481 future studies should replicate our results with this population, before to extend the conclusions
482 to the entire NF1 population. There is a real challenge to raise awareness among professionals
483 regarding the importance of visual-processing skills in NF1 children.

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485

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499 DECLARATION OF COMPETING INTEREST

500 The authors have no conflicts of interest to disclose.

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

| Measures | NF1 | | TD | | p | Effect size (r_b) |
|---------------------|--------|-------|--------|-------|------------------|-----------------------|
| | Mean | SD | Mean | SD | | |
| <i>Demographics</i> | | | | | | |
| N | 42 | - | 42 | - | 1.000 | - |
| Age (years; months) | 9;9 | 1;5 | 10;0 | 1;1 | 0.354 | 0.118 |
| Sex ratio (F/M) | 20/22 | - | 26/16 | - | 0.188 | - |
| Handedness (R/L) | 42/0 | - | 42/0 | - | 1.000 | - |
| <i>DEM-test</i> | | | | | | |
| VT (Z-score) | -0.850 | 1.425 | -0.306 | 1.149 | 0.108 | 0.204 |
| HTaj (Z-score) | -2.092 | 2.624 | -0.431 | 1.148 | < .001 | 0.447 |
| HE (Z-score) | -1.275 | 2.005 | -0.080 | 0.998 | 0.003 | 0.373 |

666 *Notes.* NF1: neurofibromatosis type 1; TD: typically developing children; M: male; F: female;
667 R: right-handed; L: left-handed; VT: Vertical Time; HTaj: adjusted Horizontal Time; HE:
668 Horizontal Errors; Significant effects appear in bold.

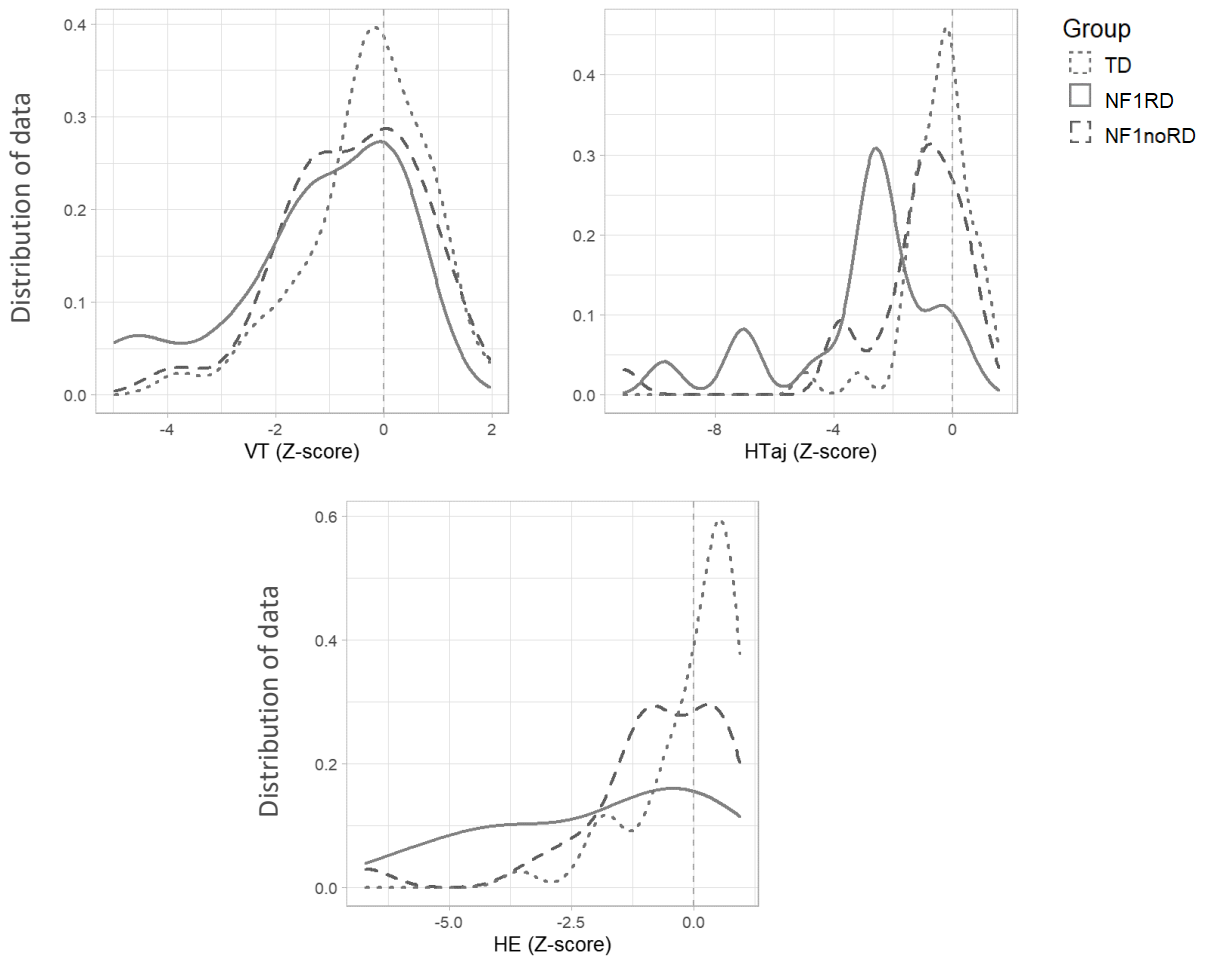
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670 Table 2. DEM-test and reading performance between NF1RD and NF1noRD children.

| Measures | NF1RD | | NF1noRD | | p | Effect size (r_b) |
|-------------------------------|-------|------|---------|------|----------------|-----------------------|
| | Mean | SD | Mean | SD | | |
| <i>Alouette test</i> | | | | | | |
| Reading accuracy (Z-score) | -3.47 | 2.07 | -0.31 | 0.66 | < . 001 | -0.892 |
| Reading fluency (Z-score) | -1.52 | 0.56 | -0.16 | 0.90 | < . 001 | -0.866 |
| <i>DEM-test</i> | | | | | | |
| VT (Z-score) | -1.25 | 1.62 | -0.58 | 1.24 | .228 | -0.224 |
| HTaj (Z-score) | -3.13 | 2.64 | -1.39 | 2.42 | .007 | -0.501 |
| HE (Z-score) | -1.95 | 2.32 | -0.81 | 1.65 | .159 | -0.261 |

671 *Notes.* NF1RD: Children with neurofibromatosis type 1 with reading disorders;
 672 NF1noRD: Children with neurofibromatosis type 1 without reading disorders; VT: Vertical
 673 Time; HTaj: adjusted Horizontal Time; HE: Horizontal Errors; Significant effects appear in
 674 bold.

675

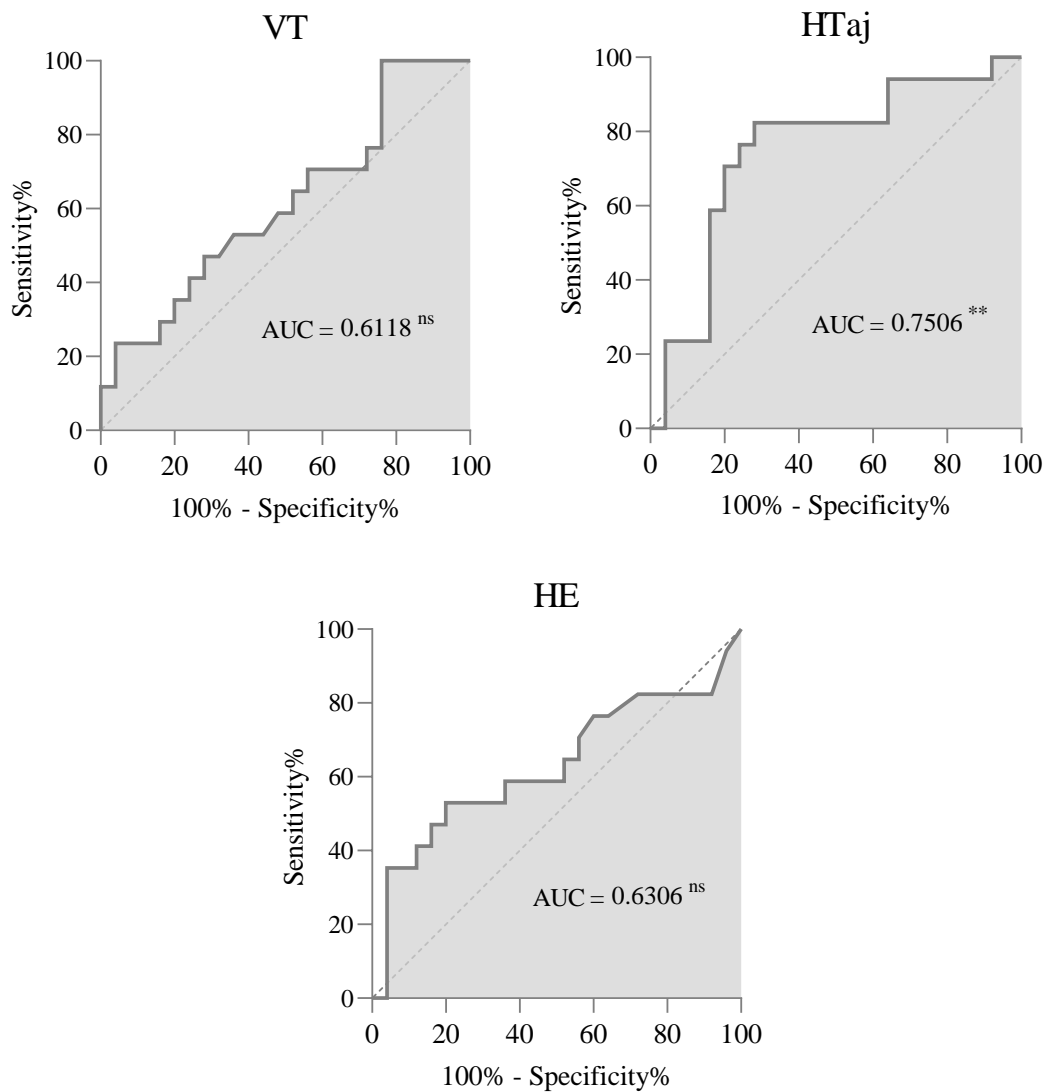


676

677 Figure 1. Data distribution for all the DEM-test indices across NF1 children
 678 with or without a reading deficit and TD children.

679 *Notes.* NF1RD: NF1 children with reading disorders; NF1noRD: NF1 children without reading
 680 disorders; TD: Typically developing children; VT: Vertical Time; HTaj: adjusted Horizontal
 681 Time; HE: Horizontal Errors.

682



683
 684 Figure 2. ROC curve analysis for each DEM-test index between NF1 children
 685 with and without reading deficits.

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

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