**Response to the Reviewers of Impact of Cannabis and Low Alcohol Concentration on Divided Attention Tasks during Driving**

We’d like to begin by thanking you for providing us the opportunity to revise and strengthen our manuscript, Impact of Cannabis and Low Alcohol Concentration on Divided Attention Tasks during Driving. We are grateful to all of the reviewers for their insightful feedback, and we appreciate the time and effort that each reviewer dedicated to our work.

In response to this feedback we’ve revised the manuscript to incorporate the points raised by the reviewers, and we provide a point-by-point response below.

**Comments from Reviewer #1**

This is an interesting paper on the impact of of THC and low levels of alcohol on driving performance during divided attention conditions. Overall the paper is of interest, but also raises some issues that the authors should address.

1. The authors state that participants inhaled 500 mg placebo (0.008±0.002% THC), low THC (2.9±0.14%), or high THC (6.7±0.05%) vaporized cannabis. However, the authors should also state the actual amount of THC that was administered in both THC conditions. That will increase comparability with other studies in the field.

Response:

As suggested, we added the amounts of THC in mg to the Dosing subsection. We’ve also added text to clarify the connection between the THC dosing conditions and blood THC. Participants inhaled ad libitum, making the amount of THC reaching the blood dependent upon an individual’s inhalation rate, depth, hold time, and lung topography. Previous research has demonstrated substantial interindividual variability in cannabinoid concentration profiles under these dosing conditions (Hartman 2015). This is why we focus on blood concentrations rather than the administered or inhaled amounts of THC.

1. Only 19 out 55 participants actually completed the study, What were the reasons for the large number of drop-outs?

Response:

Per the reviewer’s question, we’ve added the following sentence to the Participants subsection. “Reasons for noncompletion were predominantly personal owing to the rigorous nature of the data collection protocol; however, some withdrew due to nausea and/or emesis from Cannabis or simulator sickness.” In studies involving illicit substance users, higher dropout rates are typical. Because our treatment protocol required several 10-16-hour overnight stays in a controlled access facility it was extremely difficult to retain subjects despite the best efforts.

1. The authors used modeling to associate driving performance while performing a secondary task while under the influence of THC and alcohol. This approach raises two questions that should be discussed. First, duration of the secondary tasks were very short. The side mirror task lasted for 70 sec (across 14 trials), the artist search task lasted 30 secs (across 3 trials) and the message reading task lasted 60 secs (across 6 trials). In essence, these secondary data sets represent less than 2 minutes of a driving test that in total lasted 45 minutes. That really raises the question how representative and replicable these data actually are. The number of trials are extremely low and one wonders what the test-retest reliability of these data actually are. If would strengthen the current findings if the authors would provide test-retest correlations for driving parameters during secondary task performance. Second, BAC and THC were not actually assessed during these secondary task trials but modeled. It is not clear how this modelling actually occurred. It would be helpful if the modelling was described in more detail, and indicators of the strengths/reliability of modeling were provided

Response:

In response to the first part of this comment, we’ve added supplemental model information to the Appendix that includes variance components and intraclass correlations (ICC) of the repeated measures for the various outcome measures we considered, which are estimated via the variance components of our models. In a certain sense, lower ICCs are desirable from a statistical perspective given limited number of task repeats we were able to include in our study. In response to the second part of the comment, blood THC concentrations during drives were modeled via individual power-curve regression on the pre-drive (0.17 and 0.42h) and post-drive (1.4 and 2.3h) specimens. BrAC concentrations during drives were modeled by linear interpolation, as alcohol was in the post-absorptive phase, during which its pharmacokinetics are linear (Jones and Andersson, 2003). We’ve now included this information in the Data Collection subsection, including a statement directing readers to Hartman et al. 2015 for more detailed information on the modeling.

1. It is not always clear whether driving performance (ie lane departures, SDLP, speed etc) significantly differed during secondary task performance as compared to the control intervals, or between THC/BAC and placebo conditions. Perhaps the authors could elaborate?

Response:

Thank you bringing this to our attention, as you’ve suggested we added clarifying text discussion detailing that the only significant difference we found was decreased speed while engaged in the message reading task. This information can be found in Table 2 of the results section, the other non-significant differences between task and control intervals.

**Comments from Reviewer #2**

The manuscript describes the impact of cannabis and low alcohol concentration on driving performance. The manuscript is very interesting and fits into the current needs. The problems presented are on time. The still increasing marijuana use has created a demand for such research. The project seems very wide and well developed. The article is well written and although I read it twice carefully, I don't have many comments.

1. Page 3, line 20 and page 5, line 38 – the authors should present time intervals in minutes instead of hours or just add the minutes in brackets. It will be clearer then; 0.17 hour is 10 minutes, and 0.42 hour is 25 minutes.

Response:

As per the reviewer’s suggestion, we have revised the text in this location to report minutes in brackets. We agree with the reviewer that this addition increases the clarity of how the time intervals are reported.

1. Page 3, line 43 – I am not sure if keywords “Cannabis” and “Marijuana” have to start with capital letters.

Response:

To our knowledge, we believe that the keywords should be capitalized when listed as keywords, but not when appearing in the text of the manuscript. We will seek clarification from the editors on this.

1. Page 4, line 52 – why authors wrote here that participants aged 21-55 while on page 7 (line 17) the participants aged 21-37? I suspect that the data on page 3 applies to all participants in all experiments and on page 7 to those 19 participants that completed study covered by the presented manuscript. In my opinion, the data on participants should only apply to those to whom the results presented here are related. Why 36 enrolled adults did not complete the study?

Response:

The first age range (21-55) represents the acceptability criteria used to recruit participants, while the second (21-37) describes age range of the actual participants who completed the study. In agreement with the reviewer, we’ve modified the text on Page 4 to describe the acceptability criteria in more general terms to avoid any conflict between numeric values. Additionally, we’ve added the following sentence to the Participants subsection to address the 36 enrolled adults who did not complete the full study. “Reasons for noncompletion were predominantly personal owing to the rigorous nature of the data collection protocol, with some withdrawing due to nausea/emesis from Cannabis or simulator sickness.” Higher dropout rates are common in longitudinal studies of illicit substance users, and because our treatment protocol required several 10-16-hour overnight stays in a controlled access facility it was very difficult to retain subjects despite the best efforts of the research team.

1. Page 11, lines 20 and 43 (references 4 and 10) – in most references the full name journals are presented but in these two only titles abbreviations.  Page 11, line 20 (reference 4) – between journal title and between issue number and page numbers should be comma (not dot and colon). Page 12, line 11 (reference 16) – the year number should not be in brackets.

Response:

Thank you, we’ve fixed the references to now include the full journal names, we’ve replaced the dots and colons with commas, and we’ve removed the brackets around year in the 16th reference. We very much appreciate your diligence in recognizing and pointing out these inconsistencies to us.

1. Figure 1 – why subjects with placebo/placebo and placebo/alcohol have THC concentrations even up to over 5 ng/mL? This seems pretty much for occasional users who have not taken marijuana for over a week. Some concentrations in High THC subjects are even lower than in Placebo group. It would be very good to explain the reason for this in the text.

Response:

As per the reviewer’s suggestion, we’ve added the following to the Dosing subsection in the results. “Residual THC was detected in some completers—up to 6.3 ng/mL at baseline—possibly indicating inconsistency in self-reported frequency of intake. See Hartman et al. (2016) for further discussion.” The within-subject design of this study helps mitigate the residual THC levels in different participants.

1. Table 2 - what means three dots at “<0.001” in the “Message-Riding/ Speed” line and “p-values” column. It should be explained below Table.

Response:

We’ve added an explanation of the code in table legend. In short, we used it to draw attention to p-values below 0.001. If the editors believe this is confusing, we are happy to remove this code.

Overall, I think this article is very well-done.

**Comments from Reviewer #3**

The paper reports a simulator study on cannabis and driving performance. The influence of alcohol is in focus. The study is much needed and performed at a high level of expertise. The model produces weak results on the influence of cannabis and alcohol on the driving skills.

1. Given the commonly accepted fact that alcohol influence your driving skills in a non-acceptable way it would be of value to comment how sensitive this model is to document that. Is your experimental model valid?

Response:

Our analyses detected a significant negative effect of alcohol for a handful of the outcomes we considered, including SDLP in the message-reading task and lane departure durations in the side-mirror task. Considering alcohol levels were ~0.05 during the drive, and that task durations were relatively short, it is likely that some models were underpowered to detect the established detrimental effects of alcohol. We are careful to avoid interpreting this as alcohol not having negative effects.

1. You base your work and text on the relationship to THC blood concentration. Figure 1. Is used to demonstrate variability. However, the time point for sampling is in a very dynamic time point where THC concentrations are being rapidly declining. Therefore, I think your measurements are problematic to interpret.

Response:

While we measured THC blood concentrations at four different sampling points, blood THC concentrations at every moment of the drive were modeled via individual power-curve regression, an approach discussed in greater detail in Hartman et al. 2015. As per the reviewer’s comment, we’ve now included this information to the Data Collection subsection, including a statement directing readers to Hartman et al. 2015 for more detailed information on the modeling. Additionally, the within subject-design, which allows each individual participant to serve as their own control, helps address these issues because even though the actual numbers might be changing rapidly during the drive, participants are being compared to themselves. Hartman et al. 2015 discusses the consistency of measurements within subjects across sessions of the same cannabis dose.

1. Also, you seem to assume that blood concentrations of THC are golden standard for effect relationship (as for alcohol). I would challenge this as THC blood concentrations cannot representative due to the rapid redistribution to tissue and brain where effect occurs.

Response:

The reviewer is correct to point out that blood concentrations are not the gold standard for effect relationships. However, there exists a trade-off between the competing desires for the acquisition of both naturalistic driving and representative indicators of intoxication. Given the ad libitum intake and interindividual variability using blood concentrations was the best available option for this type of nature since we cannot implement any more invasive approaches without introducing additional sources of non-validity to the experiment.

1. Please speculate how representative and useful the THC blood concentrations are.

Response:

In in-vivo studies, blood THC concentrations provide an established of estimate central nervous system functioning following acute cannabis administration [CITATION(S)]. As per the reviewer’s comment, we’ve added two statements of this, one in the Data Collection subsection under methods [QUOTE STATEMENT], and another in the discussion [QUOTE STATEMENT].

1. Abstract. Is the conclusion based on the results or simply a wish?

Response:

Given the word constraints of we needed to keep the conclusion as concise as possible so as to not omit important details regarding the experiment methods and results. We chose to describe our results a safety concern rather than making a more definitive judgement. Further discussion of this is included in the discussion section, and we acknowledge that further research needs to be performed in the area of cannabis use and divided attention while driving, and we believe that the significant effects detected in our study provide a worthwhile contribution.

1. Introduction, first sentence. You mean in suspected DUI:s?

Response:

The reviewer is correct, we’ve modified the text to clarify this statement, which based upon the research of Augsburger et al. 2005 and Berning et al. 2015 (complete references given in the appendix). Because we are limited to 20 references in the main text, we did not have room to include these citations.

1. Please add a reference to your used simulator model.

Response:

As per the reviewer’s comment, we’ve added a hyperlink the NADS-1 website (https://www.nads-sc.uiowa.edu/sim\_nads1.php) to the Data Collection subsection. This official page describes the simulator in greater detail.

1. Regarding THC concentrations again. Your statement should include a reflection on how representative these are in an investigation after an accident. Problematic parameter!

Response:

This is an excellent point. We have clarified that these values are representative of THC concentrations at the time of driving rather than the time at which law enforcement would gather them following a traffic stop or crash.

1. THC measurements. Add some information regarding measurement uncertainty.

Response:

In response to the reviewer’s comment, we’ve referenced the work of Hartman et al. 2015 in the Dosing subsection of the results. This paper provides greater detail on the THC measurements in these data.

1. Results. Rather than using single concentration value did you consider using AUD values for analysis, which might be more relevant as exposure parameter?

Response:

Assuming the reviewer is referring to AUC, we did not consider AUC values as the field of DUID uses blood concentrations.

1. In the Appendix tables explain the subgroups: Urban, Interstate, Rural.

Response:

We agree that these different segments could be clarified. As per the reviewer’s suggestion, we’ve added information explaining the various drive segments in each of the Appendix tables that references them.

**Comments from Reviewer #4**

This manuscript is describing the effects of cannabis with/without alcohol compared to placebo on driving simulated tasks to explore the effects on driving safety in healthy white males (within-subject) individuals age 21-37 (n=19), using three divided attention tasks and three aspects of driving performance.  Outcomes were modeled using linear regression in response to THC or BrAC.  This is an important preliminary investigation of the combinatorial effects of THC and alcohol. As with other studies, blood concentrations of THC were highly variable across subjects.   Figure 1 (Table A1) visualizes the THC blood levels with or without co-alcohol administration.

1. It would be interesting to see statistical analysis on these values, as low THC/etOH seems to have a trend for reduced blood levels compared to THC/placebo, while high THC/etOH seems to have a trend for higher blood levels.  Do you have any explanation for these effects?  or why in two subjects the levels decreased significantly?

Response:

In general, we found there to be higher variability (and higher medians) in THC concentrations following alcohol in comparison to the same doses without alcohol. Given the space limitations of this manuscript we are unable to provide an in-depth analysis exploring this aspect of the data in this paper; however, such an analysis was performed in the citations Hartman et al. 2015 and Hartman et al. 2016 for a statistical analysis of these data that addresses the interesting patterns that the reviewer mentions.

1. Was there any change in scoring based on urban vs. rural scenarios?

Response:

We did not alter any of our outcome measures in response to the different drive scenarios. However, for tasks where some instances could take place in differing drive segments, we adjusted for task location in our statistical models. In response to the reviewer’s comment, we’ve modified the text in the final paragraph of the Statistical Analyses subsection to better indicate this.

1. The dose of THC is quite low compared to what young men are typically accessing in 'real world' cannabis use.  Can you please add a sentence or two to address this?

Response:

We agree with the reviewer on this point. To address the reviewer’s comment, we’ve added the following to the Discussion section: “Although the cannabis in this study had a lower potency than typically observed in seized materials, we do not suspect this to be a substantial limitation. Individuals inhaling cannabis can self-titrate dose to a subjective experience comfortable for them, producing similar blood concentrations across a wide range of cannabis potencies. The driving-performance effect of high-THC cannabis concentrates such as hashish were outside the scope of this study but would merit further research.”

**References Cited in the Response**

[STILL NEED TO ADD]