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RESEARCH ARTICLE

Saccade and pupil changes in children recovering from opsoclonus-myoclonus ataxia syndrome reveal midbrain alterations in oculomotor circuits

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Abstract

Objective: This study measured eye movements in children with a history of opsoclonus-myoclonus ataxia syndrome in order to identify abnormalities in saccade and pupil behavior that map onto specific alterations in brainstem pathways.
Methods: We used video-based eye tracking while participants freely viewed 10 min of short (2–4 s) video clips without instructions. Clip transitions represented a large visual perturbation and we quantified multiple characteristics of saccade and pupil responses following these transitions in 13 children recovering from opsoclonus-myoclonus and 13 healthy, age-matched control participants.
Results: The frequency of saccades and distribution of fixation durations differed between the groups. Following the clip transitions, children recovering from opsoclonus-myoclonus ataxia syndrome exhibited longer time to initiate saccades, leading to a delay in harvesting visual information. Clip transitions to lighter clips produced similar pupil constriction responses in the two groups. However, clip transitions to darker clips produced dilation responses that were initiated earlier and of greater magnitude in opsoclonus-myoclonus ataxia syndrome, suggesting removal or suppression of a signal that delays dilation.
Interpretation: Children with a history of opsoclonus-myoclonus ataxia syndrome demonstrated key abnormalities in saccade and pupil metrics. We propose a novel hypothesis in which dysfunction in the pathway from the superior colliculus to the mesencephalic and pontine reticular formation that houses the saccade and pupil premotor circuits could produce these results.

Keywords: eye movement; eye-tracking; opsoclonus; pupillometry; superior colliculus

Introduction

Opsoclonus-myoclonus ataxia syndrome (OMAS, OMS) is a rare autoimmune disorder that presents in children at approximately 18 months of age and is often associated with neuroblastoma. It is characterized by acute to subacute onset of ataxia accompanied at variable time points by rapid and irregular eye movements, myoclonus, and behavioral abnormalities.[1] Recent work has demonstrated effectiveness of early immunotherapy in reducing disease burden and hastening recovery.[2]

Knowledge about the anatomical and functional circuits involved in the uncontrolled saccadic eye movements that characterize opsoclonus is limited. In OMAS, focal abnormalities presumably occur in the brainstem and cerebellum at onset. Previous studies have implicated altered circuit

dynamics in the brainstem reticular formation to account for the uncontrolled saccades associated with opsoclonus in OMAS.[1] Specifically, disruption of intrinsic membrane properties of excitatory and inhibitory burst neurons that drive the extraocular motoneurons is hypothesized to underlie saccade oscillations,[3] and this intracellular mechanism has been successfully modeled.[4,5] During recovery, the brain can compensate for the circuit dynamics that produced the initial saccade instability observed in the acute stage, but whether ongoing alterations in circuit dynamics exist after recovery is unknown.

Video-based eye tracking is an ideal methodology to probe circuit dynamics in the cortex and brainstem because of the extensive knowledge of the brain areas and pathways controlling specific saccade and pupil behaviors.[1,6,7] Eye-tracking outcomes may therefore provide detailed clues to the brainstem pathways affected in children with OMAS, including during the recovery phase, thereby making eye tracking a particularly useful tool in the investigation of oculomotor pathway abnormalities in children with OMAS.

Here, we perform a cross-sectional study investigating the oculomotor behaviors in children with a history of OMAS using a simple free-viewing paradigm that consists of watching dynamic video clips. We hypothesize that there will be differences in saccade and pupil behavior in recovering OMAS patients compared with age-matched healthy children that reflect altered circuit dynamics in the brainstem. Specifically, we hypothesize that, because of potential brainstem and/or cerebellar dysfunction involving burst neurons[4,5] in the acute phase of OMAS,[1] the OMAS group here may have an altered saccade amplitude-velocity relationship and a higher proportion of short-duration intersaccadic intervals.

Methods

Participants

This study was reviewed and approved by the research ethics board at the Hospital for Sick Children (Toronto, ON, Canada) and Queen's University (Kingston, ON, Canada). Participants were children followed at the Neuroinflammatory Disorders Clinic (Hospital for Sick Children) who received a clinical diagnosis of OMAS (between 2012 and 2019[2]) and healthy age- and sex-matched children. Patients were included if they experienced opsoclonus and/or ataxia not explained by a visible cerebellar/pontine lesion. Children with an underlying neuroblastoma or idiopathic/postviral OMAS were included. Healthy children were recruited through word of mouth and flyer and were included if they had no preexisting significant medical diagnoses. Children were also excluded if they had a known history of developmental delay. All participants underwent a standardized protocol that included eye tracking, cognitive testing, and neurological assessment. The Mitchell-Pike OMS Severity Scale was used to grade clinical severity. The scale grades six areas of known involvement in this disorder from 0 to 3 (stance, gait, arm/hand function, opsoclonus, mood/behavior, and speech). Scores range from 0 to 18, with higher scores representing more severe manifestations.[2] Clinical information was gathered using a standardized case report form. Demographic details and patient characteristics are provided in Table 1.

Table 1. Patient characteristics.

Number of patients	13 children (10 female, 3 male)
Median age of OMAS at eye-tracking	5.3 years (IQR: 2.3–5.9)
Median age at onset of OMAS	1.8 years (IQR: 1.5–2.4)
Median OMAS score at onset	8 (IQR: 5–10)
Median time from onset to first MRI	6 days (IQR: 5–17)
Structural MRI abnormalities at onset[a]	1
Median time from first MRI to first steroids	5 days (IQR: 2–13)
Median time from onset to eye tracking	2.3 years (IQR: 1.0–5.2)
Median OMAS score at eye tracking	1 (IQR: 1–2.2)
Median opsoclonus score at eye tracking	0 (no patients with ongoing opsoclonus)
Median time from onset to follow-up MRI	2.8 years (IQR: 1.4–3.9; range: 1.1–13.3)
Number of CTRL	13 children (10 female, 3 male)
Median CTRL age at eye tracking	5.0 years (IQR: 3.3–6.9)

Abbreviations: CTRL, control; IQR, interquartile range; MRI, magnetic resonance imaging; OMAS, opsoclonus-myoclonus ataxia syndrome. [a]One patient with small, nonspecific white matter abnormalities of the parietal and frontal lobes bilaterally at onset. Unchanged through time. This patient had progressive cerebellar atrophy at follow-up.

Experimental setup and eye-tracking task

We employed a simple free-viewing eye-tracking protocol that is ideal for studying young children and is especially sensitive to abnormalities in brainstem circuitry controlling saccade and pupil responses.[8–10] Participants were seated on their caregiver's lap so that their eyes were positioned 60 cm in front of the center of a computer screen in a dark, windowless room, with a curtain drawn between them and the operator to prevent distractions. All data were collected using a video-based eye tracker (Eyelink-1000 Plus monocular-arm; SR Research), recording right pupil and eye position at 500 Hz. Head motion was monitored via a small sticker with concentric rings attached to the center of

the forehead that was also tracked by the video camera and compensated for head motion during eye tracking. Participants were calibrated using a three-point triangular pattern of fixation points. The fixation points were a small movie clip (with sound) of an animated cartoon character with a size of 1° of visual angle. Participants were calibrated to an average error <1° of visual angle.

Participants viewed a total of 10 movies that were each ~1 min and consisted of 15–17 random video clips that were each 3–5 s and composed of human actors, natural scenes, sporting events, and animals. There was no resting interval between movies unless requested by the participant. The video clips were displayed on a 17-inch LCD monitor (1280 × 1024 pixels, 32-bit color, 60 Hz refresh rate) controlled by the operator through a Dell Latitude E7440 Laptop.[8,10] The video clips switched randomly from one scene or event to another (similar to switching TV channels every 3–5 s). The task required no instruction; the participants simply viewed the video clips and were free to look anywhere on the display. The visual perturbation produced by the clip changes altered ongoing saccade and pupil behavior[8,10] that we describe here.

Data analysis

We divided the analyses into eye movement statistics that were analyzed independent of video clip content and clip-aligned analyses that revealed how the visual perturbation resulting from the clip changes affected saccade and pupil behavior. Auto-marking scripts developed in MATLAB (The MathWorks Inc.) were used to classify each trial (i.e., each video clip) and all eye movements (saccades, fixations, and pupil size).[11] The free-viewing task produced a great number of saccades of different amplitudes and directions. All saccades were marked for direction, amplitude, peak velocity, and duration and we investigated the main sequence relationship between amplitude and velocity.[12] We defined macro-saccades as all saccades ≥2° amplitude and micro-saccades as all saccades <2° amplitude following previous studies that demonstrated differences in micro- and macro-saccade characteristics in clinical populations.[10,13] Converging research has demonstrated that micro- and macro-saccades form a continuum with a common oculomotor control circuit.[14] We computed the frequency (saccade count/viewing duration) and average saccade amplitude in each of 60 different saccade directions (each bin was 6° polar angle × 60 bins = 360°). A core symptom during the acute phase of OMAS are bouts of opsoclonus, when the duration of the fixations between saccades is minimal or nonexistent.[1] We therefore measured the durations of all fixations during free viewing to determine whether the OMAS group made more short-duration fixations than the control (CTRL) group.

The clip transitions produced transient changes in saccade and pupil behavior. We computed the macro- and micro-saccade rate (saccades/s) for each participant using a peri-stimulus time histogram (2 ms bin width due to the 500 Hz sample rate) aligned on the clip changes. We then applied a Lowess model (locally weighted linear regression) to fit a smooth curve to the saccade rate data. This method preserved the underlying structure of the curves while adding just enough smoothing to discern meaningful variation in the saccade rate over time. For both macro- and micro-saccades, we computed a baseline rate for each participant (−200 to +50 ms relative to the clip change), as well as the magnitude and timing of the dip in saccade rate "saccade suppression,"[15,16] the peak macro-saccade rate after clip transition (maximum value from the time of suppression to 300 ms post clip change), and the steady-state saccade rate (averaged from 1000 to 3000 ms after clip change). We computed the magnitude and timing of the suppression in micro-saccade rate in the epoch from 100 to 300 ms after clip change.

A similar set of micro-saccade parameters was extracted for each participant. Micro-saccade peri-stimulus time histograms were created, and we computed a baseline rate (average rate from −200 to +50 ms relative to clip change). We computed the magnitude and timing of the suppression in micro-saccade rate in the epoch from 100 to 300 ms after clip change, and we computed the steady-state micro-saccade rate, which was the average over an epoch 1000 to 3000 ms after clip change.

We measured the mean global luminance of every frame of every video clip and correlated the pupil size with the screen luminance (cd/m^2) across clips for each participant. The clip changes produced luminance changes that impacted pupil size. We measured these luminance changes and ranked all clip transitions to extract the 30 clip changes with the greatest increase in luminance and the 30 clip changes with the greatest decrease in luminance to measure the impact of clip change on pupil behavior.

Statistical analyses were performed using MATLAB. All statistical comparisons used nonparametric rank sum tests (Mann–Whitney *U*), alpha level 0.05. We used nonparametric tests because our sample size was not particularly large and potentially not normally distributed. We did not adjust for multiple comparisons because of the small sample size in this exploratory study.

Results

Demographics and clinical characteristics

Thirteen children recovering from OMAS and 13 healthy age- and sex-matched children were included (Table 1). The median time from disease onset until this eye-tracking

study was 2.3 years (interquartile range [IQR]: 1.0–5.2). The median OMAS score at disease onset was 8 (IQR: 5–10), but at the time of eye tracking this had fallen to 1 (IQR: 1–6), indicating little to no disability at the time of eye tracking, and no evidence for opsoclonus was present in any children. All children received immunotherapy in the form of steroids, IVIG, plasma exchange, and/or rituximab.

Saccade statistics

We analyzed the distributions of all saccade directions and amplitudes from the 10 min of free viewing. Figure 1A,B shows the frequency of both macro- (≥2°) and micro- (<2°) saccades in 60 different angular direction bins, each representing 6° of polar angle. OMAS participants did not have any significant difference in macro-saccade frequency compared with controls (Figure 1A,C; $z = 1.64$, $p = 0.101$ for horizontal and $z = 0.26$, $p = 0.8$ for vertical); OMAS generated more micro-saccades in the vertical directions (Figure 1B,D; $z = -2.46$, $p = 0.014$, Mann–Whitney U tests). There was almost no difference in the average amplitude of saccades in the 60 different directions (Figure 1E–H; $p > 0.05$ in all but one case, Mann–Whitney U test).

Figure 2A illustrates the distribution of all fixation durations for OMAS and CTRL, normalized for overall viewing duration. We identified a short duration mode <180 ms (epoch 1) and a second, broader mode from 200 to 640 ms (epoch 2). The OMAS group made significantly more short-duration fixations than the CTRL group (Figure 2B; $z = -2.46$, $p = 0.014$; Mann–Whitney U test). In contrast, the OMAS group made significantly fewer fixations in the mode from 200 to 640 ms than the CTRL group (Figure 2C; $z = 2.21$, $p = 0.027$; Mann–Whitney U test).

We initially hypothesized that there would be group differences in the amplitude-velocity relationship of saccades. Somewhat surprisingly, these relationships for macro-saccades were similar in the OMAS and CTRL groups (Figure 3A–D). We fit a line to the logarithmic plot of amplitude versus velocity for each participant and computed the slope and y-intercept for all participants. There was no difference in the linear fits between the two groups ($z = -0.25$, $p = 0.79$ and $z = 1.49$, $p = 0.14$, for the between-group slope and y-intercept comparisons, respectively, Mann–Whitney U tests).

Clip-aligned analysis: Saccades

The abrupt perturbation produced by the changes in video clips were associated with large transient changes in saccade rate in all participants (Figure 4A). Immediately following clip change, all participants demonstrated an initial inhibition of macro-saccades after approximately 100 ms that was followed by a rebound of saccades from 150 to 300 ms, and a steady rate of about 1.2 saccades/s after 500 ms (Figure 4A).

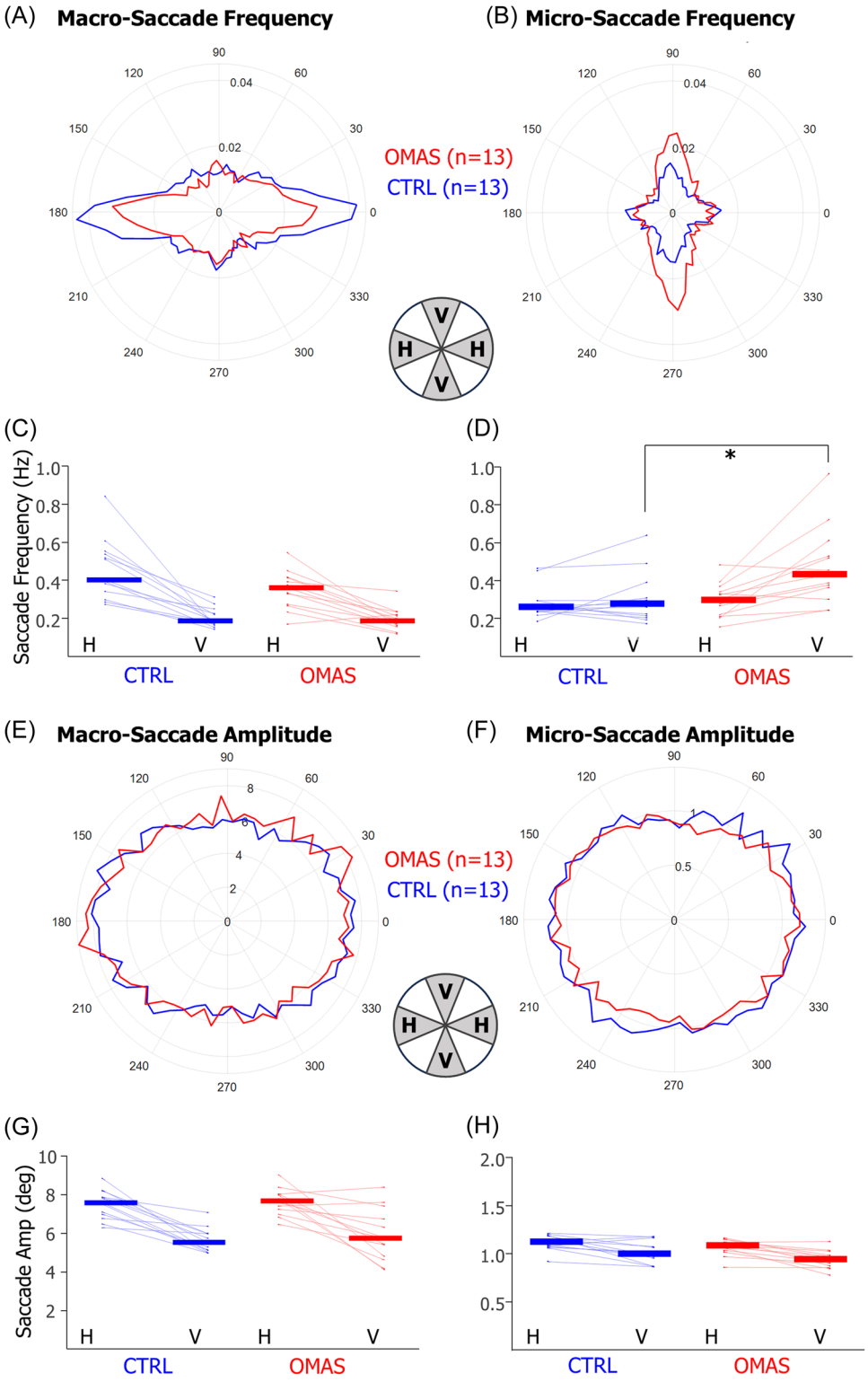
Importantly, the rebound of saccades after the clip change was delayed in OMAS participants compared with CTRL participants. For each participant, we measured the saccade rate 100–180 ms after clip change (the early part of the rebound; Figure 4C) as well as the magnitude (Figure 4D) and timing (Figure 4E) of the peak. The OMAS participants had a weaker early rebound (Figure 4C; $z = 2.21$, $p = 0.027$), a reduced peak (Figure 4D; $z = -1.98$, $p = 0.048$), delayed time to peak saccade rate (Figure 4E; $z = -2.0$, $p = 0.045$), and a lower steady-state saccade rate (Figure 4F, $z = 2.05$, $p = 0.04$, Mann–Whitney U test). No other statistically significant differences were observed.

A consequence of the apparent delayed or weaker saccade rebound in OMAS is that it may have led to a delay in harvesting visual information as the clip played out. To test this possibility, we plotted cumulative distributions of the timing of the first, second, third, and fourth macro-saccades triggered after clip change (Figure 4B). The median time for the first to fourth saccade was significantly longer in OMAS participants relative to CTRL (first saccade: 344 vs. 278 ms, $z = -8.38$; second: 997 vs. 814 ms, $z = -6.12$; third: 1634 vs. 1478 ms, $z = -3.96$; fourth: 2080 vs. 1900 ms, $z = -3.37$; $p < 0.0001$ in all cases, Mann–Whitney U tests). Thus, the delay in responding after the clip change in OMAS children persisted throughout the viewing of the clip, which would lead to a delay in harvesting new visual information.

The micro-saccade rate was also inhibited transiently after the clip change in all participants (Figure 4A). This reduction in micro-saccade rate lasted until about 400 ms after the clip change, before there was a return to the steady-state rate. This transient micro-saccade suppression was reduced in the OMAS group. The average micro-saccade rate of 100–300 ms after clip change was significantly higher in OMAS than CTRL participants (Figure 4G; $z = -2.03$, $p = 0.04$). The average steady-state micro-saccade rate of 1000–3000 ms after clip change was also significantly higher in OMAS than CTRL participants (Figure 4H; $z = -1.94$, $p = 0.05$).

Clip-aligned analysis: Pupil

To confirm that there was no difference between OMAS and CTRL participants in overall pupil size while viewing the video clips, we plotted screen luminance versus pupil size for all participants (Figure 5A). There was no significant difference in baseline pupil size (i.e., y-intercept; $z = -0.67$, $p = 0.51$; Figure 5C) or light sensitivity (i.e., slope; $z = 0.51$, $p = 0.61$; Figure 5B). Despite the



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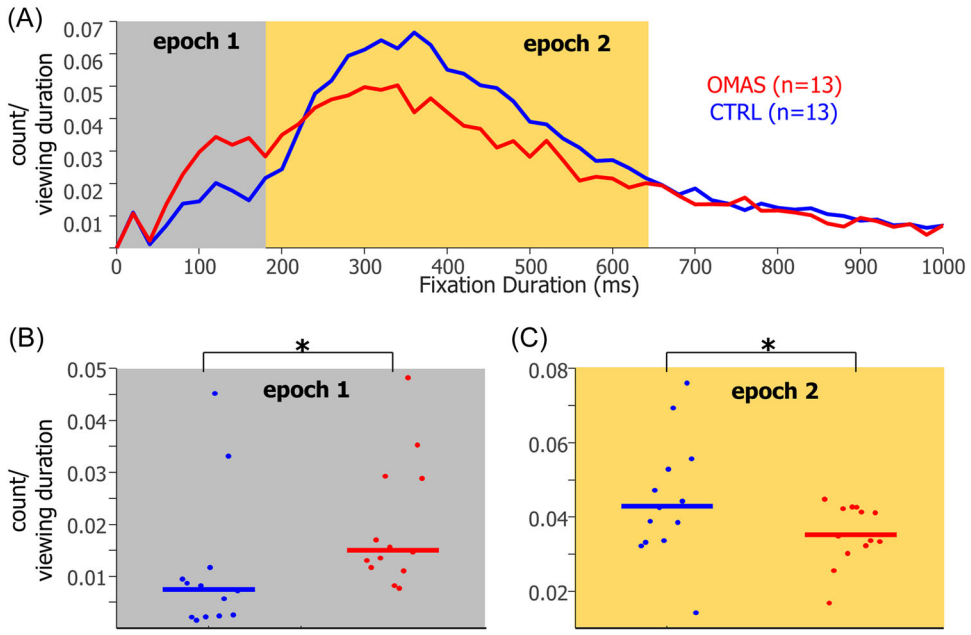


Figure 2. (A) Distribution of fixation durations for OMAS and CTRL groups. (B) The OMAS group made significantly more short-duration fixations (<180 ms, epoch 1). (C) The OMAS group had fewer fixation durations between 200 and 640 ms (epoch 2). *$p < 0.05$. CTRL, control; OMAS, opsoclonus-myoclonus ataxia syndrome.

similarity in overall pupil size between the two groups, the clip changes that resulted in luminance increases or decreases that induced transient pupil constriction or dilation, respectively, differed between the groups. Figure 6 shows how pupil constriction and dilation responses were impacted by the visual perturbation produced by the abrupt clip changes (see Methods for details). We selected the 20% of clips with the greatest luminance increase ($n = 30$ clips) and the 20% with the greatest luminance decrease ($n = 30$ clips). Consistent with the pupil light and darkness reflex, respectively, there was a systematic decrease or increase in pupil size following the clip change. After clip changes with luminance increases, the OMAS group produced constriction responses that were similar to controls (Figure 6A,C): the OMAS responses did not differ significantly from controls in timing of onset of the response (Figure 6E; $z = 0.23$, $p = 0.82$), time of peak velocity (Figure 6G, $z = -0.98$, $p = 0.35$), or magnitude of the response (Figure 6I; $z = -0.67$, $p = 0.5$ for steady-state pupil size). Although the magnitude of the dilation response following luminance decreases was not significantly different between the OMAS and CTRL groups (Figure 6J; $z = -1.44$, $p = 0.15$ for steady state), the latency of the dilation onset and the time of peak dilation velocity were both reduced significantly in the OMAS group (Figure 6B,D,F,H; $z = 2.93$, $p = 0.003$ for dilation latency, and $z = 2.79$, $p = 0.005$ for time of peak velocity). That is, the dilation response started significantly earlier in OMAS.

Discussion

We used a free-viewing paradigm to evaluate oculomotor metrics in children who had a resolution of clinical features of OMAS. We identified significant differences in gaze and pupil control compared with CTRL, despite the fact that OMAS children had largely recovered (Table 1). We identified three key differences between the groups: (1)

Figure 1. Directional distribution of all macro-sacccades (A, C) and micro-saccades (B, D) for all CTRL and OMAS participants. (A, B) All saccades were divided into 6° bins producing 60 direction bins. Note that control participants generated more horizontal macro-saccades (A), while OMAS participants generated more vertical micro-saccades (B); however, only the latter was significant. (C, D) All saccade directions were collapsed into 90° wedges centered on the horizontal and vertical meridians, showing control participants generated more horizontal macro-saccades (C), while OMAS participants generated more vertical micro-saccades (D). Directional distribution of macro- (E, G) and micro- (F, H) saccade amplitudes for all CTRL and OMAS participants. (E, F) All saccades were divided into 6° bins producing 60 direction bins. (G, H) All saccade directions were collapsed into 90° wedges centered on the horizontal and vertical meridians showing no differences between CTRL and OMAS groups. *$p < 0.05$. CTRL, control; OMAS, opsoclonus-myoclonus ataxia syndrome.

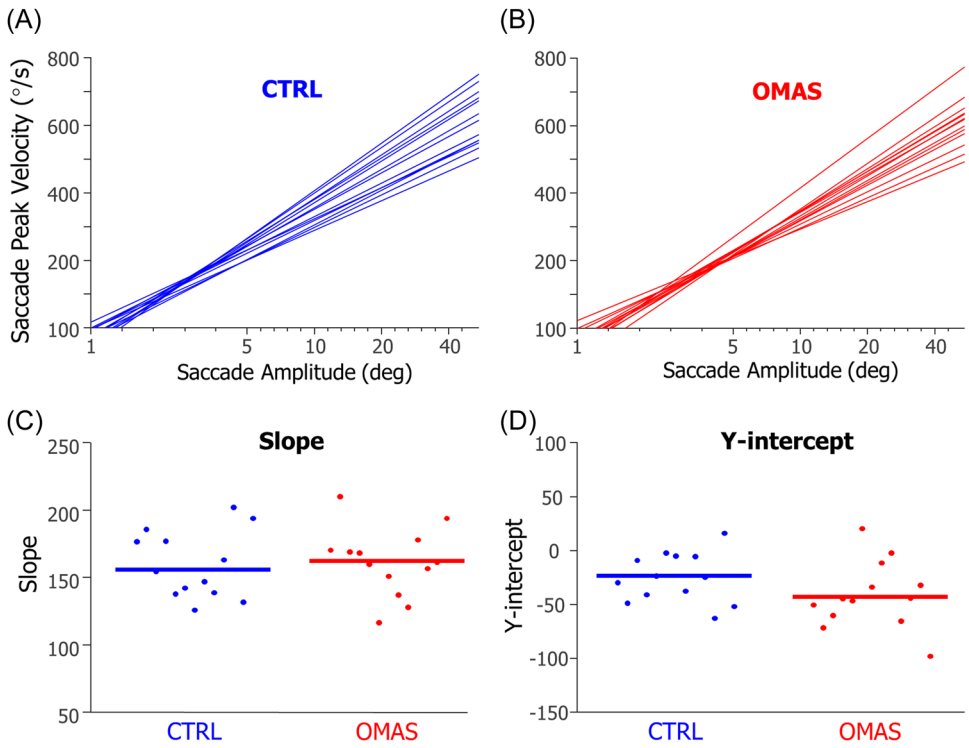


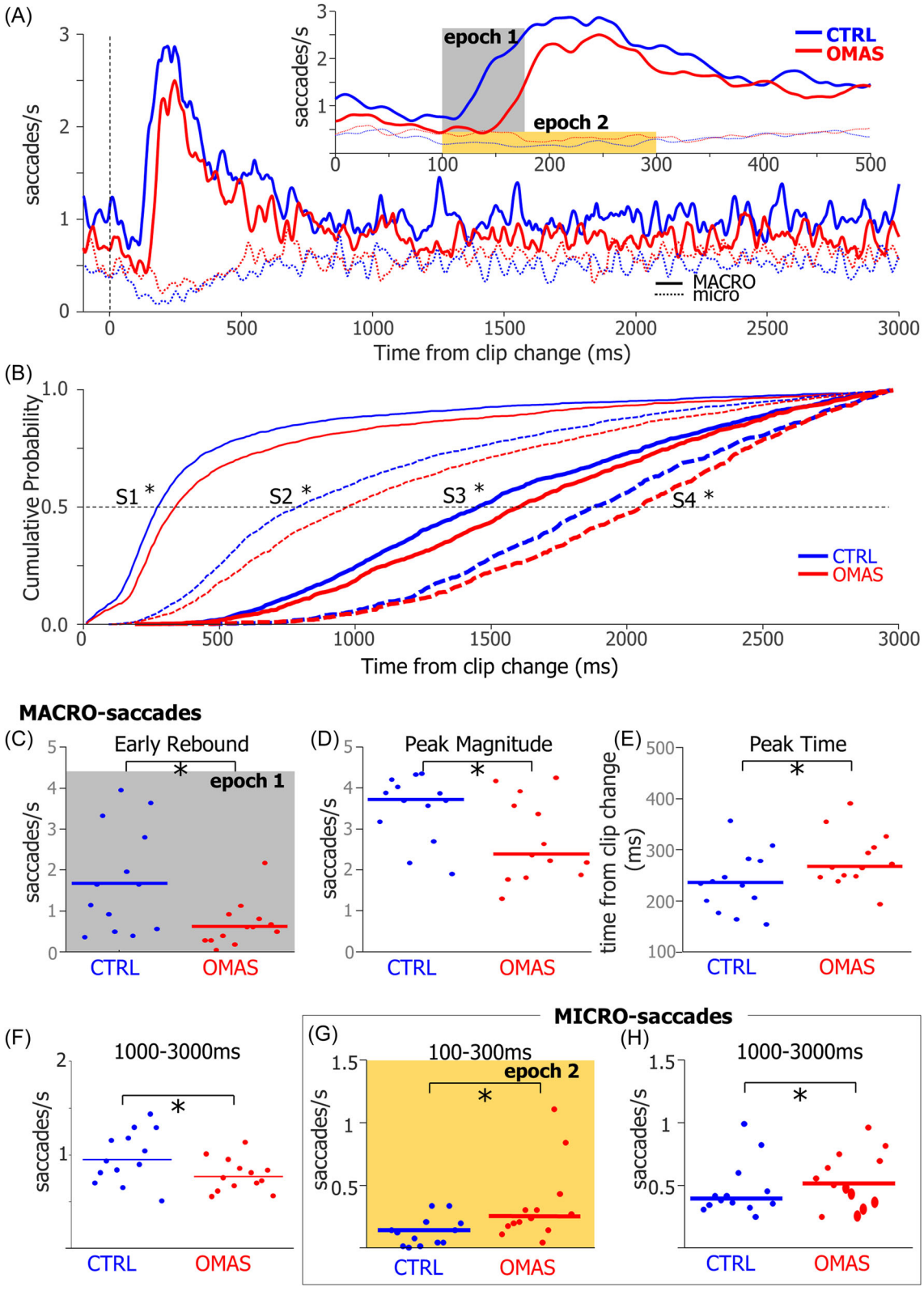
Figure 3. Amplitude velocity relationships for individual CTRL (A) and OMAS (B) participants. Plots of slope (C) and y-intercept (D) values for individual participants and the horizontal bar represents the group medians. CTRL, control; OMAS, opsoclonus-myoclonus ataxia syndrome.

OMAS children made more short-duration fixations (<180 ms) (Figure 2A,B); (2) OMAS had a delayed rebound in macro-saccade rate following clip change (Figure 4); and (3) OMAS had reduced pupil dilation latency and greater pupil dilation speed (Figure 6). There were no group differences in the amplitude-velocity relationship for saccades (Figure 3). These findings suggest that ongoing oculomotor abnormalities persist in OMAS children even 2 years after initial clinical presentation. Below we discuss possible anatomical/functional explanations for these results.

Mapping onto brainstem pathways

Structural and functional studies have provided some information on outcomes in OMAS patients. Longitudinal studies have revealed cerebellar atrophy in the vermis and flocculonodular lobe,[17] together with reduced cerebellar gray matter volume at follow-up, confirming a structure-function association between the ataxic presentation and brain abnormalities as seen via magnetic resonance imaging (MRI).[18,19] As well, decreased cortical thickness in motor and visual areas has been reported.[19] As for functional abnormalities, few publications have reported correlations between brain structure and functional abnormalities, although one older description of fMRI in two individuals with opsoclonus reported differences with healthy controls in the fastigial nucleus.[20] However, a major limitation in these imaging studies is the threshold for detection of change.

Previous research in the acute phase of OMAS has attempted to localize the anatomical and functional circuits that lead to clinical abnormalities. During gaze fixation, saccadic eye movements are inhibited by the tonic activity of brainstem omnipause neurons, a small population of neurons in the midline pons, which are tonically active during fixation and pause for all saccades.[21] They exert potent monosynaptic inhibition of saccade burst neurons that carry the saccade command to the extraocular muscle motoneurons.[22] Given the repeated bouts of opsoclonus occuring in the acute phase of OMAS, previous publications proposed that opsoclonus may be the result of dysfunction of omnipause neurons, triggering unwanted saccades.[23] However, lesion of omnipause neurons in monkeys with injection of ibotenic acid in nucleus raphe interpositus failed to reproduce the symptoms of opsoclonus and instead led to slowed saccades.[24] Alternatively, imbalance of excitatory and inhibitory inputs to the burst neurons could lead to excessive excitation or post-inhibitory rebound that could produce saccadic oscillations or opsoclonus, which has been successfully modeled.[4,5]



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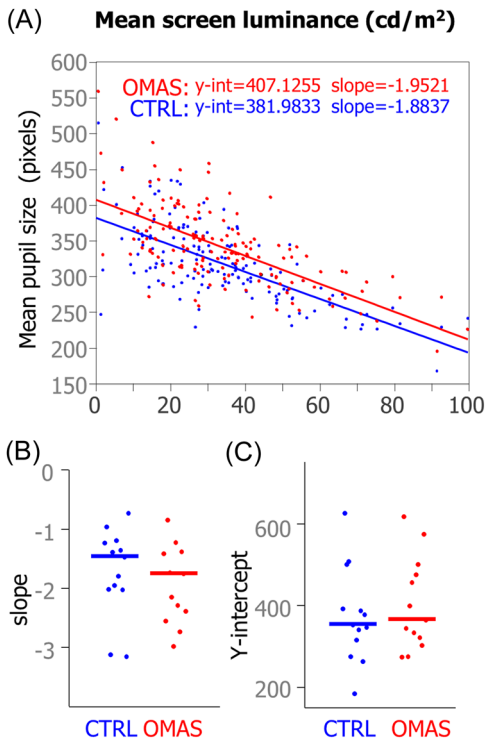

Figure 5. (A) Plot of screen luminance versus pupil size, averaged across all participants in the CTRL and OMAS groups. (B) Slope values for individual participants. (C) Y-intercept values for individual participants. There were no significant group differences in these measures. CTRL, control; OMAS, opsoclonus-myoclonus ataxia syndrome.

It has also been proposed that disruption or damage to the cerebellar vermis, which leads to disinhibition of the fastigial nucleus, could contribute to the triggering of unwanted saccades.[20,25] Indeed, the fastigial nucleus provides critical input to burst neurons to regulate the termination of the saccade burst command.[26,27] However, deactivation of the caudal fastigial nucleus in awake monkeys produces saccade dysmetria, more so than increased saccade frequency.[28] One study of eye movements in five OMAS children, however, reported saccade hypermetria.[29]

A novel hypothesis

We propose a novel hypothesis that implicates the midbrain superior colliculus (SC) and/or its input to the saccade and pupil premotor circuits that could account for the pattern of altered saccade and pupil responses identified in children recovering from OMAS. Three key observations are consistent with a disruption or down-regulation of the SC or its efferent output: (1) the saccade rebound after clip change was delayed and attenuated in OMAS participants (Figure 4); (2) OMAS participants made significantly more short-duration fixations (Figure 2A,B); and (3) pupil dilation responses after clip changes with large luminance decreases started earlier in OMAS participants (Figure 6). We discuss how these outcomes could be the result of a change in SC excitability.

Consistent with previous studies, the clip changes represented a large visual perturbation leading to short-latency saccade inhibition,[15,16] which is likely mediated via visual input to the omnipause neurons causing immediate inhibition of all saccade burst neurons. Although there was no difference in onset of saccade suppression between the groups, the saccade rebound following clip change was delayed and reduced in the OMAS group (Figure 4A,C). Because suppression onset was not altered in OMAS, the subsequent delay in saccade rebound was unlikely due to any delay in visual signals reaching the brainstem. Rather, we believe the delay in the OMAS group was due to a delay in saccade initiation commands following the suppression. This delay of short-latency visually-triggered responses is reminiscent to the loss of short-latency express saccades following a surgical ablation of the SC in monkeys.[30] After adequate time for recovery (i.e., several days), these monkeys reacquired the ability to make saccades but never reacquired the ability to produce express saccades. The longer latency saccades are presumably mediated by cortical inputs to the SC and paramedian pontine reticular formation, but the short-latency express saccades require an intact SC.[30] It is at least plausible that this short-latency pathway for express saccade generation via the SC has been reduced or silenced, possibly to adapt to the conditions of opsoclonus. Longer latency saccades would be preserved due to intact and likely enhanced cortical inputs to the brainstem premotor circuitry to overcome the reduced SC excitability. Note that micro-saccade frequency was not reduced in OMAS and vertical micro-saccades actually increased (Figure 1B,D), suggesting that not all of the SC was at reduced excitability. It is possible that the rostral pole of the SC that codes fixation[31,32] and micro-saccades[33] may actually be recruited to help inhibit the caudal SC via local collicular connectivity.

Figure 4. Analysis of the timing of macro- and micro-saccades relative to clip change. (A) Instantaneous macro- and micro-saccade rate aligned to clip change. Insert shows same curves over initial 500 ms after clip change. (B) Cumulative distributions of the first, second, third, and fourth macro-saccades after clip change revealing the delay in saccade timing in the OMAS group across the clip interval. (C–F) The early saccade rebound (C; epoch 1), peak saccade rate (D), and steady-state rate (F; 1–3 s after clip change) were significantly reduced in OMAS and the timing of the peak was delayed (E). (G) Micro-saccade suppression 100–300 ms after the clip change was reduced in OMAS (epoch 2). (H) The steady-state (1000–3000 ms) micro-saccade rate was elevated in OMAS. *$p < 0.05$. CTRL, control; OMAS, opsoclonus-myoclonus ataxia syndrome.

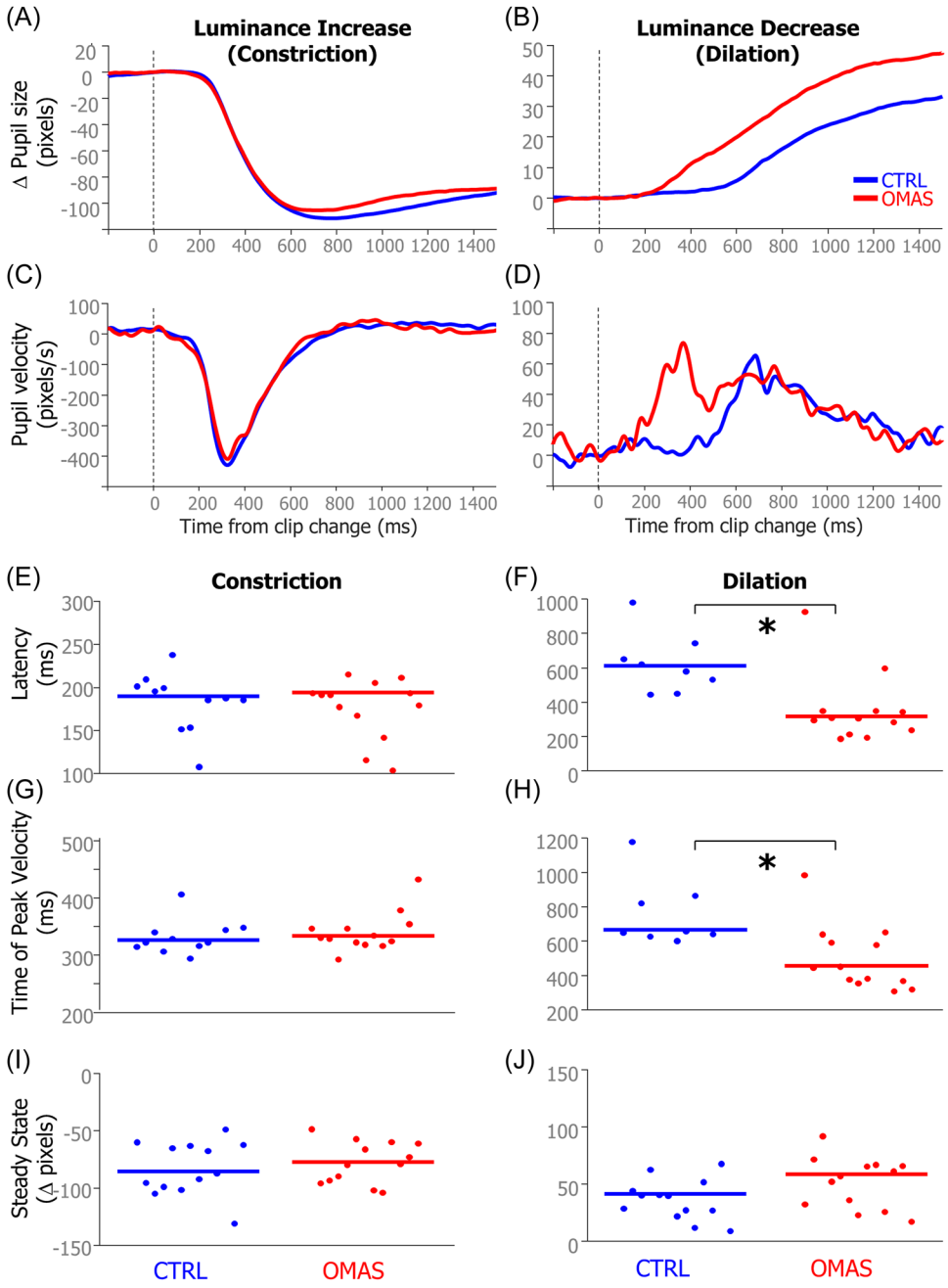

Figure 6. Pupil responses following clip changes that involved large luminance increases (A, C, E, G, and I) or decreases (B, D, F, H, J). (A, B) Time course of the average change in pupil size following clip changes with large luminance increase or decrease, respectively. (C, D) Instantaneous pupil velocity following the clip changes showing faster dilation response in OMAS. (E, F) Latency to onset of pupil change for constriction and dilation, respectively. (G, H) Time of peak pupil velocity following the clip changes. (I, J) Average pupil size 1000–3000 ms after the clip change. *$p < 0.05$.

The increase in the frequency of short-duration fixations (50–180 ms) in OMAS (Figure 2A,B) likely reflects a lack of engagement of the fixation system. Brainstem omnipause neurons (OPNs) are active during brief fixations <150 ms, while neurons in the rostral superior colliculus that are tonically active during visual fixation are usually not active during these brief fixations.[34] Most of the SC projects monosynaptically onto OPNs.[35] Reduced excitatory input to OPNs could therefore lead to excessive saccades with short fixation durations.

The altered pupil responses we observed are also consistent with altered collicular activity. Pupil constriction responses did not differ between OMAS and CTRL participants (Figure 6A,C,E,G,I), but dilation latency and the time of peak pupil velocity were unexpectedly sooner in OMAS than CTRL participants (Figure 6B,D,F,H). The possibility of altered sympathetic drive is highly unlikely because there was no difference in baseline pupil size or screen luminance sensitivity between the groups (Figure 5), both of which are likely controlled by sympathetic drive.

The presentation of salient stimuli often produces a complex pupil response that includes transient dilation followed by constriction.[36,37] These responses are independent of luminance changes. This saliency pupil response has a shorter latency than the luminance response and is likely mediated via the superior colliculus.[38,39] If collicular excitability is down-regulated in OMAS, as we hypothesize, then the pupil saliency response produced by the clip change (small dilation followed by larger constriction) should also be reduced, which would then allow the pupil dilation response to luminance decrease at clip change to start sooner, which is exactly what we observed in OMAS children (Figure 6B,D,F,H).

Clinical implications

We have identified specific eye-tracking abnormalities present in children recovering from OMAS, representing an important step in identifying a novel nonscale-based functional outcome metric that may be useful in tracking recovery of deficits. Our next steps include understanding associations between these findings and ongoing clinical and structural abnormalities in this population. This is of particular interest in this population, as poor cognitive outcome may occur in up to 75% of children with OMAS.[2] However, tools that can screen for cognitive abnormalities are limited in this age group due to the average age of onset of around 18 months. For example, the Mitchell-Pike OMS rating scale[2] is an 18-point rating scale for six categories, including stance, gait, arm/hand function, opsoclonus, mood/behavior, and speech. It provides excellent baseline information, especially for severe disease manifestations, but may fail to capture more subtle abnormalities that arise in follow-up and fail to differentiate between children who experience no to moderate motor, behavioral, or cognitive difficulties. Future studies evaluating whether eye tracking can provide more precise information on outcomes in this population are needed.

Limitations

This study is limited by the small cohort size, dictated by the rarity of the condition. Further, limitations include the cross-sectional design of the study and variability of the times from disease onset in the cohort. While selection and referral bias may be a risk in this small cohort, our registry captures all patients presenting with neuroinflammatory conditions referred to our center, and we had high uptake in participation in this study. Longitudinal studies including children in the acute phase of the disorder are needed to determine whether the same or additional measures of oculomotor control are abnormal.

Conclusions

Using video-based eye tracking and quantitative analysis, we propose a novel hypothesis regarding brain changes in children with a history of OMAS. We hypothesize that inhibition or down-regulation of the SC, as a means for the brain to reduce input to the saccade premotor burst neurons, leads to a delay in the saccade rebound after the clip changes and a decrease in the latency of pupil dilation responses. Future studies will evaluate associations of these abnormalities with quantitative brain MRI and functional metrics.

Author Contributions

Douglas P. Munoz: Conceptualization; formal analysis; funding acquisition; visualization; writing—original draft; writing—review and editing. **Brian J. White**: Conceptualization; formal analysis; visualization; writing—original draft; writing—review and editing. **Donald C. Brien**: Conceptualization. **Kajaal Parbhoo**: Data curation. **Carmen Yea**: Formal analysis; visualization. **E. Ann Yeh**: Conceptualization; data curation; funding acquisition; writing—original draft; writing—review and editing.

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Conflicts of Interest

Douglas P. Munoz, Brian J. White, and Donald C. Brien are involved in a startup company, Dynamiris Inc., that is developing eye-tracking software. Douglas P. Munoz has received research funding from CIHR, ORF, OBI, and Parkinson's Foundation. E. Ann Yeh has received research funding from NMSS, CMSC, CIHR, NIH, OIRM, SCN,

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Data Availability Statement

As per regulation of the Ethics Committee of the SickKids Hospital and University of Toronto (Toronto, Canada) and Queen's University (Kingston, Canada), the data are not publicly available as they contain information that could compromise the privacy of research participants. Nevertheless, the data that support the findings of this study are available from the corresponding author upon reasonable request.

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