Delayed oculomotor response associates with optic neuritis in youth with demyelinating disorders

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ARTICLE INFO

Keywords: Demyelinating disorders Optic neuritis Eye-tracking Pupil dynamics

ABSTRACT

Introduction: Impairment in visual and cognitive functions occur in youth with demyelinating disorders such as multiple sclerosis, neuromyelitis optica spectrum disorder, and myelin oligodendrocyte glycoprotein antibody-associated disease. Quantitative behavioral assessment using eye-tracking and pupillometry can provide functional metrics for important prognostic and clinically relevant information at the bedside.

Methods: Children and adolescents diagnosed with demyelinating disorders and healthy, age-matched controls completed an interleaved pro- and anti-saccade task using video-based eye-tracking and underwent spectral-domain optical coherence tomography examination for evaluation of retinal nerve fiber layer and ganglion cell inner plexiform layer thickness. Low-contrast visual acuity and Symbol Digit Modalities Test were performed for visual and cognitive functional assessments. We assessed saccade and pupil parameters including saccade reaction time, direction error rate, pupil response latency, and peak constriction time. Generalized Estimating Equations were used to examine the association of eye-tracking parameters with optic neuritis history, structural metrics, and visual and cognitive scores.

Results: The study included 36 demyelinating disorders patients, aged 8–18 yrs. (75% F; median = 15.22 yrs., SD = 2.8) and 34 age-matched controls (65% F; median = 15.26 yrs., SD = 2.3). Surprisingly, pro- and anti-saccade performance was comparable between patients and controls, whereas pupil control was altered in patients. Oculomotor latency measures were strongly associated with the number of optic neuritis episodes, including saccade reaction time, pupil response latency, and peak constriction time. Peak constriction time was associated with both retinal nerve fiber layer and ganglion cell inner plexiform layer thickness. Pupil response latency and peak constriction time were associated with visual acuity. Pupil velocity for both constriction and dilation was associated with Symbol Digit Modalities Test scores.

Conclusion: The strong associations between oculomotor measures with history of optic neuritis, structural, visual, and cognitive assessments in these cohorts demonstrates that quantitative eye-tracking can be useful for probing demyelinating injury of the brain and optic nerve. Future studies should evaluate their utility in discriminating between demyelinating disorders and tracking disease progression.

Abbreviations: DD, demyelinating disorders; FP, fixation point; GCIPLT, ganglion cell inner plexiform layer thickness; GEE, generalized estimating equations; HC, healthy control; IPAST, interleaved pro- and anti-saccade task; IQR, interquartile range; LCVA, low-contrast visual acuity; MOG, myelin oligodendrocyte glycoprotein; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorder; OCT, optical coherence tomography; ON, optic neuritis; PLR, pupil light reflex; RNFLT, retinal nerve fiber layer thickness; tRNFLT, temporal retinal nerve fiber layer thickness; SDMT, Symbol Digit Modalities Test; SRT, saccade reaction time.

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https://doi.org/10.1016/j.msard.2023.104969
Received 17 May 2023; Received in revised form 20 July 2023; Accepted 28 August 2023
Available online 29 August 2023
1. Introduction

Demyelinating disorders (DD), including multiple sclerosis (MS), myelin oligodendrocyte glycoprotein (MOG)-related disorders and monophasic acquired demyelinating syndromes, occur in children in 0.9/100,000 population (Banwell et al., 2009). Visual and cognition outcomes are of particular relevance to this population: over one-third of children with DD present with injury to the optic nerve in the form of overt optic neuritis (ON) or subclinical abnormalities in the optic nerve. Furthermore, cognitive impairment has been noted in up to one-third of youth with MS (Charvet et al., 2014b) and has been reported in neuromyelitis optica spectrum disorder (NMOSD) (Blanc et al., 2008) and MOG-related disorders (Fabri et al., 2022). Importantly, longitudinal studies have demonstrated progressive worsening of motor, (Renoux et al., 2007) visual, (Beck et al., 2004; Longoni et al., 2022) and cognitive function (Amato et al., 2010; Amato et al., 2014; McKay et al., 2019; Amato et al., 2006) in youth with MS and other DD, and numerous MRI studies have demonstrated altered brain maturation and progressive brain volume loss in youth (Till et al., 2011; Aubert-Broche et al., 2014) and other DD (Longoni et al., 2017). Other MS studies have revealed progressive abnormalities in the anterior visual pathway using optical coherence tomography (OCT) (Longoni et al., 2022; Costello et al., 2006). Finally, structure-function correlations have been found in visual metrics in youth with demyelination, including associations between retinal nerve fiber layer thickness (RNFLT) and visual field changes (Yeh et al., 2014).

Evaluation of functional metrics in pediatric DD may therefore provide important prognostic and clinically relevant information. However, tools used to assess functional abnormalities, such as detailed cognitive testing or visual testing, require extensive time commitment and training to administer. There is a need for a simple, accessible screening tool that can provide clinically relevant functional information in this population. Video-based eye-tracking is a low-cost, non-invasive, easy to train tool that can assess visual and cognitive functions, and provides important prognostic and clinically relevant information. However, there is a need for a simple, accessible screening tool that can assess visual and cognitive functions, and provides important prognostic and clinically relevant information in this population. Video-based eye-tracking is a low-cost, non-invasive, easy to train tool that can measure visual and cognitive functions, and provides important information about the brain regions involved in these functions. Pupil responses are a fundamental aspect of vision and orienting that are under the combined influence of visual, cognitive, and arousal processes, and have long been employed in the assessment of DD. At the bedside, pupil light reflex (PLR) is used to assess the relative afferent pupil defect that results from asymmetrical retinal pathology or optic nerve lesion (Levatin, 1959). Recent advancements in pupil research have expanded the understanding of the neural mechanisms responsible for pupil behavior involving the wider oculomotor system (Wang and Munoz, 2015; Joshi and Gold, 2020; Strauch et al., 2022). There is growing clinical interest in studying pupil responses in relation to cognitive dysfunction in neurological disease (Wang et al., 2016; Perkis et al., 2019; Joyce et al., 2018; Giza et al., 2011; Manohar and Husain, 2015; El Haj et al., 2022; Habibi et al., 2022). In MS and other DD, pupillometry studies have primarily been limited to the context of PLR and visual pathway functioning (Van Diemen et al., 1992; Surakka et al., 2008; Ellis, 1979), while the cognitive aspects of pupil behavior remain largely unexplored.

The goal of the present study is to characterize saccade and pupillometry metrics in youth with pediatric DD in comparison to healthy children. We assess oculomotor behaviors by measuring saccade and pupil responses as subjects perform the interleaved pro-/anti-saccade task (IPAST) (Coe and Munoz, 2017; Yeo et al., 2022; Wang et al., 2015), and further examine their relationship with structural, visual, and cognitive assessments. We hypothesize that a history of demyelinating events is associated with increased latency of saccade and pupil response, and that these measures are associated with structural and functional outcomes in pediatric DD.

2. Materials and methods

2.1. Participants

We recruited children and adolescents presenting with recurrent demyelinating syndromes from the Neuroinflammatory Disorders Program at the Hospital for Sick Children (Toronto, Canada). A comparison cohort of age-matched healthy control subjects (HC) was recruited through advertisement.

MS was defined following the Revised 2017 McDonald criteria (Thompson et al., 2018). NMO was defined following published consensus criteria (Krupp et al., 2012). MOGAD were identified by serum testing performed in a commercial laboratory using live, cell-based methods at Oxford University Hospital (Oxford, UK) prior to 2019 and fixed cell-based assay (Euroimmun, Germany) at London Health Sciences center (London, Ontario) from 2019 onward (Kitley et al., 2014). We defined MOGAD positivity as having one positive test at the time of their initial demyelinating event. Individuals with persistently positive MOG results were identified by serial MOG antibody testing at a minimum of 6 months after initial presentation (median 1.2 years, 0.6 IQR) (Kitley et al., 2014).

The study is in accordance with the Canadian Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans and the Declaration of Helsinki. Institutional Research Ethics Board approval and written informed consent (or assent and informed consent from a parent/legal guardian depending on child’s capacity to consent) from each participant was obtained prior to study initiation. All eligible participants were: (i) between 5 and 18.9 years of age, and (ii) spoke English as a native language or has had at least two years of schooling in English. Additional inclusion criteria for patients were (1) presence of an acute demyelinating event and (2) assessment at greater than 3 months since disease onset or relapse. Participants were excluded if they had a history of: (i) other neurological conditions, (ii) major medical comorbidities, (iii) major psychiatric comorbidity, (iv) learning disability, (v) traumatic brain injury, (vi) alcohol or illicit drug abuse, or (vii) proved or suspected non-demyelinating etiologies of white matter changes (i.e., metabolic disorders, vasculitis, and non-specific MRI abnormalities), (viii) cerebral palsy, and (ix) patients with less than 6 months since last steroid treatment.

Previous ON events were defined clinically (episodes of decreased visual acuity of presumed demyelinating origin lasting longer than 24 h). Confirmation was obtained in all cases using functional or structural metrics including (1) MRI: abnormal T2 signal or gadolinium enhancement on dedicated orbital MRI scans which included fat-saturated T2, T1, and T1 with Gadovist sequences at a minimum OR (2) VEP (obtained following International Society for Clinical Electrophysiology of Vision standards) showing prolongation of the p100 >2 SD from the laboratory’s mean (118 ms) or showing a new interocular p100 latency difference of 10 ms (Mitchell et al., 2016). Relapses were defined as neurological events lasting longer than 24 h presumed to be demyelination in origin accompanied by objective neurological findings and/or MRI abnormalities consistent with demyelination and corresponding to the neurological findings.

2.2. Recording and apparatus

2.2.1. Eye-tracking

A video-based eye-tracker (Eyelink-1000 Plus, SR Research Ltd, ON,
Canada) was used to measure eye position and pupil size with binocular recording of the two eyes at a sampling rate of 500 Hz. Stimulus presentation and data acquisition were controlled by Eyelink Experiment Builder and Eyelink software. Visual stimuli were presented on a 17-inch LCD monitor at a screen resolution of 1280 × 1024 pixels (60 Hz refresh rate), subtending a viewing angle of 32° × 26°, and distance from the eyes to the monitor and camera was set at 58 cm. Eyelink’s standard nine-point array calibration and validation procedure was performed for each participant prior to beginning the task to map gaze position. Participant eye-tracking data had to have an average validation accuracy <1.5° to be considered sufficiently accurate for further analysis.

2.2.2. Optical coherence tomography

All subjects underwent spectral domain OCT using an OCT scanner (Carl Zeiss, Meditac, Cirrus HD-OCT 5000) by a trained technician, conducted the same day of the eye-tracking experiment. Serial optic disc and macula 200 × 200 cube scans were recorded with good centration, quantifying a 6 × 6 × 2 mm volume. OSCAR 1B criteria were followed (Tewarie et al., 2012), with modifications based on the use of the Carl Zeiss, Meditac Cirrus scanner (signal strength >6 considered to be good signal strength) (Hardin et al., 2015). OCT scan quality scores >7 were considered acceptable and with no overt movements as detected by observing blood vessel discontinuity in the OCT face image. RNFLT and ganglion cell inner plexiform layer thickness (GCIIPLT) were assessed by quadrants and by average thickness; the temporal RNFLT (tRNFLT) is reported because it has been shown to demonstrate preferential axonal loss in MS (Birkeldh et al., 2017), and the average of all anatomic quadrants is reported for average GCIIPLT (µm).

2.2.3. Visual assessment

Low-contrast visual acuity (LCVA) was measured using a wall-mounted Pelli-Robson chart presented at 1 m at eye level under standardized illumination conditions. Final LCVA was scored as the lowest contrast sensitivity for which the participant correctly identified at least two of three triplet optotypes.

2.2.4. Neurocognitive assessment

Participants completed the computerized Symbol Digit Modalities Test (SDMT) from the NIH Toolbox for Assessment of Neurological and Behavioral Function (Gershon et al., 2013). As per test guidelines, only
subjects above the age of 8 years completed the assessment (26 HC and 31 DD).

2.3. Experimental paradigm

The experimental paradigm has been described previously (Yep et al., 2022; Coe et al., 2022). Participants were seated in a dark room during the experiment, and completed two blocks of 120 trials, lasting approximately 20 min. Each trial (Fig. 1A) began with the appearance of a white central fixation point (FP, 0.5° width, 44 cd/m²) that lasted for 1000 ms on a black background (0.1 cd/m²). The shape of FP provided the task instruction for the trial (O: Pro-saccade; X: Anti-saccade; matched for luminance and pixel count). Following 1000 ms of fixation, the FP was removed, and the screen remained dark for 200 ms (gap period), after which a peripheral stimulus (0.5° diameter dot; gray, 44 cd/m²) appeared, 10° horizontally to the left or right to the FP position. On pro-saccade trials (PRO), participants were instructed to look to the stimulus location as soon as it appeared. On anti-saccade trials (ANTI), participants were instructed to not look toward the stimulus, but instead look in the opposite direction from the stimulus. Trial condition (PRO, ANTI) and stimulus location (left, right) were pseudo-randomly interleaved with equal frequency.

2.4. Data analysis

2.4.1. Saccadic eye movements

Eye-tracking data processing and analysis were done using MATLAB (Version R2021a; MathWorks Inc., Natwick, MA, USA). Eye position data from the right eye were obtained for analysis. Data cleaning, saccade detection, and latency and velocity calculations were done with our standard data preprocessing pipeline (Coe et al., 2022). Saccade reaction time (SRT) was defined as the time from stimulus appearance to the first saccade away from fixation that exceeded 30°/s. Only trials with saccade latencies >90 ms after stimulus appearance were deemed viable to remove all anticipatory saccades (see Supplementary Methods) (Marino et al., 2012; Dorris and Munoz, 1998). Trials where the first saccade after stimulus appearance were generated in the incorrect direction relative to instruction were marked as direction errors, and were used to calculate direction error rate but not included in subsequent pupil analysis.

2.4.2. Pupillary responses

Pupil data from each eye were analyzed separately. Pupil data from a single eye (right) were reported, and data from both left and right eyes were only used in the GEE analysis (See Supplementary Methods). To investigate the pupil modulation by FP presentation and saccade preparation, and to avoid distortion of pupil measures by eye movements, only the fixation and gap periods were analyzed. To capture the dynamics of the pupil response, measurements for baseline, constriction, and dilation components (Fig. 1B) were calculated using our standard data processing pipeline (Coe et al., 2022). These measurements include: 1) baseline pupil size, 2) pupil response latency, 3) constriction size, 4) peak constriction time, 5) dilation size, and 6) peak dilation velocity (see Supplementary Methods). Because pupil size can be affected by blinks and eye position deviation, trials containing blinks or saccades (>2°) during the fixation period were excluded. After trial exclusion, each subject had to have a minimum of 10 viable PRO and ANTI trials for further analysis. Following these criteria, one HC and one DD subject were excluded, and subsequent analyses were conducted with 34 HC and 36 DD subjects.

2.4.3. Statistical analysis

We performed mixed ANOVAs (2 × 2 ANOVA: between-subjects factor: HC/DD x within-subjects factor: pro-/anti-saccade) for initial statistical analysis. Generalized estimating equations (GEE) were performed using the GEEQBOX toolbox (Ratcliff and Shults, 2008) to examine the relationship between the saccade and pupil parameters to clinical, structural, and functional measures. To control for subject heterogeneity within the groups, subject age, sex, group, and task condition were used as covariates for GEE analysis. Because ON history was previously reported to correlate with structural and functional measures in pediatric demyelination (Yeh et al., 2014), this was included as a covariate in the subsequent GEE analyses for TRNFLT, GCPLT, LCVA, and SDMT scores. P-values < 0.05 were considered significant. Bonferroni correction was applied to adjust for multiple comparisons when appropriate.

3. Results

Subject demographic and clinical characteristics for the 34 HC and 36 DD participants are reported in Table 1.

3.1. Saccadic performance

All saccade responses for HC and DD are summarized in Fig. 2A and B. Among viable trials (as described in Methods 2.4), there were significant within-subject effects of task condition (PRO vs ANTI) in SRT (Fig. 2C. F(1,66) = 424.012, p < 0.001) and direction error rate (Fig. 2D. F(1,66) = 282.648, p < 0.001), but no significant group difference in either SRT (F(1,66) = 0.135, p = 0.715) or direction error rate (F(1,66) = 0.019, p = 0.891).

3.2. Pupillary responses

The pupil responses during IPAST for HC and DD are shown in Fig. 3 depicting the mean relative pupil size corrected to the baseline and the mean pupil velocity, respectively. These responses were consistent with the pupil response profile previously observed in IPAST (Wang et al., 2016; Perkins et al., 2021; Wang et al., 2015). The pupil initially constricted in response to FP appearance, followed by dilation that continued until stimulus appearance. There was a robust “anti-effect” consistent with previous findings, whereby pupil dilation was greater during preparation of anti-saccades compared to pro-saccades (Wang et al., 2015). The main difference between DD and HC was a delay in the DD pupil response that was more pronounced during dilation compared to constriction, as evident in the pupil response velocity (Fig. 3C and D). Additionally, a history of ON appears to differentiate pupil responses in DD (Supplementary Fig. 1).

Because different components of pupil dynamics may be related to different underlying neural processes (Bradley et al., 2008), measures of latency, size, and velocity were extracted from components of the pupil response (Fig. 1; Supplementary Fig. 2). There were significant task effects (PRO vs ANTI) for peak constriction time, peak dilation velocity, and dilation size. DD showed longer peak constriction time and reduced dilation size compared to HC, although these effects did not reach statistical significance.

Table 1

Subject demographics and clinical information of patients with demyelinating disorders and healthy controls.

<table>
<thead>
<tr>
<th></th>
<th>HC (n = 34)</th>
<th>DD (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>22 (65)</td>
<td>27 (75)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>15.26 (2.3)</td>
<td>15.22 (2.8)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>19 (52.8)</td>
<td></td>
</tr>
<tr>
<td>MOGAD</td>
<td>11 (30.6)</td>
<td></td>
</tr>
<tr>
<td>NMOSD</td>
<td>6 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Episodes of ON, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>20 (55.6)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8 (22.2)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8 (22.2)</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 2. Saccadic performance in IPAST. Cumulative distribution of saccade responses for all (A) pro-saccade (PRO) and (B) anti-saccade (ANTI) trials of individual subjects (thin lines) and group median (thick lines) for both healthy controls (HC) and demyelinating disease patients (DD). Responses above the zero horizontal line represent correct saccades and those below represent direction errors. (C) Saccade reaction time and (D) Percentage of direction errors were reported for the viable PRO and ANTI trials. Circles represent individual subject data, and horizontal line represent group median.
3.3. Saccade and pupil associations with structural, visual, and cognitive metrics

GEE (see Methods 2.4.3) was used to examine the relationship between eye-tracking parameters with the characteristics and outcomes of DD. We hypothesized that saccade and pupil measures would be associated with ON history, structural, and functional assessments in pediatric DD. GEE analyses results are displayed in Table 2. The number of ON episodes was significantly associated with multiple latency measures including SRT ($\beta = 15.8, SE = 4.04, p < 0.0005$), pupil response latency ($\beta = 16.96, SE = 4.73, p < 0.0005$), constriction velocity ($\beta = -91.86, SE = 30.66, p < 0.005$), peak constriction time ($\beta = 92.11, SE = 14.79, p < 0.0005$), as well as dilation size ($\beta = -8.39, SE = 3.36, p < 0.05$).

For the two retinal structural measures analyzed, tRNFLT was significantly associated with pupil response latency ($\beta = 0.59, SE = 0.26, p < 0.05$), constriction velocity ($\beta = 2.65, SE = 1.2, p < 0.05$), peak constriction time ($\beta = 3.45, SE = 0.005, p < 0.005$), peak dilation velocity ($\beta = -2.65, SE = 1.2, p < 0.05$), peak constriction time ($\beta = -8.39, SE = 3.36, p < 0.05$), peak constriction time ($\beta = 15.65, SE = 0.37, p < 0.005$), peak constriction time ($\beta = 0.66, SE = 0.005, p < 0.005$), peak constriction time ($\beta = -0.65, SE = 0.005, p < 0.005$), peak constriction time ($\beta = 119.69, SE = 0.06, p < 0.0005$).

![Fig. 3. Group average pupil responses. Group mean pupil responses in (A and B) pupil size and (C and D) pupil velocity for both healthy controls (HC) and demyelinating disease patients (DD) during the fixation period in pro-saccade (PRO) and anti-saccade (ANTI) conditions. Shaded regions denote standard errors.](image_url)

Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of ON episodes</th>
<th>tRNFLT</th>
<th>GCIPIT</th>
<th>LCVA</th>
<th>SDMT z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ estimate</td>
<td>p value</td>
<td>$\beta$ estimate</td>
<td>p value</td>
<td>$\beta$ estimate</td>
</tr>
<tr>
<td>SRT</td>
<td>15.8</td>
<td>&lt;0.0005</td>
<td>0.01</td>
<td>0.98</td>
<td>0.44</td>
</tr>
<tr>
<td>Direction error rate</td>
<td>0.52</td>
<td>0.66</td>
<td>0.07</td>
<td>0.15</td>
<td>0</td>
</tr>
<tr>
<td>Baseline pupil size</td>
<td>16.6</td>
<td>0.82</td>
<td>2.38</td>
<td>0.57</td>
<td>19.46</td>
</tr>
<tr>
<td>Pupil response latency</td>
<td>16.96</td>
<td>&lt;0.0005</td>
<td>0.59</td>
<td>&lt;0.05</td>
<td>1.25</td>
</tr>
<tr>
<td>Constriction velocity</td>
<td>-91.86</td>
<td>&lt;0.0005</td>
<td>-2.65</td>
<td>&lt;0.05</td>
<td>-3.45</td>
</tr>
<tr>
<td>Peak constriction time</td>
<td>92.11</td>
<td>&lt;0.0005</td>
<td>3.61</td>
<td>&lt;0.005</td>
<td>4.6</td>
</tr>
<tr>
<td>Dilation size</td>
<td>-8.39</td>
<td>&lt;0.005</td>
<td>-0.66</td>
<td>&lt;0.05</td>
<td>-0.65</td>
</tr>
<tr>
<td>Peak dilation velocity</td>
<td>15.65</td>
<td>0.37</td>
<td>-0.11</td>
<td>0.92</td>
<td>1</td>
</tr>
</tbody>
</table>
constriction time ($\beta = 3.61$, $SE = 0.65$, $p < 0.0005$), and dilation size ($\beta = -0.66$, $SE = 0.3$, $p < 0.05$); GCIPLt significantly associated with baseline pupil size ($\beta = 19.46$, $SE = 5.88$, $p < 0.005$), pupil response latency ($\beta = 1.25$, $SE = 0.35$, $p < 0.0005$), constriction velocity ($\beta = -3.45$, $SE = 1.31$, $p < 0.05$), peak constriction time ($\beta = 4.6$, $SE = 0.87$, $p < 0.0005$), and dilation size ($\beta = -0.65$, $SE = 0.3$, $p < 0.05$).

Visual assessment as measured with LCVA also showed significant associations with latency and constriction measures, including SRT ($\beta = 31.79$, $SE = 12.19$, $p < 0.05$), baseline pupil size ($\beta = 891.68$, $SE = 280.38$, $p < 0.0005$), pupil response latency ($\beta = 68.29$, $SE = 18.88$, $p < 0.0005$), constriction velocity ($\beta = -188.79$, $SE = 69.13$, $p < 0.05$), and peak constriction time ($\beta = 210.21$, $SE = 41.84$, $p < 0.0005$).

Finally, cognitive assessment by SDMT z-scores significantly associated with SRT ($\beta = -5.27$, $SE = 2.26$, $p < 0.05$), constriction velocity ($\beta = -65.36$, $SE = 14.44$, $p < 0.0005$), dilation size ($\beta = 6.38$, $SE = 2.69$, $p < 0.05$), and dilation velocity ($\beta = 42.44$, $SE = 10.1$, $p < 0.0005$).

4. Discussion

The goal of this study was to characterize saccade and pupil behaviors in pediatric DD using eye-tracking, and further, to evaluate relationships between these metrics and visual and cognitive outcomes. We used the standardized IPAST (Yeh et al., 2022; Wang et al., 2015) to examine saccade and pupil responses in youth with MS, NMOSD, and MOGAD, and investigated the relationship between the eye-tracking measures with ON history, structural measures of RNFLT and GCIPLt, and LCVA and SDMT score as visual and cognitive functional measures with ON history, structural measures of RNFLT and GCIPLt, and investigated the relationship between the eye-tracking measures with history of ON, and that measures of saccade response and pupil dynamics were associated with structural, visual, and cognitive assessments in these cohorts. Together, these results suggest that saccade and pupil behaviors in ocularmotor tasks can be useful for probing demyelinating injury of the brain and optic nerve.

4.1. Eye-tracking behaviors and afferent visual pathway abnormalities in pediatric DD

Both ON history and retinal structural measures assessed with OCT significantly associated with multiple saccade and pupil measures (Table 2). In particular, an increase in the number of previous ON episodes was linked to delayed saccade and pupil response latencies, and after accounting for ON history, increased GCIPLt was associated with larger baseline pupil size. Increased RNFLT and GCIPLt were associated with increased time to reach peak constriction. These results collectively suggest that afferent visual pathway injury in pediatric DD may drive changes in saccade and pupil behaviors, and these ocularmotor parameters may be used to assess the integrity of the afferent visual pathway with disease progression.

Our observations of the structural and visual assessments were consistent with previous reports of degenerative retinal changes after ON episodes in DD. In MS, pediatric and adult patients with ON manifest reduced RNFLT in the affected eyes, (Yeh et al., 2009; Frohman et al., 2006; Fisher et al., 2006) and even in those children with DD who do not have a history of ON, RNFLT and GCIPLt can also be reduced. (Yeh et al., 2014) Likewise, decreased RNFLT and GCIPLt have been demonstrated in NMOSD and MOGAD (Pache et al., 2016; Sotirchos et al., 2020). Furthermore, significant visual dysfunction have long been reported following ON (Beck et al., 2004; Sabadia et al., 2016). In pediatric DD patients, decreased LCVA after ON has been demonstrated (Yeh et al., 2014; Yeh et al., 2009; Waldman et al., 2014; Pineles et al., 2020). Our findings of significant associations of structural and visual assessments with saccade latency, pupil baseline, and constriction response reflects the effect of afferent visual pathway damage from demyelination and ON episodes.

4.2. Eye-tracking behaviors and processing speed in pediatric DD

We assessed cognitive functioning using SDMT (Smith, 1982), an established test for measuring processing speed deficit in research and clinical settings with MS (Benedict et al., 2012; Portaccio et al., 2009; Akbar et al., 2011; Parmenter et al., 2007). The SDMT has been shown to be an effective cognitive screening tool in pediatric MS (Charvet et al., 2014a; Smerbeck et al., 2011). Deficits in processing speed have also been reported in NMOSD (Blanc et al., 2008; Kim et al., 2016; Hyun et al., 2017) and MOGAD (Fabri et al., 2022; Pandit et al., 2017) using SDMT and other assessments. While our data did not show significant differences in processing speed between patients and control subjects, we found associations between higher processing speed and faster pupil constriction and dilation velocities in DD. The dilation component of the IPAST pupil dynamics have been previously associated with top-down preparatory activities for upcoming saccadic response (Wang et al., 2015), and the influence may precede the dilation component thereby affecting constriction as well. Our findings further support the cognitive modulation of the pupil response in IPAST.

While the PLR modulates the amount of light entering our eyes, pupil control is not purely reflexive, as it can be modulated by various cognitive processes including attention, perception, working memory, and more (Wang et al., 2018; Ebiz and Moore, April 21, 2017; Mathôt et al., 2013; Naber and Nakayama, 2013; Van Den Brink et al., 2016; Alnæs et al., 2014). Key structures such as the superior colliculus and locus coeruleus mediate the link between cortical cognitive control circuits and the pupil premotor circuits in the brainstem (Wang and Munoz, 2015; Joshi and Gold, 2020; Strauch et al., 2022). Thus, cognitively mediated pupil responses have been useful in probing different aspects of cognition in healthy subjects and various clinical cohorts (Wang et al., 2016; Perkins et al., 2021; El Haj et al., 2022; Habibi et al., 2022). However, few studies have explored the link between pupil dynamics and processing speed. A recent large population-based cohort study (Coors et al., 2022) found that better processing speed performance was associated with larger pupil diameter during passive fixation, and suggested that this association may be due to the general levels of preparatory neural activity of saccade generation. While we found no significant associations between baseline pupil size during IPAST and processing speed, our findings of the significant association of pupil dilation velocity to processing speed is in agreement with attributing preparatory neural activity to the link with processing speed.

4.3. Limitations and future directions

While we observed delayed average pupil response in patients during IPAST performance (Fig. 3), analysis with the pupil response latency parameter did not reach significance (Supplementary Fig. 2). It is unclear whether this is a consequence of the visual characteristics of the stimulus that elicit the pupil response. While the central fixation cue in our IPAST paradigm introduced a luminance change and was capable of a evoking pupillary response in our present and previous IPAST studies (Wang et al., 2016; Wang et al., 2015), it was much weaker in comparison to that typically deployed in studies examining PLR in DD (Van Diemen et al., 1992; Surakka et al., 2008; De Seze et al., 2001) and may therefore be insufficient in evoking strong PLR differences between patients and healthy controls. Nonetheless, at present, pupilometry research in pediatric DD largely concerns PLR, and few have investigated pupil responses during ocularmotor tasks. Future investigations utilizing different ocularmotor paradigms that engage a wider visual space may be of interest for characterizing the effects of DD visual field defects on the pupil, such as using the pop-out (Wang et al., 2020) or free viewing paradigms (Habibi et al., 2022; White et al., 2017). Our findings of saccade and pupil measures in DD suggest that these
eye-tracking behaviors may have utility in tracking DD progression and functional recovery. However, these results are limited by the cross-sectional design, and different DD were considered together due to limited sample size. Future longitudinal studies evaluating longitudinal eye-tracking metrics and disease progression of different DD using other structural and functional metrics would be needed to understand whether and how these measures may be effective monitoring disease progression and treatment efficacy.

5. Conclusion

In summary, we characterized oculomotor behaviors using IPAST in pediatric DD, and observed a delay in the pupil responses induced in this task. We identified associations of saccade and pupil latency metrics with ON history, and further identified key saccade and pupil metrics associate with retinal structure, visual, and cognitive function in DD. The links between IPAST oculomotor metrics and the clinical characteristics and outcome of DD highlight the utility of oculomotor tasks in providing functional measures to assess demyelinating injury of the brain and optic nerve.

Funding

This research was funded by the Stem Cell Network, MS Scientific Research Foundation, and the Ontario Institute for Regenerative Medicine.

Role of the funding source

This research was funded by the Stem Cell Network, MS Scientific Research Foundation [grant number P20211], and the Ontario Institute for Regenerative Medicine. The funding sources were not involved in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

CRediT authorship contribution statement

Jeff Huang: Formal analysis, Software, Writing – original draft, Writing – review & editing. Visualization. Donald Brien: Methodology, Software, Validation, Writing – review & editing. Brian C. Coe: Software, Validation, Data curation, Writing – review & editing. Giulia Longoni: Writing – review & editing. Donald J. Mabbot: Writing – review & editing, Funding acquisition. Douglas P. Munoz: Conceptualization, Resources, Writing – review & editing, Supervision, Funding acquisition. E. Ann Yeh: Conceptualization, Investigation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Supplementary materials


References

Coors, A., Breterer, M.M.B., Ettinger, U., 2022. Processing speed, but not working memory or global cognition, is associated with pupil diameter during fixation. Psychophysiology, e14089. Published online.
Naber, M., Nakayama, K., 2013. Pupil responses to high-level image content. J. Vis. 13 (6), 7.
Van Den Brink, R.L., Murphy, P.R., Niemierowski, S., 2016. Pupil diameter tracks lapses of attention. PLoS One 11 (10), e0165274.