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Preliminary Eye-Tracking Data as a Nonintrusive Marker for Blood Δ-9-Tetrahydrocannabinol Concentration and Drugged Driving

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Abstract

Background: Cannabis is one of the drugs most often found in drivers involved in serious motor vehicle collisions. Validity and reliability of roadside cannabis detection strategies are questioned. This pilot study aimed to investigate the relationship between eye characteristics and cannabis effects in simulated driving to inform potential development of an alternative detection strategy.

Materials and Methods: Multimodal data, including blood samples, eye-tracking recordings, and driving performance data, were acquired from 10 participants during a prolonged single-session driving simulator experiment. The study session included a baseline driving trial before cannabis exposure and seven trials at various times over ∼5 h after exposure. The multidimensional eye-tracking recording from each driving trial for each participant was segmented into nonoverlapping epochs (time windows); 34 features were extracted from each epoch. Blood Δ-9-tetrahydrocannabinol (THC) concentration, standard deviation of lateral position (SDLP), and mean vehicle speed were target variables. The cross-correlation between the temporal profile of each eye-tracking feature and target variable was assessed and a nonlinear regression analysis evaluated temporal trend of features following cannabis exposure.

Results: Mean pupil diameter ($r = 0.81–0.86$) and gaze pitch angle standard deviation ($r = 0.79–0.87$) were significantly correlated with blood THC concentration ($p < 0.01$) for all epoch lengths. For driving performance variables, saccade-related features were among those showing the most significant correlation ($r = 0.61–0.83$, $p < 0.05$). Epoch length significantly affected correlations between eye-tracking features and speed ($p < 0.05$), but not SDLP or blood THC concentration ($p > 0.1$). Temporal trend analysis of eye-tracking features after cannabis also showed a significant increasing trend ($p < 0.01$) in saccade-related features, including velocity, scanpath, and duration, as the influence of cannabis decreased by time. A decreasing trend was observed for fixation percentage and mean pupil diameter. Due to the lack of placebo control in this study, these results are considered preliminary.

Conclusion: Specific eye characteristics could potentially be used as nonintrusive markers of THC presence and driving-related effects of cannabis.

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Keywords: cannabis; correlation; driving performance; eye-tracking; temporal trend; THC; lateral position; nonlinear regression; vehicle speed

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Introduction

Cannabis is the most widely consumed psychoactive substance after alcohol and tobacco.[1–4] According to the 2012 Canadian Alcohol and Drug Use Monitoring Survey,[5] 41.5% of Canadian adults used cannabis at least once in their lifetime.

Recent studies[6–8] in the United States and Canada reveal that the prevalence of driving under the influence of cannabis (DUIC) in some age groups is becoming similar to, or higher than, the prevalence of driving under the influence of alcohol. In a study by the Centre for Addiction and Mental Health (CAMH), drivers in Ontario, Canada, reporting DUIC within the previous 12 months had an increased risk of collision compared to those who never drove after cannabis use.[9] Other recent epidemiological research clearly shows that DUIC significantly increases the risk of motor vehicle collisions.[8,10,11] Cannabis is one of the two substances of abuse (along with alcohol), most often found in drivers involved in serious motor vehicle crashes.[12–18]

It is well known that the effects of alcohol on driving performance and associated risks increase exponentially as blood alcohol concentration increases.[6,19] On the contrary, simulated and naturalistic studies of cannabis were less consistent in terms of findings[7,8,10,11,20] and largely unsuccessful in establishing a *simple* and *direct* correlation between impairment and blood concentration of Δ-9-tetrahydrocannabinol (THC), the active compound found in blood or oral fluids after cannabis use.[21–24] Inconsistency in results of cannabis studies could be explained by differences in frequency of usage, dosage, level of driving experience, and method of substance administration.

Previous research has revealed acute and chronic effects of cannabis on driving performance measures, including lane control, reaction time, speed, steering patterns, and following distance.[25–34] Several studies showed that the standard deviation of lateral position (SDLP) increases in the presence of THC.[26,32–34] Hartman et al.[26] reported a significant association between SDLP and blood THC concentration. In this study, occasional users of cannabis participated in simulated driving sessions under various combinations of vaped cannabis and alcohol. Results indicated that cannabis (with or without alcohol) increased SDLP, while the observed effects of cannabis and alcohol combined on SDLP appeared to be additive. In another recent study,[30] we investigated the acute and residual effects of smoked cannabis on speed and lateral position, tested on a driving simulator under single- and dual-task (counting backward while driving) conditions. The results showed that mean speed was significantly reduced in the low and high THC groups compared to placebo 30 min after smoking cannabis. No evidence of residual effects of cannabis on driving 24 and 48 h later was observed. Dahlgren et al.[31] reported significant increases in pedestrial hits, speed, and lateral movements on a simulated driving task in a group of nonintoxicated, heavy, recreational cannabis users (who reported having used cannabis more than 1500 times) compared to a healthy control group. Participants with early onset of cannabis use (<16 years old) showed significantly more impairment than those with late onset of cannabis use (≥ 16 years old).

Apart from driving performance, some studies assessed the influence of cannabis on eye characteristics and movements such as fixations, smooth pursuits, saccadic movements, pupillometry, blinking, or visual search frequency.[35–41] Eye examination (including horizontal and vertical gaze nystagmus) is already practiced by law enforcement as part of drug recognition expert evaluation procedures for investigation of drug-impaired driving.[42] Some investigators reported increased latencies of reflexive visually guided saccades or decrements in smooth pursuits in young casual users.[35,39] Increased latency in saccades and fixation duration in chronic users without acute THC intoxication was also reported.[36,37] In one recent study,[38] a significant increase in pupil size following oral administration of cannabis was observed, compared to placebo; however, no significant changes were noticed following smoking or vaporization.

In view of the threat to road safety posed by cannabis use, it is important to develop strategies for roadside detection. While there is some evidence to support validity and reliability of the standardized field sobriety test (SFST) and the broader drug recognition expert evaluation for detection of cannabis,[34] these are subjective tests and potentially subject to human error. Some previous studies also reported that SFSTs are insensitive to cannabis.[33,43,44] Detection devices based on saliva or oral fluid are objective tests and were introduced in some jurisdictions; however, concerns about reliability continue to limit their use. Therefore, it is crucial to continue exploration and development of technologies for reliable roadside cannabis detection. Monitoring for drug use, including real-time monitoring, as part of fleet management is also a relevant road safety issue for commercial drivers (e.g., heavy goods vehicles, passenger buses, and taxis).[45–47]

The current pilot study used driver simulation to investigate the potential for eye-tracking data to be used as a nonintrusive marker of cannabis use. Specifically, this pilot study aimed to (1) investigate if there is a significant correlation between blood THC concentration and any eye characteristics/movements (i.e., eye-tracking features) when driving; (2) assess whether there exists a significant correlation between eye-tracking features and specific driving performance measures (i.e., SDLP, mean speed) as objective measures of impairment; and (3) identify those eye-tracking features showing a significant decreasing or increasing trend over time following exposure to cannabis.

Ultimately, our research aims to develop reliable nonintrusive artificial intelligence (AI)-based cannabis screening technologies using eye-tracking to improve road safety. These AI-based systems can either be used at roadside by law enforcement as a screening device or be deployed as in-vehicle real-time driving monitoring systems (e.g., for fleet drivers). In both applications, the eye-tracking data as a timeseries need to be segmented into time windows (epochs) for processing and feature extraction. Therefore, this pilot study also investigates the influence of epoch length as a critical variable in processing of the eye-tracking data. In a recent study,[48] we proposed specific eye-tracking features for assessment of fatigue in drivers and demonstrated effectiveness of these features in detection of drowsy driving as a form of impairment. In this work, we use the same eye-tracking features to study the relationship of eye characteristics/movements with THC concentration and driving performance under the influence of cannabis.

Materials and Methods

Participants and data collection

A total of 10 subjects (7 females; mean age ± standard deviation [SD]: 22.7 ± 2.79 years) were included in this pilot study, following eligibility assessment.[49] Participants were approached after completion of a related study[49] (REB 123/2015) to enquire as to interest in participating in this study.

This study was approved by the CAMH Research Ethics Board (REB 076/2018), conducted in accordance with the Declaration of Helsinki and registered on clinical trials.gov. All participants provided informed consent and were financially compensated for participating. Of the 10 participants, 1 had missing driving simulator data and was excluded from analyses related to driving performance (but included in all other analyses). Table 1 summarizes characteristics of participants in this study.

The experiment consisted of a single study session for each participant. At the start of each session, the participant completed a practice driving trial to refamiliarize themselves with the simulator and to be assessed for potential driving simulation sickness (i.e., nausea). In the baseline period, starting ~1 h before cannabis exposure (i.e., reference time), a blood sample was collected and the participant performed a driving simulator trial with simultaneous recording of eye-tracking data.

A single cannabis cigarette containing ~750 mg of plant material with about 10.9% THC was administrated in this study (mean ± standard error of the mean [SEM]: 63 ± 6 mg). Participants were instructed to smoke as they usually do for a maximum of 10 min and told that they could stop, in case of feeling

Table 1. Participant Characteristics, Estimated Δ-9-Tetrahydrocannabinol Dosage (mg), and Range of Blood Δ-9-Tetrahydrocannabinol Concentration (ng/mL)

Participant ID	Gender(F/M)	Age (years)	BMI (kg/m^2)	Cannabis use frequency (per week)	Estimated THC dosage (mg)[a]	Range of blood THC concentration (ng/mL)[b]
S001	M	26	23.89	3	89.49	0 to 2.9
S002	F	22	20.21	4	83.93	0 to 13.4
S003	F	20	24.91	3	38.37	0 to 9.9
S004	M	26	34.18	3	61.48	0 to 41.8
S005	F	26	22.50	1	83.93	0 to 3.8
S006	M	21	25.92	1	56.46	0 to 25.5
S007	F	20	21.97	4	48.40	0 to 8.2
S009	F	22	23.03	4	45.89	0.8 to 22
S010	F	25	31.92	3	81.42	1.1 to 30
S011	F	19	21.78	1	47.85	0 to 21.6
All: mean ± SD	—	22.7 ± 2.79	25.03 ± 4.56	2.7 ± 1.25	63.72 ± 19.15	0.19 ± 0.4 to 17.91 ± 12.5

[a]The estimated dose of THC based on the change in weight of the cannabis cigarette after smoking.

[b]Measured between ~5 min (maximum value) and 5 h (minimum value) after cannabis exposure. The baseline blood THC concentration (measured at ~ −1 h) was 0 ng/mL for all participants.

BMI, body mass index; SD, standard deviation; THC, Δ-9-tetrahydrocannabinol.

ill or achieving a high greater than they would normally experience. After completion of cannabis exposure (i.e., time zero, referring to the time that the participants stopped smoking), participants performed seven driving trials with simultaneous recording of eye-tracking data at ~15 min, 35 min, 1 h, and then hourly until 5 h. In addition, vital signs and blood samples (for THC concentration) were collected at ~5 min, 25 min, 1 h, and then hourly until 5 h. All driving trials (including the baseline) were identical. Figure 1 presents the overall blood concentration of THC over the course of the session. It is worth highlighting that the THC concentration in whole blood is about half of the concentration in plasma.[50]

In this study, a Virage VS500M driving simulator with three 50-inch screens providing a 180° field of view in the front and dynamic force feedback on the steering wheel and pedals was used. The system recorded driving metrics at 60-Hz sampling rate. SDLP and speed were used as measures of driving performance under the influence of cannabis. The simulation depicted a two-lane rural highway ~9 km in length with oncoming traffic. Participants were instructed to follow the main road, maintaining a speed of 80 km/h and their position in the center of the lane, and to interact with other vehicles and obstacles as they normally would in the real world. SmartEye Pro 8.0, a research-grade eye-tracking system with two infrared cameras,[48] was utilized to capture eye-tracking data with the sampling rate of 60 Hz and accuracy of 0.5° (gaze measurement).

Manipulation check

SDLP (mean ± SEM) increased above baseline (0.28 ± 0.01) values at 15 min (0.31 ± 0.02), 35 min (0.30 ± 0.01), 1 h (0.32 ± 0.03), 2 h (0.31 ± 0.02), 3 h (0.32 ± 0.02), and 4 h (0.32 ± 0.02) after smoking cannabis. Paired samples *t*-tests revealed that these increases were significantly different from baseline at 35 min ($t(9) = -2.390$, $p = 0.041$) and lasted until 2 h ($t(9) = 2.589$, $p = 0.029$), 3 h ($t(9) = -3.961$, $p = 0.003$), and 4 h ($t(9) = -6.558$, $p < 0.001$) after smoking.

Eye-tracking features

In this work, a set of 34 specific features, recently introduced by our research group,[48] were extracted from four main categories of raw eye-tracking data: eye

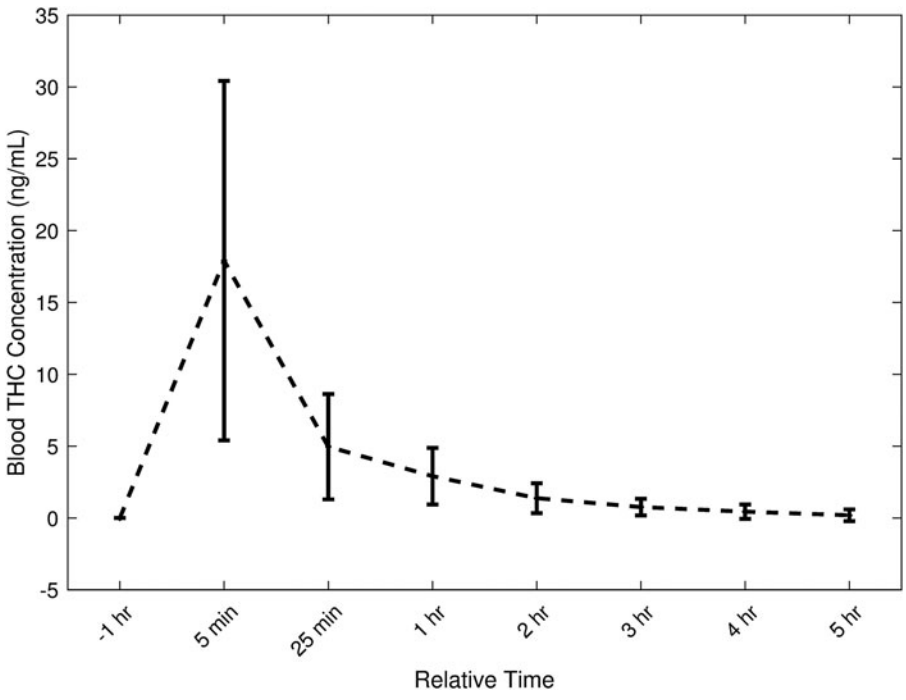

FIG. 1. The overall blood THC concentration. The *x*-axis represents the relative time with respect to the time of cannabis exposure (time: 0; the reference time). The mean and SD calculated over all participants are shown. SD, standard deviation; THC, Δ-9-tetrahydrocannabinol.

gaze, blinks, pupil diameter, and eyelid opening (Supplementary Table S1). The eye gaze data included a two dimensional timeseries representing the heading (left/right) and pitch (up/down) angles in radian. The raw gaze data were further divided into three subcategories: fixation, saccade, and general gaze (all gaze data together). Raw multidimensional eye-tracking timeseries were divided into nonoverlapping epochs (time windows) with the same length to extract features. Not only is time-windowing a necessary step to lay ground for future real-time analysis, but also considering short time intervals is an effective approach to address data nonstationarities.[51] Various epoch lengths (2, 5, 10, 15, or 30 sec) were considered in this study to evaluate the influence of this parameter. A brief description of the extracted features is provided in the following (details in Shahidi Zandi et al.[48]):

- *Mean*, *median*, *and SD* were calculated for every given epoch of the eye-tracking timeseries depending on data category.
- *Duration*, *frequency*, *and percentage:* These features were computed for every epoch of fixation, saccade, and blinking events. *Duration* was the average time interval of a specific eye-tracking event. *Frequency* was the number of incidents divided by the epoch length, and *percentage* was the length sum of all incidents divided by the epoch length.
- *Scanpath* was calculated as the sum of the absolute difference between every two consecutive gaze samples (heading or pitch dimension) for every epoch.
- The average gaze *velocity* in any given epoch was calculated for heading and pitch dimensions.
- The differential *entropy*[52] of general gaze data in each dimension was computed for every epoch.
- *Similarity Index* was computed to measure the similarity among two-dimensional gaze sample points in every epoch based on a correlation sum measure.[53]

All eye-tracking features were normalized with respect to the baseline trial to reduce the intersubject and intertrial variability.

Data analysis

In this study, the blood THC concentration, SDLP, and speed were considered target variables to evaluate the possibility of using eye-tracking features for cannabis screening.

Given a specific eye-tracking feature for every participant, the median of that feature over all epochs in each driving trial after exposure to cannabis was calculated. Then, the average of the median values was computed across all participants for each trial to form a temporal profile for that feature (i.e., average of medians vs. trial).

In addition to eye-tracking features, a temporal profile was also generated for each target variable. For driving performance measures, after windowing the corresponding timeseries into the epochs with the same length as those used for eye-tracking feature extraction, the SDLP and speed were calculated for every epoch. In the next step, the same data processing procedure used for eye-tracking features (i.e., average of medians) was used to generate a temporal profile for each of these driving performance target variables. For THC, measurements from blood samples taken either just before or at the beginning of each driving trial (after exposure to cannabis) were used to form the temporal profile.

Then, the cross-correlation between the temporal profile of each feature and that of every target variable was calculated (Supplementary Figures S1–S3 show examples of time profile of selected normalized eye-tracking features vs. the target variables). In addition, we conducted a nonlinear regression analysis to identify those eye-tracking features showing a significant semimonotonic trend (increasing or decreasing) over time. For this purpose, an exponential fit to the data was estimated. Considering that the general influence of cannabis decreases over time, this analysis could be helpful for understanding the overall effects of cannabis on eye movements/characteristics.

Results

Correlation analysis

The cross-correlation between the temporal profiles of features and target variables (after cannabis exposure) was calculated. Table 2 presents the top 5 eye-tracking features with a statistically significant correlation ($p < 0.05$) with blood THC, given different epoch lengths. The variation seen in the list and order of the top features per epoch length may be due to the differential influence of epoch length on feature distributions. Figure 2a and b show the influence of epoch length on correlation between eye tracking features and the blood THC concentration. Figure 2a presents the number of individual features with significant correlation ($r \geq 0.5$, $p < 0.05$) per epoch length, and Figure 2b summarizes the distribution of the correlation values for all features given each epoch length.

Table 2. Top 5 Eye Tracking Features with Significant Correlation to Blood Δ-9-Tetrahydrocannabinol Concentration

Epoch length	2 Sec	5 Sec	10 Sec	15 Sec[a]	30 Sec
Feature (r)[b]	Gaze SD (P) (**0.87**)	Saccade velocity (P) (**0.82**)	Fixation percentage (**0.92**)	Mean pupil diameter (**0.86**)	Gaze scanpath (P) (0.81)
	Mean pupil diameter (**0.86**)	Mean pupil diameter (0.82)	Mean pupil diameter (**0.84**)	Gaze SD (P) (**0.84**)	Mean pupil diameter (0.81)
	Gaze entropy (H) (0.73)	Gaze entropy (P) (0.81)	Gaze SD (P) (0.81)	Fixation percentage (0.73)	Gaze SD (P) (0.79)
	Saccade frequency (0.7)	Gaze entropy (H) (0.8)	Saccade velocity (P) (0.77)	Saccade frequency (0.65)	Fixation percentage (0.75)
	Fixation frequency (0.68)	Gaze SD (P) (0.79)	Saccade frequency (0.67)	—	Saccade frequency (0.6)

[a]Only four features showed a strong correlation at the significant level of $p < 0.05$ for the epoch length of 15 sec.
[b]$p < 0.05$. Bolded quantities indicate the statistically significant correlations after *Bonferroni* multiple-comparison correction ($p < 0.05$).
H, heading angle; P, pitch angle.

According to the results, mean pupil diameter and gaze SD (pitch angle) present a significant correlation with blood THC concentration for all epoch lengths, whereas saccade frequency and fixation percentage show a strong correlation in four and three epoch lengths, respectively. After correction for multiple comparisons, the correlation between mean pupil diameter and blood THC concentration remains significant at the $p < 0.05$ level for three epoch lengths. On the contrary, the one-way analysis of variance (ANOVA) revealed no significant effect of epoch length on overall correlation between blood THC concentration and eye-tracking features, $F_{(4,24)} = 0.247$, $p > 0.9$.

In the case of SDLP, a significant correlation with median gaze (heading angle), gaze scanpath (heading angle), saccade percentage/duration was observed for most epoch lengths (Table 3). Gaze median, scanpath, and SD (heading angle) showed significant correlation with SDLP ($p < 0.05$), after *Bonferroni* multiple-comparison correction, for 10- or 15-sec epoch lengths. Figure 2c and d present the number of features with significant correlation with SDLP and the corresponding distribution of correlation values for each epoch length. Overall, the effect of epoch length on correlation with SDLP was not statistically significant based on a one-way ANOVA test: $F_{(4,35)} = 1.994$, $p > 0.1$.

Considering speed, the correlation analysis revealed a strong relationship between vehicle speed and some saccade-related features. As reported in Table 4, saccade duration, saccade scanpath (heading angle), and saccade percentage are among the top 5 features showing a significant correlation with speed for almost all epoch lengths. Saccade-related features also showed significant correlation with speed at 2- or 5-sec epoch lengths, after correction for multiple comparison. Figure 2e and f present the total number of features with significant correlation to speed for each epoch length and the distribution of this correlation. A one-way ANOVA test revealed that epoch length significantly affected the overall correlation between eye-tracking features and speed: $F_{(4,39)} = 3.385$, $p = 0.018$.

Analysis of temporal trend

Due to the fact that the general influence of cannabis decreases over time, we also conducted a nonlinear regression analysis by fitting an exponential curve into the temporal profile of every eye-tracking feature for each epoch length. The goal of this analysis was to identify those features showing a significant temporal trend (increasing or decreasing) after cannabis exposure. This significant trend, if reflecting a true effect, can be interpreted as a significant correlation between the eye-tracking feature and the general effect of cannabis.

Table 5 presents the top 5 eye-tracking features with a significant increasing/decreasing temporal trend following the cannabis exposure for various epoch lengths, where adjusted R^2 (as the goodness-of-fit) and F-statistic (exponential trend vs. constant) are reported for each case. Figure 3 shows the total number of features with a significant temporal trend (adjusted $R^2 \geq 0.7$, $p < 0.01$) and the corresponding adjusted R^2 mean ($\pm$SD) as well as the distribution of adjusted R^2 for all features, given each epoch length. According to the results of this analysis, cannabis reduced saccade-related features such as velocity, scanpath, and duration (i.e., significant increasing trend observed for these features as time elapsed and the influence of cannabis decreased). On the contrary, the fixation percentage and pupil diameter (mean) significantly decreased over time as the influence of cannabis was reduced (i.e., cannabis administration increased these features in short

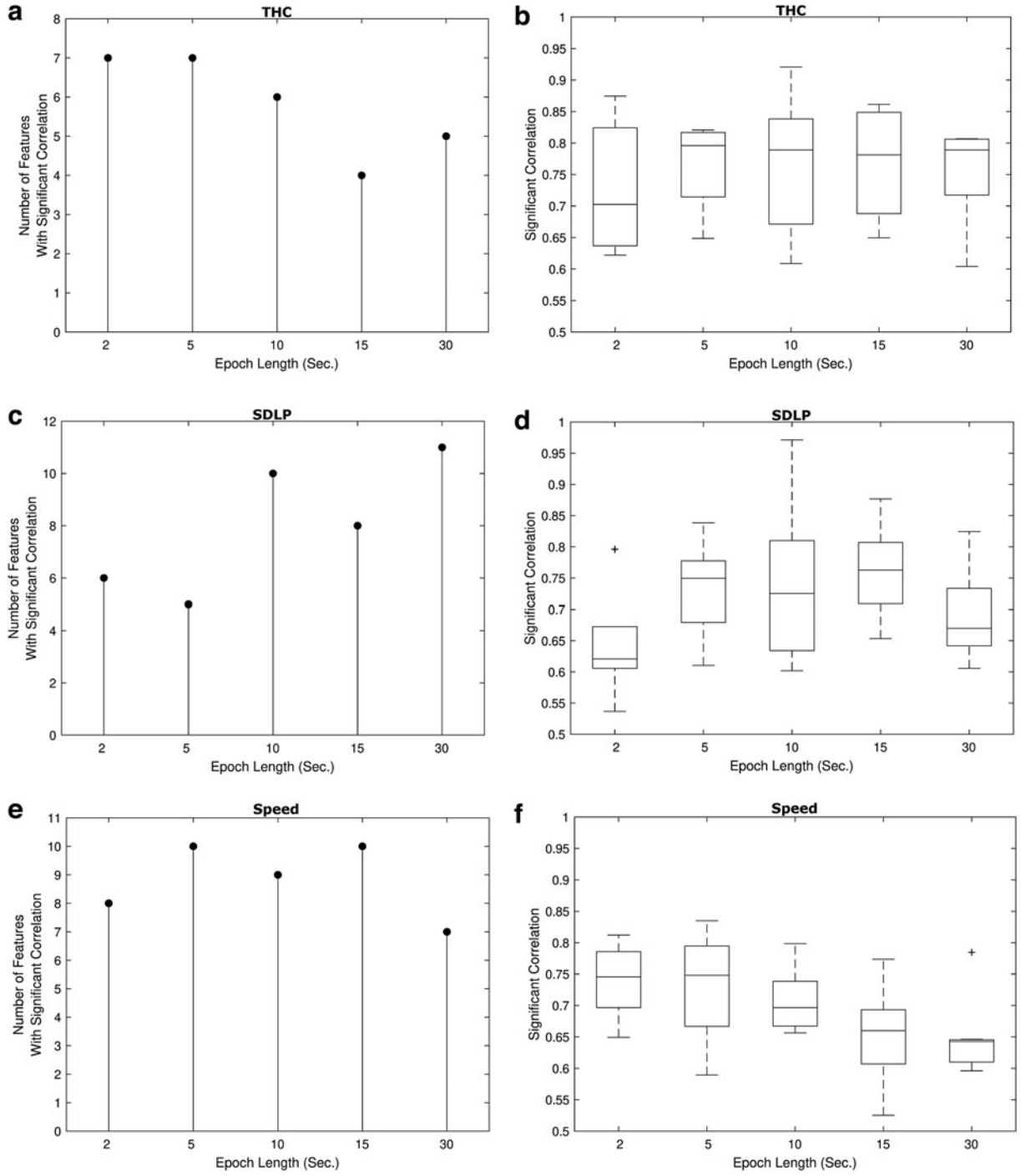

FIG. 2. Correlation between each target variable and eye-tracking features. **(a, c, e)** Number of features individually showing a significant correlation ($r \geq 0.5$, $p < 0.05$) with blood THC concentration, SDLP, and speed, respectively, for each epoch length. **(b, d, f)** The distribution of the correlations for every epoch length (with blood THC concentration, SDLP, and speed, respectively). SDLP, standard deviation of lateral position.

Table 3. Top 5 Eye Tracking Features with Significant Correlation to Standard Deviation of Lateral Position

Epoch length	2 Sec	5 Sec	10 Sec	15 Sec	30 Sec
Feature (r)[a]	Median gaze (H) (0.79)	Blink duration (**0.84**)	Gaze scanpath (H) (**0.97**)	Median gaze (H) (**0.88**)	Saccade duration (0.82)
	Saccade duration (0.67)	Median gaze (P) (0.76)	Gaze SD (H) (**0.94**)	Gaze scanpath (H) (0.82)	Saccade scanpath (H) (0.75)
	Saccade percentage (0.62)	Median gaze (H) (0.75)	Median gaze (H) (0.81)	Eyelid opening SD (0.8)	Median gaze (H) (0.75)
	Gaze scanpath (H) (0.62)	Blink percentage (0.7)	Saccade percentage (0.77)	Gaze SD (H) (0.8)	Fixation velocity (H) (0.7)
	Median gaze (P) (0.6)	Saccade percentage (0.61)	Blink duration (0.76)	Pupil diameter SD (0.73)	Fixation scanpath (H) (0.67)

[a]$p < 0.05$. Bolded quantities indicate the statistically significant correlations after *Bonferroni* multiple-comparison correction ($p < 0.05$).

time). A one-way ANOVA test revealed no significant effect of the epoch length on adjusted R^2 over all features, that is, Figure 3c: $F_{(4,116)} = 0.333$, $p > 0.85$.

Discussion and Conclusion

In this preliminary study, we investigated the use of eye-tracking information for nonintrusive assessment of the influence of cannabis on driving performance. A set of 34 specific features were extracted from eye-tracking data acquired during consecutive driving simulator trials from 10 volunteers, where the driving performance measures were simultaneously recorded and blood samples were taken before or at the beginning of each trial to measure THC concentration. The general temporal trend of these features as well as the cross-correlation between each feature temporal profile and that of every target variable (blood THC concentration, SDLP, and speed) were studied.

The overall results showed a significant correlation between some eye-tracking features and all three target variables, although the set of top features with a significant correlation varied by epoch length and target variable. Overall analysis of correlation data (one-way ANOVA) showed that the epoch length had a significant effect on the correlation between eye-tracking features and speed ($p < 0.05$); however, no significant influence of epoch length was observed for blood THC concentration or SDLP ($p > 0.1$). This implies that blood THC concentration and SDLP may be more reliable target/objective measures, which can be an important consideration in the development and assessment of real-time eye-tracking-based cannabis screening systems. As shown in Tables 2–4 (for blood THC concentration, SDLP, and speed), there existed multiple features that showed a significant correlation with the given target variable in at least three out of five different epoch lengths. It is worth noting that in assessing the correlation between a given target variable and eye-tracking features in this *exploratory* analysis, we focused on each feature behavior in the absence of all other features (i.e., one feature at a time). Although we also did correct for multiple comparisons while evaluating the statistical significance of the correlations for each epoch length, we were particularly interested in the performance of every feature individually, not the entire feature set. Therefore, the significance of the correlation between specific features and a target variable (e.g., SDLP) should not be extended to the overall correlation between the eye-tracking data and that target variable. The motivation behind this approach was to use this study as a preliminary *feature selection* phase before future phases of developing an AI-based cannabis screening system.

Table 4. Top 5 Eye Tracking Features with Significant Correlation to Speed

Epoch length	2 Sec	5 Sec	10 Sec	15 Sec	30 Sec
Feature (r)[a]	Saccade velocity (H) (**0.81**)	Saccade duration (**0.83**)	Saccade duration (0.8)	Gaze scanpath (H) (0.77)	Saccade percentage (0.78)
	Saccade duration (0.8)	Saccade velocity (H) (**0.81**)	Saccade percentage (0.74)	Saccade percentage (0.75)	Saccade duration (0.65)
	Gaze scanpath (H) (0.77)	Fixation velocity (H) (**0.79**)	Saccade scanpath (H) (0.74)	Saccade duration (0.69)	Pupil diameter SD (0.64)
	Saccade scanpath (H) (0.76)	Saccade scanpath (H) (0.79)	Blink percentage (0.71)	Blink frequency (0.69)	Blink frequency (0.64)
	Saccade percentage (0.73)	Gaze scanpath (H) (0.75)	Saccade scanpath (P) (0.7)	Saccade scanpath (H) (0.68)	Fixation velocity (H) (0.61)

[a]$p < 0.05$. Bolded quantities indicate the statistically significant correlations after *Bonferroni* multiple-comparison correction ($p < 0.05$).

Table 5. Top 5 Eye Tracking Features with Significant Increasing/Decreasing Temporal Trend (Adjusted $R^2 \geq 0.7$)

Epoch length	2 Sec	5 Sec	10 Sec	15 Sec	30 Sec
Feature [T^a, adjusted R^2, $F_{(2,8)}$]	Gaze SD (P) [**D**, 0.97, 148]	Gaze scanpath (H) [**I**, 0.97, 180]	Mean pupil diameter [**D**, 0.97, 157]	Mean pupil diameter [**D**, 0.94, 85.3]	Saccade duration [**I**, 0.97, 181]
	Mean pupil diameter [**D**, 0.94, 82.8]	Mean pupil diameter [**D**, 0.95, 100]	Fixation percentage [**D**, 0.88, 36.4]	Saccade duration [**I**, 0.83, 24.8]	Mean pupil diameter [**D**, 0.95, 90.1]
	Saccade velocity (H) [**I**, 0.94, 74.9]	Saccade velocity (H) [**I**, 0.93, 68.4]	Saccade scanpath (P) [**I**, 0.84, 27.2]	Saccade scanpath (H) [**I**, 0.81, 23]	Saccade scanpath (H) [**I**, 0.81, 21.8]
	Saccade scanpath (H) [**I**, 0.93, 70.3]	Saccade scanpath (H) [**I**, 0.92, 57.7]	Saccade duration [**I**, 0.84, 27.2]	Saccade velocity (H) [I, 0.74, 15.2]	Saccade scanpath (P) [I, 0.7, 12.4]
	Saccade duration [**I**, 0.81, 22.1]	Saccade duration [**I**, 0.87, 33.6]	Saccade scanpath (H) [**I**, 0.78, 19]	Saccade scanpath (P) [I, 0.73, 14.3]	Median gaze (H) [I, 0.7, 12.3]

[a]The temporal trend of the feature: increasing (I) or decresing (D). Bold letters indicate $p < 0.001$; otherwise the trend was significant at $p < 0.01$.

The analysis of features' temporal profiles revealed a significant increasing or decreasing trend over the course of ~5 h following exposure to cannabis for several features (Table 5 and Fig. 3). Saccade-related features, including duration, velocity, and scanpath, were significantly attenuated by cannabis (i.e., showing a significant increasing trend over time after the exposure), while other features such as the fixation percentage and mean pupil diameter significantly decreased over time following cannabis (i.e., cannabis had an

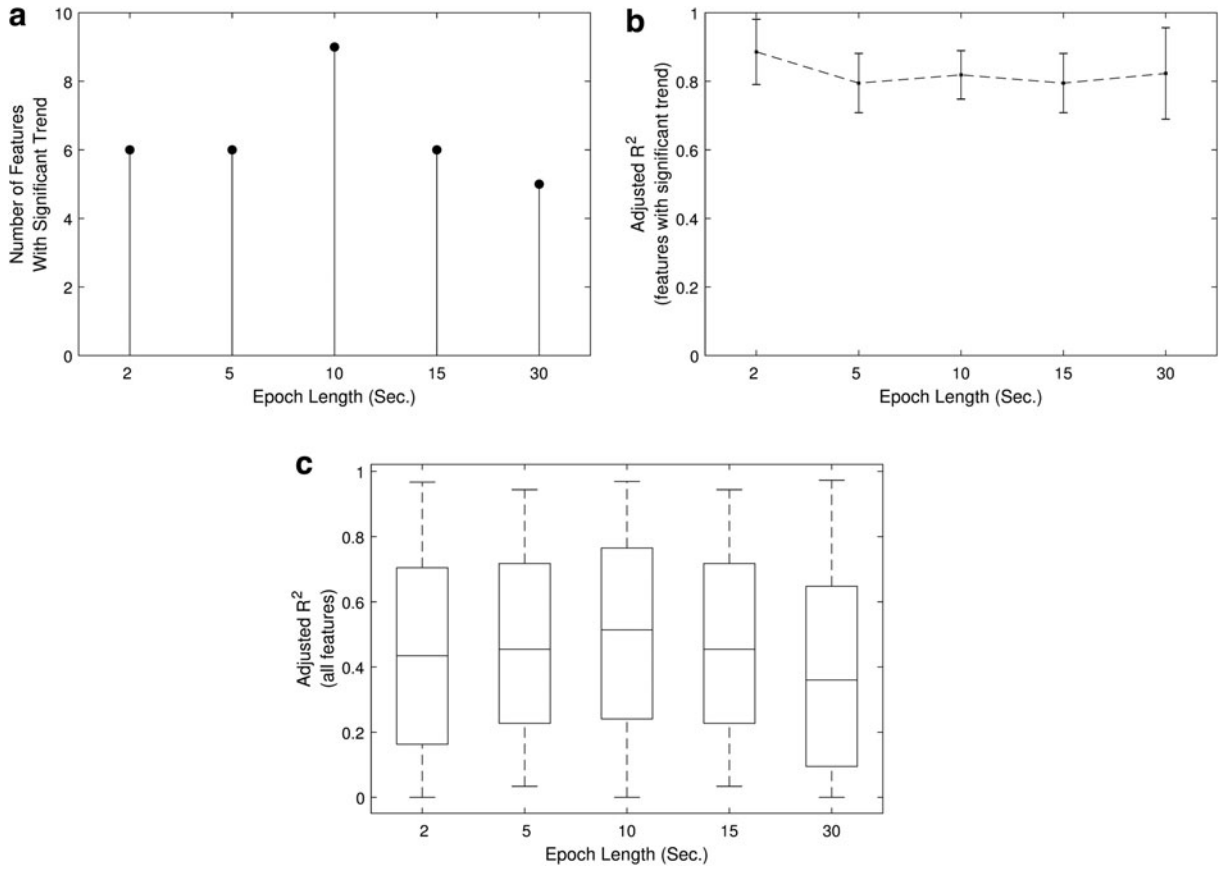

FIG. 3. Temporal trend analysis for eye-tracking features (following cannabis exposure) at different epoch lengths: **(a)** number of features showing a significant increasing or decreasing trend (adjusted $R^2 \geq 0.7$, $p < 0.01$), **(b)** the mean (±SD) of adjusted R^2 for features with significant trend, and **(c)** the distribution of adjusted R^2 over all features.

amplifying effect on these eye characteristics). Overall, results did not show a significant effect of epoch length on the goodness-of-fit measure (one-way ANOVA test).

It should be noted that continued improvement in driving simulator performance may have occurred as a result of practice effects. However, improved performance from practice is greatest early in task engagement.[54] All participants previously took part in a multisession study using this driving simulator; thus, the impact of practice effects were expected to be minimal.

This pilot study clearly suggests that specific eye-tracking features can be significantly affected by cannabis, and therefore may be used as nonintrusive markers of THC presence in the body and its influence on driving performance (i.e., assessment of impairment). The ultimate objective of this research is to develop reliable cannabis screening technologies to reduce drug impaired-driving incidents in the transport-industry, public transit, and passenger vehicles. In particular, the findings of this study may be useful in the design and development of advanced AI techniques for rapid and cost-effective roadside screening of cannabis or for in-vehicle driver monitoring, which can use a selected set of eye-tracking features as inputs and predict either the presence/probability of THC or estimate the chance of impairment, depending on the target variable used. One limitation of this pilot study is the absence of a placebo control group. As a future step, placebo-controlled studies using larger gender-balanced groups of participants with diverse histories of cannabis use need to be conducted to further investigate the influence of cannabis on the relationship between various eye-tracking features and potential target variables. It is also important to include participants from different age groups and with various levels of driving experience. The influence of various road conditions (including real driving situations) and prior driver knowledge of the road should be examined. Also, the effects of combining cannabis with other causes of driver impairment, such as alcohol, fatigue, and other drugs, on eye-tracking data need to be investigated.

Author Disclosure Statement

Dr. Shahidi Zandi is an ACS employee and has no competing financial interests to report. Mr. Felix Comeau is the ACS President/CEO and has no competing financial interests to report. Dr. Mann has no competing financial interests to report. Dr. Di Ciano, Mr. Arslan, and Mr. Murphy have no conflicts to report. Dr. Le Foll has obtained funding from Pfizer (GRAND Awards, including salary support) for investigator-initiated projects. Dr. Le Foll has/will received some in-kind donation of cannabis product from Canopy and Aurora and medication donation from Pfizer and Bioprojet and was provided a coil for TMS study from Brainsway. Dr. Le Foll has performed research with industry funding obtained from Canopy (through research grants handled by CAMH or University of Toronto), Bioprojet, ACS and Alkermes. Dr. Wickens has no confict of interest to report.

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Supplementary Material

Supplementary Table S1
Supplementary Figure S1
Supplementary Figure S2
Supplementary Figure S3

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Abbreviations Used

AI = artificial intelligence
ANOVA = analysis of variance
CAMH = Centre for Addiction and Mental Health
DUIC = driving under the influence of cannabis
SD = standard deviation
SDLP = standard deviation of lateral position
SEM = standard error of the mean
SFST = standardized field sobriety test
THC = Δ-9-tetrahydrocannabinol