Pain Sensitivity Among Young Adult Recreational Cannabis Users

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0. ABSTRACT

Substantial effort has been directed toward understanding associations between cannabis and pain processing, yet we have many, and at times conflicting, perspectives regarding cannabinoid-related pain modulation. Although cannabis's short-term and intermediate-term effects on experimental and clinical pain have received considerable attention, long-term effects remain understudied. In two experiments, we measured pain ratings and pain tolerance in response to repeated mechanical nociceptive stimulation in young adult recreational cannabis users ($n = 33$) and demographically similar cannabis non-users ($n = 31$). Linear mixed-effects models demonstrated that: (1) regarding pain ratings, there was an interaction between *trial* and *group* such that subjective ratings in response to repeat pain stimulation increased faster among users, (2) regarding pain tolerance, there was an interaction between *trial* and *group* such that maximum pain tolerance was lower during earlier trials among users and increased faster, and (3) cannabis use characteristics, including onset age, past-month use, and recent use, differentially moderated temporal effects on pain outcomes. Importantly, cannabis-related pain sensitivity differences remained statistically significant even after adjusting for age, sex, and alcohol use. Considerable variance was observed in between-subject trends regarding ratings and tolerance, suggesting that individual differences in pain responses warrant careful consideration in cannabis use research involving pain. When taken together, these outcomes suggest that recreational cannabis is associated with pain sensitivity differences in young adult users; however, additional studies are needed to provide a more thorough understanding of the biological, psychological, and social contexts and consequences.

Cannabis Associated with Pain Sensitivity Differences Among Young Adult Recreational Users

Normative processing of acute pain signals is an important aspect of the human experience. However, normal pain can outlast its survival-related utility, resulting in maladaptive, chronic pain. Globally, one-in-five people experience chronic pain (Goldberg & McGee, 2011). In the United States, an estimated 50 million people live with chronic pain, while another 20 million experience high-impact chronic pain (Dahlhamer, 2018). In addition to having enormous personal impact (Fine, 2011), chronic pain is associated with considerable economic impact. Recent estimates suggest that pain-related expenses, including healthcare needs, medication use/misuse, and reduced earnings, cost Americans between \$560 billion and \$635 billion annually (Henschke et al., 2015). Despite this pressing individual and collective burden, effective pain management strategies are lacking. In recent decades, evolving societal attitudes toward cannabis have increased interest in cannabis-based medicines for the treatment of normal acute pain, chronic pain, and pain associated with various clinical conditions (Hill, 2015; Hill et al., 2017).

Converging evidence suggests that cannabis and cannabis-based medicines reduce pain, with several literature and systematic reviews summarizing cannabis-related outcomes across pain populations (Abrams, 2018; Hill, 2015; Muecke et al., 2018; Nugent et al., 2017; Stockings et al., 2018). Those reports concluded that cannabis preparations are promising pain reduction options, while citing concerns about adverse mental health effects. Similarly, recent meta-analyses have attempted to provide quantitative resolution regarding cannabinoid analgesia. Coalescing results from published studies provide some support for cannabis-related pain reduction in experimental acute pain (Vita et al., 2018) and clinical pain across diagnoses (Aviram & Samuelly-Leichtag, 2017; Whiting et al., 2015; Yanes et al., 2019), with mixed support by condition: cancer (Haeuser et al., 2019), HIV

(Phillips et al., 2010), multiple sclerosis (Iskedjian et al., 2007), neuropathic pain (Andreae et al., 2015; Finnerup et al., 2015), non-cancer pain (Stockings et al., 2018), and rheumatoid arthritis (Richards et al., 2012). Critically, these meta-analytic outcomes overwhelmingly reflect studies that considered short-term (e.g., single dose) and intermediate-term (e.g., clinical trial) cannabis administrations. As such, the extent to which long-term cannabis use modulates pain processing, such as in recreational, regular, and heavy users, remains understudied. With medicinal (Cerdá et al., 2012; Park & Wu, 2017) and non-medicinal (Grucza et al., 2016; Lloyd & Striley, 2018; Miech et al., 2020) cannabis use on the rise, one important open research question involves characterizing pain processing alterations among users that may represent causes, consequences, or both, linked with long-term use.

To provide clarification regarding associations between recreational cannabis use and pain, young adult cannabis users and non-users completed experimental acute pain assessments involving repeated experimental mechanical nociceptive stimulation. Outcomes measured were pain ratings and pain tolerance. We used linear mixed-effects models to test associations between cannabis use and pain-related outcomes. In general, we tested two overarching hypotheses: that (i) pain ratings were lower among users and (ii) pain tolerance was greater among users. In ancillary analyses, we examined relationships between pain outcomes and cannabis use characteristics, including onset age, regular use years, past-month use, and recent use.

2. METHODS

Participants were enrolled in a between-groups, quasi-experimental protocol involving two primary outcomes: pain ratings and pain tolerance. During each task, participants completed repeated acute pain trials involving mechanical pressure-based

nociceptive stimulation. Laboratory data collection spanned from January 2018 to October 2018.

2.1. Ethics and Open Science Practices

To protect participant privacy, the investigators secured a Certificate of Confidentiality from the National Institute on Drug Abuse (CC-DA-17-177) before data collection commenced. Participants were admitted to the protocol following written informed consent and inclusion/exclusion criteria evaluation. All procedures were approved by the Auburn University Office of Human Subjects Research and Institutional Review Board (17-037 MR 1702). In line with current recommendations and open science best practices (Magezi, 2015; Meteyard & Davies, 2020), we have made data and corresponding code associated with this work freely available on Open Science Framework (<https://osf.io/b2kf3/>).

2.2. Participants

Participants were men and women between ages 19 and 24 (for demographics, please see Table 1). Promotional materials, including advertisements with links to recruitment assessments, were located online and on the Auburn University main campus and surrounding areas. During recruitment, participants completed several assessments including: a demographics questionnaire, Beck Anxiety Inventory (BAI)(Beck, Epstein, et al., 1988), Beck Depression Inventory (BDI) (Beck et al., 1961; Beck, Steer, et al., 1988), Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994), Marijuana Smoking History Questionnaire (MSHQ) (Bonn-Miller & Zvolensky, 2009), Patient Health Questionnaire 15 (PHQ-15) (Kroenke et al., 2002), and Prodromal Questionnaire, Brief Version (PQB) (Loewy et al., 2011; Xu et al., 2016). Alcohol consumption was measured using the demographics questionnaire. Specifically, participants indicated whether they drink: “more than three drinks per week” (3), “about three drinks per week” (2), “less than three drinks per week”

(1), or “abstain” (0). Participants meeting specific inclusion/exclusion criteria outlined below were then invited to complete experimental acute pain tasks in the laboratory.

Participants were considered “recreational cannabis users” and included in the protocol if they endorsed four or more cannabis use episodes in the preceding 30-day period (i.e., at least one episode per week) as indicated on the MSHQ. This threshold was strategically selected to enhance participation among young adult users while maximizing observed effects of cannabis on pain. Alternatively, participants were considered cannabis non-users if they endorsed no more than three cannabis use episodes ever. Once a user had been enrolled, corresponding age-matched and sex-matched non-users were selected from the participant pool and invited to complete the laboratory study. For completing the laboratory study, participants received \$20 cash compensation. Also, those participants currently enrolled at Auburn University received credit toward eligible coursework.

Both users and non-users were excluded if they endorsed current chronic pain as indicated on the BPI, used prescription/over-the-counter pain medications in the eight-hour period before acute pain assessments, were currently taking medications that could cause/increase bleeding, or had current or previous neurologic or psychiatric conditions. Participants with recreational substance use histories (i.e., more than three use episodes ever) other than alcohol, cannabis, and nicotine (e.g., opioids, psychedelics, psychomotor stimulants) were also excluded. Before commencing data collection, participants were asked whether their cannabis use patterns had changed between online recruitment and pain assessments. Those participants who reported such changes were excluded. Regarding acute cannabis intoxication effects, although enrollment did not involve drug screening to assess recent cannabis use, participants were informed beforehand that suspected intoxication would result in dismissal from the study.

2.3. Pressure-Based Pain Apparatus and Experimental Pain Assessments

Nociceptive stimulation involved a pressure-based pain apparatus developed and validated at Auburn University (Davis et al., 2016). During nociceptive stimulation, a commercial sphygmomanometer was secured to participants' non-dominant hand, and rapid inflation/deflation across trials caused discomfort or pain by pressing on a 3D-printed plastic disk placed between the index and middle fingers on the dorsal surface of the non-dominant hand. The pain apparatus reports pressure levels in millimeters of mercury (mmHg). Before commencing the experimental pain assessments, participants were reminded that they could withdraw at any time. In separate tasks, we assessed pain ratings (Hashmi & Davis, 2009; Sarlani & Greenspan, 2002; Seminowicz & Davis, 2006) and pain tolerance (Davis et al., 2016) in response to repeat nociceptive stimulation.

During the pain ratings task, stimulus trains involved 10 repetitions of fixed nociceptive stimulation (Sarlani & Greenspan, 2002). Trials involved a(n): on-ramp phase (5 sec), fixed nociceptive stimulation phase (10 sec), off-ramp phase (5 sec), and rating phase (10 sec) (Figure 1A). Nociceptive stimulation was not varied between trials, participants, or groups. That is, each participant experienced stimulation 10 times at approximately the same target pressure of 100 mmHg that was expected to elicit moderate pain based on previous observations (Davis et al., 2016). Participants provided one rating following each off-ramp phase. In the rating phase, participants were instructed to rate the immediate-past pain experience using a visual analog scale (VAS)(Jensen et al., 1986) anchored by 0 ("No Pain") and 100 ("Most Pain Possible"). Pain ratings were operationally defined as the point along the VAS (0-100 points) that participants used to describe each trial.

During the pain tolerance task, stimulus trains involved 10 repetitions of nociceptive stimulation that varied from trial-to-trial at participants' discretion (Davis et al., 2016). Trials involved a(n): baseline phase (5 sec), maximum nociceptive stimulation phase (~10 sec),

off-ramp phase (5 sec), and recovery phase (10 sec) (Figure 1B). During the maximum stimulation phase, apparatus pressure increased linearly until participants indicated that the pain was “too uncomfortable to continue,” at which point pressure was immediately relieved. Pressure was increased at a rate of approximately 10 mmHg/second consistently across participants. Duration times during the maximum stimulation phase ranged between approximately 5 and 15 seconds and varied between participants. The recovery phase allowed pain responses to return to baseline between trials. Pain tolerance was operationally defined as the pressure in mmHg (20-240 mmHg) when participants ended each trial. Apparatus pressure was never increased to more than 240 mmHg during pain tolerance due to instrument limitations.

Pain tasks were counterbalanced between participants and within groups to prevent order effects, and every participant completed both tasks. One experimenter who was blind to participant group assignment operated the pressure-based pain apparatus across participants to prevent between-experimenter variation in reaction times and inflation/deflation rates.

2.4. Data Analysis

All data analyses, including handling, statistical modeling, and visualizations, were carried out in the R software environment (version 4.1.1). Because our repeated-measures design resulted in a hierarchical data structure with non-independent observations, we used linear mixed-effects models to test experimental hypotheses, which incorporate both random and fixed effects (Baayen et al., 2008). Random effects account for data non-independence by modeling variation in intercepts and/or slopes associated with distinct observational units (Snijders & Bosker, 2011). In this way, error variance between participants (random intercepts) and within participants (random slopes) can be simultaneously modeled alongside fixed effects. To concurrently estimate random and fixed

effects, we used the *lme4: Linear Mixed-Effects Models* R package (Bates et al., 2015), version 1.1-27.1, and fit models using restricted maximum likelihood (REML). Results were reported using field-specific best practice guidelines for linear mixed-effects models (Meteyard & Davies, 2020). In both pain tasks, *trial* (1-10) and *group* (users versus non-users) were modeled as fixed effects, and *participant* was modeled as random effects (i.e., random intercepts). Models of interest are specified below (Model 1, 2).

Model 1: Ratings ~ $B0 + B1(\text{Trial}) + B2(\text{Group}) + B3(\text{Trial} * \text{Group}) + (B0 | \text{Participant}) + e$

Model 2: Tolerance ~ $B0 + B1(\text{Trial}) + B2(\text{Group}) + B3(\text{Trial} * \text{Group}) + (B0 | \text{Participant}) + e$

In exploratory assessments, we tested whether associations between *trial* and pain ratings and pain tolerance were moderated by cannabis use characteristics, including onset age, years of regular use (i.e., “use once or twice per week”), past-month use (i.e., “use episodes during the last 30 days”), and recent use (i.e., “use within the last 48 hours”).

Data were inspected for univariate outliers [i.e., values greater/less than the within-trial median observation $\pm$ two interquartile ranges (Tukey, 1970)]; ultimately, no observations were deemed outliers using these criteria. Predictors were grand-mean centered to facilitate model intercept interpretations (Enders & Tofighi, 2007). Adherence to standard linear model assumptions was checked using the *performance* R package (Lüdtke et al., 2021), version 0.7.3.

3. RESULTS

We report results from two experiments examining recreational cannabis’s effects on pain ratings and pain tolerance. Outcomes are reported as percentages, means (M) $\pm$ one standard deviation, or estimates from appropriate statistical tests, accordingly.

3.1. Participants

During recruitment, 1,243 respondents completed online materials. Those respondents who met inclusion/exclusion criteria described above were invited to enroll on

a first come, first served basis. Overall, 71 respondents were enrolled, of which seven were excluded (five met exclusion criteria (e.g., consuming pain relievers in the previous eight-hour period), one reported changes in patterns (i.e., from non-user to user), and one withdrew during the consent process), yielding a sample of 64 participants: 33 users and 31 non-users. Table 1 conveys group-level enrollee characteristics. Results from independent samples mean difference tests and chi-square tests for independence demonstrated no between-group differences among most considered characteristics, including race, age, height, weight, body mass index, and symptom severities regarding depression (BDI), anxiety (BAI), psychosis (PQB), and somatic symptoms (PHQ-15). There was, however, a difference between response distributions regarding alcohol use ($X^2(2, N = 64) = 13.52, p = 0.004$). Models were rerun after adjusting for alcohol use. In general, users started consuming cannabis during late adolescence, reported some years of regular use, and endorsed past-month use. Moreover, most users disclosed recent use (i.e., “use within the last 48 hours”). Complete correlation and variance-covariance tables are available here (<https://osf.io/b2kf3/>).

3.2. Pain Ratings Task

Regarding pain ratings (0-100 VAS), the mean rating across trials was $M_{\text{rating}} = 46.89 \pm 26.55$ VAS in users versus $M_{\text{rating}} = 46.12 \pm 23.50$ VAS in non-users (Figure 2A). Linear mixed-effects models demonstrated (Table 2): (1) ratings increased as a function of *trial*; (2) considering cannabis use status showed no *group* main effect on ratings; and (3) there was a synergistic interaction between *trial* and *group*, suggesting that the association between *trial* and ratings differed between users and non-users. Specifically, among users, ratings increased faster across trials (Figure 2B, 2C). Subgroup analyses confirmed that the effect of *trial* was stronger among users versus non-users (Supplementary Materials, Table 1). Moreover, the interaction term remained statistically significant even after adjusting for

participant age, sex, and alcohol use (Supplemental Materials, Table 2). Furthermore, in ancillary analyses involving users, cannabis onset age, past-month use, and recent use moderated the association between trial and ratings (Supplementary Materials, Table 3). However, regular use years did not moderate the association. Finally, there was considerable variance observed among participant-level intercepts, and modeling random and fixed effects explained more variance (Conditional $R^2 = 0.88$) than modeling fixed effects alone (Marginal $R^2 = 0.01$).

3.3. Pain Tolerance Task

Regarding pain tolerance (0-240 mmHg), the mean tolerance across trials was $M_{\text{tolerance}} = 139.47 \pm 51.91$ mmHg in users versus $M_{\text{tolerance}} = 160.74 \pm 56.12$ mmHg in non-users (Figure 3A). Linear mixed-effects models demonstrated that (Table 3): (1) tolerance increased as a function of *trial*; (2) considering cannabis use status showed no *group* main effect on tolerance; and (3) there was a synergistic interaction between *trial* and *group*, suggesting that the association between trial and tolerance differed between users and non-users. Specifically, among users, tolerance was lower during earlier trials and increased faster across trials (Figure 2B, 2C). Subgroup analyses confirmed that the effect of *trial* was stronger among users versus non-users (Supplementary Materials, Table 4). Moreover, the interaction term remained statistically significant even after adjusting for participant age, sex, and alcohol use (Supplemental Materials, Table 5). Furthermore, in ancillary analyses involving users, cannabis onset age moderated the association between trial and tolerance (Supplementary Materials, Table 6). However, regular use years, past-month use, and recent use did not moderate the association. Finally, there was considerable variance observed among participant-level intercepts, and modeling random and fixed effects explained more variance (Conditional $R^2 = 0.89$) than modeling fixed effects alone (Marginal $R^2 = 0.04$). Across pain tolerance trials, tolerance was not recorded

in approximately 2.5% ($n_{\text{trials}} = 17/640$) due to technical/human errors. In these trials, missing data were handled using subject-level mean imputation such that participants' own data were leveraged to estimate missing values.

Several participants reached the pain tolerance ceiling (i.e., 240 mmHg) in some or all trials, suggesting that their true pain tolerance was outside the measurable range. To explore the possibility that the number of participants whose pain tolerance was outside the measurable range differed between users and non-users, we used a chi-squared test for independence to compare the number of participants who reached the ceiling between groups. Although fewer users reached the tolerance ceiling (i.e., 240 mmHg) on one or more trials compared to non-users ($N_{\text{users}} = 5$, $N_{\text{non-users}} = 11$), between-group differences regarding tolerance distributions did not reach statistical significance ($X^2(1, N = 64) = 2.52$, $p = 0.112$). Importantly, rerunning linear mixed-effect models while omitting ceiling observations had moderate, albeit influential, impact on the *trial* $\times$ *group* interaction term ($B = 0.85$ (95% CI: -0.27, 1.97) mmHg, $p = 0.138$).

4. DISCUSSION

Our approach leveraged experimental acute pain assessments to discern effects of recreational cannabis use on pain outcomes. First, we observed that pain ratings in response to repeat nociceptive stimulation increased faster over time among cannabis users. Second, cannabis use was associated with lower pain tolerance during earlier trials that increased faster over time. Importantly, these outcomes were contrary to our experimental hypotheses. Third, we observed that various cannabis use characteristics differentially moderated temporal effects on ratings and tolerance. The results reported here suggest that, notwithstanding considerable evidence demonstrating that acute cannabis is associated with analgesic effects, long-term cannabis use is associated with marginally, yet statistically significant, increased pain sensitivity.

4.1. Is Recreational Cannabis Associated with Increased Pain Sensitivity?

Despite perceived efficacy often reported by medicinal and recreational cannabis users across a range of psychological and physiological symptoms (Cuttler et al., 2018; Sexton et al., 2016), a growing empirical corpus supports the supposition that users may experience worse pain outcomes compared to non-users (G. Campbell et al., 2018; Degenhardt et al., 2015; Jamal et al., 2019; Jefferson et al., 2013; Liu et al., 2019; Salottolo et al., 2018; Sturgeon et al., 2020; Touil & Lavand'homme, 2019). In one seminal study involving adult heavy cannabis users (Jefferson et al., 2013), researchers tracked adults undergoing elective orthopedic operations during the postoperative period. In the first hour post-operation, users (N = 42) reported greater mean pain intensities than non-users (N = 31). In a more recent study involving adult users (Sturgeon et al., 2020), pain clinic intake data were retrospectively compared between users (N = 899) and non-users (N = 6,126), including pain intensity, pain interference, and several psychological endpoints. Importantly, cannabis was associated with increased pain sensitivity across considered variables, with the largest between-group differences observed for pain interference, depression, anxiety, and social isolation. It is worth noting that previous reports assessed pain in adult and older adult cannabis users, with the reported mean age ranging from 28 to 57 years across studies. Therefore, our outcomes extend earlier research by demonstrating pain sensitivity differences among young adult users with minimal use histories and without chronic pain conditions, potentially pointing toward early onset of cannabis-related pain sensitization seen in older populations. Moreover, results presented here extend recent reports about cannabis and pain sensitivity associations (St Pierre et al., 2020), which found no differences between users and non-users, by highlighting the importance of considering temporal effects on pain outcomes in statistical models. When taken together, these outcomes point toward two possible, and not necessarily mutually exclusive (Ditre et al.,

2011, 2019), frameworks for understanding cannabinoid pain modulation, which are discussed below.

It is possible that pain sensitivity is a consequence, cause, or both, of cannabis use (i.e., the cause-consequence controversy) (Khantzian, 1997). For example, repeat exposure to endogenous cannabinoid system modulators (e.g., delta-9-tetrahydrocannabinol (THC)) could lead to increased pain through peripheral and/or central mechanisms, such as central sensitization, rendering long-term users more vulnerable to pain states. Cannabinoid receptor agonism influences mesolimbic connections between the ventral tegmental area and nucleus accumbens, which are involved in learning and reward processing (Stahl, 2013). Importantly, considerable overlap exists between neural systems that mediate reward and pain behavior (Leknes et al., 2011; Leknes & Tracey, 2008). As such, increased stimulation in reward circuits during repeat cannabis episodes can have deleterious within-system effects (e.g., anhedonia or aberrant learning) and tandem effects on associated pain circuits (e.g., hyperalgesia) via cross-sensitization (Ditre et al., 2019; Elman et al., 2012; Elman & Borsook, 2016; Goeders, 2003; Southwick et al., 1999; Yehuda & Antelman, 1993), a process by which repeat exposure to one stimulus class (e.g., drug) increases responding to that same stimulus class and a different stimulus class (e.g., stress, pain). Indeed, similar links have been reported between pain and non-cannabinoid drug classes, including alcohol (Lawton & Simpson, 2009), nicotine (Hahn et al., 2006), and opioids (Ho et al., 2011). Importantly, our ancillary analyses revealed that onset age moderated the association between trial and ratings, such that those participants who initiated cannabis use at earlier ages experienced greater within-study sensitization. Past-month use also moderated temporal effects on ratings. Regarding tolerance, earlier onset ages were also associated with less within-study habituation across trials. Importantly, however, substance use/abuse measures that rely solely on self-report (e.g., MSHQ) may

not be sufficiently sensitive to capture true dose-response associations. That is, measures that involve guided interviews [e.g., Timeline Followback (Robinson et al., 2014)] or drug screening may be necessary to understand nuanced associations between recreational cannabis use and associated effects on pain sensitivity. Therefore, cannabis-induced alterations in pain processing represent an open research question that warrants additional consideration.

On the other hand, people who have pain, or are at greater risk for developing pain and pain-related symptoms (e.g., hyperalgesia, allodynia, negative affect), might turn to recreational/medicinal cannabis to obtain reprieve (Fales et al., 2019; Lake et al., 2019; Ouellette et al., 2019; Pledger et al., 2016; Ware et al., 2003). That is, they may believe that their symptoms would have been worse had they not used cannabis. This perspective is broadly compatible with several substance use/abuse and addiction models, including the negative reinforcement model of addiction (Baker et al., 2004; Wikler, 1948) and self-medication hypothesis (Khantzian, 1997). In general, these models propose that alleviating or preventing negative affective states (e.g., acute withdrawal symptoms) represents a central motivation in repeat substance use (Koob & Le Moal, 2008; Zorrilla & Koob, 2019). Similarly, various pain models, such as the four-stage model of pain processing (Price, 1988; Wade et al., 1992, 1996) and fear-avoidance model (Vlaeyen & Linton, 2000), suggest that normal pain can lead to maladaptive behaviors in those trying to mitigate pain-related negative affect (e.g., avoidance, guarding, substance use). Indeed, that we observed that within-study pain sensitization was *positively* moderated by past-month use but *negatively* moderated by recent use (i.e., previous 48 hours) is consistent with these perspectives, as it suggests that very recent cannabis use may counteract acute withdrawal effects associated with more regular, long-term use. Moving forward, longitudinal studies that track pain among cannabis-naïve users are warranted to

understand potential pain-related consequences associated with long-term cannabis use. This becomes particularly important given recent trends regarding cannabis-based medicines used as adjunctive or even replacement treatments to opioid analgesics (Hutchison et al., 2019).

4.3. Limitations and Future Directions

The observed outcomes reported here should be considered within the context of several methodological limitations. First, as is common with cross-sectional studies, interpretations regarding causal associations were constrained due to the experimental design, which did not involve a cannabis use manipulation. As such, plausible bidirectional relationships between cannabis use and pain were considered similarly. Second, participants were 87.50% white and therefore may not constitute representative samples. Indeed, previous studies have documented sociocultural and ethnic differences regarding pain (C. M. Campbell & Edwards, 2012; Losin et al., 2020), which would not be reflected here. Third, and related to the previous point, our sample was composed of undergraduate college students despite efforts to recruit from the surrounding communities, further constraining generalization. Third, one curious outcome was that among cannabis users, and to a lesser extent among non-users, pain ratings increased with repeat stimulation (evidence of temporal summation) as did pain tolerance (evidence of habituation). Importantly, examining group-specific models provided some additional clarification. Namely, while increasing pain ratings may represent within-session pain sensitization across trials, it is possible that changes in pain tolerance represent participants' comfort with the task over time. Indeed, participants were instructed to signal when pain was "too uncomfortable to continue," which may have interacted with baseline trait/state anxiety levels toward the start of the task. In support of this claim, cannabis users endorsed having more general anxiety symptoms than non-users (Table 1), and users reported considerably

lower pain tolerance versus non-users during trial 1 compared to trial 10 (Figure 3B). This would be consistent with previous studies showing that pain responses habituate over time (Bingel et al., 2007; Hashmi & Davis, 2009; Rennefeld et al., 2010), albeit across longer timescales. In light of these outcomes, moving forward, well-powered studies, particularly those that consider mental health effects (e.g., trait/state anxiety), are necessary to interrogate associations between cannabis use and pain sensitivity and provide clarification regarding cannabis-related pain modulations.

4.4. Conclusions

Results reported here demonstrate that recreational cannabis is associated with pain sensitivity differences among young adult users. As public perceptions continue to evolve regarding the role for cannabis and cannabinoid-based medicines in pain management, it becomes increasingly important to consider both the potential motivations and unintended consequences associated with regular, long-term cannabis use.

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Variable	Users		Non-Users		t, X ²	p
Participants n	33		31			
% Men	39		42			
% Women	61		58			
Age (yrs)	20.18	+ 1.31	19.94	+ 1.03	0.83	0.420
BMI	23.06	+ 3.29	23.31	+ 3.47	0.30	0.768
% Race (A/B/H/I/W)	0/9/0/0/91		6/18/0/6/70		1.27	0.736
% Hispanic	0		6		3.35	0.187
Health						
BAI	13.09	+ 7.43	12.19	+ 9.21	0.43	0.668
BDI	11.85	+ 8.64	11.26	+ 9.27	0.26	0.793
PHQ-15	6.85	+ 3.61	6.06	+ 4.75	0.75	0.455
PQB	3.33	+ 2.70	2.94	+ 3.23	0.54	0.601
% Alcohol (0/1/2/3)	6/30/18/46		39/28/20/13		13.52	0.004
Cannabis						
Onset Age	17.06	+ 1.48				
Regular Use Years	1.08	+ 1.07				
Past-Month Use	6.39	+ 1.77				
% Recent Use	79					

Table 1. Laboratory Study Group-Level Characteristics. N = 64 (n = 33 users, n = 31 non-users) participants were enrolled. Values are means $\pm$ one standard deviation or percentages. Groups were compared using independent samples mean difference tests and chi-square tests for independence as appropriate ($\alpha = 0.05$). Regarding alcohol use, participants indicated whether they drink: “more than three drinks per week” (3), “about three drinks per week” (2), “less than three drinks per week” (1), or “abstain” (0). Regarding cannabis use, participants indicated: onset age, years of regular use (i.e., “use once or twice per week”), past-month use (i.e., “use episodes during the last 30 days”), and recent use (i.e., “use within the last 48 hours”).

A, Asian; B, Black; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BMI, body mass index; eps, episodes; H, Hawaii/Pacific Islander; I, American Indian/American Native; PHQ-15, Patient Health Questionnaire 15; PQB, Prodromal Questionnaire Brief Version; W, White.

Fixed Effect	Estimate	95% CI		p
		LL	UL	
Intercept	46.52	40.37	52.68	<0.001
Trial ^a	0.74	0.50	0.98	<0.001
Group ^b	0.77	- 11.54	13.09	0.902
Trial * Group	0.68	0.19	1.17	0.006
Random Effect	SD	95%		
		LL	UP	
Intercept ^c	82.17	73.11	92.12	

Table 2. Linear Mixed-Effects Model Parameters for Pain Ratings. N = 64 participants (n = 33 cannabis users, n = 31 cannabis non-users) completed the pain ratings task. Marginal $R^2 = 0.01$. Conditional $R^2 = 0.88$. Estimates are unstandardized beta coefficients. Statistical significance determined using $\alpha = 0.05$.

CI, confidence interval; LL, lower limit; SD, standard deviation; UL, upper limit.

^a1-10; ^b0 = non-user, 1 = user; ^c between-participant variance (participant number).

Fixed Effect	Estimate	95% CI		p
		LL	UL	
Intercept	149.77	136.55	163.00	<0.001
Trial ^a	1.58	1.06	2.11	<0.001
Group ^b	- 21.27	- 47.74	5.20	0.115
Trial * Group	1.31	0.27	2.36	0.014
Random Effect	SD	95%		
		LL	UP	
Intercept ^c	376.21	334.74	421.75	

Table 3. Linear Mixed-Effects Model Parameters for Pain Tolerance. N = 64 participants (n = 33 cannabis users, n = 31 cannabis non-users) completed the pain ratings task. Marginal $R^2 = 0.04$. Conditional $R^2 = 0.89$. Estimates are unstandardized beta coefficients. Statistical significance determined using $\alpha = 0.05$.

CI, confidence interval; LL, lower limit; SD, standard deviation; UL, upper limit.

^a1-10; ^b0 = non-user, 1 = user; ^c between-participant variance (participant number).

Figure 1. Overview of Pressure-Based Pain Tasks. In two tasks, we measured pain ratings and pain tolerance, using a pressure-based pain apparatus (commercial sphygmomanometer) secured to participants' non-dominant hand. During the pain ratings task (A), participants were asked to read instructions completely (1). Then, 10 trials involved a(n): on-ramp phase (2), fixed nociceptive stimulation phase (3), off-ramp phase (4), and rating phase (5). The point along a VAS (0-100 points; 0 = no pain, 100 = most pain possible) that participants used to describe each trial was recorded as pain ratings. During the pain tolerance task (B), participants were asked to read instructions completely (1). Then, 10 trials involved a(n): baseline phase (2), maximum nociceptive stimulation phase (3), off-ramp phase (4), and recovery phase (5). The pressure (20-240 mmHg) when participants ended each trial was recorded as pain tolerance.

max, maximum; sec, seconds; VAS, visual analog scale.

Figure 2. Pain Ratings Across Trials. $n = 64$ participants (33 users, 31 non-users) completed stimulus trains involved 10 repetitions of fixed nociceptive stimulation (100 mmHg) and pain ratings measurements. Participants provided pain ratings during each trial using a VAS (0 = no pain, 100 = most pain possible). Pain ratings were operationally defined as the point along the VAS that participants used to describe each trial. (A) Group-level pain ratings data (green = user, gray = non-user) by trial. Data are shown as means $\pm$ one standard error of the mean. (B) Group-level pain ratings trends across trials. Shading represents 95% confidence intervals around group-level trends. (C) Individual pain ratings trends across trials.

VAS, visual analog scale.

Figure 3. Pain Tolerance Across Trials. $n = 64$ participants (33 users, 31 non-users) completed stimulus trains involving 10 repetitions of nociceptive stimulation that varied from trial-to-trial at participants' discretion and pain tolerance measurements. Pain tolerance was operationally defined as the pressure in mmHg (20-240 mmHg) when participants ended each trial. (A) Group-level pain tolerance data (green = user, gray = non-user) by trial. Data are shown as means $\pm$ one standard error of the mean. (B) Group-level pain tolerance trends across trials. Shading represents 95% confidence intervals around group-level trends. (C) Individual pain tolerance trends across trials.
mmHg, millimeters of mercury.

Fixed Effect	Users				Non-Users			
	Estimate	95% CI		p	Estimate	95% CI		p
		LL	UL			LL	UL	
Intercept	46.89	37.83	55.95	<0.001	46.12	37.85	54.40	<0.001
Trial ^a	1.07	0.75	1.39	<0.001	0.39	0.02	0.76	0.041
Random Effect	SD	95%			SD	95%		
		LL	UP			LL	UP	
Intercept ^b	26.41	20.74	33.88		23.31	18.12	30.18	

Supplementary Materials, Table 1. Linear Mixed-Effects Model Parameters for Pain Ratings by Group. N = 64 participants (n = 33 cannabis users, n = 31 cannabis non-users) completed the pain ratings task. Estimates are unstandardized beta coefficients. Statistical significance determined using $\alpha = 0.05$.

CI, confidence interval; LL, lower limit; SD, standard deviation; UL, upper limit.

^a1-10; ^b between-participant variance (participant number).

Fixed Effect	Age				Sex				Alcohol			
	Estimate	95% CI		p	Estimate	95% CI		p	Estimate	95% CI		p
		LL	UL			LL	UL			LL	UL	
Intercept	46.52	40.35	52.69	<0.001	46.52	40.32	52.72	<0.001	46.52	40.35	52.69	<0.001
Trial ^a	0.74	0.50	0.98	<0.001	0.74	0.50	0.98	<0.001	0.74	0.50	0.98	<0.001
Group ^b	0.23	- 12.19	12.64	0.972	0.73	- 11.68	13.15	0.908	3.28	- 10.37	16.93	0.638
Trial * Group	0.68	0.19	1.17	0.006	0.68	0.19	1.17	0.006	0.68	0.19	1.17	0.006
Age	2.22	- 3.08	7.52	0.412								
Sex ^c					1.50	- 11.13	14.14	0.815				
Alcohol ^d									- 2.60	- 8.63	3.44	0.399
Random Effect	SD	95%			SD	95%			SD	95%		
		LL	UP			LL	UP			LL	UP	
Intercept ^e	25.03	20.68	29.42		25.15	20.79	29.57		25.02	20.67	29.41	

Supplementary Materials, Table 2. Linear Mixed-Effects Model Parameters for Pain Ratings with Statistical Controls. N = 64 participants (n = 33 cannabis users, n = 31 cannabis non-users) completed the pain ratings task. Models control for participant age, sex, and alcohol use [“more than three drinks per week” (3), “about three drinks per week” (2), “less than three drinks per week” (1), or “abstain” (0)]. Estimates are unstandardized beta coefficients. Statistical significance determined using $\alpha = 0.05$.

CI, confidence interval; LL, lower limit; SD, standard deviation; UL, upper limit.

^a1-10; ^b0 = non-user, 1 = user; ^c0 = female, 1 = male; ^d1-4; ^e between-participant variance (participant number).

Onset Age					Regular Use Years				
Fixed Effect	Estimate	95% CI		p	Fixed Effect	Estimate	95% CI		p
		LL	UL				LL	UL	
Intercept	46.89	37.76	56.03	<0.001	Intercept	46.89	37.70	56.09	<0.001
Trial ^a	1.07	0.75	1.39	<0.001	Trial ^a	1.07	0.75	1.39	<0.001
Onset	2.22	- 4.06	8.50	0.488	Years	0.99	- 7.75	9.74	0.824
Trial * Onset	- 0.24	- 0.46	- 0.02	0.030	Trial * Years	- 0.29	- 0.59	0.02	0.063
Random Effect	SD	95%			Random Effect	SD	95%		
		LL	UP				LL	UP	
Intercept ^b	26.63	20.58	33.62		Intercept ^b	26.82	20.72	33.85	
Past-Month Use					Recent Use				
Fixed Effect	Estimate	95% CI		p	Fixed Effect	Estimate	95% CI		p
		LL	UL				LL	UL	
Intercept	46.89	37.77	56.02	<0.001	Intercept	46.52	37.22	55.83	<0.001
Trial ^a	1.07	0.76	1.39	<0.001	Trial ^a	0.97	0.65	1.29	<0.001
30d ^c	1.94	- 3.30	7.19	0.468	48h ^d	- 5.34	- 27.78	17.09	0.641
Trial * 30d	0.37	0.19	0.55	<0.001	Trial * 48h	- 1.43	- 2.20	- 0.66	<0.001
Random Effect	SD	95%			Random Effect	SD	95%		
		LL	UP				LL	UP	
Intercept ^b	26.62	20.57	33.60		Intercept ^b	26.75	20.67	33.77	

Supplementary Materials, Table 3. Linear Mixed-Effects Model Parameters for Pain Ratings with Cannabis Use Characteristics. $n = 33$ cannabis users completed the pain ratings task. Models test interactions between trial and cannabis use characteristics [onset age, years of regular use (i.e., “use once or twice per week”), past-month use (i.e., “use episodes during the last 30 days”), and recent use (i.e., “use within the last 48 hours”)]. Estimates are unstandardized beta coefficients. Statistical significance determined using $\alpha = 0.05$.

CI, confidence interval; LL, lower limit; SD, standard deviation; UL, upper limit.

^a1-10; ^b between-participant variance (participant number); ^c 0-8; ^d 0 = no, 1 = yes.

Fixed Effect	Users				Non-Users			
	Estimate	95% CI		p	Estimate	95% CI		p
		LL	UL			LL	UL	
Intercept	139.47	121.76	157.18	<0.001	160.74	140.99	180.50	<0.001
Trial ^a	2.22	1.46	2.98	<0.001	0.91	0.19	1.63	0.014
Random Effect	SD	95%			SD	95%		
		LL	UP			LL	UP	
Intercept ^b	51.52	40.39	66.15		55.81	43.48	72.19	

Supplementary Materials, Table 4. Linear Mixed-Effects Model Parameters for Pain Tolerance by Group. N = 64 participants (n = 33 cannabis users, n = 31 cannabis non-users) completed the pain tolerance task. Estimates are unstandardized beta coefficients. Statistical significance determined using $\alpha = 0.05$.

CI, confidence interval; LL, lower limit; SD, standard deviation; UL, upper limit.

^a1-10; ^b between-participant variance (participant number).

Fixed Effect	Age				Sex				Alcohol			
	Estimate	95% CI		p	Estimate	95% CI		p	Estimate	95% CI		p
		LL	UL			LL	UL			LL	UL	
Intercept	149.77	136.53	163.02	<0.001	149.77	136.64	162.91	<0.001	149.77	136.44	163.11	<0.001
Trial ^a	1.58	1.06	2.11	<0.001	1.58	1.06	2.11	<0.001	1.58	1.06	2.11	<0.001
Group ^b	- 22.57	- 49.22	4.08	0.097	- 21.75	- 48.04	4.55	0.105	- 21.07	- 50.58	8.44	0.162
Trial * Group	1.31	0.27	2.36	0.014	1.31	0.27	2.36	0.014	1.31	0.27	2.36	0.014
Age	5.26	- 6.11	16.64	0.365								
Sex ^c					18.63	- 8.12	45.39	0.172				
Alcohol ^d									- 0.21	- 13.26	12.84	0.975
Random Effect	SD	95%			SD	95%			SD	95%		
		LL	UP			LL	UP			LL	UP	
Intercept ^e	53.72	44.39	63.14		53.27	44.01	62.61		54.08	44.69	63.57	

Supplementary Materials, Table 5. Linear Mixed-Effects Model Parameters for Pain Tolerance with Statistical Controls. N = 64 participants (n = 33 cannabis users, n = 31 cannabis non-users) completed the pain tolerance task. Models control for participant age, sex, and alcohol use ["more than three drinks per week" (3), "about three drinks per week" (2), "less than three drinks per week" (1), or "abstain" (0)]. Estimates are unstandardized beta coefficients. Statistical significance determined using $\alpha = 0.05$.

CI, confidence interval; LL, lower limit; SD, standard deviation; UL, upper limit.

^a1-10; ^b0 = non-user, 1 = user; ^c0 = female, 1 = male; ^d1-4; ^e between-participant variance (participant number).

Onset Age					Regular Use Years				
Fixed Effect	Estimate	95% CI		p	Fixed Effect	Estimate	95% CI		p
		LL	UL				LL	UL	
Intercept	139.47	121.49	157.44	<0.001	Intercept	139.47	121.48	157.46	<0.001
Trial ^a	2.22	1.48	2.97	<0.001	Trial ^a	2.22	1.46	2.98	<0.001
Onset	- 1.65	- 14.00	10.70	0.794	Years	- 0.89	- 18.00	16.23	0.919
Trial * Onset	0.83	0.31	1.34	0.002	Trial * Years	0.08	- 0.64	0.80	0.823
Random Effect	SD	95%			Random Effect	SD	95%		
		LL	UP				LL	UP	
Intercept ^b	52.31	40.36	66.08		Intercept ^b	52.35	40.38	66.14	
Past-Month Use					Recent Use				
Fixed Effect	Estimate	95% CI		p	Fixed Effect	Estimate	95% CI		p
		LL	UL				LL	UL	
Intercept	139.47	121.50	157.44	<0.001	Intercept	139.56	121.31	157.81	<0.001
Trial ^a	2.22	1.46	2.98	<0.001	Trial ^a	2.33	1.57	3.10	<0.001
30d ^c	- 1.47	- 11.80	8.86	0.781	48h ^d	1.36	- 42.65	45.38	0.952
Trial * 30d	0.01	- 0.42	0.45	0.949	Trial * 48h	1.61	- 0.23	3.46	0.086
Random Effect	SD	95%			Random Effect	SD	95%		
		LL	UP				LL	UP	
Intercept ^b	52.29	40.34	66.06		Intercept ^b	52.36	40.39	66.15	

Supplementary Materials, Table 6. Linear Mixed-Effects Model Parameters for Pain Tolerance with Cannabis Use Characteristics. $n = 33$ cannabis users completed the pain tolerance task. Models test interactions between trial and cannabis use characteristics [onset age, years of regular use (i.e., “use once or twice per week”), past-month use (i.e., “use episodes during the last 30 days”), and recent use (i.e., “use within the last 48 hours”)]. Estimates are unstandardized beta coefficients. Statistical significance determined using $\alpha = 0.05$.

CI, confidence interval; LL, lower limit; SD, standard deviation; UL, upper limit.

^a1-10; ^b between-participant variance (participant number); ^c 0-8; ^d 0 = no, 1 = yes.