TITLE: Detecting Changes in Pupil Response Trajectories to Light after Cannabis Consumption

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INTRODUCTION:

According to the National Survey on Drug Use the rates of cannabis consumption has increased in adults over 26 and adults aged 18-25 from 4.0% to 7.9% and from 17.3% to 22.1%, respectively (Lira 2021). Along with increases in consumption, there have been increases in cannabis involved motor vehicle fatalities from 9.0% in 2000 to 21.5% in 2018 (Lira 2021), and while cannabis consumption at- or before- work is of concern to employers with regards to occupational injury, the literature on the topic is mixed (Biasutti, 2020 and Zhang 2020) with temporality of exposure being a major concern. However, there is strong biological evidence of the impairment caused by cannabis consumption depend on the route of administration (Goldsmith 2015 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4410963/> ). To better understand the impairment of cannabis in driving and in the workplace an impairment test is needed.

There are a variety of tests that may have the potential to detect impairment under the influence of cannabis; however, many of these tests have shown a reduction in effectiveness when administered on frequent cannabis users. A more general test used for alcohol and drug impairment is the Standardized Field Sobriety Tests, which is composed of the horizontal gaze nystagmus, walk and turn and one-leg stand with an additional component of head movements and/or jerks added specifically to improve assessment of impairment due to drugs (Downey 2015). While shown to an accurate and reliable assessment for alcohol impairment, it has limited ability to identify drug use (Downey 2015). Another test possibility is a plasma concentration of THC and its metabolite THCCOOH from a blood draw; however predictive models have better performance in participants abstaining for several days compared to daily users (Burt 2021 <https://www.sciencedirect.com/science/article/pii/S037907382100222X> ) Additionally, for frequent users who maintain elevated levels of blood plasma THC, the reduction in performance shows a tolerance effect so that the levels of THC and performance correspond less (Burt 2021).

One test that may have a resistance to the tolerance effect is the pupillary light reflex. This test is administered by shining a light in the eye of the subject and measuring the pupil constriction and rebound dilation over the course of several seconds. Evidence on the acute effect of THC on pupillary light reflex is mixed with several studies showing decrease, increase and no effect on the static pupil diameter (Brown et al., 1977; Ortiz-Peregrina et al., 2020; Stark et al., 2003; Merzouki et al., 2008; Shahidi Zandi et al., 2021; Fant et al., 1998; Newmeyer et al., 2017). In two studies, the pupillary light reflex was diminished after cannabis consumption (Fant 1998 and Campobasso 2020).

There are three objectives to this analysis. First, we will compare the ability of a model using the full trajectory of the pupillary light reflex versus a model using single values feature summaries to discriminate between smokers and non-smokers. Second, we will estimate differences in the pupillary light reflex based on self-reported cannabis consumption frequency categories and finally we examine the effect of a time delay in testing after cannabis consumption on the estimating full trajectories of the pupillary light reflex.

METHODS:   
*Sample Information:*

Pupillary light reflex trajectories were collected in 101 healthy participants with enrolled in groups of daily, occasional and no cannabis consumption. Daily cannabis consumption was defined as smoking or vaping a cannabis flower product at least one time per day, every day of the week for 30 days prior to enrollment (N = 33); occasional consumption was defined as smoking or vaping cannabis flower product on at least one day but no more than two day per week in the 30 days prior to enrollment (N=36); and no cannabis consumption was defined as not having used cannabis in the month prior to enrollment (N=32). Videos of the pupillary light reflex test were recorded prior and post cannabis consumption on the study visit date and processed using task-specific video segmentation techniques (Steinhart Thesis), to create a frame-level trajectory of percent change from baseline values of pupil size for each eye on each participant at time point (prior and post consumption). After video segmentation and pre-processing, 88 post consumption trajectories of the right eye were collected, and after removing one outlier and matching to pre-consumption a total of 84 participants were used in this analysis.

In this sample of 84 participants, there were 29 non-users, 30 occasional and 25 daily users. Participants ranged in age from 25.1 to 45.3 years with an average of 32 years (sd = 5.02); an average BMI of 25.4 kg/m2 (sd. 4.41); and approximately 58% male (N = 49) (see Table 1). Time between cannabis consumption and post testing varied from 53 – 84 minutes with a median of 62 minutes. Participants in the no use category were allowed to rest with their eyes closed for approximately equal time as allowed for cannabis consumers to use cannabis.

*Functional Data Analysis*

Functional data analysis (FDA) is a field of statistics that models curves or trajectories of information without extracting pre-defined specific features. It allows examination of differences in the patterns of the curves as it relates to an outcome, and how the patterns of the curves differ based on individual characteristics. Two methods of FDA were used in this analysis (1) scalar-on-function regression (SoFR) and (2) function-on-scalar regression (FoSR). In SoFR, an outcome, such as cannabis consumption status, is regressed on the trajectories to find differences in the trajectories that are associated with the outcome. However, in FoSR the trajectories are regressed on covariates such cannabis use frequency to determine how the trajectories differ by the covariate. In this analysis, a SoFR model was used to determine the subtle differences in the pupillary light reflex that discriminate between cannabis users versus non-users, while the FoSR models were used to distinguish trajectory patterns that are associated with cannabis use frequency. Additionally, due to the variability in the time from cannabis consumption to the post test, a FoSR model was used to explain differences in trajectories due to cannabis use frequency and time differences in wait time between cannabis use and testing.

Although, the pupillary light reflex trajectories had been preprocessed and smoothed through the video segmentation pipeline (Ben’s thesis), adequate representation across the domain (i.e. test time) is required for the estimation of differences in trajectories by covariate and especially when using the trajectories to discriminate between smokers and non-smokers (i.e. SoFR modeling), so the trajectories were truncated to 400 frame, approximately 13.3 seconds after the start of the light test. This truncation seemed to compass the full reflex response for most of the sample, although specific ends to the test were not annotated in the videos.

*Prediction Analysis*

Two separate logistic regression model were used to predict cannabis user and not users. The first model used single value summaries of the trajectory data which included: (a) minimal constriction, the magnitude of peak decrease as a percentage of the pre-illumination diameter; (b) AUC, the magnitude of rebound dilation after the point of minimal constriction; and (c) the slope of the rebound after the point of minimal constriction (Steinhart thesis). The second model used the prediction from the SoFR model, which assessed information from the full trajectory of the pupillary light reflex during the post test. Receiver operating characteristic curves (ROCs) for each model were used to assess the accuracy of the models with area under the curve.

Analysis Software

All analyses were conducted in R (version 4.0.2) using with the mgcv package used for the analysis.

RESULTS:

The ROC curves for the prediction analysis compared the discrimination ability for two models; one uses summary features of the trajectory of the pupillary light reflex and the second used the full trajectory of the pupillary light reflex (Figure 1). The AUCs, used to quantify the discrimination ability of the model, for these prediction models ranged from 0.68 to 0.71, with the model using the full trajectory of pupillary light reflex having the higher AUC. This indicates that models using full trajectory information of pupillary light reflex may have the ability to discriminate between cannabis smokers and non-smokers better than feature-based models.

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| Figure 1: ROCs Evaluating the Discrimination Ability between Smokers and non-Smokers for Summary Feature vs Full Trajectory Models |
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| Receiver Operator Characteristic curves (ROCs) evaluate the prediction accuracy for different models, with a higher prediction accuracy indicated by a higher AUC and the ROC curve following the left and top edge of the graph. The model depicted with the blue line was constructed with summary features of pupillary light reflex which included the point of minimal constriction, the area under the curve after the point of minimal constriction and the rebound dilation slope after the point of minimal constriction. The model depicted with the yellow was constricted with the full trajectory of pupillary light reflex without creating summary features. Although similar, the model utilizing the full trajectory data has better discrimination ability between smokers and non-smokers. |

The full trajectory model used in the prediction analysis was a SoFR model that found differences in the average trajectory of smokers and non-smoker to predict the group for each trajectory. A plot of the odds ratio between smoker and non-smoker trajectories is shown. From this plot in Figure 2, and statistically significant differences are seen between 2.03 and 3.73 seconds with a maximum difference at 2.97 seconds (OR: 2.66, 95% CI: [1.28, 5.50]) and between 5.7 and 7.3 seconds with a peak difference at 6.57 seconds (OR: 0.37, 95% CI: [0.17, 0.81]).

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| Figure 2: Plot of Logistic Regression Model to Discriminate between Smokers and non-Smokers |
| Chart, line chart  Description automatically generated |
| The dashed lines indicate the 2\*SE confidence interval around the Odds Ratio (OR) estimate.  The plot depicts the odds ratio (OR) of being a smokers vs non-smokers across the time course of the pupillary light reflex. High ORs would increase the probability of predicting a smoker. The red line indicates no difference between smokers and non-smokers, and areas where the confidence interval (both dashed lines) are above or below the red line indicate statistically significant differences between smokers and non-smokers. |

The FoSR model was used to show differences between the average trajectories of pupillary light reflex in daily, occasional and non-users. A separate model estimated the average trajectory of smokers and non-smokers. In Figure 3, the average trajectories are plotted with solid lines for cannabis use frequency and a dashed line was overlaid for all smokers. The non-user and non-smokers encompass the same individuals and therefore overlap completely. From the figure, we can see a stronger initial constriction in non-users and a steady rebound after the light test; however, in smokers of both groups there is less initial constriction, and the slope of the rebound dilation is shallower.

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| Figure 3: Average Pupillary Light Reflex Trajectories by Cannabis Use Frequency |
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| Average pupillary light reflex trajectories are plotted by cannabis use frequency. An additional dotted lined based on the average trajectory for smokers, was included to show differences between smokers and non-smokers (non-users). |

Using the FoSR model, we depict the differences between the average trajectories for occasional and non-users, daily and non-user and daily and occasional users (Figure 4). These plots show regions of significant difference between occasional and non-users as well as daily and non-user; however, there are no significant differences in the average trajectories of daily and occasional users. When comparing occasional and non-user the most prominent differences are seen between 1.77 to 3.97 seconds with a peak difference at 2.87 seconds of 4.00% (95% CI : 1.32%,6.68%), and between daily and non-users there is significant difference region in a similar time period from 2.1 to 2.73 seconds with a peak difference at 2.5 seconds of 2.88% (95% CI: 0.14%, 5.62%).

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| Figure 4: Plot Depict the Difference between Occasional, Daily and Non-users of cannabis in Pupillary Light Reflex |
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| The plot shows the difference in average trajectories between pairs of occasional, daily and non-user of cannabis. The red line indicates no difference between the average trajectory of two groups, while a region where the confidence interval (both dashed lines) is above or below the red line indicate statistically significant differences between trajectories. The figure demonstrates significant regions of difference between occasional and non-users and daily and non-users; while there is no significant difference between occasional and daily users. |

The effects of the testing delay after cannabis consumption may impact the results of the previous analyses, so we examined the distribution of this testing delay and modelled it’s effects the mean trajectories of smokers at delay times of 60, 65, and 70 minutes from cannabis consumption. The distribution of the testing delay is show in Figure 5. The testing delay ranged from 53 to 84 minutes with a mean of 62.22 minutes (sd = 5.57). Figure 6 depicts the average trajectory of non-smoker and smokers with a 60-, 65-, and 70-minute delay in testing. As shown in the figure, the initial pupil constriction after the start of the light test is reduced in smokers with less delay in testing and reaches constriction similar to non-smoker with a longer delay in testing. However, the slope of the rebound dilation is still shallower in smokers with any of test delay compared to non-smokers.

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| Figure 5: The distribution of time delay in testing post cannabis consumption |
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| The plot shows the distribution of the time delay from cannabis smoking to the post pupillary light reflex test for cannabis smokers. The red line indicates the mean of the distribution at 62.7 minutes with an interquartile range between 59 – 66 minutes. |

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| Figure 6: The Effect of delayed testing post consumption on the average trajectory of the pupillary light reflex for smokers |
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| The plot depicts the differences in the average pupillary light reflex response as the time from smoking increases from 60 minutes to 70 minutes (lighter color). The red line shows the average trajectory of a non-smoker. With longer delays in the test time, the point of minimal constriction seems to match that of non-smokers while the rebound dilation appears to remain distinct. |

DISCUSSION:

The ability to detect impairment while under the influence of cannabis is a necessary tool for individuals concerned with occupational and traffic safety. While there have been multiple efforts to define a test for cannabis impairment, many have suffered from tolerance effects with regular cannabis consumption. The current analysis provides evidence that pupillary light reflex has the potential to discriminate between cannabis smokers and non-smokers and that the discrimination ability is better when using the full trajectory of the reflex than using summary features of trajectory. Additionally, the current modelling paradigm demonstrates differences in trajectories of the pupillary light reflex between non-users and occasional users after cannabis consumptions, and those differences persist between non-user and daily user showing a robustness to the effects of drug tolerance which is not seen with other tests. By examining the effects of time delays from consumption to test, we were able to show that the while time delays mitigated the effect on initial pupil constriction, the differences in the rebound effect were maintained, so that a test focusing on rebound effects may be able to discriminate between smokers and non-smokers.

However, there are several limitations to this analysis for which further analysis and more sophisticated instrumentation will be need. Of primary concern were data quality issues that persisted after data processing, imputation and smoothing from the video segmentation pipeline. While most pupillary light reflex trajectories reflected the characteristic pattern of the light reflex there were a minority that were removed because there was no characteristic features of the reflex. This led to a reduction in the sample size from a collection of 101 participant to usable data in 84. While it speaks to the robustness of the method that significant differences were still detected, it also limits the precision of the estimated differences. Additionally, due to improper fit of the pupil tracking googles used in the study, it was not feasible to estimate the baseline pupil size of individual, which is directly related to the amount of change pupils can undergo when exposed to a light stimulus. Being unable to account for the baseline pupil size also increases the imprecision in the estimation of differences in pupillary light reflex trajectories by marijuana use frequency.

Limitations:

1. Sample size small
2. Data noisy, no systematic length of light stimulus; recording googles did not fit well on all subjects
3. Did not adjust for baseline pupil size
4. Prediction analysis did not use an independent test set.

Strength:

1. Participant did not “over” consume cannabis during the test may not have gotten as “high” as they would on a regular basis – but we can still measure an effect difference (not really a limitation)

HOW DOES THIS FIT INTO A LARGE CONTEXT?