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The Effects of β-myrcene on Simulated Driving and Divided Attention: A Double-Blind, Placebo-Controlled, Crossover Pilot Study

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ABSTRACT

Background. ß-myrcene, one of the most common terpenes found in cannabis, has been associated with sedation. We propose that ß-myrcene contributes to driving impairment even in the absence of cannabinoids. **Aim.** To conduct a double-blind, placebo-controlled crossover pilot study of the effect of ß-myrcene on performance on a driving simulator. **Method.** A small sample (n=10) of participants attended two experimental sessions, one in which they were randomized to receive 15 mg of pure ß-myrcene in a capsule versus a canola oil control. Each session, participants completed a baseline block and three follow-up blocks on a STISIM driving simulator. **Results.** ß-myrcene was associated with statistically significant reductions in speed control and increased errors on a divided attention task. Other measures did not approach statistical significance but fit the pattern of results consistent with the hypothesis that ß-myrcene impairs simulated driving. **Conclusions.** This pilot study produced proof-of-principle evidence that the terpene ß-myrcene, an agent commonly found in cannabis, can contributes to impairment of driving-related skills. Understanding how compounds other than THC affect driving risk will strengthen the field's understanding of drugged driving.

Key words: = cannabis; ß-myrcene; terpene; driving impairment; simulator

Recent legalization of cannabis has spurred interest in the relationship between acute cannabis use and impairment. Cannabis — measured through the presence of tetrahydrocannabinol (THC) — is the most prevalent drug (including alcohol and prescription medications) found among U.S. drivers (Kelley-Baker et al., 2017; Ramirez et al., 2016). In fact, the number of drivers testing positive for cannabis appears to be on the rise (Berning et al., 2015; Johnson et al., 2012; Masten & Guenzburger, 2014; Salomonsen-Sautel et al., 2014). A recent report by the Centers for Disease Control and Prevention (Azofeifa et al., 2019) found that over 12 million Americans drove after using cannabis in the past year, and the National Roadside Survey found that 12.6% of weekend nighttime drivers tested positive for THC (up from 8.6% in 2007) (Kelley-Baker et al., 2017; Lacey et al., 2009).

While double-blind, placebo-controlled studies have routinely found that cannabis impairs cognitive and psychomotor skills, as well as simulated driving (Hartman et al., 2015; Hartman & Huestis, 2013), recent epidemiological research has proved more inconsistent. Four major relative crash risk studies conducted in the past decade have produced varying results (Bernhoft et al., 2012; Brubacher et al., 2019; Drummer et al., 2020; Lacey et al., 2016), and a meta-analysis also found that 1 in 3 studies reviewed found no significant association between cannabis and

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crash risk (Gjerde et al., 2015). Other recent reviews (e.g., Pearlson, Stevens & D'Souza, 2021) suggests relatively low risk, with some meta-regression odds ratios as small as 1.22 and considerable variability among individual studies (Rogeberg & Elvik, 2016).

In contrast, across decades and locations, results of *alcohol* crash risk studies have been relatively consistent (Blomberg et al., 2005; Borkenstein et al., 1964; Krüger & Vollrath, 2004; Lacey et al., 2016). Thus, while the methods for estimating relative crash risk can produce stable results, fundamental differences between alcohol and cannabis may account for the wide variability in observed crash ratios attributed to cannabis use.

The pharmacokinetics of cannabis may be one contributing factor. For example, THC can be detected in both blood and oral fluid for weeks after last use, long after impairing effects would have disappeared (Andås, Krabsth, Enger, et al., 2014; Bergamaschi, Karschner, Goodwin, et al., 2013). The separation between detection of the drug and impairment might hamper observing clear dose-response relationships.

But another factor may be the chemical complexity of the cannabis plant. Cannabis consists of over 400 cannabinoids, terpenes, and flavonoids, few of which have received careful examination (Atakan, 2012). However, research on cannabis and crash risk to date has focused almost exclusively on THC, the primary psychoactive agent in cannabis, as the cause of cannabis-induced driving impairment. However, cannabis compounds other than THC may play a role as well, and their presence may obfuscate the true driving risk associated with cannabis use.

For example, while THC and THC-based medications are themselves associated with drowsiness (Issa, Narang, Jamison, et al., 2014; Schimrigk, Marziniak, Neubauer, et al., 2017; May & Glode, 2016), research has suggested that cannabis high in cannabidiol (CBD) produces *particularly* strong sedating effects (Crippa et al., 2004; Pearce et al., 2014; Zhornitsky & Potvin, 2012). We have argued (Johnson, 2020; Johnson, 2022) that the *sedating* properties of alcohol and drugs, not just the *intoxicating* properties, are understudied agents of crash risk, and accordingly, in earlier research investigated both THC and CBD as predictors of driving impairment. In Johnson (2019), habitual cannabis users drove an instrumented vehicle for a period of 6-10 days and provided one or more oral fluid samples each driving trip they took; we were able to link THC and CBD concentrations to vehicle performance. The study found that only high CBD/high THC levels predicted driving impairment. In fact, we found no evidence of driving impairment at any THC level when subjects tested negative for CBD (Johnson, 2019).

Similarly, Arkell, Lintzeris, Kevin et al. (2019) experimentally examined cognitive performance as a function of THC-dominant cannabis, THC/CBD equivalent cannabis, and a placebo. Although subjective ratings of experience (e.g., feeling "stoned") did not differ as a function of CBD content, performance on some attentional tasks was significantly worse under THC/CBD than versus THC-dominant dosing. And while not all research has found that CBD exacerbates cannabis impairment (Arkell et al., 2020), it is noteworthy that the Food and Drug Administration recently issued a warning about driving under the influence of a CBD-based medication specifically because of its sedating effects (U.S. Food and Drug Administration, 2019).

Interpretation of these findings is further complicated by the suggestion that CBD is not, by itself, sedating. Although cannabis high in CBD can produce lethargy (Crippa et al., 2004; Pearce et al., 2014; Zhornitsky & Potvin, 2012), it has been argued (Russo, 2011, 2016, 2017) that those effects actually are caused by the terpene β-myrcene, which often co-occurs with CBD. And because concentrations of β-myrcene vary considerably among strains, it follows that sedating properties of these strains, and possibly the crash risk, may vary as well.

However, β-myrcene is not limited to cannabis; it also occurs in plants such as basil, lemongrass, and hops. In fact, β-myrcene is thought to be the sedating agent in some traditional sleep aids based on hops and lemongrass preparations (Lorenzetti et al., 1991; Wichtl, 2004). Furthermore, animal studies show that β-myrcene acts as a muscle relaxant and demonstrates other sedating effects (Vale et al., 2002; Vale et al., 1999).

We have a broad interest in better clarifying the role between cannabis use and motor vehicle crash risk, and this involves exploring cannabis compounds other than THC. Based on the

evidence that ß-myrcene has sedating properties, we conducted an experiment to test the hypothesis that ß-myrcene can directly impair driving skills. In this proof-of-principle pilot study, we examined ß-myrcene as an isolate, derived from non-cannabis sources (citrus fruit), and free from THC, CBD, and other cannabinoids, and examined its impact of simulated driving performance and divided attention. To our knowledge, no other research on cannabis-impaired driving, whether epidemiological or experimental, has measured or modeled ß-myrcene as a predictor of driving skills or behavior.

METHODS

This pilot study was internally funded and designed to generate proof-of-principle evidence of the effect of ß-myrcene on simulated driving. Sample size (N=10) was not based on a power analysis, but rather on the availability of funds and time restrictions. All procedures were reviewed and approved by the Pacific Institute for Research and Evaluation (PIRE) Institutional Review Board (IRB).

Participants and Recruitment

Participants were recruited by placing advertisements in Craigslist that sought occasional cannabis users to take part in paid research. Cannabis users were selected because of likely prior experience consuming ß-myrcene. Interested persons were directed to an online prescreening instrument, from which qualified individuals were contacted and invited to take part in two 2.5-hour experimental sessions. An incentive of $150 was offered for participation, along with up to $20 each session (as necessary) to help cover the costs of rideshare service; participants were not allowed to drive away from the research sessions as a precaution against drowsy driving.

Data collection during the time of COVID-19 required a variety of methodological adjustments to reduce risk of transmission. These including using a spacious physical location, providing N95 masks, social distancing, sanitization, and symptom screening. However, because of the isolation of the data collection space, and the fact that all research staff present were male, the IRB only approved for us to recruit male participants in order to avoid any discomfort or concern that female participants might experience. We were also limited by participant age, as individuals older than 50 were deemed to have higher risk of serious complications due to COVID-19.

Eligibility was based upon gender (male) and age (21-50), as well as lifetime cannabis use. Respondents who reported using cannabis more than weekly were excluded, as were respondents who reported use of other illicit drugs in the past year.

Protocol

Each subject was scheduled for two sessions. In a randomized order, in one session participants were dosed with 15 mg (19 µl) of ß-myrcene extract (www.elevationterpenes.com) in a vegetarian capsule (mixed with ~ 480 µl canola oil). In the second (control) session, participants received a vegetarian capsule containing only canola oil. Neither the subject nor the data collector knew which dose participants received during a given session.

For this proof-of-principle study, the dose was meant to exacerbate impairment; but it was also determined by the physician on our team to reflect what a particularly sedating daily dose of medical cannabis might contain. As a concrete example, the cannabis strain Blue Dream has been reported to have ß-myrcene concentrations as high as 2.7% (see https://cannigma.com/strains/blue-dream). Accordingly, it is feasible that a person could consume 27 mg (at 100% absorption) in 1 gram of cannabis from a strain with a particularly high ß-myrcene content; consuming 15 mg of ß-myrcene in 1 gram of cannabis is realistically possible.

Only one participant was scheduled per day, and sessions averaged 4 days apart. Upon arrival to the session, the data collector recorded the participant's temperature completed a COVID-19 symptoms checklist. Participants were breathalyzed to ensure alcohol sobriety at the start of the research (participants with BACs $\geq$ .02 g/dl were rescheduled). This pilot study did not have the resources to screen participants for drugs, although we excluded self-reported heavy/frequent users from taking part in the research with the prescreening questionnaire. We relied on random assignment to balance out any potential drug-positive participants.

At the start of each session, subjects first completed a 10-minute guided warm-up drive on the driving simulator (described below) to acclimate to the controls. This warm-up included all the measures used in the study routes, and so participants had the opportunity to become familiar with the specific tests. Participants then completed a 20-minute *baseline* driving session. This was followed by a dosing period, where subjects took the capsule provided to them. After the dosing period there were three 20-minute post-dosing simulator blocks. At the end of the final driving scenario, participants were released and took their arranged transportation home.

Driving Simulator, Scenarios, and Measures

The research used a STISIM M100 driving simulator. The research scenarios consisted of driving on a rural road with one lane in each direction and occasional oncoming cars. Two similar versions of the scenario were created, which were counterbalanced and used to reduce the likelihood that participants would be able to memorize features of the drive.

The scenarios included static speed control and dynamic speed control tasks, which alternated over the course of the drive. The static task involved explicit instructions for the participant to drive as close to the posted speed limit as possible; there was an audio announcement of each speed limit change so that participants were less likely to simply miss the new speed sign. The dynamic speed task involved the appearance of another vehicle (a cargo van) in the driver's lane. This vehicle would begin at 35, 45, or 55 miles per hour and would change speeds twice before vanishing. Participants were tasked with maintaining a constant distance behind the vehicle (i.e., matching that vehicle's speed based on observation) as it accelerated and decelerated.

Over the course of each 20-minute driving block there were 17 static speed control trials and 16 dynamic speed control trials. The mean difference (based on 30 readings per second) between participants' driving speed and the target speed (posted speed limit or speed of the cargo van) was recorded for each of the 33 trials. In addition, we recorded the standard deviation of lane position (SDLP) for each of the 33 trials. Whereas the speed control measures reflect longitudinal control of the vehicle, SDLP reflects lateral control (or lack thereof). In addition, for the 16 dynamic speed trials per block, we also recorded the minimum *time-to-collision* (TTC) with the cargo van. Time-to-collision reflects the combination of speed and distance from the vehicle in front and is used as a measure of risk-taking (Van Dyke & Fillmore, 2017) (although risk-taking is not necessarily a hypothesized effect of β-myrcene).

The simulator scenarios also included an embedded measure of divided attention. In the lower left and right corners of the screen were grey boxes with red diamond shapes. During the session, the diamonds were occasionally replaced by red left-pointing arrows in the left box or red right-pointing arrows in the right box. These arrows remained for 5 seconds or until the participant responded by pushing the appropriate button on the steering wheel. Arrows appeared during periods in which participants were attending to speed limits or the speed of the cargo van, creating a need to divide attention. There were 41 divided attention trials per driving block. We recorded mean reaction time as well as divided attention errors (missed signals, incorrect responses).

Due to our desire for conducting as brief a study as possible (for COVID protection), as well as because of our small sample size (which would produce low statistical power outside of numerous repeated measures), we did not include self-report assessment of subject experience.

Analytic Approach

Data were analyzed using *generalized linear mixed modeling* (PROC GLIMMIX) in SAS, where subject was treated as a random effect. Logit link functions (logistic regression) were modeled for analysis of data with dichotomous outcomes.

Per the manufacturer, vegetarian capsules take 25-30 minutes to dissolve before the contents can be absorbed. Normally, a dosing experiment would include a drug *absorption period* before data collection. However, due to the desire to limit the duration of the research (because of possible COVID-19 exposure) our IRB would not approve an empty 30-minute time block for this purpose. Rather, after discussion with the IRB, we decided to *a priori* that for analytic purposes we would combine the baseline and first post-dosing block into the pre-drug effect category and the second

and third post-dosing blocks into a post-drug effect category. It seemed unreasonable to test for drug affects when the ß-myrcene would still sitting in an undissolved capsule.

Our statistical model, therefore, was a pre- versus post-dose, ß-myrcene versus placebo control design factorial design with multiple measures within each session. Analyses compared the Block (Baseline v Post-Dose) × Condition (ß-myrcene v control) interaction, but also included the main effect of session (1st versus 2nd) to control for the effects of time. The analytic approach did not assume equivalency at baseline, but rather tested for changes from baseline. We predicted increased driving impairment post-dose for subjects under ß-myrcene compared to potential changes in the placebo-controlled condition (which might experience improved performance due to learning). Specifically, for the post-dose ß-myrcene condition we expected: significantly greater deviations between participant speed and the target speed for both static and dynamic speed control tasks, significantly greater SDLP, significantly lower TTC, and significantly slower divided attention responses and increased attention error rates.

In addition to presenting test statistics (focusing on the Block x Condition interaction), we depict results using bar graphs and 95% confidence intervals. It is important to note, however. that eyeballing overlap between confidence intervals is not identical to interpreting the results of significance tests. Significance tests are based on pooled errors around differences, not errors around independent estimates, and thus confidence intervals are underpowered reflections of actual tests (Cumming & Finch, 2005; Goldstein & Healy, 1995). Furthermore, confidence intervals do a poor job reflecting crossover interactions.

RESULTS

Participants

A total of 41 individuals responded to the prescreening survey. We selected 10 eligible individuals, mean age 34.9 (median age=32.5), of whom 6 were White, 3 were Black, and 1 was of South Asian descent. All 10 participants completed both experimental sessions, although one participant needed to be rescheduled for arriving at the session with a BAC of .06 g/dl. Most non-selected respondents were female, reported using cannabis too frequently, and/or reported illicit drug use other than cannabis.

Speed Control

The Block × Condition interaction was statistically significant, $F(1, 1266) = 3.9$, $p = .049$, on the static speed control task, with increased speed deviations (reduced speed control) under ß-myrcene (versus placebo control) (see Figure 1a). For the dynamic speed task, the Block × Condition interaction was not statistically significant ($p = .30$), but the pattern mirrored that observed for the static speed task (see Figure 1b).

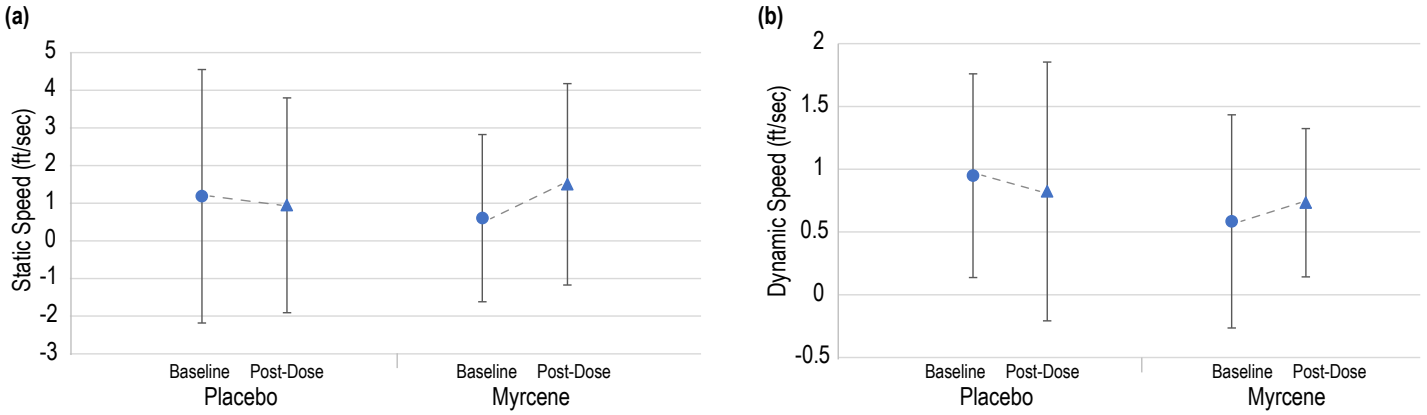

Figure 1. *The effects of ß-myrcene on (a) static speed control and (b) dynamic speed control.*

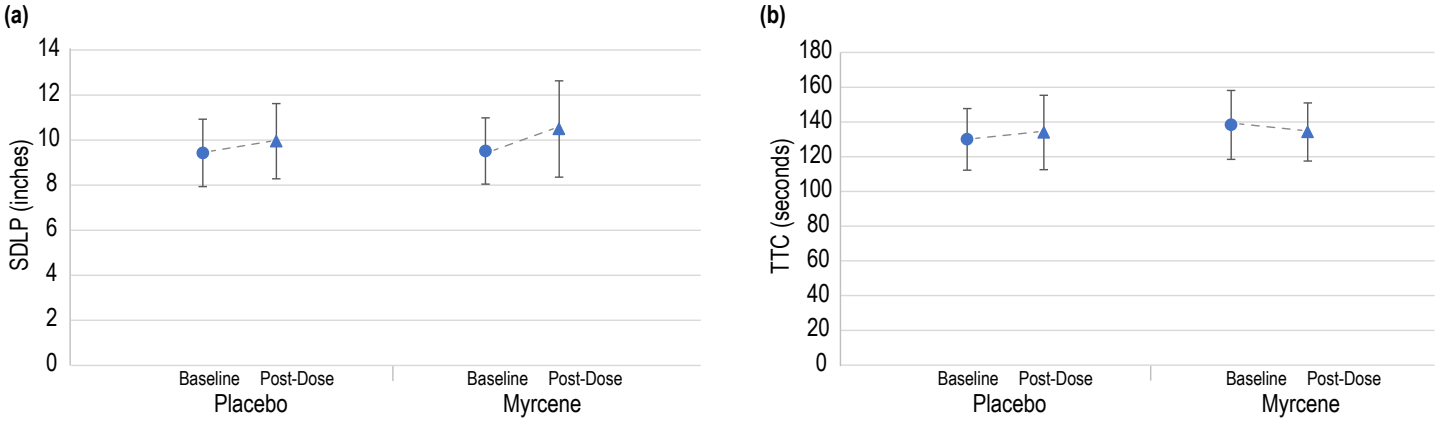

Figure 2. *The effects of β-myrcene on (a) standard deviation of lane position (SDLP) and (b) time-to-collision (TTC).*

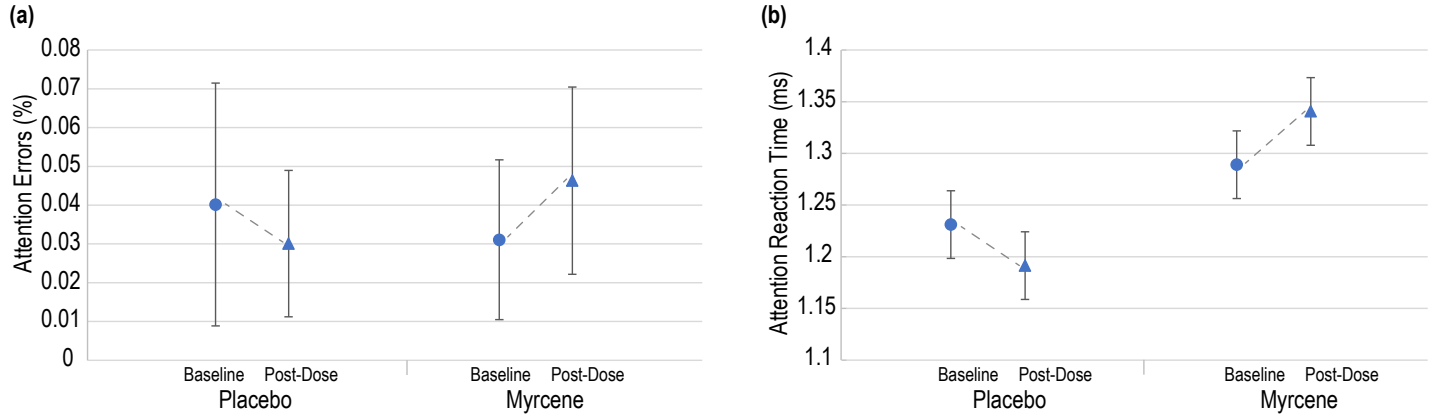

Figure 3. *The effects of β-myrcene on (a) divided attention errors and (b) divided attention reaction time.*

SDLP and TTC

Block × Condition interactions were not significant for both SDLP (p = .58) and TTC (p = .20), although patterns were generally consistent with predictions (see Figure 2).

Divided Attention

Under β-myrcene, participants made significantly more errors on the divided attention task (i.e., missing the cue, indicating the incorrect direction) relative to the placebo control. For attention errors, the Block × Condition interaction was statistically significant, $F(1, 3267) = 7.7$, p = .006 (see Figure 3a). For reaction time, the Block × Condition interaction was not statistically significant on the divided attention task (where responses were capped at 5 seconds), $F(1, 3267) = 1.4$, p = .24).

Four-Block Patterns

Because we could not include a drug absorption period in our design, we aggregated the first data collection after dosing with the baseline period given that the β-myrcene would not yet have been dissolved. However, given that little is known about pharmacokinetics of β-myrcene, for descriptive purposes, in Figures 4 – 6 below we present the predicted outcomes for each measure and for each of the four time-blocks as a function of drug.

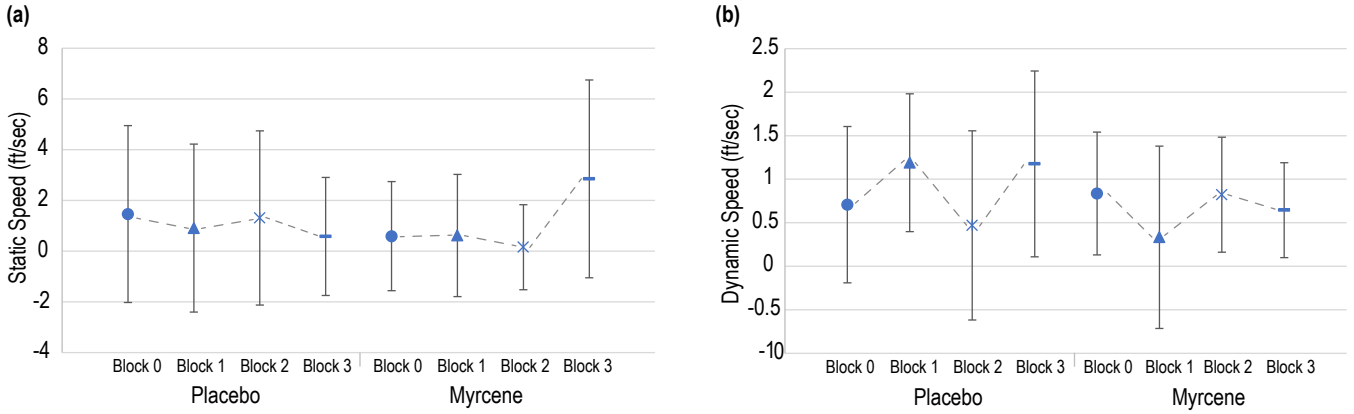

Figure 4. *The effects of β-myrcene on (a) static speed control and (b) dynamic speed control over four time blocks.*

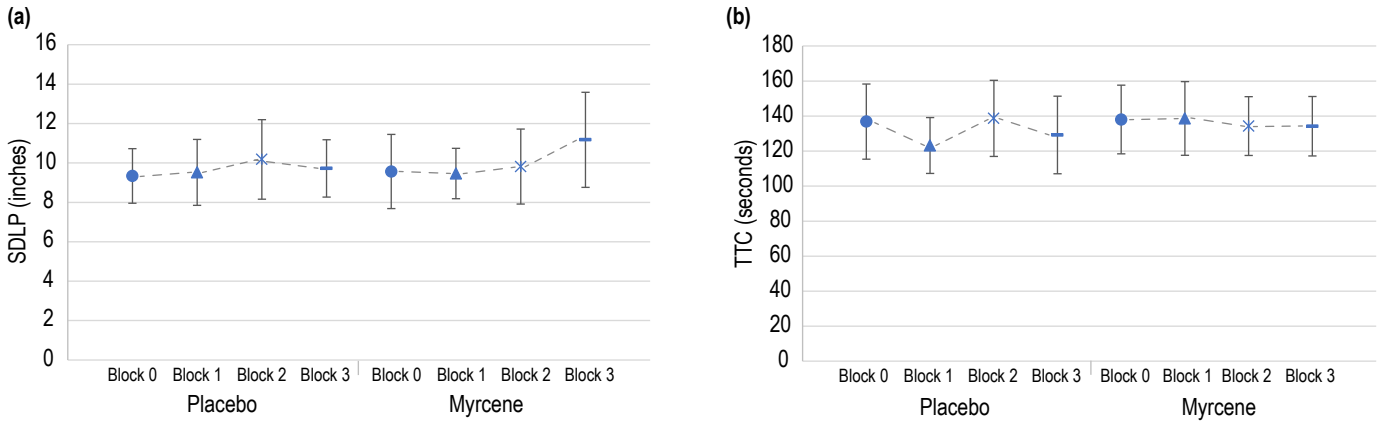

Figure 5. *The effects of β-myrcene on (a) standard deviation of lane position (SDLP) and (b) time-to-collision (TTC) over four time blocks.*

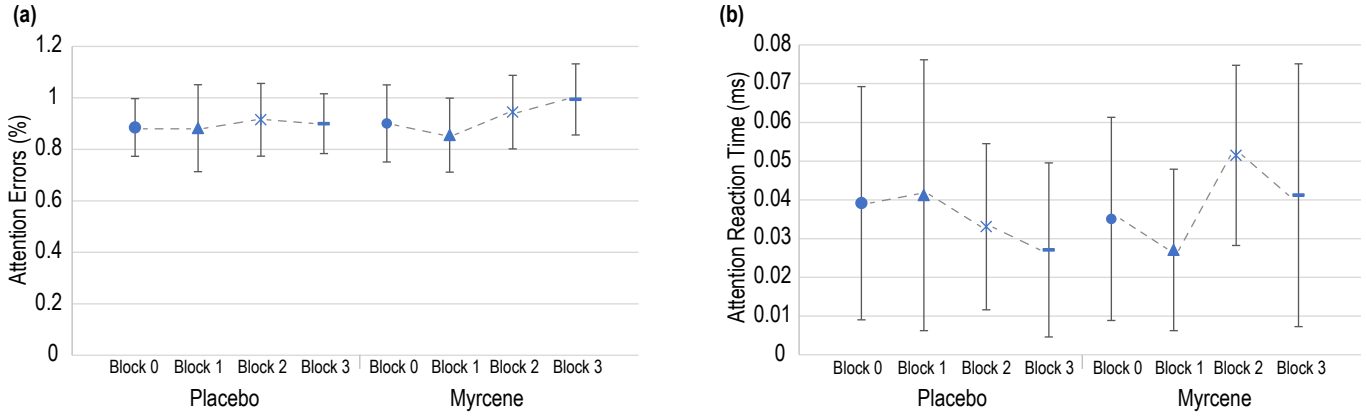

Figure 6. *The effects of β-myrcene on (a) attention errors and (b) attention reaction time over four time blocks.*

DISCUSSION

Participants dosed with 15 mg of β-myrcene performed significantly worse than placebo controls on divided attention and static speed control tasks. Non-significant patterns consistent with those findings emerged for the dynamic speed control test, SDLP, and TTC. Somewhat surprising is that the lack of significant, or even suggestive, findings regarding SDLP, which is among the measures most sensitive to THC. It is possible that β-myrcene and THC interfere with driving skills through different mechanisms.

To our knowledge, this is the first research examining the effects of a cannabis terpene on behavior related to driving. Importantly, β-

myrcene was dosed outside of any cannabis product, based on earlier research that β-myrcene alone might have sedating properties. Given that THC by itself can be sedating, the combined effects of THC and high concentrations of β-myrcene might be considerably stronger. A crossover trial comparing high β-myrcene cannabis, low β-myrcene cannabis, versus β-myrcene without cannabis, might be a more thorough approach.

Undoubtedly, this pilot study was underpowered, and the design suffered several limitations. Although we capitalized on the extensive repeated measures data, a sample of 10 subjects was likely too few to overcome individual differences in responses to the β-myrcene. Still, in nearly all of the driving simulator measures, the patterns were suggestive.

Although we breathalyzed participants at the start of each experimental session, and we excluded individuals with self-reported recent and frequent cannabis use, this pilot study did not have the resources to screen for recent cannabis use. Thus, thus we relied on random assignment within our crossover design to mitigate bias, treating possible recent cannabis use like any other uncontrolled or unmeasured variable that might have affected driving (e.g., mood, distraction, etc.). However, by definitively identifying and excluding drug positive participants we may have been able to reduce noise. Further, collecting measures of subjective experience, such as drowsiness, as mediators of performance impairment would strengthen future research.

The observed relationship between cannabis use and motor vehicle crashes has been inconsistent and widely varying across studies (e.g., Rogeberg & Elvik, 2016). This inconsistency is attributed, in part, to the pharmacokinetics THC and the fact that the substance can be detected weeks after use. However, we have argued that the complexity of cannabis is also an important but understudied factor (Johnson, 2019). While research on cannabis use and crash risk has focused almost exclusively on THC, the drug itself contains hundreds of other compounds (Atakan, 2012), some of which may have implications for safe driving (Arkell et al., 2019; Crippa et al., 2004; Johnson, 2019; Pearce et al., 2014; Zhornitsky & Potvin, 2012; Vale et al., 2002). We believe that by failing to measure and model these other cannabis compounds in relative crash risk research, the field is undermining its ability to inform the public health consequences of cannabus-involved driving.

Basic experimental research can be essential step in identifying compounds that impair driving skills. In this proof-of-principle study, we found suggestive evidence that β-myrcene, a terpene common in some strains of cannabis, can reduce drivers' ability to maintain consistent speed and interfere with attention. Our understanding of the relationship between cannabis and crash risk, and of cannabis in general, can only be improved through the examination of compounds other than THC that comprise the cannabis plant.

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