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# **Eye movements and postural control in children; biomarkers of neurodevelopmental disorders: evidences toward new forms of therapeutic intervention?**

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## **Disclosure statement**

The authors declare no competing interests exist.

**Abstract:**

Autism (ASD), attention deficit/hyperactive disorders (ADHD) and dyslexia (DYS) are defined in DSM-5 as neurodevelopment disorders (NDDs) and several times they are comorbid disorders. Several studies reported poor oculomotor performance and postural instability in this children population confirming the cerebellar deficit hypothesis in subjects with NDDs. In this paper we summarized oculomotor and posture findings collected during the last decade in order to find out biomarkers for children with NDDs; at our knowledge, such issue has never been studied; the present study was designed to fill this gap. Oculomotor parameters (the number of express and anticipate saccades, the number of saccades during fixations and the number of catch-up saccades during pursuits) and the postural instability index measured in two viewing conditions (eyes open and eyes closed, on stable and unstable platform) were compared in four groups of 40 children. One way ANOVA reported significant difference in oculomotor parameters between the three groups of children with NDDs with respect to typically developing (TD) children group: the number of anticipatory saccades were found significantly ( $p < 0.001$ ) higher in ADHD ( $32.4 \pm 5.9$ ) and DYS ( $34.7 \pm 5.3$ ) group; the occurrence of express saccades and catch-up saccades were significantly ( $p < 0.001$ ) more frequent in ASD group ( $26.8 \pm 1.8$  and  $55.3 \pm 4.2$ , respectively); unwanted saccades occurred more in ADHD ( $8.5 \pm 0.7$ ) and DYS ( $7.3 \pm 1.1$ ) and in the fixation with distractor task they were significantly ( $p < 0.001$ ) higher in ADHD group ( $36.3 \pm 3.9$ ). In addition, the mixed repeated ANOVA on the postural instability index (measured under eyes open and eyes closed condition, on stable and unstable platform) reported a significant difference ( $p < 0.001$ ) of such parameter in children with NDDs (ASD:  $2.8 \pm 0.6$ ; DYS:  $2.6 \pm 0.5$ ; ADHD:  $2.7 \pm 0.5$ , respectively) with respect to the TD group ( $1.9 \pm 0.3$ ); however, postural instability index failed to distinguish between the different neurodevelopmental deficits. Such abnormal oculomotor and postural performances are

in line with poor cerebellar activity; oculomotor measures only could be used as phenotype biomarkers for children with NDDs. Finally, these results could be useful to clinicians in order to develop specific oculomotor and/or postural training types based on visual fixations and body stability exercises for reinforcing motor abilities in children with NDDs.

**Keywords:** eye movements; postural control; children; neurodevelopment disorders; frontal eye field; cerebellum

### **Highlights**

1. Children with neurodevelopmental disorders reported poor eye movements as well as postural performance with respect to children with typically development.
2. Such motor abnormalities could be due to a deficit in cerebellar activity.
3. Oculomotor measures only allow to distinguish between hyperactivity, autism spectrum disorder and dyslexia; some of these parameters can be used as phenotype biomarkers for such disorders.

## **Introduction**

Neurodevelopmental disorders are disabilities related with the function of the brain; their occurrence is variable between countries but recently it is grown up most likely due to the better diagnosis and training of clinicians who care for children and adolescents. Recently the America's Children and the Environment (ACE) reported that in children from 5 to 17 years old examined between 1997-2021 in the world, autism spectrum disorders (ASD) was found in 3.1% of children, attention deficit/hyperactive disorders (ADHD) in 10.8% of children and dyslexia (DYS) in 7.9% of children tested. It is also well know that single NDD is quite rare and that frequently child presents comorbidity that is an overlap between such different disorders (Francés et al. 2022). The hypothesis that a cerebellum deficit could be at the origin of DYS, firstly suggested by Nicolson et al. (2001) was expanded also on the other types of NDDs such as ASD and ADHD (see review Brughhage et al. 2018). Indeed, Stoodley (2016) reviewed cerebellar dysfunction related to developmental disorder such as ASD, ADHD, and DYS and she reported evidences for which specific regions of the cerebellum were affected in these developmental disorders and that distinct cerebro-cerebellar networks could lead to behavioral characteristics of ASD, ADHD and DYS. In other words, specific deficits in these circuits maybe responsible of social and cognitive disabilities reported in children with these disorders.

The key role of the cerebellum in motor control is also well known; a recent review of Shemesh and Zee (2019) pointed out specific structures of the cerebellum responsible in the triggering of different types of eye movements and several neuroimaging studies (see meta-analysis from Dijkstra et al. 2020) reported that cerebellum is involved in postural activity. Several studies have been done showing poor performance in both eye movements and postural abilities in children with NDDs.

For instance, in the domain of eye movements, inhibitory and executive function play a major role for a correct performance of saccades; when a visual stimulus appears, a saccade has to be prepared and specific cortical and subcortical structures need to be activated (Leigh and Zee 2015); indeed in order to trigger and process a saccade, visual attention should be oriented toward the new stimulus, the fixation has to be disengaged and new parameters has to be calculated in order to bring the object of interest into the fovea (see Findlay and Walker 1999). From the retina, the visual input goes to the primary visual cortex and then via the dorsal stream to parietal and frontal cortex (McDowell et al. 2008 for review). Several other regions are involved in this network as cerebellum, striatum, thalamus and superior colliculus before transmitting the motor command to the extra-ocular muscles (Robinson, 2022). The frontal eye field is also well known to be important for controlling the saccades and their suppression (Dash et al. 2020); indeed, studies on patients with frontal lesions reported the occurrence of undated saccades suggesting a deficit in the fixation control system (Takahashi et al. 2022). In laboratory various paradigms can be used to explore eye movements performance in children with NDDs allowing to assess the basic oculomotor behavior as well as their abilities in executive functions and inhibitory control. Firstly Rommelse et al. (2008) reported distinct oculomotor deficits in children with ASD, ADHD and DYS; several other studies have been conducted by researchers group showing poor oculomotor performances in such pathologies reporting distinct oculomotor behavior in these children and difficulties in executive functions (here the list of some of these studies that is not at all exhaustive ASD: Kelly, Walker & Norbury, 2013; Mosconi, Kay, D’Cruz, Seidenfeld, Guter et al., 2009; a review of O’Hearn et al. 2008; a more recent review Johnson et al. 2016; Kowarski et al. 2018; Caldani et al. 2023a,b; ADHD: Hanisch et al., 2006; Mahone et al., 2009; Cui et al. 2020; Fernandez-Ruiz et al. 2020; Chamorro et al. 2020; Caldani et al. 2020a, b; DYS (note that

studies leading with eye movements during reading has been excluded: Tiadi et al. 2016; Lukasova et al. 2016; Caldani et al. 2020; Jafarlou et al. 2021; the review of Macambira et al. 2022). Note also that more recent meta-analyses on oculomotor recordings in ADHD subjects (Chamorro et al., 2022; Maron et al., 2021) advanced the hypothesis that instability in visual fixation and difficulties to initiate saccades could be promising biomarkers for ADHD population.

To summarize, oculomotor deficits in children with NDDs are as follows: *i)* children with ASD showed an elevated occurrence of errors during saccades and inhibition functions related to disturbances in the frontal cortical structures; *ii)* children with ADHD reported inability to suppress unwanted saccades and to maintain a good fixation most likely due to poor functioning of the dorsolateral prefrontal cortex in relation with cerebellum and thalamus network; *iii)* Finally, literature on non-linguistic eye movement recordings in DYS showed atypical pattern during pursuits with several catch-up saccades and unstable fixations suggesting immaturity of cortical areas responsible of eye movement's performance. Furthermore, several imaging studies advanced the hypothesis that visuo-motor impairment reported in children with NDDs could be due to cerebellar dysfunctions as already mentioned (D'Mello and Stoodley, 2015; review of Stoodley, 2016).

Postural control has been also strongly explored in children with NDDs (Lim et al. 2017; Gouleme et al. 2017; Bucci et al. 2017; Bucci et al. 2018; Caldani et al. 2019; Meachon et al. 2023). We reviewed studies shown motor impairment in children with ASD and children with ADHD (Bruchhage et al. 2018); sensorimotor deficits could be at the origin of poor fine and gross motor skills, postural instability and deficient body coordination reported in these children. We assumed that these children have difficulties in integrating the specific sensorial inputs (such as visual, vestibular and somatosensory) essential to achieve body balance. Con-

sisting studies reported also body instability in children with dyslexia; and the broaden use of platforms to measure postural abilities allowed researchers to examine postural control under different conditions in dyslexia population (Moe-Nilssen et al. 2003; Stoodley et al. 2005; Pozzo et al. 2006; Gouleme et al. 2017; Barela et al. 2022; Wu et al. 2022). A recent study from Zoccante et al. (2021) compared postural stability in different conditions in ASD, and ADHD children and they found that children with ASD were significantly more severely impaired than ADHD children. The authors suggested that posture difficulties in NDDs children could be a useful biomarker for children with an atypical neurodevelopment.

In conclusion, postural control in children with NDDs has been observed to be poor and they showed difficulties to compensate body instabilities occurring in the natural environment. The cerebro-cerebellar network seems to play an important role in motor control in line with the hypothesis of Nicolson et al. (2001) in dyslexia but also with the findings recently reported in the review of Cundari et al. (2023).

While several are the studies exploring eye movements or postural capabilities in children with ASD, ADHD or dyslexia; indeed, studies in which such visual/motor abilities are tested at the same time and with the same experiment design in these three types of neurodevelopmental disorders are lacking. This study would like to do that by compared oculomotor parameters (the number of anticipatory and express saccades during a visually guided horizontal saccades paradigm, the number of catch-up saccades made during horizontal pursuits and the number of saccades made during a fixation task) and the postural sways (the postural instability index) in typically developing children and in children with NDDs (ASD, ADHD, dyslexia). Based on literature above described in NDDs children inhibitory visual mechanisms and motor compensation of natural environmental are lacking, consequently we make the hypothesis that such visual/motor capabilities could be tested in a large population of chil-



dren with NDDs (examined in the same hospital center) in order to explore potential biomarkers of these deficits. An eye-tracker was used to stimulate and record eye movements and a platform was used to measure postural sways of participants respectively with eyes open and eyes closed on stable and unstable support. Note that several clinicians and physiotherapists use these types of instruments during their medical activities. Our objective was to try to find out eventual specific biomarkers for these diseases that could be used by clinicians for a rapid and objective screening of neurodevelopmental disorders (in details, autism spectrum disorder, hyperactivity with attention deficit and dyslexia). Indeed, our final goal is to develop tools for an easy detection, rehabilitation and follow up of neurodevelopmental disorders.

## **Materials and Methods**

### *Subjects*

Four groups of 40 children, matched for sex, age, and IQ, participated in the study (Table 1): group 1 included TD children, groups 2 to 4 included respectively children with ASD, children with ADHD and DYS children.

Inclusion criteria for children of the groups 2, 3 and 4 were: children with IQ in normal range; and they should have the diagnosis of ASD, ADHD and DYS based on DSM-5 criteria (see below). All children from groups 2, 3 and 4 were enrolled at the Child and Adolescent Psychopathology Department, Robert Debré Hospital (Paris, France) and their diagnosis was based on DSM-5 criteria (APA, 2013) and done by a group of clinicians' specialist in NDDs. Note that this department is specialized in the diagnostic evaluation and therapeutic orientation of children with developmental and/or behavioral disorders.

**Table 1.** Clinical characteristics (mean, SD) of the four groups of children tested.

	<b>Group 1 Children with TD n = 40</b>	<b>Group 2 Children with ASD N = 40</b>	<b>Group 3 Children with ADHD N = 40</b>	<b>Group 4 Children with dyslexia n = 40</b>
Age (years)	9.8 ± 0.2	10 ± 0.5	10.2 ± 0.4	9.9 ± 0.3
Boys/girls	28/12	26/14	29/11	28/12
<b>ADHD-RS total score:</b>				
	4.5 ± 3.3	4.8 ± 2.1	36.8 ± 4.2	5.7 ± 3.8
<b>L2MA standard deviation from the mean:</b>				
<i>Oral Language</i>				2.7
<i>Written Language</i>				2.8
<i>Memory</i>				2.5
<b>Autism Diagnostic Interview-Revised (ADI-R) scores:</b>				
<i>Social Reciprocal Interaction</i>		19.5 ± 3.3		
<i>Communication</i>		13.3 ± 2.3		
<i>Stereotyped Patterns of Behaviors</i>		5.0 ± 2.3		
<b>Autism Diagnostic Observation Schedule (ADOS) scores:</b>				
<i>Social Reciprocal Interaction</i>		8.5 ± 3.2		
<i>Communication</i>		4.1 ± 1.8		
<b>Wechsler scale (WISC-IV) scores:</b>				
<i>Verbal Comprehension</i>		97 ± 5	96 ± 6	95 ± 7
<i>Perceptual reasoning</i>		90 ± 4	92 ± 5	96 ± 6
<i>Working memory</i>		93 ± 5	94 ± 4	97 ± 4
<i>Processing Speed</i>		95 ± 6	96 ± 5	98 ± 7
<i>Similarities</i>	10 ± 1			
<i>Matrix reasoning</i>	11 ± 2			

All children had a neurological exam in the normal range and were naïve of psychotropic treatment at inclusion; their mean intelligence quotient (IQ) was in the normal range (between 85 and 115). Psychiatric comorbidities were systematically screened during the interviewing and if present, child was excluded by the study. The diagnosis of ASD was based using the Autism Diagnostic Interview-Revised (ADI-R, Lord et al. 1994) and the Autism Diagnostic Observation Schedule (ADOS, Lord et al. 2000) associated to the clinical expertise. The diagnosis of ADHD was carried out using the Kiddie-SADS-EP (Goldman et al. 1998). ADHD symptom severity was assessed using the parental report of the ADHD Rating Scale (ADHD-RS). For children with dyslexia, the L2MA (Langage Oral Écrit Mémoire Attention) battery by Chevrie-Muller et al. (1997) was used. This battery is largely used by clinicians in France allowing to explore the oral and written language capabilities (text comprehension, ability to read words and pseudo-words) and memory capabilities. All children with DYS had a score on the L2MA more than two standard deviations below the normal mean.

Typically developing children (group 1) were sons and daughters of hospital employees. Inclusion criteria were: children with IQ in normal range; children with any neurological or psychiatric abnormalities, no history of reading difficulty. The IQ in typically developing children was estimated using two subtests, assessing the verbal and the logic abilities (similarities and matrix reasoning tests, respectively). The normal range for both tests is  $10 \pm 3$  (WISC-IV Sattler & Dumont, 2004). All TD children had normal verbal ( $10 \pm 1$ ) and logic ( $11 \pm 2$ ) capabilities.

Exclusion criteria were: children taking medications; children with co-morbidity (i.e. hyperactivity); visual impairment, orthopedic disorder or surgeries.

All these inclusion and exclusion criteria have been already used in previous research studies of our group.

The investigation followed the principles of the Declaration of Helsinki and the protocol was approved by our Institutional Human Experimentation Committee (Comité de Protection des Personnes CPP Île-de-France I). Written consent was obtained from the children's parents after they were explained the experimental procedure.

### *Oculomotor task*

Eye movements were recorded using the Mobil EBT, an eye tracker with infrared cameras that captures the movements of each eye independently with a recording frequency of 300 Hz. The precision of the system is  $0.25^\circ$ .

In a dark room, child was seated in front of a flat screen with the head stabilized by a headrest supporting both the forehead and chin. Viewing was binocular and distance of 60 cm. Calibration was done at the beginning of eye movement's recordings. During the calibration procedure, child was asked to fixate a grid of 13 points (diameter 0.5 deg) mapping the screen. Each calibration point required a fixation of 250 ms to be validated. A polynomial function with five parameters was used to fit the calibration data and to determine the visual angles. After the calibration procedure, the visual tasks were presented to the child. Duration of the each task was kept short (lasting a couple of minutes) allowing an accurate evaluation of eye movement recordings (Bucci et al. 2013). Four types of oculomotor tasks were run: 1) visually-guided saccades, 2) simple fixation, 3) fixation with distractor, 4) pursuits. These tasks were elicited randomly; briefly the procedure is explained below (see also Caldani et al.

2023).

*Visually guided saccades:* the stimulus was a red filled circle subtending a visual angle of  $0.5^\circ$ , positioned at the center of the screen for a variable delay comprised between 2000 and 3500 ms. After this period the central target was switched off and a target on the left or on the right side of the screen (at  $20^\circ$ ) was simultaneously switched on for 1000 ms. The central fixation target then reappeared, signaling the beginning of the next trial. Each child performed two blocks of 30 visually-guided saccades randomly presented to the left and to the right side. In the *simple fixation task*, the child was asked to fix the gaze on the target appearing on the monitor in front of him/her during 30 sec. In the *fixation with distractor* task the child was asked to fix the central target and to inhibit saccades toward the distractors (a white smile target of  $0.5^\circ$ ) stimulating a saccade from  $5$  to  $15^\circ$  on the monitor appearing randomly for a duration from 500 to 2000 ms.

The *pursuit task* requires child to follow a slowly moving visual target. The stimulus was moving horizontally from the right to left and reversing direction at a constant velocity ( $15^\circ/s$ ) on the screen. A total of nine trials (right-left/right-left) were run and included in the analysis. Child was instructed to keep their eyes on the target. Each oculomotor task was run twice. Before recording, child was tested in each of these four oculomotor task to ensure that the instructions are well understood.

#### *Postural task*

To evaluate postural ability the medical device Multitest Equilibre ([www.framiral.fr](http://www.framiral.fr)) was used (Gouleme et al. 2015; Bucci et al. 2017). The surface of the center of pressure displacement (CoP) has been measured in two postural conditions (stable and unstable platform) and under two different viewing conditions: eyes open (EO), fixating a target ( $0.5^\circ$ ) at a distance of 250

cm (target projected on a screen in front of the subjects at their eye level), eyes closed (EC). The unstable platform conditions are dynamic sway-referenced conditions in which the platform could move in all axes, in a free-float manner, in reference to the participants' sway directions. In the referenced dynamic sway conditions, the platform itself moves in the same direction as the pressure exerted by the subject's feet. As a result, this sway condition dramatically decreases the ability of the plantar sole's exteroceptors to discriminate against the pressure and shear exerted by the subject on the ground and thereby increased the demand on the participant's visual and vestibular systems to maintain the balance. The displacement of the Center of Pressure (CoP) was sampled at 40 Hz and digitized with 16-bit precision. Postural recording was performed in a dark room while child stood on the platform; child was instructed to stay as still as possible with their arms along the side of the body and the feet position standardized on footprints (distance and angle between heels: 11 cm and 30°, respectively). Each postural condition was recorded during 30 s with 15 s of rest to avoid possible tiredness effects.

### *Data analysis*

For visually guided saccades we measured the percentage of anticipatory and express saccades, that are saccades made with shorter latency (< 120 ms). Anticipatory saccades are saccades made with latencies shorter than 80 ms; while express saccades are saccades with latency between 80 and 120 ms; this is consistent with other developmental oculomotor studies (Fisher et al 1997, Munoz et al. 1998).

Detection of catch-up saccades during pursuit was based on criteria of minimum amplitude (2 deg) and velocity (30/s). Catch-up saccades were saccades in the direction of the target, allowing a reduction of the position error. The number of these saccades was counted.

For the simple fixation and fixation with distractor task, we counted the number of saccades  $> 2^\circ$  given that microsaccades are normally smaller than  $2^\circ$  (for details, Tiadi et al. 2016). Postural control performance was evaluated measuring the postural instability index (PII) (see Bucci et al. 2017). The PII is calculated as follows:  $PII = \frac{\sum_x \sum_y PI(F1, F2, F3)}{CT(F1, F2, F3)}$ , where  $x$  is in mediolateral and  $y$  is in anteroposterior direction, PI and CT are spectral power index and cancelling time, respectively for different frequency bands (F1: low frequency between 0.05–0.5 Hz; F2: medium frequency, between 0.5–1.5 Hz and F3: frequency higher than 1.5 Hz, see Bernard-Demanze et al. 2014). The PI is calculated as the decimal logarithm and allows us to know the postural oscillation and the energy cost involved to maintain postural control. CT is the time, in seconds, during which the spectral power index of the body sway was almost canceled by the posture control mechanisms. Thus, use PII is a relevant choice to report postural performance in children (Gouleme et al. 2018). Note that this parameter is a global postural index used during routine test by clinicians and allowing an easy and quick evaluation of the child's postural instability. The larger is the PII, the greater is the instability.

### *Statistical analysis*

Normality (Shapiro-Wilk test) and homogeneity of variance (Levene test) were tested before running ANOVA. We performed a one way ANOVA with the four groups of children (ASD, ADHD, DYS and TD) as between-subject factor and clinical findings and oculomotor variables (percentage of anticipatory and express saccades, the number of catch-up saccades and the number of saccade made in the fixation simple and with distractor task) as within-subject factor. A mixed repeated ANOVA was run for comparing the postural instability index between the two postural conditions (2 levels: stable and unstable platform) in the two visual

conditions (2 levels: EO and EC) as within-subject factor and between the four groups of children as between-subject factor. Data were processed using JASP software version 0.16.4.0 (a free statistical analysis program developed by the University of Amsterdam). Post-hoc comparisons were made with the Bonferroni test. A difference was considered significant when the p-value is less than 0.05.

## Results

Table 2 shows oculomotor parameters measured in the four groups of children tested. For the percentage of anticipatory saccades one-way ANOVA reported a significant group effect ( $F_{(156,3)} = 41.2$ ,  $p < 0.001$ ,  $\eta^2 = 0.41$ ); Bonferroni test showed that anticipatory saccades occurred significantly more frequent in the group of children with ADHD than in the TD group ( $p < 0.001$ , Cohen's  $d = 2.3$ ) and in children with ASD ( $p < 0.001$ , Cohen's  $d = 1.8$ ); also anticipatory saccades occurred significantly more frequent in the DYS group with respect to TD ( $p < 0.001$ , Cohen's  $d = 2.5$ ) and ASD groups ( $p < 0.001$ , Cohen's  $d = 2.0$ ). For the occurrence of express saccades, one-way ANOVA reported a significant group effect ( $F_{(156,3)} = 18.2$ ,  $p < 0.001$ ,  $\eta^2 = 0.25$ ). Bonferroni test showed that the occurrence of express saccades of the ASD group was significantly greater with respect to the other three groups (all  $p < 0.001$ , all Cohen's  $d > 1.3$ ).

**Table 2.** Mean and standard deviation of the percentage of anticipatory and express saccades made during visually guided saccades, the number of catch-up saccades made during pursuits and the number of saccades occurred during simple fixation and fixation with distractor in the four groups of children tested.



	<b>TD</b>	<b>ASD</b>	<b>ADHD</b>	<b>DYS</b>
<b>Percentage of anticipatory saccades</b>	4.0 ± 1.3	7.7 ± 0.8	32.4 ± 5.9	34.7 ± 5.3
<b>Percentage of express saccades</b>	5.7 ± 1.2	26.8 ± 1.8	4.1 ± 2.6	4.9 ± 1.1
<b>Number of catch-up saccades</b>	22.2 ± 1.9	55.3 ± 4.2	39.8 ± 3.1	45 ± 4.4
<b>Number of saccades in the simple fixation task</b>	2.2 ± 0.3	2.9 ± 0.4	8.5 ± 0.7	7.3 ± 1.1
<b>Number of saccades in the fixation with distractor task</b>	3.6 ± 0.4	4.8 ± 0.5	36.3 ± 3.9	6.7 ± 1.3

The number of catch-up saccades one-way ANOVA reported a significant group effect ( $F_{(156,3)} = 16.36$ ,  $p < 0.001$ ,  $\eta^2 = 0.24$ ): the TD group made significantly less catch-up saccades with respect to those measured in the other groups (all  $p < 0.001$ , all Cohen's  $d > 1.2$ ). Also the number of catch-up saccades made by the ASD group was significantly higher to those reported in the ADHD group ( $p < 0.02$ , Cohen's  $d = 1.1$ ).

For the number of saccades made during simple fixation and fixation with distractor task by the four groups of children tested, one-way ANOVA showed a significant group effect ( $F_{(156,3)} = 21.79$ ,  $p < 0.001$ ,  $\eta^2 = 0.21$  and  $F_{(176,3)} = 33.36$ ,  $p < 0.001$ ,  $\eta^2 = 0.45$ , respectively in the simple fixation and fixation with distractor task). Bonferroni showed that the number of saccades made during simple fixation task by ADHD group and DYS group was significantly higher to those made by the TD and ASD group (both  $p < 0.001$ , Cohen's  $d = 1.0$  and  $1.2$ , respectively); also the number of saccades made during fixation with distractor task by the ADHD group

was significantly greater compared with the other three groups (all  $p < 0.001$ , all Cohen's  $d > 1.1$ ).

Finally, Table 3 reports the postural instability index (PII) with eyes open and eyes closed condition on stable and unstable platform in the four groups of children tested. ANOVA showed a significant group effect ( $F_{(156,3)} = 10.29$ ,  $p < 0.001$ ,  $\eta^2 = 0.13$ ). Bonferroni showed that the PII of the TD group was significantly smaller with respect to those measured in the other three groups (all  $p < 0.01$ , Cohen's  $d = 1.0$ ,  $1.2$  and  $1.2$ , respectively for the ASD, ADHD and DYS group). There was also a significant postural and visual conditions effect ( $F_{(156,1)} = 85.5$ ,  $p < 0.001$ ,  $\eta^2 = 0.12$  and  $F_{(156,1)} = 36.09$ ,  $p < 0.001$ ,  $\eta^2 = 0.38$ , respectively): the PII was greater in the unstable postural condition and eyes closed condition, respectively. Note that it is well known that PII is larger when vision can not be used to control postural sway and also on unstable platform (when somatosensory inputs are not available).

**Table 3:** Postural instability index (PII) in eyes open (EO) and eyes closed (EC) condition on stable and unstable platform of the four groups of children tested.

	Stable platform		Unstable platform	
	EO	EC	EO	EC
<b>TD</b>	1.6 ± 0.1	1.7 ± 0.1	1.9 ± 0.1	2.3 ± 0.1
<b>ASD</b>	2.1 ± 0.1	2.6 ± 0.2	2.9 ± 0.1	3.5 ± 0.1
<b>ADHD</b>	2.1 ± 0.1	2.5 ± 0.1	3.0 ± 0.1	3.3 ± 0.1
<b>DYS</b>	2.0 ± 0.1	2.3 ± 0.1	2.8 ± 0.1	3.1 ± 0.1

## Discussion

The oculomotor and postural findings observed in TD children group were similar to those reported previously by other studies already mentioned in the Introduction. Next we will focus on the discussion of findings observed in children with NDDs and their difference with respect to TD children.

Several studies already mentioned in the Introduction reported deficits at the level of both visual as well as motor functions in ASD, ADHD and DYS, but quite rare, at our knowledge, are the studies in which these deficits are compared at the same time in children with these neurodevelopmental disorders. As previously described few meta-analyses/reviews showed visual and/or motor deficits in children with NDDs (see Johnson et al. 2016; Macambira et al. 2022; Bruchhage et al. 2018; Zoccante et al. 2021), but this is the first study in which eye movements and postural capabilities are recored in a large number of children with NDDs.

The goal of the present study was to try to point out oculomotor and/or postural biomarkers of children with NDDs in order to help clinicians to assess these disabilities using objective tool. Indeed, we well known that such neurodevelopment disabilities are diagnosed by using several tests and questionnaires exploring behavioral observation depending on the feeling of child, and symptoms reported by parents and teachers.

Table 4 summarizes the oculomotor findings reported here: i) children with dyslexia and ADHD had an abnormal occurrence of anticipatory saccades; ii) children with ASD showed an high number of express saccades; iii) the pursuit task allows to distinguish between children with ASD and children with ADHD; indeed children with ASD made several catch-up saccades during pursuits with respect to children with ADHD; iv) the difficulty to fixate a target and avoid unwanted saccades is more difficult for children with ADHD and children with dyslexia; interestingly, the fixation with distractor task could be allow to distinguish children with ADHD with respect to other NDDs.

**Table 4.** Summary of oculomotor findings could be used as biomarkers for each type of NNDs (ADHD, ASD and DYS).

	<b>ADHD</b>	<b>ASD</b>	<b>DYS</b>
<b>Visually guided saccades task</b>	Anticipatory saccades	Express saccade	Anticipatory saccades
<b>Pursuit task</b>		Catch-up saccades	
<b>Simple Fixation task</b>	Unwanted saccades		Unwanted saccades
<b>Fixation with distractor task</b>	Unwanted saccades		

Similar findings have been observed also by other researchers examining eye movement's abnormalities in children with one of these disorders. Indeed, in a recent meta-analysis Maron et al. (2021) reported fixation abnormalities and inhibition deficits in relation the several problems associated with ADHD such as poor attention capabilities, instable concentration etc. Saccades with shorter latencies have been reported also in children with ASD (Kovarski et al. 2018) and Takarae et al. (2014) showed poor pursuit performance in ASD. Finally, Biscaldi et al. (1998), and Bednarek et al. (2006) showed abnormal shorter saccades latency in children with dyslexia.

Note that all oculomotor tests reported here requires a correct control of the inhibitory mechanism including attentional network (Leigh & Zee, 2015); these activities are under control of cortical regions as the frontal and inferior frontal cortex and the pre-supplementary motor area as responsible of showed by Wessel and Aron (2017). Several studies have reported also a cortical network in relation with the cerebellum for adaptive mechanisms of saccades (Guillaume et al. 2018, Metais et al. 2022). Recently, Kaufman et al. (2023), testing stroke patients

confirmed the concept that cognitive functions such as visuospatial attention and inhibition capabilities used in everyday life activities are together controlled by several cortical regions in line with the recent ‘multiple-demand’ network model (Assem et al. 2020). In other words, these authors defended the idea that cognitive functions could share similar fields not only behavioral but also neuroanatomical. The present study reported that cortical network controlling cognitive performances is deficient in children with NDDs, and it highlighted a specific deficiency for each of these neurodevelopmental disorders allowing to classify precise and distinct oculomotor biomarkers for these children. Based on these findings we could assume that a simple oculomotor test could improve the examination of children with NDDs; several eye trackers are already commercially available and their use is simplified for clinicians and psychomotor therapists.

About the findings on postural instability, the results reported a significant larger instability in all three groups of children with NDDs with respect to TD children; however the PII measured in the different visual and postural conditions did not allow to discriminate between ASD, ADHD and dyslexia. We could assume that for all these children compensatory mechanisms working for adapting body balance are deficient and cannot be useful in the phenotyping of these disorders. Finally, these results confirm previous works showing worst postural control, when sensorial inputs are not anymore available (see review of Peterka, 2018) regardless children examined; indeed, for all children groups tested, postural instability was more important when vision was significantly greater in EC condition and on unstable platform in line with previous reports from other groups (Lim et al. 2017; Meachon et al. 2023) and ours (Bucci et al. 2017; Gouleme et al. 2018). Note, however that in the present study we measured the PII only, consequently other postural measures and/or other types of analysis, for instance

machine learning analysis, could allow to distinguish a different postural behavior for these different types of NDDs. Further studies on such issue will be useful.

As already mentioned in the Introduction such oculomotor as well as postural deficiencies confirm the poor cerebellar activity in children with NDDs in line with already cited studies (Nicolson et al., 2001; D’Mello and Stoodley, 2015; Stoodley, 2016; Bruchhage et al. 2018).

We have to point out that also abnormal cortical structures are involved at the origin of neurodevelopmental disorders as several imaging studies reported (Shi et al. 2013, Williams et al. 2018; Lukito et al. 2020; He et al. 2021); further exploration comparing in the same study different types of NDDs will be necessary to better understand central and cortical network involved in these types of disabilities.

Another important point to be mentioned is that based on such oculomotor and postural biomarkers researchers could develop specific training types for these children. Currently, several groups of researchers (Ramezani et al. 2021; Garcia-Baos et al. 2019; Kadri et al. 2019; Bertoni et al. 2024) and ours (Gouleme et al. 2015; Caldani et al. 2019; Caldani et al. 2020; Caldani et al. 2023) have tested the improvements after visual, attentional and motor rehabilitation in these children, and the results are promising even if further studies on larger number of subjects will be necessary to confirm the results. For instance, video-games or other alternative therapies such as cognitive training has been tested in ADHD children and/or in children with dyslexia (Garcia-Baos et al. 2019; Bertoni et al. 2024); improvement in selective attention has been observed also after a martial art programs (Kadri et al. 2019). Verbal working memory balance training was tested in dyslexic children by Ramezani et al. (2021) and these authors reported an improvement in automatized skills highlighting the role of the cerebellum in such disease. Our group tested several types of training in children with ASD, ADHD or DYS in order to improve both oculomotor/visual capabilities, but also body stabili-

ty. Children with dyslexia (Caldani et al. 2020) and children with ADHD (Caldani et al. 2020; Caldani et al 2023) after a short visual attentional training period (searching tasks for about 10 min) significantly improved their oculomotor performances. Also for children with ASD inhibitory mechanisms were improved after a short cognitive training period (a revised Stroop test, Caldani et al. 2023). Visuo-postural training had also a beneficial effect on children with dyslexia (Gouleme et al. 2015) as well as on children with ASD (Caldani et al. 2020); such improvement could be due to the important implication of cerebellum allowing these children to use all sensory information and to better integrate them. Note, however, that all these studies need to be confirmed by testing a larger number of subjects as well as combining imagine studies in order to further explore the central/cortical network involved in these adaptive mechanics.

Finally, ongoing studies from our group try to train children with NDDs by using dual tasks (postural and visual stimuli at the same time) in order to induce eventual larger benefit from these adaptive responses. We believe that training types need to be developed to place the child in a more natural and comfortable situation; this is an essential point to obtain benefits from rehabilitation. Researchers have to develop outils in which children are in natural 3D space and they can freely move their body (for exemple by using an immersive rehabilitation system) and also can move their head (with an eye tracker able to compensate head movements). These steps constitute the next challenge to improve the care of these children.

## **Conclusion**

The goal of this study was to explore the presence of promising objective oculomotor and postural biomarkers for children with NDDs. The present findings show the presence of significant impairment in both oculomotor as well as postural functions in children with NDDs

with respect to TD children; however, only oculomotor tasks are able to distinguish between ASD, ADHD and DYS. Finally we have to remember that such screening types could be also done early during childhood, leading to a better medical care of these neurodevelopmental disorders. We suggest that such oculomotor measures can be used as phenotype biomarkers for these disorders and that they can be used for rehabilitation activities of these children.

### **Limitations**

In all studies conducted until now, we failed to show any significant correlation between such oculomotor and postural biomarkers and neuropsychological tests done during the screening of children for their diagnostic. This is an important point needs to be further explored in order to obtain objective assessment tools largely used by clinicians and practitioners specialized in NDDs. Finally, other types of analysis on postural measure could be useful in order to find out eventual postural biomarkers, most likely by increasing the number of children tested and the environmental settings of the tests.

**Data availability:** The datasets generated and/or analyzed during the current study are available from the author on reasonable request. The data are not publicly available due to ethical restriction.

**Institutional Review Board Statement:** The investigation adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Human Experimentation Committee of CPP Ile de France I.



**Informed consent Statement:** Written informed consent was obtained from all children involved in the study and the children's parents after the experimental procedure had been explained to them.

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