TITLE: Detecting changes in pupil response to light associated with cannabis consumption

Authors: Suneeta Godbole, MS

Andrew Leroux, PhD

Ashley Brooks-Russell, PhD

Prem S. Subramanian, MD, PhD

Michael J. Kosnett, MD, MPH

Julia Wrobel, PhD

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 [1]. 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 [1], 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 [2, 3] 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 [4]. 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 [5]. While shown to an accurate and reliable assessment for alcohol impairment, it has limited ability to identify drug use [5]. 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 [6]. 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 [6].

One test that may have not be affected by tolerance to cannabis 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 as shown in Figure 1. Evidence on the acute effect of cannabis on pupillary light reflex is mixed with several studies showing decrease, increase and no effect on the static pupil diameter [7-13]. In two studies, the pupillary light reflex was diminished after cannabis consumption [8, 14]. There is some evidence that there is less pupil constriction and slower rebound dilation due to acute cannabis consumption, but evidence is mixed and warrants further study.

Steinhart et al [15] examined pupil light response in participants with patterns of daily cannabis use, occasional cannabis use, and a no-use control group. After accounting for pre-smoking baseline pupil response, they found evidence that acute cannabis consumption was significantly associated with less pupil constriction in both the daily and occasional use groups. In addition, no significant differences were found between the daily and occasional use groups, indicating that the pupil light response may pick up on physiological responses to cannabis consumption that do not display tolerance effects. However, that study only found significant effects when accounting for pre-smoking baseline pupil response, making it inappropriate for roadside assessments where baseline measurements are not available. In addition, Steinhart et al [15] used single number summaries extracted from the full pupillary response trajectories depicted in Figure 1; collapsing these trajectories results in a loss of information that could potentially be exploited to better discriminate between cannabis use groups.

Using only data from after acute cannabis use, this analysis uses a statistical subfield called functional data analysis (FDA) to leverage the full pupil light response trajectories and examine differences between cannabis use groups and no use controls.. The main conceptual underpinning of FDA is to model the whole trajectory as a unit of observation, and to use the temporal structure and ordering of the trajectory to estimate time-specific effects. In this analysis, , we will first compare the ability of a model using the full trajectory of the pupil light response versus a model using single values feature summaries to discriminate between the cannabis use group and the no-use control group. Second, we will estimate differences in the pupil light response based on self-reported cannabis use frequency categories and finally we examine the effect of a time delay in testing after cannabis use on estimating full trajectories of the pupil light response.

METHODS:   
*Sample Information:*

Data are part of a larger study examining effects of acute cannabis consumption on simulated driving among participants with occasional and daily cannabis use histories, and participant enrollment as well as screening criteria are described in Brooks-Russell et.al., 2021. [16] 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; 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; and no cannabis consumption was defined as not having used cannabis in the month prior to enrollment. Participants in the daily and occasional use groups were observed to consume cannabis flower during a 15-minute interval and were instructed to smoke ad-libitum “the amount you commonly use for the effect you most commonly desire”, and participants in the no use group were invited to relax for the equivalent amount of time.

Videos of pupil response during a light test were collected using SafetyScanTM infrared videography goggles developed by Ocular Data Systems. Trajectories of pupillary light response like that shown in Figure 1 were extracted from the videos using the video segmentation pipeline described in Steinhart et al, 2023. These trajectories represent percent change from baseline values of pupil size for each eye after cannabis consumption (occasional and daily use groups) or after a short rest period (no use control group). Pupillary light reflex trajectories were truncated to 400 frames, approximately 13.3 seconds after the start of the light test.

In the sample of 84 participants used in this analysis, there were 29 participants in a no-use group, and 30 and 25 participants in the occasional and daily use groups, respectively. 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 the pupil light response test varied from 53 – 84 minutes with a median of 62 minutes (see Figure 4).

*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. The term “functional” in FDA refers to the structure of the data instead of a characteristic of the participant or covariates. For the pupil light response, a single functional unit is denoted with yi(t) or xi(t), depending on whether the trajectory is modelled as the outcome or covariate, with t specifying the time at which the measurement was assessed.

Our analysis uses two distinct FDA methods to model differences in pupil response to light across cannabis use groups; these models differ in whether the pupil response trajectory is treated as a covariate or the outcome. The first method is known as scalar-on-function regression (SoFR)[17, 18] in the FDA literature, and treats smoker vs. non smoker as a binary outcome with pupil response trajectory as a covariate. This model is analogous to logistic regression and is given by

As with logistic regession, the binary outcome of smoker vs non-smoking is transformed into the log-odds with a logit function, is an estimated odds of being a smoker in the whole population. For the SoFR model the coefficient is the most interesting since it estimates the log odds of being a smoker at a specific time (t) during the pupil light response test. When this coefficient is exponentiated is interpreted as the odds ratio of being a smoker at a specific time (t) during the pupil light response test. The is a random effect for each individual and the is random noise in the model. In this analysis, a SoFR model will be used to determine the subtle differences in the pupil light response that discriminate between the cannabis use group versus no-use group.

The second FDA method used is function-on-scalar regression (FoSR), which is analogous to linear regression and relates functional responses to scalar covariates (e.g. age, cannabis use group, gender). The FoSR model is

This model is akin to a linear regression with indicator variables for the occasional and daily use groups, estimates the average trajectory of a participant in the no use control group and and estimate the average difference at a specific time (t) between the occasional and control group, and the daily and control group, respectively. Again in this model is a subject level random effect estimating the difference in trajectories for each individual and estimates random noise across the trajectory.

FoSR models will be used to distinguish pupil trajectory patterns that are associated with acute cannabis use in the daily and occasional use groups with pupil trajectory patterns associated with no use. Additionally, due to the variability in the time from cannabis consumption to testing , a separate FoSR model was used to explain differences in trajectories due to time differences in wait time between cannabis use and testing. In this model, the cannabis use groups were collapsed to use and no use control groups and the time delay (TD) from smoking to testing was grand mean centered This model was specified as

In the model the estimate would have the same interpretation as the previous FoSR (e.g the average pupil light response trajectory in the no use control group), can be interpreted as average difference in trajectories at a specific time (t) between no use controls and smokers with an average time delay from smoking to testing, and is interpreted as the average difference at a specific time for an additional minute delay in time to test for smokers. Again, and refer to subject-specific random effects and random noise, respectively.

*Prediction Analysis*

The goal of this portion of the analysis is to build a model that best discriminates between those who recently smoked cannabis (designated “cannabis use” group, combining daily and occasional use groups) and those who did not (designated “no use”). Our main model is the SoFR functional logistic regression model described above; we compare the to a model that uses single value summaries of the trajectory data, including (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, 2023 #18}.We compare both models in their ability to predict cannabis use status, and expect better prediction from the SoFR model because it leverages information from the full pupil response trajectories. Receiver operating characteristic curves (ROCs) for each model were compared to assess the discrimination ability of each model with the metric of area under the curve, where values closer to 1 are interpreted as having a higher discrimination ability.

Analysis Software

All analyses were conducted in R (version 4.0.2).[19] The R packages mgcv[20] and refund [18]were used for functional data models.

RESULTS:

Table 1 (shown below) describes demographic characteristics, THC the active component of cannabis and the delays in time from cannabis consumption to testing. :

|  | **Cannabis Use Group** | | |  |
| --- | --- | --- | --- | --- |
|  | **no-use** (N = 29)1 | **occasional** (N = 30)1 | **daily** (N = 25)1 | **Total** (N = 84)1 |
| **Age (years)** | 32.29 (4.70) | 31.15 (4.75) | 32.75 (5.71) | 32.02 (5.02) |
| **Sex** |  |  |  |  |
| Female | 16 (55%) | 10 (33%) | 9 (36%) | 35 (42%) |
| Male | 13 (45%) | 20 (67%) | 16 (64%) | 49 (58%) |
| **Body Mass Index (kg/m^2)** | 24.94 (4.72) | 24.49 (3.96) | 27.08 (4.26) | 25.42 (4.41) |
| **THC, post consumption (mg/dL)** | 0.00 (0.00) | 9.52 (12.20) | 34.91 (37.26) | 13.84 (25.82) |
| **Time Delay after Cannabis Consumption (mins)** | 0.00 (0.00) | 63.93 (6.26) | 60.16 (3.78) | 40.74 (30.10) |
| 1Mean (SD); n (%) | | | | |

|  |
| --- |
|  |
| Figure 1: A typical pupil light response trajectories, starting a light shining at 0 seconds and then pupil constriction to the point of minimal constriction and finally rebound dilation to pre-light shine pupil size. |

*Prediction analysis between recent cannabis use and no use results*

The ROC curves for the prediction analysis compared the discrimination ability for two models; one used summary features of the trajectory of the pupil light response and the second used the full trajectory of the pupil light response (Figure 2A). The model based on the full trajectory of pupil light response had a higher AUC value (AUC = 0.71) compared to the model based single value summary features (AUC = 0.68). This indicates that models using full trajectory information of pupil light response may have a better ability to discriminate between the cannabis use group and no-use controls than feature-based models.

|  |
| --- |
|  |
| Figure 2: *Panel A*: Receiver Operator Characteristic curves (ROCs) for our two logistic regression models. Higher accuracy in predicting recent cannabis use is indicated by a higher AUC and the ROC curve following the left and top edge of the graph. The model depicted with blue line was constructed with single value summary features of pupil light response. The model depicted with the yellow was constructed with the full trajectory of pupil light response. Although similar, the model utilizing the full trajectory data has better discrimination ability between cannabis users and no-use controls.  *Panel B*: The dashed lines indicate the point wise 95% confidence interval around the Odds Ratio (OR) estimate between smokers and non-smokers. The plot depicts the odds ratio (OR) of being a smokers vs non-smokers across the time course of the pupil light response. High ORs would increase the probability of predicting a smoker. The red dotted segments indicate areas where the confidence interval (both dashed lines) are above or below the critical value, demonstrating statistically significant differences between smokers and non-smokers. |

Because the functional logistic regression model in the yellow line of Figure 2A leverages information in the full pupil response trajectories it is better able to discriminate between participants who have recently used cannabis from those who have not. An added benefit of this model is the ability to visualize the odds of cannabis use over the 10 seconds of the pupil light response test (Figure 2B). This plot shows two regions with statistically significant differences between cannabis uses and no-use controls. The first region between 2.03 and 3.73 seconds with a maximum difference at 2.97 seconds (OR: 2.66, 95% CI: [1.28, 5.50]) corresponds to the time period where the point of minimal constriction is typically observed, and shows that individuals with less pupil constriction have higher odds of being smokers. The second region between 5.7 and 7.3 seconds with a peak difference at 6.57 seconds (OR: 0.37, 95% CI: [0.17, 0.81]), occurs during the period of rebound dilation and shows that higher values of rebound dilation decrease the odds of being a smoker.

*Visualizing patterns in pupil response trajectories across cannabis use group*

The function-on-scalar regression (FoSR) model, which shows differences in the full pupil light response trajectories by characteristic such as age or cannabis use group was used to show differences between the average trajectories of pupillary light reflex in daily, occasional and no-use groups. 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 no-use group and non-smokers encompass the same individuals and therefore overlap completely. From Figure 3A, we can see a stronger initial constriction in the no-use group 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.

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 3B-3D). 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%).

|  |
| --- |
|  |
| Figure 3 A-D: Panel A shows average pupil light response trajectories plotted by cannabis use frequency. An additional dotted lined based on the average trajectory for smokers, was included to show differences between use and no-use groups. Panel B 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 4. The testing delay ranged from 53 to 84 minutes with a mean of 62.22 minutes (sd = 5.57). Figure 5 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.

|  |
| --- |
|  |
| Figure 4: 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. |

|  |
| --- |
|  |
| Figure 5: 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:

It is necessary for occupation health and traffic safety settings to establish a tool that can detect recent cannabis use. While there have been multiple efforts to define tests for recent cannabis use and cannabis impairment, many have suffered from tolerance effects with regular cannabis consumption. The current analysis provides evidence that pupil light response, when paired with functional data analysis methods that leverage information from the full pupil response trajectory, has the potential to discriminate between participants who recently smoked cannabis and those with no history of recent use. Additionally, FDA methods allow visualization of the average trajectories for daily and occasional users and no-use controls, as well as estimating differences in trajectories between these groups. We found differences between the occasional and no use groups for time periods that correspond to the point of minimal constriction and this difference remained significant when examining differences between the daily use and no-use controls, indicating some robustness to the tolerance effect seen in other tests. Finally, there was no statistically significant difference between the daily use and occasional use group. 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 with the average trajectory of smokers with any time delay still appearing shallower than in the no-use control, so that a test focusing on rebound dilation may be able to discriminate between smokers and non-smokers even have an hour after consumption .

However, there are several limitations to this analysis for which further analysis and more sophisticated instrumentation will be needed. 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. Currently, we are collecting data on a large sample with a better validated devices and will replicate this analysis in that sample. 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. Finally, due to the sample size constraints of the current dataset the prediction analysis showing better discrimination using functional data method did not use an independent validation data set; this will be corrected in with the larger dataset. Lending support to the robustness of these results are comments from participants relayed by investigator that the participant did not over consume cannabis during the testing and they did not get as “high” as they usually do. Although anecdotal, these comments were indicate that the results from this analysis may be conservative, with larger differences seen in real world setting where there is no monitoring of cannabis consumption.

Results from this analysis are the first foray into pairing functional data analysis with pupil light response trajectories to better understand the utility of these methods discriminating between acute cannabis use and no use. While cautiously optimistic these results show an advantage in using the full pupil light response trajectory to discriminate between cannabis users and a no-use control with only data collected after consumption, as well as differences in trajectories by frequency of use compared to no use. With larger samples and better validated data collection methods, functional data analysis methods should lead to tests with high specificity providing accountability and ensuring safer workplaces and reducing driver impairment on our roads.

References:

1. Lira M.C., Heeren T.C., Buczek M., Blanchette J.G., Smart R., Pacula R.L., Naimi T.S. Trends in Cannabis Involvement and Risk of Alcohol Involvement in Motor Vehicle Crash Fatalities in the United States, 2000‒2018. *Am J Public Health*. **2021**, 111, 1976-85. <https://doi.org/10.2105/AJPH.2021.306466>

2. Biasutti W.R., Leffers K.S.H., Callaghan R.C. Systematic Review of Cannabis Use and Risk of Occupational Injury. *Subst Use Misuse*. **2020**, 55, 1733-45. <https://doi.org/10.1080/10826084.2020.1759643>

3. Zhang J.C., Carnide N., Holness L., Cram P. Cannabis use and work-related injuries: a cross-sectional analysis. *Occup Med (Lond)*. **2020**, 70, 570-7. <https://doi.org/10.1093/occmed/kqaa175>

4. Goldsmith R.S., Targino M.C., Fanciullo G.J., Martin D.W., Hartenbaum N.P., White J.M., Franklin P. Medical marijuana in the workplace: challenges and management options for occupational physicians. *J Occup Environ Med*. **2015**, 57, 518-25. <https://doi.org/10.1097/JOM.0000000000000454>

5. Downey L.A., King R., Papafotiou K., Swann P., Ogden E., Boorman M., Stough C. Detecting impairment associated with cannabis with and without alcohol on the Standardized Field Sobriety Tests. *Psychopharmacology (Berl)*. **2012**, 224, 581-9. <https://doi.org/10.1007/s00213-012-2787-9>

6. Burt T.S., Brown T.L., Milavetz G., McGehee D.V. Mechanisms of cannabis impairment: Implications for modeling driving performance. *Forensic Sci Int*. **2021**, 328, 110902. <https://doi.org/10.1016/j.forsciint.2021.110902>

7. Brown B., Adams A.J., Haegerstrom-Portnoy G., Jones R.T., Flom M.C. Pupil Size After Use of Marijuana and Alcohol. *American Journal of Opthalmology*. **1977**, 83, 350-4. <https://doi.org/https://doi.org/10.1016/0002-9394(77)90732-2>

8. Fant R.V., Heishman S.J., Bunker E.B., Pickworth W.B. Acute Residual Effects of Marijuana in Humans. *Pharmacology Biochemistry and Behavior*. **1998**, 60, 777-84.

9. Merzouki A., Molero Mesa J., Louktibi A., Kadiri M., Urbano G.V. Assessing changes in pupillary size in Rifian smokers of kif (Cannabis sativa L.). *J Forensic Leg Med*. **2008**, 15, 335-8. <https://doi.org/10.1016/j.jflm.2007.08.001>

10. Newmeyer M.N., Swortwood M.J., Taylor M.E., Abulseoud O.A., Woodward T.H., Huestis M.A. Evaluation of divided attention psychophysical task performance and effects on pupil sizes following smoked, vaporized and oral cannabis administration. *J Appl Toxicol*. **2017**, 37, 922-32. <https://doi.org/10.1002/jat.3440>

11. Ortiz-Peregrina S., Ortiz C., Castro-Torres J.J., Jimenez J.R., Anera R.G. Effects of Smoking Cannabis on Visual Function and Driving Performance. A Driving-Simulator Based Study. *Int J Environ Res Public Health*. **2020**, 17. <https://doi.org/10.3390/ijerph17239033>

12. Shahidi Zandi A., Comeau F.J.E., Mann R.E., Di Ciano P., Arslan E.P., Murphy T., Le Foll B., Wickens C.M. Preliminary Eye-Tracking Data as a Nonintrusive Marker for Blood Delta-9-Tetrahydrocannabinol Concentration and Drugged Driving. *Cannabis Cannabinoid Res*. **2021**, 6, 537-47. <https://doi.org/10.1089/can.2020.0141>

13. Stark M.M., Englehart K., Sexton B.F., Tunbridge R., Jackson P. Use of a pupillometer to assess change in pupillary size post-cannabis. *J Clin Forensic Med*. **2003**, 10, 9-11. <https://doi.org/10.1016/S1353-1131(02)00162-1>

14. Campobasso C.P., De Micco F., Corbi G., Keller T., Hartung B., Daldrup T., Monticelli F. Pupillary effects in habitual cannabis consumers quantified with pupillography. *Forensic Sci Int*. **2020**, 317, 110559. <https://doi.org/10.1016/j.forsciint.2020.110559>

15. Steinhart B., Brooks-Russell A., Kosnett M.J., Subramanian P.S., Wrobel J. A Video Segmentation Pipeline for Assessing changes in Pupil Response to Light After Cannabis Consumption. *bioRxiv*. **2023**. <https://doi.org/10.1101/2023.03.17.533144>

16. Brooks-Russell A., Brown T., Friedman K., Wrobel J., Schwarz J., Dooley G., Ryall K.A., Steinhart B., Amioka E., Milavetz G.; et al. Simulated driving performance among daily and occasional cannabis users. *Accid Anal Prev*. **2021**, 160, 106326. <https://doi.org/10.1016/j.aap.2021.106326>

17. Ramsay J.O., Dalzell C.J. Some Tools for Functional Data Analysis. *Journal of the Royal Statistical Society Series B (Statistical Methodology)*. **1991**, 53, 539-72.

18. Reiss P.T., Goldsmith J., Shang H.L., Ogden R.T. Methods for scalar-on-function regression. *Int Stat Rev*. **2017**, 85, 228-49. <https://doi.org/10.1111/insr.12163>

19. Team. R.C. (2020) R: A language and environment for statistical computing., available from: <https://www.R-project.org/> (accessed on:

20. Wood S.N. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*. **2011**, 73, 3-36. <https://doi.org/> <https://doi.org/10.1111/j.1467-9868.2010.00749.x>