Pressure-Based Pain Tolerance and Cannabis: A Neuropsychological Assessment of Pain Processing in Recreational Cannabis Users

by

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Abstract

Chronic pain, including pain associated with medical diagnoses, is an ever-growing concern in the United States. Pain-related healthcare costs, lost labor, and medication overdoses cost Americans more $600 billion every year. From a pharmaco-therapy perspective, cannabis represents a promising pain treatment option. Although acute cannabis administration has been associated with anti-pain effects across pain populations, whether such effects endure remains unclear. Characterizing therapeutic windows is one important step towards providing enhanced understanding about if/how cannabis may be used to treat pain. Here, I used an MR-compatible pressure-based pain apparatus to examine mean pain ratings and mean maximum pain tolerance among recreational cannabis users and age- and sex-matched non-users. I found that mean pain ratings were lower among recreational cannabis users than among non-users. Moreover, I found that mean maximum pain tolerance was greater among recreational cannabis users than among non-users. Furthermore, comparing accuracy and reaction times during a color/word interference task (i.e., “Stroop” task) revealed no differences between users and non-users. Enhanced understanding about cannabinoid-induced pain modulations is important for informed decision-making regarding therapeutic potential.

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The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

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List of Abbreviations

CBD	Cannabidiol
THC	Tetrahydrocannabinol
PNS	Peripheral Nervous System
CNS	Central Nervous System
BS	Box Score
HIV	Human Immunodeficiency Virus
BAI	Beck Anxiety Inventory
MSHQ	Marijuana Smoking History Questionnaire
PQ-B	Prodromal Questionnaire- Brief Version
ms	millisecond
MR	Magnetic Resonance
mmHg	millimeters/mercury
NRS	Numeric Rating Scale
s	Second
ANOVA	Analysis of Variance
SSB	Sum of Squares Between
SST	Sum of Squares Total
IQR	Interquartile Range
BMI	Body Mass Index

CE	Common Era
CB	Cannabinoid Receptor
fMRI	Functional Magnetic Resonance Imaging
CAST	Cannabis Abuse Screening Test
CUDIT	Cannabis Use Disorders Identification Test- Revised

Pressure-Based Pain Tolerance and Cannabis:

A Neuropsychological Assessment of Pain Processing in Recreational Cannabis Users

Although medicinal cannabis applications date back more than 3000 years (Booth, 2003), social norms and public policies concerning cannabis are constantly changing. As recently as 2018, 31 states, as well as the District of Columbia, Guam, and Puerto Rico, had enacted legislation that permits public comprehensive medical cannabis programs, with 27 states citing pain-related conditions as inclusionary criteria (National Conference of State Legislatures, 2018). These policies perhaps stem from emerging evidence that cannabis can treat various medical conditions and/or symptoms associated with medical conditions, including nausea/vomiting (Cross-Mellor, Ossenkopp, Piomelli, & Parker, 2007), eating disorders (Hao, Avraham, Mechoulam, & Berry, 2000), sleep/wake disorders (Gorelick et al., 2013), anxiety (Crippa et al., 2012), epilepsy (Devinsky et al., 2015), multiple sclerosis (Baker et al., 2000), post-traumatic stress disorder (Roitman, Mechoulam, Cooper-Kazaz, & Shalev, 2014), and acute and chronic pain states (for a review and meta-analysis, see Hill, 2015). Narrative reviews and meta-analytic reports have linked cannabis to desirable health outcomes, including pain reduction in several pain models (e.g., neuropathic pain), despite producing unwanted cognitive (for a review, see Broyd, van Hell, Beale, Yucel, & Solowij, 2016), psychomotor (Bondallaz et al., 2016; Rogeberg & Elvik, 2016), and psychotic side effects (for a review and meta-analysis, see Marconi, Di Forti, Lewis, Murray, & Vassos, 2016). The ever-widening disparities between (i) local, state, and federal policies that prohibit cannabis use – which has been attributed to weak evidence regarding cannabis' addictive potential when compared to alcohol, heroin, and cocaine (Joy, Watson, & Benson, 2000) – and (ii) emerging evidence that

suggests cannabis may have valuable biomedical properties, underscores the need for objective, quantitative investigations regarding cannabis. Such investigation may reveal potential targets for the development of novel, therapeutic agents that capitalize on cannabis's desirable properties without unwanted side effects.

Cannabis and America: Changing Landscapes

The term *cannabis* comes from the ancient Greek word *kannabis* (meaning "hemp") and commonly refers to three species: *C. sativa, C. indica,* and *C. rederalis*, with *sativa* being the most used worldwide (Booth, 2003). When consumed, cannabis can have powerful psychoactive effects on users. These effects are likely the result of the 450+ chemical constituents associated with cannabis, with more than 50 known exogenous cannabinoids. Common cannabinoids include cannabidiol (CBD), cannabichromene, cannabigerol, cannabicyclol, cannabitriol, and delta-9-tetrahydrocannabinol (THC) (Elsohly & Slade, 2005), with THC constituting as much as 5% of the plant's weight/volume in some strains (Booth, 2003). Responsible for the "high" that is associated with cannabis consumption (Gaoni & Mechoulam, 1964), THC represents the most commonly studied psychoactive cannabinoid compound. Other constituents, such as CBD, are non-psychoactive, and have demonstrated links to various physiological processes, including associations with anti-inflammation (Iuvone, Esposito, De Filippis, Scuderi, & Steardo, 2009) and appetite regulation (Nelson, Walsh, Deeter, & Sheehan, 1994).

It is estimated that in 2014, there were 22.2 million past-month cannabis users in the United States (Center for Behavioral Health Statistics and Quality, 2015). Moreover, recent studies have examined national prevalence rates for cannabis use and cannabis-

use disorders (Hasin et al., 2015), and found dramatic increases in reported use between 2001-2002 (4.1%) and 2012-2013 (9.5%). Although cannabis-use disorder prevalence rates have decreased among current users since 2001-2002, those researchers observed overall increases across subpopulations, suggesting that cannabis could be rising among new and/or infrequent, recreational users. In one assessment, users in the southern states were among those with the biggest increases (Hasin et al., 2015). In addition, several states, counties, and local jurisdictions have legalized recreational cannabis use and/or decriminalized minor cannabis possession. When taken together, these unprecedented changes may contribute to increased permissiveness about cannabis use among Americans (Palamar, Ompad, & Petkova, 2014). For example, although cannabis has been linked to negative or undesirable outcomes, including poor cognitive performance (Meier et al., 2012), visuospatial processing deficits (Pope, Jacobs, Mialet, YurgelumTodd, & Gruber, 1997), impairments operating motor vehicles (Bondallaz et al., 2016; Rogeberg & Elvik, 2016), psychotic symptoms (Moore et al., 2007), cannabis-use disorder and cannabis-withdrawal syndrome, and use/abuse of other, sometimes more severe substances (Joy et al., 2000), Americans support broadening cannabis legalization more than ever (Jones, 2015), according to recent polling.

The Experience of Pain: Central and Peripheral Mechanisms

Chronic pain, including pain associated with various medical diagnoses, such as diabetes, cancer, and others, is an ever-growing concern in the United States. Indeed, recent estimates suggest that pain-related healthcare costs, lost labor, and medication overdoses, cost Americans more $600 billion every year (Institute of Medicine, 2011). According to the International Association for the Study of Pain, pain is “an unpleasant

sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." (Merskey & Bogduk, 2011). However unpleasant, pain is believed to have a role in the navigation of one's external environment, providing important information that could mean the difference between life and death. According to Melzack (1984), pain can benefit the system in three ways: (1) short-lasting pain can cause the organism to withdraw from a noxious stimulus/environment (e.g., reflex response) and subsequent damage, (2) long-lasting pain can increase recuperative behaviors, including feeding and drinking, sleeping, grooming, and dormancy, and (3) pain expression can serve as a means of communication between conspecifics, promoting both survival behaviors and nurturing behaviors. Pain can have origins in the peripheral nervous system (PNS) and central nervous system (CNS), with several pain states involving both.

Findings from several studies suggest that pain states, including such as neuropathic pain (i.e., pain caused by nerve lesions and/or diseases that lead to nerve lesions), have distinct pathologies, affecting PNS and/or CNS neurons (Honroe et al., 2000; Voscopoulos and Lema, 2010). In one example, Honroe and colleagues (2000) found that *decreased* concentrations in various protein kinases and neuropeptides were associated with neuropathic pain onset, but that *increased* concentrations were associated with inflammation-related pain onset. Moreover, those researchers found that cancer-related pain was associated with changes in astrocytes. In any case, peripheral pain (i.e., pain that originates within the PNS) is believed to involve two common mechanisms: peripheral nociceptor sensitization and silent nociceptor recruitment (Schaible & Richter, 2004). Peripheral nociceptor sensitization refers to the relaxation of

excitation thresholds needed to “excite” pain fibers, and occurs following long-lasting exposure to pain (Wolf & Salter, 2000). These maladaptive relaxed thresholds can make normally non-painful stimulation, such as moderate temperature, light, and touch, seem extremely painful. On the other hand, silent nociceptor recruitment refers to the excitation of mechanosensitive fibers that do not normally respond to noxious stimuli (Schaible & Schmidt, 1988). It is through these pathological mechanisms that long-lasting exposure to peripheral pain can produce structural alterations in spinal and neuronal circuits (i.e., CNS) that process pain, perpetuating the pain state (Stahl, 2014).

Long-lasting noxious stimulation can cause CNS neuron sensitization as well, or increases in spinal cord neuron excitability (Schaible, Schmid, & Willis, 1987). In CNS neuron sensitization, spinal cord neurons become more sensitive to input from peripheral pain fibers, effectively amplifying signals stemming from noxious stimulation. This process has been linked to three underlying mechanisms (Schaible & Richter, 2004): (1) increased responding to signals from affected neurons, (2) increased responding to signals from regions near affected neurons, and (3) an increase in the areas from which specific spinal cord neurons process noxious stimuli. Importantly, CNS neuron sensitization has been seen across pain states (Bourke, Langford, & White, 2015), and is associated with spinal structures (e.g., dorsal horn) and supraspinal structures (e.g., brainstem, higher cortical centers) (Melzack, 2001). Many pain states, including chronic pain, can be characterized by central neuron sensitization that endures even when the peripheral noxious stimulation has ended (Sandkühler & Liu, 1998).

Cannabis and Pain: Evidence for Analgesic Properties

From a pharmaco-therapy perspective, cannabis represents a promising option for pain treatment and management. Data from more than 40 clinical trials provide evidence for cannabis's analgesic effects in several pain models, including neuropathic pain (Hill, 2015). Indeed, several reviews and meta-analytic reports have corroborated these findings (Blake, Robson, Ho, Jubb, & McCabe, 2006; Iskedjian, Bereza, Gordon, Piwko, & Elnarson, 2006; Lynch & Campbell, 2011; Martin-Sanchez, Furukawa, Taylor, & Martin, 2009). In one example of acute administration, Wissel and colleagues (2006) examined the effects of low-dose treatment with a synthetic cannabinoid on chronic pain using a randomized, double-blind, placebo-controlled cross-over design. Eleven non-cannabis-using patients with chronic upper motor neuron syndrome were treated with Nabilone, a derivate synthetic cannabinoid (Rubin et al., 1977), and placebo, for four weeks each. Pain was assessed using the Box Score (BS)-11 scale, a rating scale that is commonly used for clinical pain measurement (Hartrick, Kovan, & Shapiro, 2003). Those researchers found that cannabinoid treatment significantly reduced pain ratings among patients, while placebo treatment had no effect. In another example of acute administration, Ellis and colleagues (2009) examined the effects of smoked cannabis on neuropathic pain using a randomized, double-blind, placebo-controlled cross-over design. Twenty-eight non-cannabis-using patients living with human immunodeficiency virus (HIV) smoked cannabis cigarettes – ranging from 1% to 8% in THC content – or placebo cigarettes, for one week each (i.e., four use episodes per day, five days per week). Pain was assessed using the Descriptor Differential Scale, a commonly used ratio scale in subjective pain measurement (Gracely & Kwilosz, 1988). Those researchers

found that cannabis was more effecting regarding pain reduction compared to placebo. Finally, in an example of long-term cannabis use followed by acute administration, Cooper and Haney (2016) examined the effects of active cannabis (3.56% - 5.60% THC) to inactive cannabis (0.00%) on pain sensitivity and pain tolerance using a double-blind, crossover design. Forty-two recreational cannabis users smoked active-cannabis cigarettes and non-active-cannabis cigarettes during counterbalanced experimental sessions. Users completed a cold pressor paradigm, which involves suspending one's hand a in cold bath (4^{o} C) and enduring noxious thermal stimulation as long as possible. The cold pressor paradigm can provide estimates of both pain sensitivity (i.e., latency to first feeling pain) and pain tolerance (i.e., latency to withdraw hand from water). Those researchers found that, among recreational cannabis users, smoking active cannabis produced anti-pain outcomes (i.e., decreased pain sensitivity and increased pain tolerance) compared to smoking non-active cannabis. When taken together, these (and other) findings provide some evidence that cannabis has therapeutic potential regarding pain. However, whether such effects endure beyond acute intoxication remains unclear. Moving forward, one challenge facing biomedical research is determining whether cannabis is associated with long-lasting (i.e., residual) pain reduction effects. Characterizing therapeutic windows is one important step towards providing enhanced understanding about if/how cannabis may be used to treat pain.

To determine whether recent cannabis was associated with pain reduction effects, and to determine whether cannabis-related pain reduction differs between emotion/motivation pain dimensions (i.e., pain ratings) and sensation/perception pain dimensions (i.e., pain tolerance), recreational cannabis users and non-users were

recruited to this quasi-experimental cross-sectional study. Following online recruitment and screening, eligible participants were asked to complete in-laboratory pain testing. Overall, I expected that mean pain ratings (i.e., a subjective pain measure) would be different between recreational cannabis users and non-users following pressure-based pain (Hypothesis 1). Moreover, I expected that mean maximum pain tolerance (i.e., an objective pain measure) would be different between recreational cannabis users and non-users (Hypothesis 2). Furthermore, to determine the extent to which recreational users demonstrated expected cannabis-related cognitive problems (for an extended review, see (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013), participants completed a color-word interference task. I expected that task performance, including accuracy and reaction time, would be worse among recreational cannabis users compared to non-users (Hypothesis 3A, 3B).

Methods

Participants

Participants were men and women, between ages 19 and 24, and currently enrolled in undergraduate psychology coursework at Auburn University in Auburn, Alabama, USA. Recruitment advertisements were circulated via Sona Systems, a cloud-based participant pool management system. During recruitment, participants completed several scales and questionnaires online. Recruitment scales and questionnaires included: a demographics questionnaire, Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown, & Steer, 1988), Marijuana Smoking History Questionnaire (MSHQ) (Bonn-Miller & Zvolensky, 2009), and Prodromal Questionnaire- Brief Version (PQ-B) (Xu et al., 2015) (Appendix A-D). Participants received class credit towards undergraduate psychology

coursework for completing the recruitment scales and questionnaires. Participants meeting specific inclusion/exclusion criteria (described in “Procedure”) were then invited to the laboratory to complete data collection. Participants were deemed “recent cannabis users,” and included in the protocol, when they reported four (or more) cannabis use episodes in the preceding 30-day period (i.e., at least one episode per week). Those participants that reported not having used cannabis in the preceding 30-day period were deemed “non-cannabis users” and included in the protocol. Importantly, non-cannabis users endorsing more than three lifetime use episodes were excluded. For completing laboratory data collection, participants received additional class credit towards undergraduate psychology coursework and $20 cash compensation. Participants were excluded when they had consumed pain relievers in the eight-hour period before data collection, reported repeated substance use (i.e., more than three use episodes) other than cannabis and/or alcohol (e.g., cocaine), and were currently taking over-the-counter or prescription medications to treat medical conditions, including attention deficit hyperactivity disorder, depression, pain, and seizures. Exclusion criteria included severe anxiety as determined by BAI scores (BAI $\geq$ 36) and excessive risk for developing psychosis as determined by PQ-B scores (PQ-B > 6).

To protect participant privacy, the research team 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 evaluation. All procedures were approved by the Auburn University Office of Human Participants Research and Institutional Review Board (17-037 MR 1702).

Apparatus

Marijuana Smoking History Questionnaire (MSHQ). Cannabis use patterns were determined using the Marijuana Smoking History Questionnaire (MSHQ) (Bon-Miller & Zvolensky, 2009). The MSHQ is a 21-question self-report assessment that estimates cannabis use patterns (lifetime, previous 30-day period), representative amount consumed (per use episode, per week), administration route (e.g., cannabis cigarette or "joint," bowl, edible), and consumption context, such as whether respondents consume cannabis alone or in social settings. The assessment is shown in Appendix D, pp. 41-42.

MR-compatible pressure-based pain apparatus. The MR-compatible pressure-based pain apparatus was developed by an interdisciplinary research team from Auburn University (Davis et al., 2016). The apparatus involved a blood pressure armband, which had been outfitted with a neoprene plastic disk and secured to participants' non-dominant hand between the first and second knuckles. The researcher administered experimental pain via increasing pressure within the armband, which pressed the disk into the sensitive tissue in the hand. Pressure was described in millimeters/mercury (mm/Hg). A baseline pressure was reached (20 mmHg) before experimental pain is administered. Pressure was increased via pumps delivered at a variable rate (average rate = 1 pump/s). In the preliminary validation (Davis et al., 2016), the MR-compatible pain apparatus produced reliable results across ten trials (Cronbach's α = 0.98) compared to a commercially available pain apparatus across five trials (i.e., algometer [Cronbach's α = 0.97]), demonstrating that pressure-based pain measurements were reliable using both devices. Within participants, pain tolerance was correlated between devices (r = 0.78, p < 0.001),

indicating comparable performance across devices. The MR-compatible pressure-based pain apparatus is shown in Appendix E, pp. 43.

Color/word interference task. Between counter-balanced pain rating and pain tolerance conditions (described in "Procedure"), participants completed a color/word interference task (i.e., "Stroop" task) (Stroop, 1935). The task involved word/color pairings shown in rapid succession under incongruent conditions (e.g., the word "red," shown in non-red ink, the word "yellow," shown in non-yellow ink). The words/colors used were: red, yellow, green, and blue. Individual trials involved a fixation cross (1,000 ms), a color/word stimulus (max, 1,000 ms), and feedback (1,000 ms). During the color/word stimulus, participants were shown an incongruent color/word pairing at the center of the screen and response options (i.e., 1 = red, 2 = yellow, 3 = green, 4 = blue) at the bottom of the screen. Participants were instructed to respond via button press, striking the number that corresponded to the stimulus color, not the stimulus word. During feedback, participants were shown "Correct," "Incorrect," or "No Response Detected," regarding the response made during the preceding color/word stimulus. Participants completed 12 practice trials to become familiar with the task. Following practice trials, participants completed 100 trials. Primary outcomes during the color/word interference task were response accuracy and response time.

Procedure

Data collection spanned from January 2018 to October 2018. Data were collected from participants across two time points: (1) during online recruitment via Sona Systems and (2) during one in-laboratory pain testing session. In general, pain testing sessions were scheduled between 10:00 AM and 2:00 PM, and were one hour in duration. Before

starting each session, participants were asked whether their cannabis use patterns had changed between recruitment and pain testing. Participants reporting pattern changes were excluded from data collection. This double-blind, between-participants, quasi-experimental protocol had two co-primary outcomes: mean pain ratings and mean maximum pain tolerance. The first co-primary outcome, mean pain rating, was operationally defined as the value along a numeric scale which participants selected to describe the preceding pressure-based pain stimulation, averaged across ten trials. Within each trial, a baseline pressure was reached (20 mmHg). Following baseline pressure, pain was administered by increasing pressure within the device at a variable rate (average rate = 10 mmHg/s). Importantly, using a variable rate ensured that participants could not track their progress across trials. Once pressure reached 100 mm/Hg, participants were instructed to "monitor the current pain" during a five-second interval. Then, the researcher deactivated the pain apparatus. Following deactivation, participants were instructed to evaluate the pain using a numeric rating scale (NRS) (Hartrick et al., 2003), anchored with 0 on the far-left (indicating "no pain"), and 100 on the far-right (indicating "most pain possible"). Trial-specific pain ratings were averaged across trials to produce subject-level mean pain ratings, which were then averaged to produce group-level mean pain ratings. The NRS is shown in Appendix F, pp. 46. The second co-primary outcome, mean maximum pain tolerance, was operationally defined as the pressure in millimeters/mercury (mmHg) when participants indicated that the current pain was "too uncomfortable to continue," averaged across ten trials. Within each trial, a baseline pressure was reached (20 mmHg). Following baseline pressure, pain was administered by increasing pressure with the apparatus at a variable rate (average rate

= 10 mmHg/s). Participants indicated that the pain was too uncomfortable to continue via keyboard response, which prompted the researchers to record the end-point pressure reading and deactivate the apparatus. Trial-specific end-point pressure readings were averaged across trials to calculate subject-specific mean maximum pain tolerance scores, which were then averaged to produce group-level mean maximum pain tolerance scores.

Participant recruitment/scheduling and data collection were handled by separate research team members to ensure double-blind adherence (undergraduate research assistant and J.A.Y, respectively). Once participants were deemed recent cannabis users and enrolled, corresponding age-matched and sex-matched non-cannabis users were selected to complete data collection.

Data Analysis

One-way, between-subjects analyses of variance (ANOVA) were conducted to test main hypotheses regarding subjective pain ratings and objective pain tolerance between recreational cannabis users and non-users. Statistical significance was determined using an $\alpha = 0.05$, two-tailed. Eta-squared (η^2) was calculated as the sum of squares between (SSB) over the sum of squares total (SST). Data were examined using assumptions of ANOVA, including normality, residual normality, and equal variances. Observations deemed outliers [i.e., median observation +/- interquartile range (IQR) x 1.5] were replaced with upper/lower quartile values. Following upper/lower quartile replacement, observations with residual outliers were determined to be those observations with a Cook's distance > 4, and were removed from subsequent one-way ANOVAs.

Results

Demographic information is shown in Table 1. During recruitment, 1,208 participants complete online questionnaires. Following screening, 33 recreational cannabis users and 33 age- and sex-matched non-users completed in-laboratory pain testing sessions. Importantly, no statistically significant differences were observed between users and non-users regarding sex ratio (61% men), age, weight, height, body mass index (BMI), and anxiety and prodromal symptoms. On average, users endorsed between six and seven cannabis use episodes (M = 6.39, SD = 1.77) in the 30-day period preceding the experimental session, and 51% had used cannabis in the preceding 48-hour period.

First, to test the assertation that recreational cannabis was associated with marked alterations in pain ratings (i.e., Hypothesis 1), I conducted a one-way between-subjects ANOVA to compare mean pain ratings between recreational cannabis users and non-users. ANOVA results indicated that pain ratings among users (M = 40.60, SD = 24.59) were lower than among non-users (M = 51.92, SD = 24.172), and that this difference reached statistical significance [$F(1, 63)$ = 4.70, p = 0.03, η^2 = 0.07] (Figure 1). One observation was altered via IQR replacement in the previous analysis. Also, two observations were associated with residual outliers as determined by Cook's distance scores and were excluded. Second, to test the assertion that recreational cannabis was associated with marked alterations in pain tolerance (i.e., Hypothesis 2), I conducted a one-way between-subjects ANOVA to compare mean maximum pain tolerance between cannabis users and non-cannabis users. ANOVA results indicated that mean maximum pain tolerance among users (M = 160.46, SD = 55.29) was greater than mean maximum

pain tolerance among non-users (*M* = 141.76, *SD* = 53.74), but that this difference did not reach statistical significance [*F(1, 64)* = 1.94, *p* = 0.17, η^2 = 0.03] (Figure 2). There were no observations altered via IQR replacement in the previous analysis. Also, there were no observations associated with residual outliers. When taken together, these outcomes suggest that recreational cannabis may mitigate emotion/motivation pain dimensions (i.e., pain ratings) without affecting sensation/perception dimensions (i.e., pain tolerance). Third, to test the assertion that recreational cannabis is associated with marked problems in cognitive functioning (Hypothesis 3A, 3B), I conducted a one-way between-subjects ANOVA to compare mean accuracy, and another one-way between-subjects ANOVA to compare mean reaction time, between users and non-users during a color/word interference task. ANOVA results indicated that mean accuracy among users (*M* = 0.98, *SD* = 0.02) did not differ from mean accuracy among non-users (*M* = 0.98, *SD* = 0.02)) [*F(1, 58)* = 2.59, *p* = 0.11, η^2 = 0.04]. Two observations were altered via IQR replacement in the previous analysis. Also, six observations were associated with residual outliers as determined by Cook's distance scores and were excluded. Also, ANOVA results indicated that mean reaction time among users (*M* = 713.42, *SD* = 168.13) were no different from mean reaction times among non-users (*M* = 715.94, *SD* = 163.55) [*F(1, 59)* = 0.26, *p* = 0.61, η^2 = 0.01]. Four observations were altered via IQR replacement in the previous analysis. Also, five observations were associated with residual outliers as determined by Cook's distance scores and were excluded.

Discussion

In the current assessment, I examined relationships between recreational cannabis and subjective pain dimensions and objective pain dimensions. Specifically, I

used an MR-compatible pressure-based pain apparatus to compare experimental pain outcomes, including mean pain ratings and mean maximum pain tolerance, between recreational cannabis users and non-users. Results reported here demonstrate that recreational cannabis is associated with lower pain ratings following experimental pain administration, but not associated with greater pain tolerance. Overall, these outcomes provide some evidence that cannabis can assuage emotion/motivation pain aspects while leaving sensation/perception aspects unchanged. Moving forward, more research is needed to provide enhanced understanding regarding differences in cannabis-induced pain modulations between short-term use, such as acute administration during experimental and clinical trials, and more long-term use, such as medical and/or recreational use.

Overall Neuropsychological Effects

That cannabis was associated with reduced pain evaluations among recreational users is not surprising when one considers that cannabinoids have been associated with therapeutic techniques throughout human history (Parker, 2017), with the earliest documented treatments centered around pain in 400 common era (CE) (Zias et al., 1993). However, it was not until recent decades that scientists discovered an endogenous neuromodulatory system – dubbed the endogenous cannabinoid (endocannabinoid) system – dispersed throughout the central nervous (Devane et al., 1992) and peripheral nervous system (Munro et al., 1993). The endocannabinoid system includes dense type-1 cannabinoid receptor (CB1 receptor) concentrations within cortical and subcortical brain regions, including the cingulate cortex, thalamus, and cerebellum (Glass et al., 1997); brain regions with demonstrated associations to pain processing dimensions (Wager et

al., 2013), including salience signal processing, somatic-specific activation (DaSilva et al., 2002), and information integration from peripheral pain pathways (Moulton et al., 2010). As such, it is possible that cannabinoid-receptor agonism reduces pain via complex interactions with brain regions that process various pain aspects, including emotional/motivational dimensions. Such an account would be consistent with reports that cannabinoid-based medicines reduce pain ratings among pain patients. For example, in one neuroimaging report, Lee and colleagues (2013) used functional magnetic resonance imaging (fMRI) to examine cannabinoid-induced pain modulations following experimental (i.e., chemical) pain. Those researchers observed that, when compared to placebo, cannabinoid administration (i.e., 15 mg THC) reduced pain unpleasantness, but not pain intenseness. That is, cannabinoid administration modulated pain perception (unpleasantness) without affecting pain sensation (intenseness). Indeed, a recent meta-analysis of cannabinoid-induced modulations in experimental pain reported related conclusions (De Vita et al., 2018). Moreover, cannabinoid-induced reductions in pain unpleasantness correlated with less ACC activation. Indeed, ACC functioning has been implicated in various affective-motivational components in higher-order pain processing, such as conditioned place avoidance (Johansen et al., 2001; LaGraize et al., 2004), perceived threat from noxious stimulation (Foltz & White, 1962), and monitoring survival-relevant goals (Lieberman & Eisenberger, 2015). Despite evidence that acute cannabinoid-receptor agonism may mitigate emotional/motivational pain features via brain activation alteration, whether these effects endure beyond short-term intoxication remains unclear. Recently, Yanes and colleagues (2018) synthesized functional neuroimaging outcomes from studies on long-term cannabis users. Those researchers

found that sustained cannabis was associated with marked modulations in brain activation within the cingulate and striatum, among other brain regions. Moreover, ancillary assessments revealed that those modulations were associated with pain-related taxonomic descriptors (i.e., *Pain, Pain Monitor/Discrimination*) across the functional neuroimaging literature. Altogether, these neuroimaging outcomes may point towards higher-order, brain-level mechanisms that support cannabis-related pain modulations. Moving forward, critical challenges facing biomedical research involve expanded research efforts to provide enhanced understanding about (1) cannabis-related modulations in brain regions that process pain, (2) how such modulations work in concert to reduce the pain experience, and (3) the costs/benefits associated with using cannabinoid-based medicines to treat pain despite demonstrated unwanted side-effects.

Limitations

The results presented here should be considered with respect to several methodological concerns. First, at the time of the study, regulations regarding cannabis consumption in the United States prevented a methodological design that involved experimental cannabinoid administration, which would have permitted observation of direct cause and effect relationships between cannabis and pain. Thus, associations discussed herein must be evaluated with respect to the cross-sectional methods used to derive them. Second, a preliminary power analysis revealed that an increased sample size would have been needed to achieve sufficient power (i.e., N = 176, given effect size = 0.50). A post-hoc power analyses revealed that the pain rating experiment achieved 48% power, while the pain tolerance experiment achieved 28.5% power. As such, it is possible that alternative conclusions could be reached with increased sample sizes.

Third, the current study was limited to undergraduate students, and did not consider other populations (e.g., adolescents, older adults, etc.), which may be differentially affected by cannabis (Meier et al., 2012). Recently, there has been increasing concern over problematic research practices (Open Science Collaboration, 2015), including reliance on "convenience samples" (Peterson & Merunka, 2014). Critically, such practices produce variant (and on occasion, contradicting) conclusions. For example, results presented here demonstrate that recreational cannabis users were no different than non-users regarding accuracy and reaction time during a color/word interference task. Indeed, cannabis-related problems have been reported in users across cognitive functions (for an extended review, see Crane et al., 2013), including interference (Sagar et al., 2015). For example, Sagar and colleagues (2015) measured performance during a color/word interference task among cannabis users and non-cannabis users. Those researchers found that users made more errors than non-users, and that among users, those endorsing early onset use (i.e., before age 16) made more errors than those endorsing late onset use. That no between-group differences were observed here may reflect the convenience sample used (i.e., undergraduate students), as opposed to community samples used in other studies (e.g., Sagar et al., 2015). On the other hand, it is possible that the task demands associated with the current report were not sufficiently challenging to produce cannabis-related between-group differences, especially among college students. Finally, although accepted practices were used to determine cannabis use patterns among participants (i.e., MSHQ), one recent meta-analysis considered results from 25 cannabis-related instruments (Lopez-Pelayo et al., 2015), and concluded that the Cannabis Abuse Screening Test (CAST) and Cannabis Use Disorders Identification Test- Revised

(CUDIT-R) performed best. Moreover, novel instruments that assess cannabis use frequency, onset, and magnitude have recently become available (Cuttler & Spradlin, 2017). It is possible that using such screening materials (e.g., CAST, CUDIT-R) could have produced participant groups with more consistent cannabis use patterns. Moving forward, subsequent research efforts would benefit from these important considerations.

Conclusions and Future Directions

Lagging behind changes to state and federal policies regarding cannabis is the scientific understanding needed to justify such actions. Despite growing evidence that cannabis use has analgesic properties, studies that examine the psychophysiological, neurobiological, and neurochemical mechanisms that support these effects remains unclear. Eventually, this work will shape my dissertation work, which will leverage sophisticated neuroimaging techniques to examine neural circuits involved in pain perception through the lens of recreational and medicinal cannabis use. Enhanced understanding of cannabis's impact on the human brain is important for providing patients, healthcare providers, and law makers with a theoretical foundation allowing for informed decision-making regarding cannabis use.

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	Non-Cannabis	Cannabis	Difference
Demographic			
n	33	33	
Men/n	20/33	20/33	
Age	20.06 ± 1.12	20.18 ± 1.31	$p = 0.68$
Height	67.91 ± 3.66	68.61 ± 3.65	$p = 0.44$
Weight	151.09 ± 26.38	157.73 ± 32.01	$p = 0.36$
BMI	22.96 ± 3.07	23.57 ± 3.63	$p = 0.50$
Mental Health			
BAI	14.21 ± 10.47	13.64 ± 7.98	$p = 0.80$
PQB	2.55 ± 2.09	3.09 ± 2.17	$p = 0.30$
Cannabis Use			
Pre. 30 D	0	6.39 ± 1.77	$p < 0.05$ *
Pre. 48 H	0	51%	

Table 1. Participant Characteristics. Table depicting group-level characteristics among recreational cannabis users and non-users, including group size (n), sex ratio (Men/n), age (Age), height (Height), body mass index (BMI), anxiety symptoms (BAI), prodromal symptoms (PQ-B), and recent cannabis use (Pre. 30 D, Pre. 48 H). Values denoted * reached statistical significance.

BMI, body mass index; BAI, Beck Anxiety Inventory; PQ-B, Prodromal Questionnaire- Brief Version; Pre. 30 D, cannabis use during last 30 days; Pre. 48 H, cannabis use during last 48 hours.

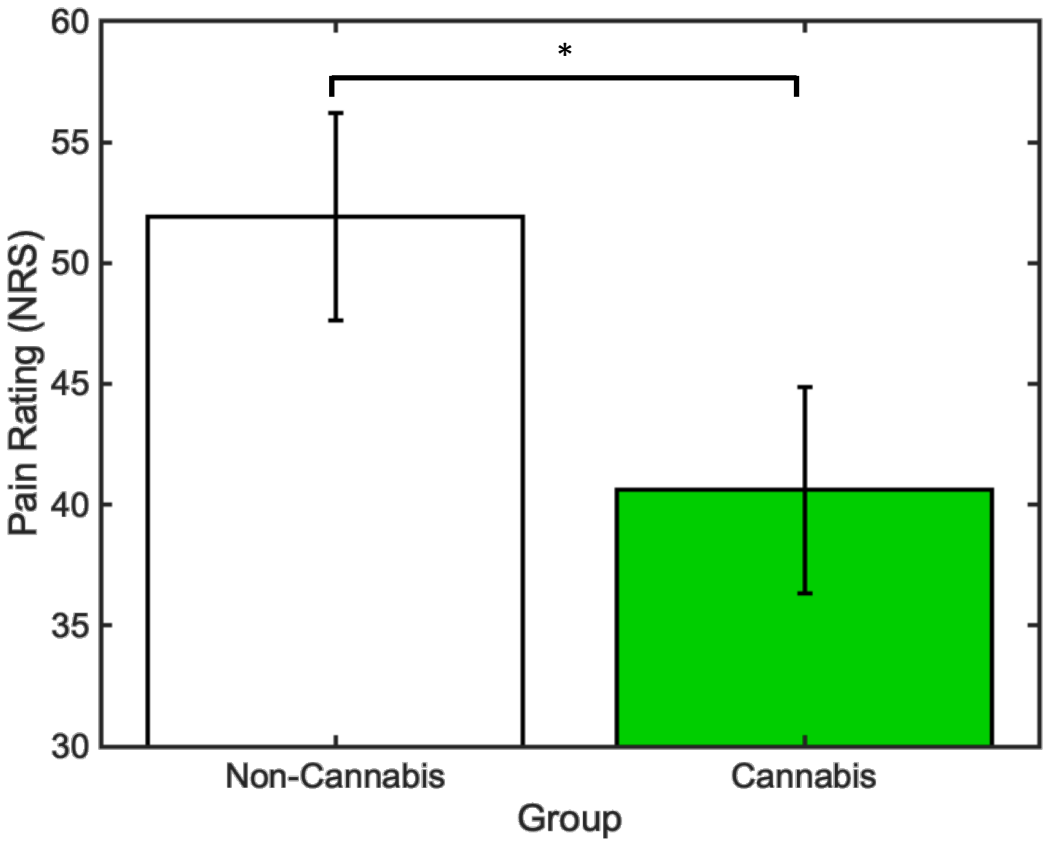

Figure 1. Mean Pain Ratings. Histogram depicting group-level pain ratings averaged across ten trials. Mean pain ratings were lower among recreational cannabis users (*M* = 40.60, *SD* = 24.59) than among non-users (*M* = 51.92, *SD* = 24.172). One-way ANOVA (between-subjects factor = group) indicated that the difference between means reached statistical significance [$F(1, 63) = 4.70$, $p = 0.03$, $\eta^2 = 0.07$].

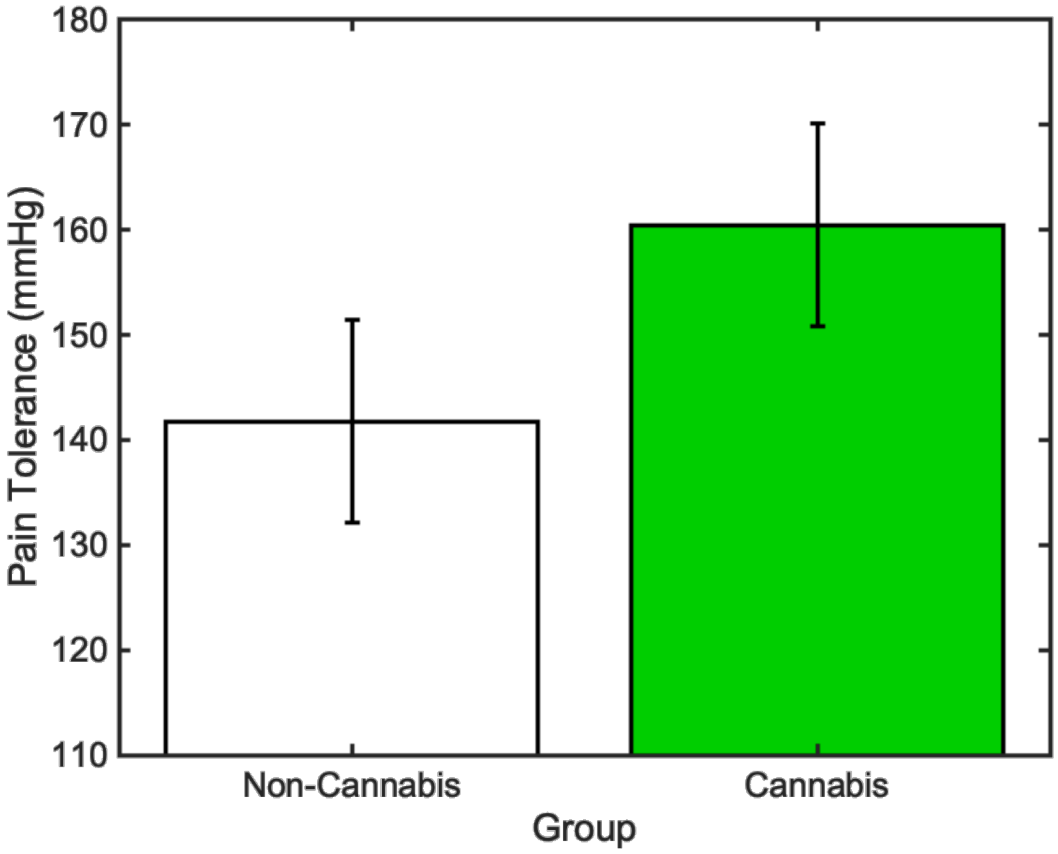

Figure 2. Mean Maximum Pain Tolerance. Histogram depicting group-level maximum pain tolerance averaged across ten trials. Mean maximum pain tolerance was greater among recreational cannabis users (*M* = 160.46, *SD* = 55.29) than among non-users (*M* = 141.76, *SD* = 53.74). One-way ANOVA (between-subjects factor = group) indicated that the difference between means difference did not reach statistical significance [*F(1, 64)* = 1.94, *p* = 0.17, η^2 = 0.03].

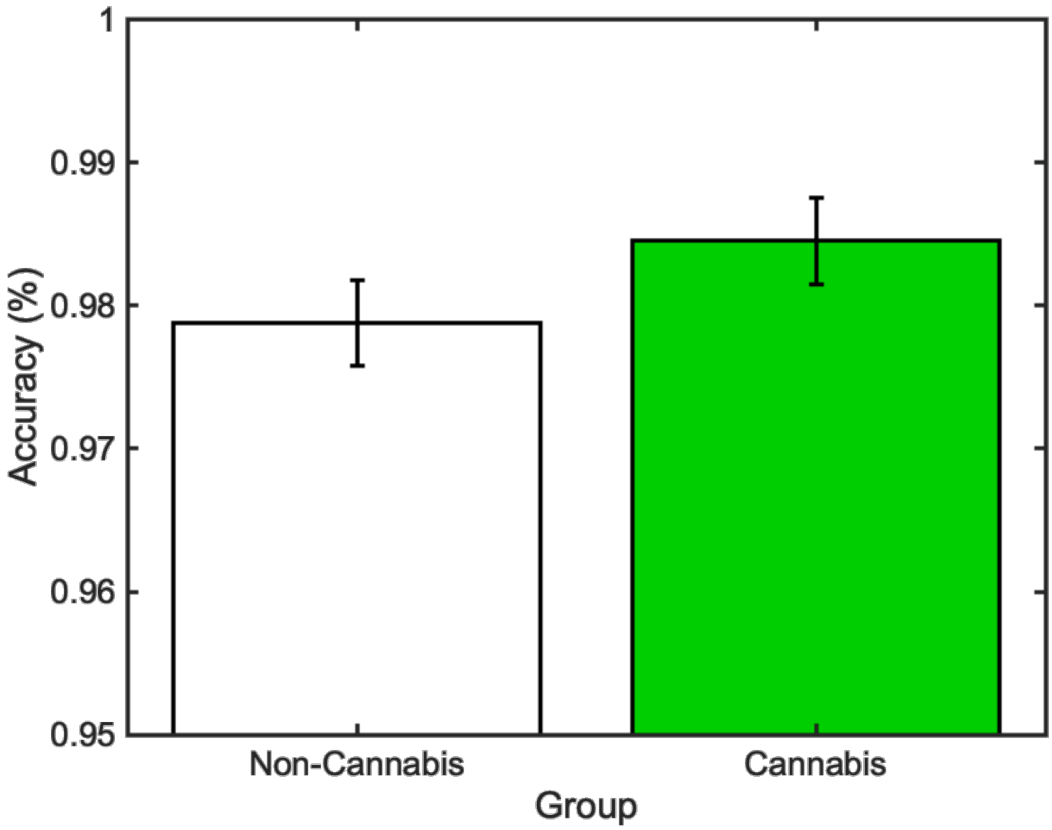

Figure 3. Mean Color/Word Interference Accuracy. Histogram depicting group-level accuracy during color/word interference task completion averaged across 100 trials. ANOVA results indicated that mean reaction times among recreational cannabis users (*M* = 0.98, *SD* = 0.02) were no different from mean reaction times among non-users (*M* = 0.98, *SD* = 0.02) [*F(1, 58)* = 2.59, *p* = 0.11, η^2 = 0.04].

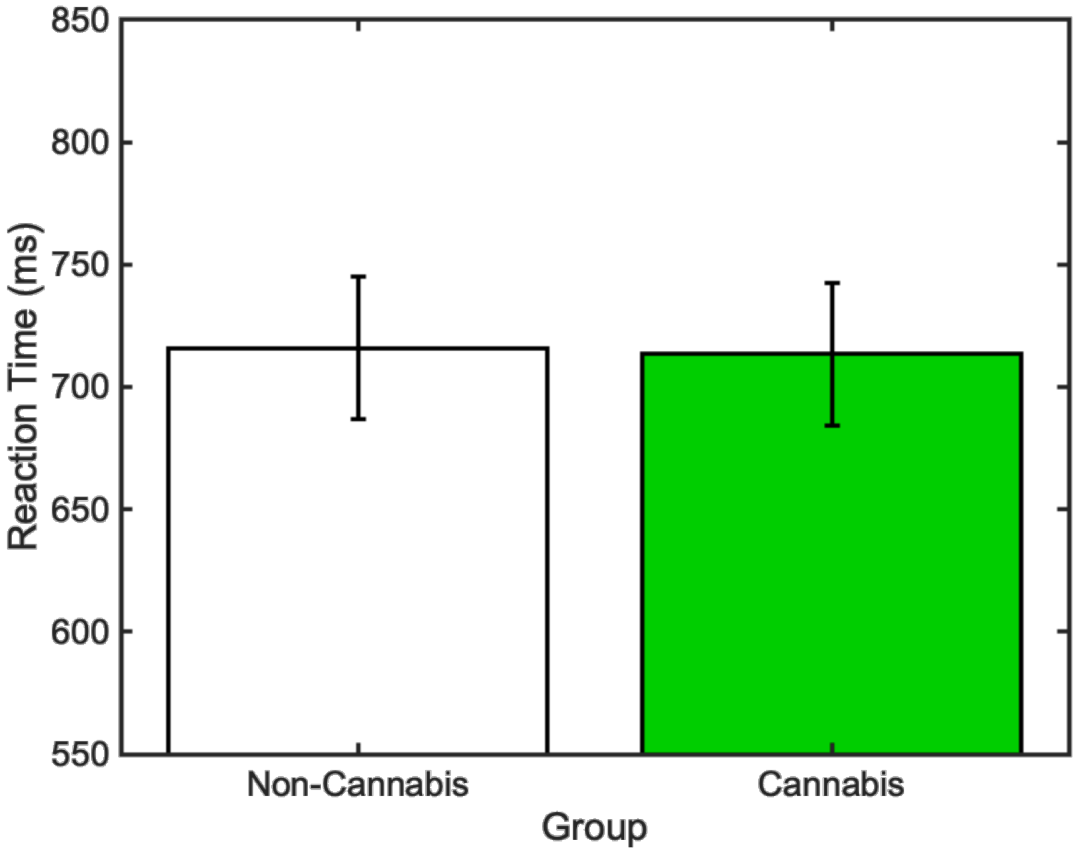

Figure 4. Mean Color/Word Interference Reaction Time. Histogram depicting group-level reaction times during color/word interference task completion averaged across 100 trials. ANOVA results indicated that mean reaction times among recreational cannabis users (*M* = 713.42, *SD* = 168.13) were no different from mean reaction times among non-users (*M* = 715.94, *SD* = 163.55) [*F(1, 59)* = 0.26, *p* = 0.61, η^2 = 0.01].

Appendix A: Demographics Questionnaire

1. What is your age in years? _____

2. What is your sex? Male Female

3. How do you describe yourself? (please check the one option that best describes you)—Be sure consisted with NIH

American Indian or Alaska Native

Hawaiian or Other Pacific Islander

Asian or Asian American

Black or African American

White

4. How do you describe yourself?

Hispanic or Latino

Non-Hispanic White

5. Are you:

Married

Divorced

Widowed

Separated

Never been married

A member of an unmarried couple

6. Are you currently:

Employed for wages full-time

Employed for wages part-time

Out of work for more than 1 year

Out of work for less than 1 year

A student

Retired

Unable to work

7. What is the highest grade or year of school you completed?

Never attended school or only attended kindergarten

Grades 1 through 8(Elementary)

Grades 9 through 11 (Some high school)

Grade 12 or GED (High school graduate)

College 1 year to 3 years (Some college of technical school

College 4 years (College graduate)

Graduate School(Advance Degree)

8. What is the primary language you speak at home?

English

Spanish

Other

9. Have you ever taken medication for psychological/psychiatric reasons? _____Yes _____No

10. Have you received counseling or psychotherapy previously?
_____Yes _____No

11. Have you ever been hospitalized for psychological/psychiatric reasons?
_____Yes _____No

12. Has anyone in your family (parents, grandparents, siblings, other relative) been diagnosed and/or treated for psychological/psychiatric condition(s)? _____Yes
_____No

Appendix B: Beck Anxiety Inventory (BAI)

Beck Anxiety Inventory

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not At All	Mildly but it didn't bother me much.	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky / unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint / lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3
Column Sum				

Scoring - Sum each column. Then sum the column totals to achieve a grand score. Write that score here _____ .

Interpretation

A grand sum between **0 – 21** indicates very low anxiety. That is usually a good thing. However, it is possible that you might be unrealistic in either your assessment which would be denial or that you have learned to "mask" the symptoms commonly associated with anxiety. Too little "anxiety" could indicate that you are detached from yourself, others, or your environment.

A grand sum between ***22 – 35*** indicates moderate anxiety. Your body is trying to tell you something. Look for patterns as to when and why you experience the symptoms described above. For example, if it occurs prior to public speaking and your job requires a lot of presentations you may want to find ways to calm yourself before speaking or let others do some of the presentations. You may have some conflict issues that need to be resolved. Clearly, it is not "panic" time but you want to find ways to manage the stress you feel.

A grand sum that **exceeds 36** is a potential cause for concern. Again, look for patterns or times when you tend to feel the symptoms you have circled. Persistent and high anxiety is not a sign of personal weakness or failure. It is, however, something that needs to be proactively treated or there could be significant impacts to you mentally and physically. You may want to consult a physician or counselor if the feelings persist.

Appendix C: Prodromal Questionnaire- Brief Version (PQ-B)

Figure(s)

Appendix A. PQ-B Rachel Loewy, PhD and Tyrone D. Cannon, PhD

Please indicate whether you have had the following thoughts, feelings and experiences **in the past month** by checking "yes" or "no" for each item. **Do not include experiences that occur only while under the influence of alcohol, drugs or medications that were not prescribed to you.** If you answer "YES" to an item, also indicate how distressing that experience has been for you.

1. **Do familiar surroundings sometimes seem strange, confusing, threatening or unreal to you?**

   ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:

   ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

2. **Have you heard unusual sounds like banging, clicking, hissing, clapping or ringing in your ears?**

   ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:

   ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

3. **Do things that you see appear different from the way they usually do (brighter or duller, larger or smaller, or changed in some other way)?**

   ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:

   ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

4. **Have you had experiences with telepathy, psychic forces, or fortune telling?**

   ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:

   ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

5. **Have you felt that you are not in control of your own ideas or thoughts?**

   ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:

   ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

6. **Do you have difficulty getting your point across, because you ramble or go off the track a lot when you talk?**

   ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:

   ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

7. **Do you have strong feelings or beliefs about being unusually gifted or talented in some way?**

   ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:

   ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

8. **Do you feel that other people are watching you or talking about you?**

   ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:

   ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

9. **Do you sometimes get strange feelings on or just beneath your skin, like bugs crawling?**

   ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:

   ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

10. **Do you sometimes feel suddenly distracted by distant sounds that you are not normally aware of?**

    ☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:

    ☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

PLEASE TURN PAGE OVER>>

11. Have you had the sense that some person or force is around you, although you couldn't see anyone?

☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

12. Do you worry at times that something may be wrong with your mind?

☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

13. Have you ever felt that you don't exist, the world does not exist, or that you are dead?

☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

14. Have you been confused at times whether something you experienced was real or imaginary?

☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

15. Do you hold beliefs that other people would find unusual or bizarre?

☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

16. Do you feel that parts of your body have changed in some way, or that parts of your body are working differently?

☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

17. Are your thoughts sometimes so strong that you can almost hear them?

☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

18. Do you find yourself feeling mistrustful or suspicious of other people?

☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

19. Have you seen unusual things like flashes, flames, blinding light, or geometric figures?

☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

20. Have you seen things that other people can't see or don't seem to see?

☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

21. Do people sometimes find it hard to understand what you are saying?

☐ **YES** ☐ **NO** ***If YES:*** When this happens, I feel frightened, concerned, or it causes problems for me:
☐ Strongly disagree ☐ disagree ☐ neutral ☐ agree ☐ strongly agree

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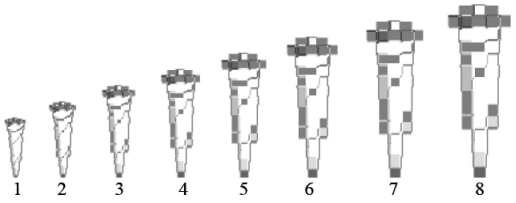
APPENDIX

Marijuana Smoking History Questionnaire (MSHQ)

1. Do you currently or have you ever smoked marijuana?

   1 = YES 0 = NO *If NO, skip the remainder of this page and the next.
2. Please rate your marijuana use in the past 30 days.

   0 1 2 3 4 5 6 7 8
   No use Once a week More than once a day
3. On average, how much marijuana do you smoke per occasion (circle one)?

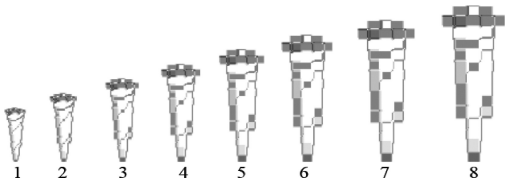


4. In your lifetime how many days have you smoked marijuana?

   0 1 2 3 4 5 6
   No days More than 300 days
5. What is the **typical** means by which you consume marijuana (circle one)

   a. Joint b. Bowl c. Bong d. One-hitter
   e. Ingestion (e.g. food)
6. In which of the following situations do you **typically** smoke marijuana (circle one)

   a. Alone b. With two or three people c. With more than three people
7. How old were you when you **first** smoked marijuana? (years)
8. How old were you when you started regular daily marijuana smoking? (years)
9. For how many years, altogether, have you been a regular daily marijuana smoker?
10. Think about your smoking during the **last week**, how much marijuana did you smoke per occasion in an average day (circle one)?



11. Think about your smoking during the **last week**, how often did you smoke marijuana in an average day?
12. When were you smoking the **heaviest**? (year)
13. How many times in your life have you made a serious attempt to quit using marijuana? (If more than 9 times, put 9)
14. As best as you can remember, how long ago did you make your first attempt to quit marijuana smoking? (years)
15. How many years have you smoked marijuana? (total number of years)
16. How many different times in you life have you made an attempt to quit smoking marijuana where you have stayed off marijuana for 12 or more hours? (Do not include time sleeping)

17. Since you started smoking marijuana regularly, have you ever quit for a period of at least 24 hours?
    1 = YES 0 = NO _____
18. Since you first started smoking marijuana, what was the **longest** period of time that you were able to stay off marijuana? (If less than 1 day, do not include time sleeping)
    Years _____
    Months _____
    Days _____
    Hours _____
19. Have you in the **past** had a disease or illness you believe was caused or aggravated by your smoking marijuana?
    1 = YES 0 = NO _____
20. Do you have any symptoms **now** that you believe are caused by your smoking marijuana?
    1 = YES 0 = NO _____
21. Do you have a disease or illness **now** that you believe is caused by or aggravated by your smoking marijuana?
    1 = YES 0 = NO _____

Appendix E: Pressure-Based Pain Apparatus

Appendix F: Numeric Rating Scale (NRS)