7T Functional MRS/MRI Assessment of Pain in Cannabis Users

by

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Abstract

Despite analgesic efficacy reported by medicinal and recreational cannabis users, mounting empirical evidence suggests that long-term cannabis use is associated with worse pain outcomes. In the US, 33 states have enacted policies that permit cannabis use to treat a range of pain conditions, including chronic lower back pain, arthritis, fibromyalgia, and clinical pain associated with various disease states. As such, the focus of considerable scientific efforts has been to understand the neurobiological mechanisms that underpin cannabinoid-related pain modulation. Unfortunately, lacking robust research practices has contributed to mixed – and at times contradictory – conclusions regarding cannabinoid pain control. To provide clarification regarding the impact of cannabis use on neurochemical and neurobiological correlates of pain processing, the current study combined functional magnetic resonance spectroscopy (fMRS) and functional magnetic resonance imaging (fMRI) to examine metabolite level changes and functional responses to acute nociceptive stimulation among cannabis users (n = 17) and non-users (n = 23). Participant eligibility was determined using accepted cutoff scores across several assessments regarding anxiety, depression, prodromal, and somatic symptom severity, as well as dependence severity scores regarding amphetamine, cocaine, heroin/opioids, and psychomotor stimulant use. To be included, cannabis users needed to be recent, frequent users (i.e., $\geq$ 4 use episodes in preceding 30-day period) and non-users were not permitted to endorse more than 3 lifetime cannabis use episodes. Regarding fMRS, there was modest evidence that cannabis use impacts dorsal anterior cingulate (dACC) glutamate and glutamate + glutamine (Glx) levels but not glutamine levels. Moreover, exploratory assessments revealed associations between cannabis use

and dACC aspartate. Regarding fMRI, dACC functional responses during moderate nociceptive stimulation were not associated with dACC metabolite level changes, including glutamate, glutamine, Glx, and aspartate. Importantly, understanding neurochemical and neurobiological impacts associated with cannabis among frequent, long-term cannabis users is an important step toward developing effective pain management strategies as access to medicinal and recreational cannabis continue to expand.

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List of Abbreviations

AEA	Anandamide
AFNI	Analysis of Functional Neuroimages
Ala	Alanine
ALE	Activation Likelihood Estimation
ACC	Anterior Cingulate Cortex
Asp	Aspartate
CAN	Cannabis
CB	Cannabinoid Receptor
CBD	Cannabidiol
Cr	Creatine
dACC	Dorsal Anterior Cingulate Cortex
DLPFC	Dorsolateral Prefrontal Cortex
fMRI	Functional Magnetic Resonance Imaging
fMRS	Functional Magnetic Resonance Spectroscopy
FTND	Fagerström Test for Nicotine Dependence
GAD	Generalized Anxiety Disorder
GABA	Gamma-Aminobutyric Acid
GCPS	Generalized Chronic Pain Scale
Gln	Glutamine
Glu	Glutamate
Glx	Glutamate + Glutamine
GPC	Glycerophosphocholine

GSH	Glutathione
Ins	*Myo*-inositol
IU	Institutional Unit
Lac	Lactate
MACM	Meta-Analytic Coaction Map
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NAA	*N*-acetylaspartate
NPS	Neuropathic Pain Scale
NRS	Numeric Rating Scale
PCr	Phosphocreatine
PCh	Phosphocholine
PE	Phosphoethanolamine
PET	Positron Emission Tomography
PHQ	Patient Health Questionnaire
PQB	Prodromal Questionnaire Brief
PSS	Perceived Stress Scale
RAPI	Rutgers Alcohol Problem Index
RCT	Randomized Control Trial
ROI	Region of Interest
Tau	Taurine
THC	Tetrahydrocannabinol
VAS	Visual Analog Scale

WBS	Well Being Scale
2AG	2-Arachidonoylglycerol

Chapter 1

General Introduction

Normative processing of acute pain signals represents one important aspect of the human experience. However, normal pain can outlast its survival-related utility, resulting in maladaptive, chronic pain. 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 narrative and systematic reviews summarizing cannabis-related outcomes across pain populations (Abrams, 2018; Hill, 2015; Hill et al., 2017; Muecke et al., 2018; Nugent et al., 2017; Stockings et al., 2018). Those reports concluded that cannabis preparations represent promising pain treatment options, while citing concerns about adverse mental health effects. Similarly, recent meta-analytic assessments have attempted to provide quantitative resolution regarding cannabinoid analgesia. Coalescing results from published studies provides some support for cannabis-related pain reduction

in acute experimental 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 reported between specific conditions: cancer (Haeuser et al., 2019), HIV (Phillips et al., 2010), multiple sclerosis (Iskedjian et al., 2007), neuropathic pain (Andreae et al., 2015; Phillips et al., 2010), 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 moderate-term (e.g., clinical trial) cannabis administrations. As such, the extent to which cannabinoid analgesia endures in long-term 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 in the United States, one important open research question involves characterizing pain processing alterations among users that may represent motivations, consequences, or both, linked with long-term use.

Despite perceived efficacy often reported by medicinal and recreational cannabis users across a range of psychological and physiological symptoms (Cuttler et al., 2018, 2019, 2020; Sexton et al., 2016), a growing empirical corpus supports the supposition that users may experience worse pain outcomes when 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). Regarding worse pain-related outcomes among cannabis users, it is possible that more pain is a consequence, cause, or both, of regular cannabis use (i.e., the cause-consequence controversy) (Khantzian, 1997). For example, repeated exposure to cannabinoid receptor agonists (e.g., delta-9-tetrahydrocannabinol (THC), cannabidiol

(CBD)) might 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 neural connections involved in reinforcement learning and reward processing (Stahl, 2013). Importantly, rewarding aspects associated with acute cannabis administration, such as relaxation, openness, and analgesia, are likely facilitated via indirect VTA-NAc connections (i.e., glutamatergic, GABAergic, acetylcholinergic, serotonergic, and opioidergic connections) rather than direct VTA-NAc connections (i.e., dopaminergic connections) (Nutt et al., 2015; Stahl, 2013). These regions have distributed whole-brain connections targets, including to the anterior cingulate cortex (ACC), via the cortico-ventral basal ganglia circuit (Haber, 2011).

Considerable overlap exists between neural systems that mediate reward and pain behavior (Leknes et al., 2011; Leknes & Tracey, 2008). Accordingly, increased stimulation in reward neural circuits during repeat cannabis-use episodes can have deleterious within-system effects (e.g., anhedonia, aberrant learning) and tandem effects on associated pain neural 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 (i) that same stimulus class and (ii) a different stimulus class (e.g., stress, pain). Indeed, similar links have been reported between other drug classes that target indirect mesolimbic connections and increase pain: alcohol (Lawton & Simpson, 2009), nicotine (Hahn et al., 2006), and opioids (Ho et al., 2011). In one recent report, an association was observed between pain-related interference, but not pain tolerance, and use duration (regular use years) among cannabis users, such that

those participants with longer use histories reported more interference (Yanes et al., 2020). However, no associations were observed between pain outcomes and other cannabis use characteristics, including onset age, past-month use, and recent use. Moreover, previously reported longitudinal results have shown no association between previous cannabis use and subsequent pain intensity or interference after controlling for baseline pain, pain self-efficacy, and clinical covariates (G. Campbell et al., 2018). Accordingly, potential cannabis-induced alterations in pain processing represents an open research question which warrants further 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, catastrophizing), might turn to recreational and/or 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, their symptom severities might be worse if not for having used cannabis. This perspective is broadly compatible with several substance 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 and/or preventing negative affective states represents a central motivation in repeat substance use. 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 people trying to mitigate pain-related negative affect (e.g., avoidance, guarding, substance use). Moving forward, longitudinal studies that track pain and cannabis-use characteristics among drug-naive (new) users are warranted to

understand potential pain-related consequences associated with long-term cannabis. 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).

Therefore, the research program presented herein centers around understanding cannabis-related neurobiological consequences and associated effects on pain processing. The following chapters have been included in complete detail.

In Chapter 2, results from a meta-analysis of functional neuroimaging studies involving whole-brain comparisons between cannabis users and non-users are discussed (Yanes et al., 2018). Importantly, these studies were not restricted to one task paradigm or domain (e.g., working memory, reward processing). Rather, included studies represented several psychological phenomena, including cognitive control, motor coordination, facial recognition, emotion processing, and more. Critically, despite increasing attention to the effects of cannabis on pain (Hill, 2015; Hill et al., 2017), functional neuroimaging studies regarding cannabis-related pain modulation were lacking. Nevertheless, ancillary assessments demonstrated that cannabis was associated with differential activation in brain regions important in pain processing, namely, the anterior cingulate cortex (ACC) and striatum. However, it remained unclear whether these neurobiological meta-analytic outcomes translate to observable changes in pain sensitivity.

In Chapter 3, results are reviewed from a subsequent meta-analysis that sought to provide clarification regarding cannabinoid-related pain modulation in populations that experience pain (e.g., chronic pain, neuropathic pain, cancer-related pain) (Yanes et al.,

2019). When considering collective outcomes from across considered studies, there was strong evidence that cannabinoid-based treatments (e.g., whole-plant cannabis, cannabis extracts, synthetic cannabinoids) were more efficacious versus corresponding placebo treatments regarding pain ratings. Given meta-analytic evidence that *long-term* cannabis use is associated with functional changes in pain brain regions, and given meta-analytic evidence that *short-term* cannabis administration is associated with measurable pain reduction, one open research question involves characterizing pain outcomes among cannabis users and non-users to understand neurobiological mechanisms associated with cannabis-related pain modulation.

To that end, Chapter 4 describes the current study, wherein cannabis users and non-users underwent combined functional magnetic resonance spectroscopy (fMRS) and functional magnetic resonance imaging (fMRI) while receiving acute mechanical nociceptive stimulation. Because functional changes were observed in the dorsal ACC (dACC) among users (Yanes et al., 2018), and because the dACC represents an important pain processing brain area (Wager et al., 2013), hypotheses were centered around dACC metabolite levels (fMRS) and functional responses (fMRI). Moreover, recent meta-analytic evidence suggests that glutamate-related metabolite level changes, as measured by fMRS, are associated with experimental pain (Archibald et al., 2020). Specifically, it was hypothesized that: (1) dACC glutamate-related metabolite levels would be lesser among cannabis users versus non-users, (2) dACC glutamate-related metabolite levels would track nociceptive stimulation, and (3) dACC glutamate-related metabolite levels would be associated with dACC functional responses during nociceptive stimulation. Importantly, understanding cannabis-related changes in brain areas

important in pain processing is one important step toward developing effective pain management strategies as access to medicinal and recreational cannabis continue to expand.

Chapter 2

Neuroimaging Meta-Analysis of Cannabis Use Studies Reveals Convergent Functional Alterations in Brain Regions Supporting Cognitive Control and Reward Processing

Cannabis, the flowering plant genus that includes three species, *C. sativa*, *C. indica*, and *C. ruderalis*, contains psychotropic and non-psychotropic compounds, including delta-9-tetrahydracannabinol (THC) and cannabidiol (CBD). These compounds interact with endogenous cannabinoid receptors, albeit to different degrees, distributed throughout the central nervous system, with particularly high receptor densities found in the thalamus, cingulate cortex, and primary and supplementary motor areas (Freund et al., 2003; Howlett et al., 2002). In 2015, there were an estimated 22.2 million past-month cannabis users in the United States (US), a number expected to continue rising in the coming years according to the Substance Abuse and Mental Health Services Administration. As of September 2017, 29 states within the US and the District of Columbia have enacted legislation that permits cannabis use for the treatment of various medical conditions, with several states even permitting recreational use. Lagging behind these rapid changes to state laws, as well as societal views and medical practice, is insight into the cognitive, behavioral, and neurobiological consequences of cannabis use. Deeper understanding of cannabis's impact on brain functioning is important for informed decision-making about its use.

Functional neuroimaging modalities – including functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) – provide a means to examine the effects of substance use and abuse on the human brain (Jia et al., 2011; Sutherland et al., 2015; Volkow et al., 2013). Regarding cannabis, some insights into region-specific

effects are beginning to emerge. Specifically, previous studies suggest attenuated activity among users in brain regions supporting executive functions, such as cognitive control, error processing, and learning, yet enhanced activity in regions supporting reward processing. For example, (Hester et al., 2009) examined the neural correlates of error processing among cannabis users employing a modified Go/No-Go response inhibition task. Those authors observed behavioral deficits in error awareness (but not error commission) among users versus non-users, and that more severe reductions in anterior cingulate cortex (ACC) activation were associated with greater error awareness deficiencies. Similarly, (Jager et al., 2007) documented reduced activation in the dorsolateral prefrontal cortex (DL-PFC), among other regions, in abstinent cannabis users completing an associative memory paradigm, such that cannabis-related reduced activation within prefrontal regions was more pronounced during associative learning relative to retrieval task phases. In another example, (Nestor et al., 2010) used a monetary incentive delay paradigm to examine reward anticipation and evaluation among cannabis users. Those researchers reported increased ventral striatum responding during reward anticipation among users versus non-users. Importantly, cannabis-use patterns (i.e., lifetime joints consumed) were positively correlated with increased striatal activation, providing evidence for heightened sensitivity to reward-predictive stimuli with increasing exposure. Moving forward, an important challenge facing the field is to synthesize findings from functional neuroimaging studies on cannabis use to establish aggregate patterns of neurobiological changes associated with non-acute exposure.

Towards this goal, several narrative reviews have sought to summarize the neural, cognitive, and behavioral consequences of cannabis use (Bhattacharyya, Atakan, et al.,

2012; Bhattacharyya & Sendt, 2012; G. Bossong et al., 2014; Kowal et al., 2013; Martín-Santos et al., 2010; Wrege et al., 2014). En masse, these reviews provide variant yet complementary perspectives. Specifically, some reports have advocated that cannabis use has detrimental effects on cognitive processes, such as attention and decision-making (Bhattacharyya, Atakan, et al., 2012; Martín-Santos et al., 2010; Wrege et al., 2014), which have been ascribed to decreased activation within frontal and prefrontal regions, including the ACC (Eldreth et al., 2004; Gruber et al., 2012; Hester et al., 2009) and DL-PFC (Bolla et al., 2005). Others have focused on salience processing and impulsiveness among cannabis users, highlighting enhanced activation within reward circuits (Bhattacharyya, Atakan, et al., 2012; Wrege et al., 2014), including the striatum (Bhattacharyya, Crippa, et al., 2012). Despite these high-level interpretations, results from specific studies have been inconsistent, with several reports suggesting discordant outcomes (Volkow et al., 2016). For example, (Gruber et al., 2012) used a multi-source interference task to examine impulsive-behavior inhibition among cannabis users. Using a region-of-interest (ROI) approach, those authors identified increased ACC activation among users, despite comparable behavioral performance to non-using controls. In another example, (Martz et al., 2016) demonstrated decreased striatal responsiveness among young adult users during reward anticipation relative to controls in a monetary incentive delay task. These variant, and at times contradicting outcomes may not be surprising when one considers the limited, yet growing corpus of functional neuroimaging studies that have examined the non-acute effects of cannabis (e.g. long- term recreational use) on brain function. Accordingly, unbiased procedures that assess statistical

convergence across published neuroimaging studies are needed to determine which brain regions most consistently show cannabis-related alterations.

Neuroimaging meta-analytic tools present opportunities to quantitatively synthesize and more fully interpret published neuroimaging results. As such, we sought to determine which brain regions most consistently demonstrate functional alterations among cannabis users (across various neuroimaging tasks) by examining published findings within the activation likelihood estimation (ALE) framework (Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002). To do so, we first identified studies reporting functional brain differences between cannabis users and non-users using fMRI or PET in the context of cognitive, social cognitive, affective, perceptual, and motor tasks. This holistic approach permitted the consideration of an expanded experiment assortment, enhancing statistical power, and revealing cannabis-related neurobiological effects irrespective of ontological task classifications (Sutherland et al., 2015). In a primary assessment, we identified convergent cannabis-related activity decreases (users < non-users) and increases (users > non-users) across functional neuroimaging studies. In a first ancillary assessment, we then determined the brain networks in which cannabis-affected regions were embedded using meta-analytic connectivity modeling (MACM). MACM delineates those brain areas that tend to coactivate with user-specified ‘seed’ regions across various task classifications, revealing potential network-level targets of drug-related effects. In a second ancillary assessment, we aimed to provide enhanced insight into brain–behavior relationships. Specifically, we performed a functional decoding assessment using data from a large repository of published neuroimaging coordinates and associated meta-data terms (BrainMap, http:// www.brainmap.org) to characterize

psychological processes potentially linked to functional alterations among cannabis users via quantitative forward- and reverse-inference analyses. Here, we use the term "functional decoding" to represent the statistical approaches used to determine which psychological processes (e.g. working memory) are implicated given the observed meta-analysis results. This approach provides objective interpretations about the potential behavioral consequences of the convergent neurobiological alterations associated with cannabis use. We anticipated that users would demonstrate region-specific differential activation relative to non-users across brain regions. Moreover, we expected these neurobiological alterations to be associated with expansive task-based neural networks, and to correspond with distinct psychological constructs and processes. Clarifying cannabis's effects on specific brain regions, delineating broader brain networks potentially impacted, and characterizing psychological processes that may be disrupted among users may provide a more complete and coherent understanding of the health-related impacts of cannabis.

Methods

Literature Search and Selection

We conducted a comprehensive literature search to locate neuro- imaging studies that reported brain activation differences between cannabis users and non-users. Primary searches were conducted using PubMed (www.ncbi.nlm.nih.gov/pubmed) and Web of Science (http://webofknowledge.com) with the search terms: MRI OR magnetic resonance imaging OR fMRI OR functional magnetic resonance imaging OR PET OR positron emission tomography OR neuroimaging AND cannabis OR marijuana. To expand our assemblage, we then reviewed the reference sections from the papers

identified in the primary search as well as from several narrative reviews (Bhattacharyya et al., 2012a, 2012b; Bhattacharyya and Sendt, 2012; Bossong et al., 2014; Chang and Chronicle, 2007; Kowal et al., 2013; Martin-Santos et al., 2010; Wrege et al., 2014).

The current meta-analysis included studies that: (1) described between-group brain differences between cannabis users and non-users, (2) used fMRI and/or PET measures to derive these differences, (3) expressed differences as statistical parametric contrasts, encompassing the whole brain, with coordinates reported in standard stereotaxic space, and (4) utilized cognitive, social cognitive, affective, perceptual, and/or motor tasks. As a consequence, studies that assessed anatomical differences (e.g. voxel-based morphometry), functional resting-state differences, functional connectivity differences, and/or findings derived using ROI methods were excluded. Moreover, the current meta-analysis was limited to contrasts between cannabis users and non-users, omitting contrasts involving groups specifically selected for having mental health disorders and diseases. Published papers that examined one or more clinical groups (e.g. schizophrenia, bipolar disorder) were carefully reviewed using the inclusion/exclusion criteria. We note that although some studies reported results from several group-level comparisons (e.g. schizophrenia patients with cannabis-use histories > non-schizophrenia patients with cannabis-use histories > controls), coordinate extraction was restricted to just those comparisons between otherwise normal users and non-users (e.g. non-schizophrenia patients with cannabis-use histories > controls). In addition, pharmacologic assessments characterizing acute cannabis administration were not considered. This meta-analysis reflects papers published through December 2016.

Coordinates that expressed decreased activation were taken from contrasts that reported attenuated activation among cannabis users compared with non-users (cannabis users < non-users), while increased activation coordinates were taken from contrasts that reported enhanced activation among users compared with non-users (cannabis users > non-users). Considering decreased and increased activation across included studies is common among neuroimaging meta-analyses (Cortese et al., 2016; Dehghan et al., 2016; Etkin & Wager, 2007; Radua et al., 2012). This approach can produce detailed interpretations about neurobiological differences reported across sampled studies. Moreover, by incorporating coordinates across task classifications (Sutherland et al., 2015), we allowed our meta-analytic outcomes to represent more general aspects of task-based processing. That is, results reported here may represent cannabis-related functional brain changes that supersede task-specific and domain-specific demands, revealing neurobiological consequences that are not constrained by variable neuroimaging ontologies and methodologies.

Primary Assessment: ALE meta-analysis

To establish which brain regions showed consistent cannabis-related changes across functional neuroimaging studies, we conducted two coordinate-based ALE meta-analyses usingGingerALE (version 2.3.6; http://brainmap.org/ALE/), which implements an updated version of the ALE algorithm (Eickhoff et al., 2009, 2012). ALE meta-analysis is used to assess statistical convergence across results from reported neuroimaging studies (Turkeltaub et al., 2002), producing quantitative outcomes that are otherwise unobtainable using more traditional narrative review approaches (Laird et al., 2005). In ALE, activation coordinates (foci) are modeled as centers of three-dimensional Gaussian

probability distributions to account for uncertain variance associated with functional neuroimaging experiments. The extent of the aforementioned distribution is weighted using the given experiment's sample size. The GingerALE software computes one modeled brain activation map per experiment, and then aggregates these maps to compute spatial convergence. The resulting ALE map provides statistical measures, via the ALE statistic, for every voxel in the brain, characterizing the extent to which that voxel is implicated in a given dataset. First, we assembled coordinates of cannabis-related decreased and increased activation into a database along with associated experimental characteristics as described elsewhere (detailed description of BrainMap taxonomy and workflows provided in (Laird, Eickhoff, Kurth, et al., 2009)) (Figure 2.1). This included relevant meta-data, including: experiment sample size, mean subject age, sex distribution, time since last cannabis-use episode, mean lifetime cannabis-use episodes, and task classification or paradigm used. Coordinates that were reported in Montreal Neurological Institute (MNI) space were transformed to Talairach space (Lancaster et al., 2007). These coordinates were then used to compute two distinct ALE meta-analysis maps, revealing clusters of convergent cannabis-related decreased activation and increased activation ($p_{cluster\text{-}corrected} < 0.01$; $p_{voxel\text{-}level} < 0.001$) (Eickhoff et al., 2017). When considering decreased activations, clusters > 3600 mm^3 survived cluster-level thresholding, while for increased activations, clusters >2960 mm^3 survived thresholding. We note that one inherent limitation of ALE meta-analysis is that the approach cannot consider null results (i.e., no observed activation differences between users and non-users). Thus, included studies do not represent the complete corpus of available cannabis-related neuroimaging studies, but rather the corpus of available studies that

reported activation differences between users and non-users. Resultant meta-analytic clusters were reported as coordinates in Talairach space. Extrema labels were determined via the Talairach Daemon application (Lancaster et al., 2000, 2007). To facilitate future research, ROIs created using resultant meta-analytic clusters have been made available via NeuroVault (http://neurovault.org/ collections/2508).

Ancillary Assessment: MACM

To delineate the large-scale brain networks in which cannabis- affected regions were embedded, we used MACM and computed whole-brain coactivation patterns for each resultant ALE meta-analysis cluster. MACM leverages the BrainMap database (www.brainmap.org), an online repository of human neuroimaging studies and associated meta-data, to determine which regions coactivate with a given user-specified seed region (Cauda et al., 2012; Clos et al., 2013; Eickhoff et al., 2012; Robinson et al., 2010, 2012). Results from published functional neuroimaging studies are archived in the database using a rigorous classification scheme and taxonomy that describes peak-activation coordinates in the context of experimental conditions used to derive them (for a complete listing of meta-data terms, please see http://www.brainmap.org/scribe/BrainMapLex.xls). Using Sleuth (version 2.4; www.brainmap.org/sleuth), we searched the database for studies that reported foci within the resulting meta-analysis clusters (i.e. seed regions). Sleuth is an online application that searches the BrainMap database for relevant studies, given user-specified search parameters. Inclusion was limited to databased statistical contrasts that reported activations (i.e. task > baseline) and normal mapping (i.e. non-patient populations), as described in (Robinson et al., 2010, 2012). At the time of analyses, the database contained 116,639 foci from 3,026 papers, representing functional

neuroimaging data from more than 60,000 subjects. Contrasts that reported coordinates within the seed regions were extracted from the database and assessed for statistical convergence using ALE meta-analysis to establish each cluster's whole-brain coactivation pattern ($p_{cluster\text{-}corrected} < 0.01$ $p_{voxel\text{-}level} < 0.001$). MACM maps were computed in Talairach space.

Ancillary Assessment: Functional Decoding

To quantify potential psychological, physiological, or behavioral processes associated with each meta-analysis cannabis-affected cluster, we used a data-driven forward- and reverse-inference analytic approach that capitalizes on the BrainMap database's meticulous classification protocol (Cieslik et al., 2013; Laird et al., 2015; Nickl-Jockschat et al., 2015). Forward inference describes the likelihood that a specific volume (e.g. voxel, anatomically-defined region, network) will activate given the recruitment of mental processes (e.g. working memory, fear, finger tapping), while reverse inference describes the likelihood that various mental processes are being recruited given activation within some volume. Together, these techniques provide important information about brain–behavior relationships (Yarkoni et al., 2011). Here, we used intact primary meta-analysis cluster volumes to search the database, effectively circumventing error or bias associated with creating three-dimensional ROIs centered around local maxima. In addition, forward- and reverse-inference analyses were constrained to foci from databased studies that reported activations - as opposed to deactivations - from otherwise normal subjects. Having identified these studies, we examined the distribution of meta-data terms used to catalog them, including various task classifications (e.g. Stroop Task, Monetary Incentive Delay, Flashing Checkerboard). To establish statistical significance,

we examined the relations between the representation of meta-data terms contributing to the (a) volume and (b) complete database (Poldrack, 2006; Yarkoni et al., 2011). That is, we used forward inference to examine the relations between the conditional probability of activation (P(Activation|Process)) and the baseline probability of activation (P(Activation)) being observed within each meta-analytic cluster (pFDR-corrected < 0.05). For forward inference, statistical significance was calculated using a binomial test. These measures (i.e. P(Activation), P(Process), and P(Activation|Process)) were then used to calculate reverse inference (P(Process|Activation)) using Bayes' rule (pFDR-corrected < 0.05). For reverse inference, statistical significance was calculated using a Chi-square test. When considering functional decoding interpretations, we note that subject-level inferences about psychological processes that may be impacted among cannabis users (e.g. working memory) are made using modern machine learning techniques that leverage cross-validation to make out-of-sample generalizations (Bzdok & Yeo, 2017; Yarkoni & Westfall, 2017). These analytic approaches produce models with better predictive value, providing augmented understanding about the relationship between brain regions and associated psychological processes.

Results

Our systematic search yielded 35 peer-reviewed papers meeting inclusion criteria (Table 2.1; Figure 2.1). The corpus of published results included 88 task-based statistical contrasts, reporting 202 coordinates representing decreased activation among 472 cannabis users and 466 non-users, as well as 161 coordinates representing increased activation among 482 cannabis users and 434 non-users.

No.	Reference	Users			Non-Users			Details Regarding Cannabis Users			
		n	Age	%M	n	Age	%M	Use	Co-use	Abstinent	Paradigm
1	Abdullaev et al. (2010)	14	19.5	71	14	19.7	71	673.2 EPL *	Alcohol	48 h	Attention
2	Acheson et al. (2015)	14	17.6	76	14	17.3	76	6.7 EPW	Alcohol; Tobacco	~12 h	Reward
3	Behan et al. (2014)	17	16.5	94	18	16.1	94	4,168.1 EPL	Alcohol; Tobacco	~12 h	Go/No-Go
4	Block et al. (2002)	18	N/R	N/R	13	N/R	N/R	7 EPW	Alcohol	26 h	Working Memory
5	Bolla et al. (2005)	11	26	100	11	31	100	41 EPW	Alcohol; Tobacco	25 d	Iowa Gambling
6	Carey et al. (2015)	15	22.4	73	15	23.27	86	7341.4 EPL	Alcohol; Tobacco	101 h	Associate Recall
7	Chang et al. (2006)	24	28.77	63	19	30.57	58	2,709 EPL	Alcohol	4 h / 38 m	Tracking
8	Cousijin et al. (2012b)	32	21.4	66	41	22.2	63	1,611.2 EPL	Alcohol; Tobacco	1.6 d	Iowa Gambling
9	Eldreth et al. (2004)	11	25	100	11	29	100	34.7 EPW	Alcohol; Tobacco	25 d	Stroop
10	Enzi et al. (2015)	15	26.33	100	15	27.13	100	13.27 EPW	Alcohol; Tobacco	1.1 d	Monetary Incentive Delay
11	Filbey et al. (2013)	59	23.49	78	27	30.32	18	7467.9 EPL	Alcohol	72 h	Monetary Incentive Delay
12	Gruber et al. (2009)	15	25	93	15	26	93	25.6 EPW	Alcohol	12 h	Faces
13	Heitzeg et al. (2015)	20	19.84	60	20	20.51	70	618.12 EPL	N/R	48 h	Emotion Elicitation
14	Hester et al. (2009)	16	24.6	94	16	25.2	94	11,628 EPL	Alcohol	38 h	No/No-Go
15	Jager et al. (2007)	20	24.5	65	20	23.6	65	1,900 EPL	Alcohol; Tobacco	7 d	Encoding
16	Kanayama et al. (2004)	12	37.9	83	10	27.8	60	19,200 EPL	N/R	6-36 h	Perception /Working Memory

17	King et al. (2011)	30	21.75	53	30	23.75	53	9.75 EPW	Alcohol	~12 h	Finger Tapping
18	Kober et al. (2014)	20	26.65	100	20	29.2	100	2,611.44 EPL *	Tobacco	N/R	Stroop
19	Lopez-Larson et al. (2012)	24	18.2	92	24	18	71	1,500.6 EPL	N/R	24-48 h	Finger Tapping
20	Nestor et al. (2008)	14	24.4	86	14	24.1	86	7,925 EPL	Alcohol	80.8 h	Encoding
21	Nestor et al. (2010)	14	22.1	86	14	23.1	79	7,256 EPL	Alcohol; Tobacco	108 h	Monetary Incentive Delay
22	Padula et al. (2007)	17	18.06	82	17	17.9	71	477.06 EPL	Alcohol	28 d	N-Back
23	Pillay et al. (2008)	11	37.7	36	16	29.7	63	17,637 EPL	N/R	28 d	Finger Tapping
24	Pillay et al. (2004)	9	37.3	89	16	29.4	63	16,711.5 EPL	N/R	4-36 h	Finger Tapping
25	Riba et al. (2015)	16	N/R	N/R	16	N/R	N/R	42,000 EPL	Tobacco	N/R	Working Memory
26	Roser et al. (2012)	15	26.5	100	14	27.3	100	13.1 EPW	Tobacco	25.1 h	Theory of Mind
27	Schweinsburg et al. (2008)	15	18.1	73	17	17.9	70	480 EPL	Alcohol; Tobacco	60.4 d	N-Back
28	Smith et al. (2010)	10	20	60	14	20	64	2,697 EPL	Alcohol; Tobacco	N/R	N-Back
29	Sneider et al. (2013)	10	20.3	80	18	22.8	61	2268.4 JPL *	N/R	12 h	Morris Water Maze
30	Tapert et al. (2007)	16	18.1	75	17	17.9	71	475.6 JPL	Alcohol; Tobacco	28 d	Go/No-Go
31	Vaidya et al. (2012)	46	24.32	61	34	24.72	53	589.92 JPL	Alcohol; Tobacco	24-29 h	Iowa Gambling
32	Van Hell et al. (2010)	14	24	93	13	24	85	3,841 JPL	Alcohol; Tobacco	7 d	Monetary Incentive Delay
33	Wesley et al. (2011)	16	26.4	56	16	26.6	38	29.4 D/M	Alcohol	12 h	Iowa Gambling
34	Wesley et al. (2016)	17	25.1	53	16	27.1	31	8, 466.528 EPL *	Tobacco	~12 h	Emotion Elicitation

35	Yip et al. (2014)	20	26.7	100	20	29.2	100	N/R	Tobacco	21 d	Monetary Incentive Delay

Table 2.1. Published Papers Meeting Inclusion Criteria. Numbering (no.) corresponds with published papers (reference) meeting specific inclusion criteria. Subjects were cannabis users (n = 647, mean age = 24.0 years) and non-users (n = 625, mean age = 24.3). Extracted variables were cannabis-use patterns (cannabis use), other substance-use patterns classification used (paradigm).

d: days; D/M: days per month; EPL: reported episodes per lifetime; EPL*: estimated episodes per lifetime; EPW: episodes per week; h: hours; JPL: joints per lifetime; m: months; M%: percent of participant sample that was male; N/R: not reported.

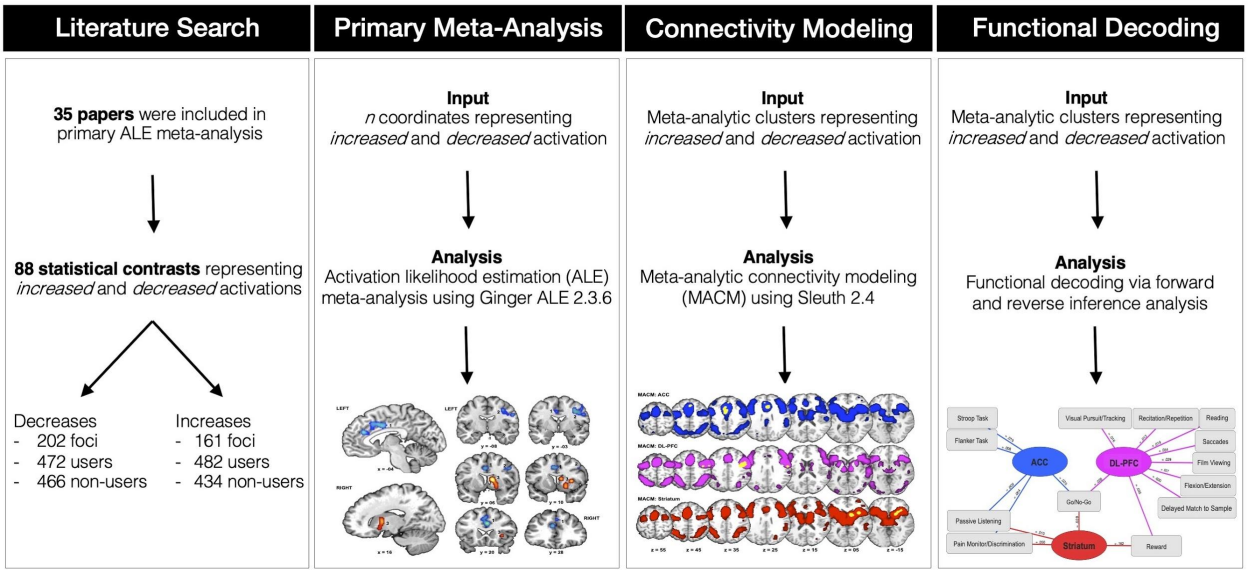

Figure 2.1. Meta-Analytic Data Pipeline. Schematic illustration of the meta-analytic tools employed to identify convergent functional alterations among cannabis users and provide enhanced interpretation of such alterations. Step 1 (literature search): Published papers that reported functional brain alterations among cannabis users relative to non-users were identified. Step 2 (primary meta-analysis): Statistical convergence among reported coordinates was assessed using GingerALE to produce separate maps delineating regions showing decreased activations (users < non-users) and increased activations (users > non-users). Step 3 (connectivity modeling): Using the BrainMap database, MACM was implemented to locate archived neuroimaging experiments that reported co-activations with resultant meta-analytic clusters. Step 4 (functional decoding): Quantitative forward- and reverse-inference analysis techniques were applied to determine which commonly used functional neuroimaging paradigms were associated with cannabis-affected regions.

ALE: activation likelihood estimation; MACM: meta-analytic connectivity modeling.

Cannabis-Related Functional Alterations

Regarding the neurobiological impact of cannabis use, our primary meta-analytic assessments revealed convergent decreased and increased activation among cannabis users versus non-users across neuroimaging studies (Table 2.2; Figure 2.2). Specifically, clusters of convergent decreased activation were observed among cannabis users in the bilateral ACC (volume = 4920 mm^3) and right DL-PFC (volume = 3744 mm^3). In contrast, one cluster of convergent increased activation was observed among cannabis users in the right striatum (i.e. caudate, claustrum, putamen) extending into the insula (volume = 4200 mm^3). We note that simultaneous inspection of decreased and increased activation clusters via conjunction analysis revealed no regions of spatial overlap among clusters, suggesting that our meta-analytic results speak to dissociable effects of cannabis use on the brain. Given considerable variance across included studies with respect to time since last cannabis-use episode (Table 2.1), we completed an exploratory assessment that involved parsing included studies into two groups: studies reporting short-term and long-term abstinence among users.

Cluster No.	Extrema Label (within +/-5mm)	BA	Hemisphere	x	y	z
Decreases (Users < Non-Users)						
1 (ACC)						
	Cingulate Gyrus	24	B	4	20	28
	Anterior Cingulate Gyrus	32	B	-4	34	22
	Cingulate Gyrus	24	B	-4	2	36
	Medial Frontal Gyrus	8	B	0	22	42
	Medial Frontal Gyrus	6	B	4	36	36
2 (DL-PFC)						
	Middle Frontal Gyrus	6	R	36	-6	42
	Precentral Gryus	6	R	38	-4	36
	Precentral Gyrus	6	R	56	-6	28
	Middel Frontal Gyrus	6	R	48	2	38
Increases (Users > Non-Users)						
3 (Striatum)						
	Caudate	NA	R	12	6	8
	Claustrum	NA	R	32	12	4
	Putamen	NA	R	20	10	-10
	Insula	13	R	34	22	-2

Table 2.2. Convergent Functional Alterations Associated with Cannabis Use. Numbering (left) corresponds to brain regions shown in Figure 2.2. Cluster 1, ACC, volume = 4920 mm3. Cluster 2, DL-PFC, volume = 3744 mm3. Cluster 3, Striatum,

volume = 4200 mm3. Extrema labels were determined via the Talairach Daemon. Hemisphere column denotes in which cerebral hemisphere resultant meta-analytic clusters were observed. Coordinates (x, y, z) indicate location of local extrema in Talairach space.

ACC: anterior cingulate cortex; B: bilateral; BA: Brodmann area; DL-PFC: dorsolateral prefrontal cortex; L: left; NA: not applicable; R: right.

MACM of Affected Brain Regions

In a first ancillary assessment, we used the BrainMap database to delineate which brain regions tend to coactivate with the cannabis-affected meta-analytic clusters described above (Figure 2.3). MACM analyses revealed that Cluster 1 (ACC) was characterized by extensive whole-brain coactivation patterns, including associations with the insular cortex and caudate, medial frontal cortex, precuneus, fusiform gyrus, culmen, thalamus, and cingulate cortex (Figure 2.3, top row). In addition, Cluster 2 (DL-PFC) demonstrated considerable coactivation with the orbitofrontal cortex, parietal regions, fusiform gyrus, and occipital cortex (Figure 2.3, middle row). Finally, Cluster 3 (striatum) was associated with whole-brain coactivations that included the insular cortex, frontal cortex, superior parietal lobule, fusiform gyrus, and culmen (Figure 2.3, bottom row). These MACM outcomes demonstrate that cannabis-affected brain regions interact with broader brain networks across various neuroimaging tasks. Moreover, close inspection of each coactivation network suggested considerable spatial overlap within the medial frontal cortex, lateral frontal cortex, lateral parietal regions, insula, and limbic areas.

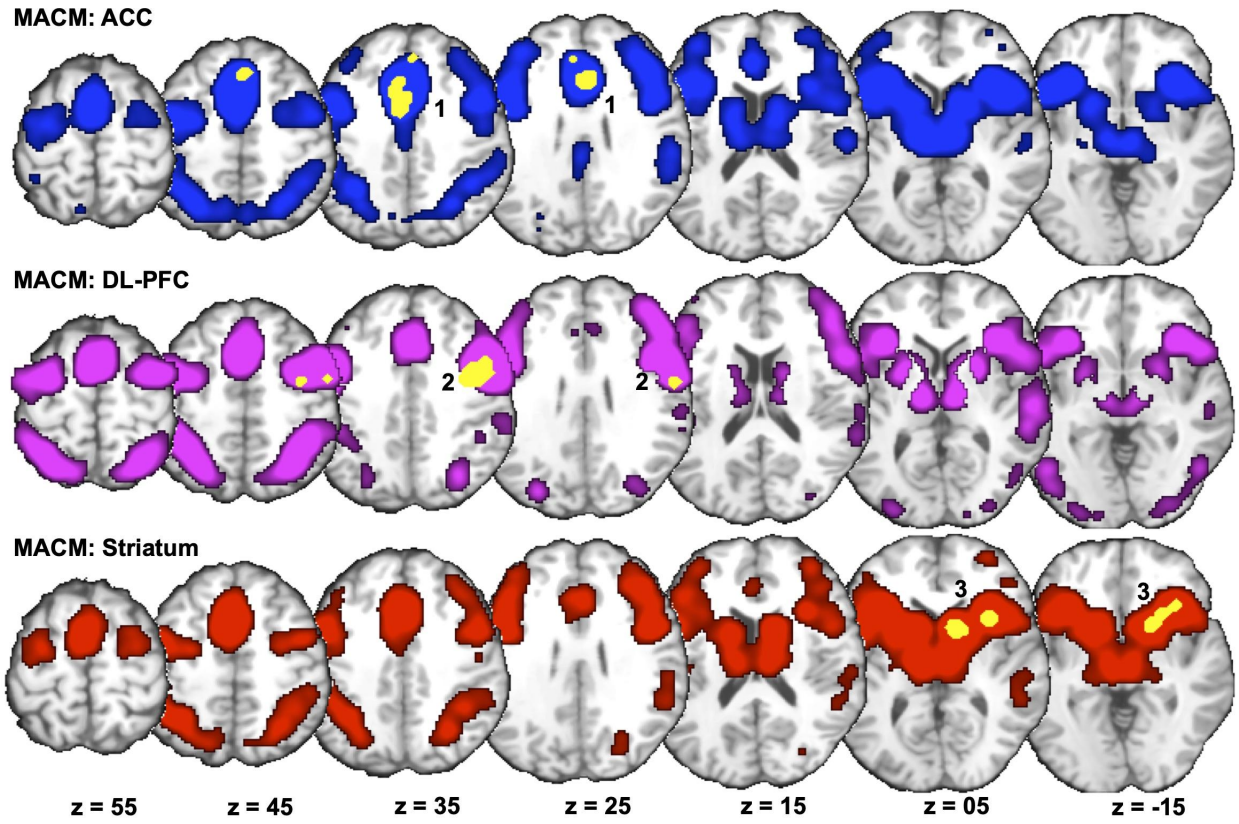

Figure 2.2. MACM of Impacted Regions. MACM delineated other brain areas showing significant co-activation with resultant meta-analytic clusters impacted by cannabis (yellow) when considering all neuroimaging experiments archived in the BrainMap database. Modeled co-activation maps ($p_{cluster\text{-}corrected} < 0.01$; $p_{voxel\text{-}level} < 0.001$) were visualized in Talairach space within the MRIcron environment. Cluster 1 (ACC, top row, blue) demonstrated co-activation with the insular cortex, caudate, medial frontal cortex, precuneus, fusiform gyrus, culmen, thalamus, and cingulate cortex. Cluster 2 (DL-PFC, middle row, purple) showed co-activation with the orbitofrontal cortex, fusiform gyrus, and occipital cortex. Cluster 3 (Striatum, bottom row, red) demonstrated co-activation with the insular cortex, frontal cortex, superior parietal lobule, fusiform gyrus, and culmen.

ACC: anterior cingulate cortex; DL-PFC: dorsolateral prefrontal cortex; MACM: meta-analytic connectivity modeling.

Functional Decoding of Primary Meta-Analytic Clusters

In a second ancillary assessment, we used quantitative forward- and reverse-inference analyses to characterize which psychological phenomena were linked to those regions showing cannabis-related functional alterations. Because we were interested in describing the likelihood that mental processes were being recruited given activation in specified brain regions, the results from the reverse-inference analysis are reported in Figure 2.4. Functional decoding revealed significant associations between Cluster 1 (ACC) and the BrainMap task classifications: Stroop Task, Flanker Task, Passive Listening, Pain Monitor/Discrimination and Go/No-Go (Figure 2.4, ACC). Cluster 2 (DL-PFC) showed significant associations with the task classifications: Delayed Match to Sample, Visual Pursuit/Tracking, Flexion/Extension, Recitation/ Repetition, Film Viewing, Saccades, Reading, Reward, and Go/ No-Go (Figure 2.4, DL-PFC). Finally, decoding results identified significant associations between Cluster 3 (striatum) and the task classifications: Pain Monitor/Discrimination, Passive Listening, Reward, and Go/No-Go (Figure 2.4, Striatum). We note that several tasks demonstrated associations with more than one cluster, including Pain Monitor/Discrimination and Passive Listening (ACC, striatum), Reward (DL-PFC, striatum), and Go/No-Go (ACC, DL-PFC, and striatum).

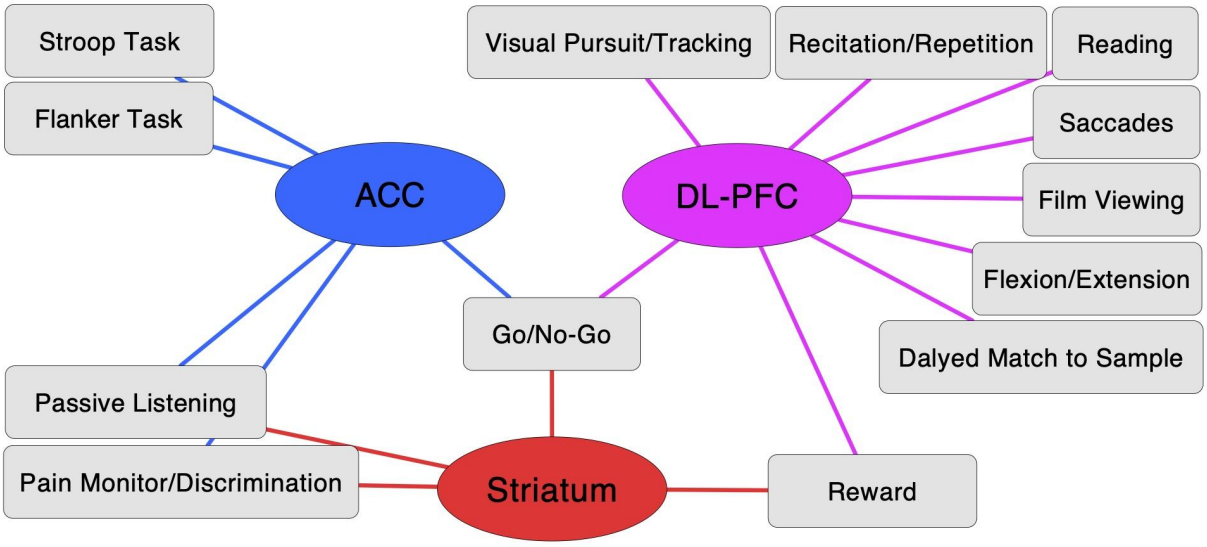

Figure 2.3. Functional Decoding of Primary Meta-Analytic Clusters. Reverse-inference analysis characterized psychological processes that were significantly associated with functionally impacted brain regions among cannabis users. Meta-data term associations were visualized using Cytoscape version 3.4.0 (Shannon et al., 2003). Lines between meta-data terms (squares, task classifications) and meta-analytic clusters (circles, impacted brain regions) indicate that the observed probability reached statistical significance. Probabilities next to each line (p_{FDR}-corrected < 0.05) express the likelihood that a specific psychological process is engaged given activation in a specified brain region (P(Process|Activation)), where higher values

indicated greater likelihoods.

ACC: anterior cingulate cortex; DL-PFC: dorsolateral prefrontal cortex.

Discussion

To clarify the neurobiological impact of cannabis use, we compiled results from 35 task-based functional neuroimaging papers, which compared cannabis users and non-users, within the ALE meta-analysis framework. In a primary meta-analytic assessment,

we identified statistical convergence of reported decreased activation (users < non-users), revealing functional alterations in the ACC and DL-PFC, and of increased activation (users > non-users), showing convergent disruptions in the striatum. In two ancillary assessments, we used archived functional neuroimaging coordinates and associated meta-data to more thoroughly characterize these meta- analytic outcomes. Specifically, we observed coactivation between the ACC and frontal, parietal, and limbic system regions, with demonstrated associations to cognitive, inhibitory, and pain processing tasks. Additionally, the DL-PFC was characterized by coactivation patterns with frontal, parietal, and occipital regions, and was linked to tasks involving cognitive and visual processes. Finally, we observed extensive coactivation between the striatum and frontal, parietal, and limbic regions, and associations to tasks involving reward, inhibition, and pain.

Overall Neurobiological Impact of Cannabis Use

Aberrant ACC activation among cannabis users is perhaps not surprising, given the known architecture of the endocannabinoid system. Indeed, several studies have shown dense concentrations of endogenous cannabinoid (CB1) receptors within the ACC (Eggan & Lewis, 2007; M. Glass et al., 1997; Herkenham et al., 1990, 1991; Svíženská et al., 2008). Despite these concentrations, findings regarding structural alterations within the ACC among users are mixed (Cousijn et al., 2012; Weiland et al., 2015). A critical region in task-dependent and task-independent, or resting-state, processes (Binder et al., 1999; Laird, Eickhoff, Li, et al., 2009; Mazoyer et al., 2001; Shulman et al., 1997), the ACC has been linked to error monitoring, conflict detection, and engaging the DL-PFC to resolve such conflicts (Botvinick et al., 2004; Carter et al., 1998; Carter & Van Veen, 2007;

Laird et al., 2005). Increased activation within the ACC, specifically following high-conflict challenges, is thought to promote enhanced DL-PFC activation to reduce conflict and error commissions on subsequent challenges (Kerns et al., 2004). In this way, the ACC, working in concert with the DL-PFC, is believed to modulate cognitive control processes following high-conflict situations including error detection. Furthermore, the DL-PFC is involved in sustained attention, important for maintaining sensory, motor, and cognitive information “online” for subsequent encoding and retrieval (Miller & Cohen, 2001). Our primary meta-analytic results identified convergent cannabis-related decreased activation in the ACC and DL-PFC. One interpretation of these outcomes is that functional alterations within cognitive control nodes and their associated brain networks may underlie task-performance disruptions among cannabis users. Indeed, several studies have reported poorer performance among users relative to non-users when considering tasks which probe cognitive control and executive functions (e.g., (Crane, Schuster, Fusar-Poli, et al., 2013; Crane, Schuster, & Gonzalez, 2013; Gruber & Yurgelun-Todd, 2005; Sagar et al., 2015; Thames et al., 2014)). Results from our functional decoding assessments are consistent with such accounts, suggesting that the ACC and DL-PFC were associated with behavioral control paradigms, including Flanker and Stroop Tasks, and with paradigms involving learning and memory, including Delayed Match to Sample and Recitation/Repetition (Figure 2.4, DL-PFC, purple).

Mesocorticolimbic and nigrostriatal dopaminergic systems are implicated in various aspects of reward processing, including evaluating social judgments (Bzdok et al., 2011; Kampe et al., 2001), and substance use (Delgado, 2007; Haber & Knutson, 2010; Wise, 2009). Specifically, drug-related hyperactivation throughout dopaminergic

circuitry, including the striatum, has been linked to long-term substance use across various drugs, including opioids (Chu et al., 2015), heroin (Q. Li et al., 2012), alcohol (Gilman et al., 2012; van Holst et al., 2014), cocaine (Jia et al., 2011), amphetamines (O'Daly et al., 2014), nicotine (Addicott et al., 2012), and cannabis (Abdullaev et al., 2010; Acheson et al., 2015; Cousijn et al., 2012; Enzi et al., 2015; Hester et al., 2009; Nestor et al., 2010; van Hell et al., 2010). Our meta-analytic results are consistent with these reports, as we observed increased activation within the striatum among cannabis users. In addition, functional decoding revealed an association between the striatum and the task classification of Reward, suggesting that users may demonstrate cannabis-related enhanced activation in brain regions that subserve reward processing. These conclusions are supported by previous accounts that link the striatum to reward-processing features, including anticipation and appraisal (Delgado, 2007; Haber & Knutson, 2010; Wise, 2009) (Delgado, 2007; Haber and Knutson, 2010; Wise, 2009). Indeed, increased reward-seeking behavior following cannabis exposure has been demonstrated in animal (for an extensive review, see (Tanda & Goldberg, 2003) and human studies (Gilman et al., 2012; Lyvers et al., 2013)). Moreover, a large-scale longitudinal assessment of adolescent risky decision-making found that increased substance use, including cannabis, correlated with attentional biases towards reward-predictive cues (van Hemel-Ruiter et al., 2013). However, across drugs of abuse, both decreased and increased striatal responding has been reported during reward anticipation. Regarding cannabis, such discrepant outcomes may reflect distinct methodological decisions made across studies. For example, one study (van Hell et al., 2010), which required cannabis-using participants to have a negative THC urine toxicology screen before scanning, reported comparable striatal

activity during reward anticipation relative to non-users. In another study (Nestor et al., 2010), in which users were required to have a positive THC toxicology screen, cannabis-using participants showed increased striatal activity despite similar task demands as in the previous example. As such, it is plausible that these seemingly discordant results are indicative of residual intoxication/pharmacological effects among users with positive toxicology results (Balodis & Potenza, 2015). Nevertheless, the convergent increased striatal activation observed among users here, coupled with quantitatively demonstrated associations to reward-related tasks, provides a potential neurobiological explanation for previously characterized links between cannabis use and sensitization towards reward-predicting cues and associated outcomes. The evolution from recreational substance use to dependence is believed to represent a transition from cortical-mediated to striatal-mediated behavioral control processes (Volkow et al., 2013). For example, functional neuroimaging studies have shown decreased activations in the ACC and PFC among cocaine users; deficits that persisted more than 3 months following detoxification (Volkow et al., 1992). Such alterations in cognitive control neurocircuitry have been linked to impulsive behaviors (Holmes et al., 2016). Taken together, decreased activation of the ACC and DL-PFC, paired with increased activation of the striatum, may represent a systems-level neurobiological mechanism through which problematic, and potentially addictive cannabis use patterns develop. From a related perspective, it is noteworthy that each of the three meta-analytic clusters observed were associated with the Go/No-Go task classification, a behavioral inhibition paradigm requiring participants to make/withhold motor responses. These results are consistent with contemporary views about the relations between the PFC, striatum, and one's abilities to regulate problematic

behaviors (Goldstein & Volkow, 2011). Here, the fact that distinct region-specific disruptions were linked with the same task classification may be indicative of a cannabis-related compound effect manifest across studies. In other words, a diminished capacity to inhibit problematic behaviors may be linked to concurrent reduction of prefrontal activity (ACC and DL-PFC) and elevation of striatal activity.

Implications from Functional Decoding

Given the absence of pain-related studies in this meta-analysis, it is noteworthy that two clusters, the ACC and striatum, were linked with the pain monitor/discrimination meta-data task classifications (Figure 2.4). Indeed, these structures have demonstrated involvement in distinct aspects of pain processing (Freund et al., 2009; Jahn et al., 2016; Lieberman and Eisenberger, 2015). From a pharmacotherapy perspective, cannabinoids represent a potential option for pain treatment and management. Data from more than 40 clinical trials using cannabinoids provide evidence for its antinociceptive effects in both chronic and neuropathic pain (Hill, 2015). A recent meta-analysis explored the beneficial and adverse effects of cannabinoids for medical use (Whiting et al., 2015). When considering data from 79 studies, representing 6,462 participants, those researchers found a 37% pain reduction among medicinal cannabis users. Despite these and other findings, the antinociceptive properties of cannabis remain poorly understood at the neurobiological level. Results from one pharmacologic neuroimaging investigation involving cannabis administration suggest that a potential mechanism for THC-related analgesic effects may be through cingulate-limbic connectivity (Lee et al., 2013). Our meta-analytic outcomes and subsequent functional decoding results demonstrate the utility of using meta-analytic approaches to coalesce results from published neuroimaging

studies involving substance use, revealing neuroimaging paradigms that may warrant additional investigation among cannabis-using populations (e.g. pain processing).

Limitations

When interpreting these results, we considered several methodological issues. First, the observed meta-analytic effects of cannabis should be considered preliminary, given the sample of studies included (N = 35). In addition, similar limitations barred the meta-analytic assessment of structural differences (e.g. voxel-based morphometry), acute cannabis effects (e.g. drug- administration studies), and null effects (i.e. studies reporting no differences between users and non-users). Second, as is the case with most reviews and meta-analytic reports, our results are constrained by the current state of the functional neuroimaging literature. Studies included here used tasks designed to probe specific psychological constructs, such as working memory, spatial memory, reward processing, and response inhibition. Importantly, the range of tasks used to identify use-related functional brain alterations may be constrained by a priori conceptualizations about cannabis's impact on brain and behavior. That is, it is possible that the findings reported here reflect an overabundance of cognition- and reward-related investigations, and that the inclusion of more affective, perceptual, or motor investigations would refine the current results, revealing alternative brain regions that may be impacted among cannabis users. Third, the studies included in this meta-analysis were all cross-sectional, which limits causal inferences that can be made about the observed functional brain alterations and cannabis use. With large-scale longitudinal assessments currently underway, such as the Adolescent Brain Cognitive Development study, dissociable antecedents and consequences of cannabis use will become more evident. Fourth, we

note that these findings represent cannabis-related decreased and increased activation that are task-general. The included studies represent the expanding corpus of functional neuroimaging studies on cannabis use that used fMRI or PET, and reported whole-brain findings. As new neuroimaging data are assembled, a more dissociative approach should become possible, permitting assessment of task-specific effects (e.g. cannabis users versus non-users during working-memory challenges). Fifth, the studies included here did not adequately consider sex-specific effects of cannabis use on brain function. Specifically, women were under-sampled among included studies, with 79% of users and 73% of non-users being men. Additionally, whole-brain contrasts comparing men and women are sparse, despite emerging indications of sex-specific effects. For example, one recent report showed that men, but not women, were responsive to the antinociceptive effects of cannabis, showing significant reductions in pain sensitivity (Z. D. Cooper & Haney, 2016). Similar sex differences have also been reported regarding neurocognitive performance (Crane et al., 2013a, 2013b). Future studies should take into consideration potential sex differences when assessing the neurobiological effects of cannabis. Finally, cannabis-use assessment, including amount and frequency estimates, as well as duration since last cannabis-use episode, varied across the included studies. Despite considerable variance regarding these measures, with some studies reporting recreational use and others reporting more severe, problematic use patterns, convergent results were indeed detected. Furthermore, an exploratory assessment that involved parsing included studies using abstinence measures revealed distinct neurobiological changes associated with short-term versus long-term durations since last use episode (see online Supplemental Figure 2.2). Future investigations should take into consideration these critical factors to

provide additional clarification regarding the impact of the amount, frequency, and currency of cannabis use on brain function.

Conclusions

The meta-analytic outcomes reported here suggest that cannabis use is linked with differential, region-specific effects on the brain, including decreased activation in the ACC and DL-PFC, and increased activation in the striatum. Ancillary analyses revealed that these cannabis-related functional alterations were embedded within expansive coactivation networks, and that several psychological processes may be impacted among users. Specifically, these functional alterations may manifest as alterations in cognitive control performance, enhanced reward seeking and responsiveness, and disrupted pain processing. This study highlights the utility of using meta-analytic tools to synthesize published neuroimaging results thereby elucidating neurobiological, cognitive, and behavioral processes associated with cannabis use. As policies and societal norms regarding cannabis undergo rapid changes, enhanced understanding of the impact of cannabis on the human brain is important for providing patients, healthcare providers, and policy makers with scientific information allowing for informed decision-making regarding cannabis use.

Chapter 3

Effects of Cannabinoid Administration for Pain: A Meta-Analysis and Meta-Regression

Chronic pain is an ever-growing concern in the United States. There is a rising economic burden—currently estimated to be between $560 billion and $635 billion annually—that stems from pain-related costs to patients, patient-care providers, health care systems, and poor treatment outcomes among clinical pain populations (e.g., chronic lower back pain, neuropathic pain, and fibromyalgia). These, and other, conditions have resulted in an overreliance on opioid-based pharmacotherapies. Although some patients are appropriate for focused treatments involving opioids (e.g., acute pain), patients with more chronic conditions (e.g., cancer) can achieve better outcomes by managing pain through more comprehensive approaches. Thus, it has become increasingly important to explore additional therapeutic opportunities. In recent decades, cannabinoids, such as molecular compounds found in cannabis, including delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), have been considered viable treatment options regarding pain . As recently as 2018, 30 states had enacted policies that permit cannabis use to treat various medical conditions, with 27 states citing pain-related conditions as inclusionary criteria. Despite growing access to medicinal cannabis, mixed (and on occasion, null) effects have been reported, underscoring the need to expand research efforts regarding cannabinoid-induced pain mitigation.

Recently, several reports have examined cannabinoid administration effects on subjective reports of pain . However, these accounts have produced variant, and sometimes contradictory, conclusions. In one example, (J. R. Johnson et al., 2010) examined the impact of nabiximols (Sativex), a standardized whole-plant cannabis extract

oromucosal spray, on cancer-related pain. In that double-blind, randomized controlled trial (RCT), patients with intractable cancer pain entered a 2-week administration regimen and received THC: CBD extract (2.7 mg THC and 2.5 mg CBD), THC extract (2.7 mg THC), or placebo. Patients were free to titrate their dosage as needed. Following the drug administration regimen, Johnson et al. observed significant reductions in subjective pain ratings among patients receiving THC:CBD extract compared to patients receiving placebo. THC alone was less effective. In a similar example, (Portenoy et al., 2012) evaluated nabiximols as an add-on therapy for advanced cancer patients with opioid-refractory (unresponsive) pain. Patients were placed into low-, medium-, or high-administration conditions and pain was measured following a 5-week intervention interval. At the end of treatment, Portenoy et al. found that THC:CBD extract was associated with greater pain reduction in the low-administration condition (one-to-four sprays per day), but not in the medium-administration (six-to-10 sprays per day) or high-administration conditions (11-to-16 sprays per day). Taken together, these outcomes suggest that cannabinoids may represent potential pharmacological tools for pain reduction. On the other hand, several studies have shown no difference between cannabinoids and corresponding placebo administrations. For example, (Lichtman et al., 2018) leveraged a double-blind RCT to examine pain outcomes among cancer patients with uncontrolled pain following a 2-week nabiximols administration period. Following the intervention, Lichtman et al. compared pain modulations from baseline between cannabinoid and placebo conditions, revealing no superior effects associated with THC:CBD extract. Moving forward, an important challenge facing biomedical research involves coalescing

results from studies involving various pain populations receiving cannabinoid administrations to determine overall therapeutic potential.

Toward this goal, several systematic reviews have endeavored to summarize cannabis's putative pain-related therapeutic effects (Abrams, 2018; F. A. Campbell et al., 2001; Colombo et al., 2006; Deshpande et al., 2015; Sznitman & Zolotov, 2015). These reviews have provided competing conclusions. In one review, Campbell and colleagues (2001) considered outcomes from nine randomized active- and placebo-controlled trials involving cannabinoids (five trials involved cancer-related pain, two involved chronic pain, and two acute postoperative pain), with a focus on pain intenseness scores, pain relief scores, and adverse effects. Those authors concluded that the cannabinoids considered were no more effective than active control conditions, including the opioid analgesic codeine, stressing that cannabinoid administration to treat postoperative pain would be "undesirable," given unwanted central nervous system depressant effects. However, opioids have also been linked with depressant/sedative effects (Chou et al., 2009). Moreover, other, perhaps more severe, opioid-related adverse effects include respiratory depression, especially when paired with other substances, such as benzodiazepines and alcohol (Chou et al., 2009). Given the abuse potential associated with opioids, these (and other) side effects underscore the need to consider replacement and/or adjunctive pain management approaches. Additionally, Campbell et al. noted that, among RCTs considered in the systematic review, none had examined active cannabis. That is, the trials examined pain reduction associated with THC, nitrogen-containing benzopyran derivative, benzopyranoperidine, or levonantradol. Importantly, cannabinoid-induced analgesia may stem from compound or synergistic effects associated with several

cannabinoids. For example, preclinical evidence suggests that high-dose CBD modulates antinociceptive effects associated with low-dose THC, indicating that both cannabinoids may be involved in pain reduction (Varvel et al., 2006). Furthermore, work from (Comelli et al., 2008) demonstrated that whole-plant cannabis extract provides improved nociceptive efficacy compared to corresponding doses of constituent cannabinoids. As such, as the corpus of cannabis-related pain investigations continues growing, it is possible that more comprehensive assessments could reach alternative conclusions regarding cannabinoid analgesia. In a more recent review, The National Academies of Sciences, Engineering, and Medicine considered more than 10,000 peer-reviewed abstracts to characterize cannabis's potential therapeutic utility across several domains, including pain. That committee concluded that "there was conclusive or substantial evidence that Cannabis or cannabinoids are effective for the treatment of pain in adults," (Abrams, 2018, p. 7). However, narrative and systematic reviews often omit representative estimates of effect magnitude and therefore cannot provide quantitative conclusions about outcomes of interest. As such, objective techniques that determine statistical convergence across published studies involving cannabinoid-induced pain reduction are needed to more accurately characterize potential therapeutic effects.

Meta-analyses present powerful opportunities to coalesce conventional effect size estimates (e.g., Cohen's d) across published studies, providing clarification regarding results and permitting assessments not possible within the original, single report. Within this framework, several study-level effect size estimates derived under comparable experimental conditions are averaged, producing one pooled (representative) effect size estimate. Regarding pharmacologic manipulations, pooled effect sizes are used to

characterize cross-study drug administration effects on specific endpoints (Wilkinson et al., 2018), or to make comparisons between two (or more) drug administration conditions (Bushe et al., 2016). Toward this goal, several meta-analyses have provided some insight into cannabinoid-related pain reduction (Andreae et al., 2015; Aviram & Samuelly-Leichtag, 2017; Goldenberg et al., 2017; Iskedjian et al., 2007; Phillips et al., 2010; Vita et al., 2018; Whiting et al., 2015). For example, Iskedjian and colleagues (2007) synthesized results from six studies examining cannabinoid administration within the limited context of multiple sclerosis (MS). When considering baseline versus endpoint pain ratings among 298 patients, Iskedjian et al. observed that cannabinoids were associated with greater pain reduction relative to placebo. However, whether these effects extend beyond MS-related pain (e.g., neuropathic pain) remained unclear. In a more comprehensive meta-analysis, Aviram and Samuelly-Leichtag (2017) examined pain reduction associated with cannabinoid-based medicines across 24 RCTs. Those researchers considered several pain populations, including neuropathic pain, cancer-related pain, noncancer pain, and postoperative pain, as well as active-control and placebo-control designs. Overall, Aviram and Samuelly-Leichtag reported “limited” support for cannabinoid-based medicines across considered RCTs. However, a more focused assessment that excluded active-control designs, which were believed to have increased analgesic efficacy compared to placebo, demonstrated improved analgesic outcomes associated with cannabinoid-based medicines. Surprisingly, the extent to which specific study-level characteristics, such as sample size, age, and sex composition (sex ratio), may modulate observed pain outcomes remains to be meta-analytically explored. Indeed, these active research areas have received considerable attention in

recent years. Here, we address this open-ended question using meta-regression to examine cannabinoid and placebo-related pain reduction with respect to several study-level characteristics (Baker et al., 2004).

To determine cross-study cannabinoid-related standardized effect sizes regarding self-reported pain reduction, and to examine potential associations with important study-level characteristics, we leveraged a combined meta-analysis and meta-regression approach. In a primary assessment, we used meta-analysis techniques to coalesce drug-induced pain reduction standardized effect sizes associated with cannabinoid and placebo administrations to produce pooled effects and enable statistical comparison. In a second assessment (G. V. Glass et al., 1981), we used meta-regression to examine relationships between various continuous and categorical explanatory variables and drug-induced pain reduction effect sizes. Specifically, we used multiple linear regression to examine relationships between several study-level characteristics (sample size, age, sex composition, experimental design, and pain population) and drug administration conditions. Overall, we posited that cannabinoid administration would be associated with pain reduction across included studies, and that placebo administration would be less effective. Furthermore, we expected that study-level characteristics would be associated with pain reduction standardized effect sizes. Providing clarification about potential pain-mitigating effects associated with cannabinoids should enable enhanced scientific understanding about possible therapeutic applications.

Methods

Search

We conducted a literature search to identify pharmacological manipulation studies that assessed cannabinoid-induced alterations in subjective pain ratings. Primary searches were carried out using PubMed (www.ncbi.nlm.nih.gov/pubmed/) and Web of Science (http://webofknowledge.com) with the search terms: cannabis OR cannabinoids OR delta-9-tetrahydrocannabinol OR THC OR cannabidiol OR CBD OR marijuana OR nabilone OR dronabinol OR nabiximols AND pain OR noxious OR analgesia OR visual analog scale OR VAS OR numeric rating scale OR NRS. We further reviewed the reference sections of each record identified during the exhaustive search, in particular, systematic and narrative review papers (F. A. Campbell et al., 2001; Colombo et al., 2006; Deshpande et al., 2015; Sznitman & Zolotov, 2015; Wright, 2007) and existing meta-analyses (Andreae et al., 2015; Aviram & Samuelly-Leichtag, 2017; Goldenberg et al., 2017; Iskedjian et al., 2007; Phillips et al., 2010; Vita et al., 2018).

Screen

During screening, record abstracts were inspected to determine appropriateness. Specifically, records that did not represent peer-reviewed original research studies were removed from the meta-analysis review pipeline (e.g., letters to editors, reviews, conference proceedings). Records involving nonhuman models were also not considered. This meta-analysis was restricted to RCTs that (a) assessed drug-induced pain reductions following cannabinoid administration across studies, including whole-plant cannabis, whole-plant cannabis extracts, and synthetic cannabinoids (i.e., Dronabinol, Nabilone, CT3) and corresponding active or placebo administrations; (b) described pain reductions as differences between baseline (pre-administration) and endpoint (post-administration)

measurements; and (c) used a parallel-groups (i.e., independent samples) or crossover (i.e., repeated measures) design to examine pain reductions. Importantly, although active control studies were considered in the current meta-analysis, drug-induced pain reductions associated with active control administration (e.g., ibuprofen) were not included in placebo subgroup analyses. The current meta-analysis reflects papers published through August 2018.

Data Extraction and Primary Meta-Analysis

Remaining records were obtained as complete published articles and assessed by two reviewers (J.A.Y and Z.E.M). Reviewers cross-checked extracted data points and resolved disagreement before commencing meta-analyses. Extracted data points included author, publication year; sample size(s); pharmacological manipulation(s) such as whole-plant cannabis, whole-plant cannabis extract, synthetic cannabinoid, and placebo; pain population (pain linked with various medical conditions); baseline mean pain score; endpoint mean pain score; and associated variance estimates. Studies that involved more than two (k_x) administration conditions (e.g., THC:CBD extract, THC extract, and placebo) contributed k_x (e.g., k = 3) mean gain standardized effect sizes to quantitative assessment, where k describes total standardized effect sizes considered in the current meta-analysis. Because we sought to pool cannabinoid-related standardized effect sizes across included studies, and because we sought to pool placebo-related standardized effect sizes across included studies, baseline and endpoint pain severity scores were extracted from cannabinoid and placebo conditions separately. Studies that omitted baseline and/or endpoint pain severity scores were excluded. When required, pain severity scores were computed using available summary data (e.g., mean pain

percent. Data points collected from one record required reverse scoring. Although baseline and endpoint pain severity scores were necessary for inclusion, several records omitted associated variance estimates. In such cases, we employed several strategies to secure missing variance data. First, we contacted the lead and/or corresponding authors with data requests. Second, to supplement remaining records, we leveraged the freely available service WebPlotDigitizer (https://automeris.io/WebPlotDigitizer) to compute variance estimates using article figures, an accepted technique to extract numeral data from data visualizations. Third, when data requests and data extraction from visualizations were not possible, missing variance estimates were reconciled via mean imputation using assembled variance estimates (H. Cooper et al., 2019). Notably, imputed variance estimates represented approximately 35% (46/130) of total variance data. Outcome measures included quantitative pain-rating scales, such as numeric rating scales (Hartrick et al., 2003) and visual analog scales (Ferraz et al., 1990). Quantitative pain-rating scales involve asking participants to describe pain severity, routinely anchored by 0, (no pain) and 10 (worst pain). Results from studies using 100-point ranges were scaled to enable pooling and comparison. Following data extraction, baseline pain severity scores, endpoint pain severity scores, and associated variance estimates, were used to compute study-level standardized mean gain effect sizes (i.e., Cohen's d; Becker, 1988). Standardized effect sizes were used to calculate associated standard errors and confidence intervals. To facilitate meta-analytic comparison, study-level standardized effect sizes were then inverse-variance weighted and pooled to produce an average cannabinoid-induced effect and an average placebo-induced effect. Monte Carlo simulations suggest that inverse-variance weighting produces optimal pooled effect sizes

in meta-analysis assessments (Sanchez-Meca & Marín-Martínez, 2016). Forest plots were created to visualize standardized effect sizes. We assessed the degree to which variation among cannabinoid and placebo administrations was attributed to chance via the I^2 statistic and associated Cis (Higgins & Thompson, 2002). Pooled effects were compared with an independent-samples mean difference test (Hedges & Pigott, 2001).

Multiple Linear Regression (Meta-Regression)

Meta-regression examines the relationships between continuous and/or categorical explanatory variables (e.g., sample size, sample age, sample sex composition) and a continuous outcome variable (e.g., study-level standardized effect sizes. Specifically, we used an exploratory fixed-effects multiple linear regression (meta-regression) approach (Greenland, 1987) (Greenland, 1987), to explore relationships between pain reduction effects and drug administration condition (placebo, cannabinoid [whole-plant, whole-plant extract], synthetic cannabinoid [Dronabinol, Nabilone, CT3]), sample size (reported sample size), sample age (mean sample age), sample sex composition (sample sex ratio), experimental design (parallel vs. crossover), and pain population (abdominal pain, arthritis, cancer, chronic pain, diabetes, fibromyalgia, headache, HIV, multiple sclerosis, neuropathic pain, postoperative pain, and “various” or mixed-pain populations within one effect). Data were examined using statistical assumptions associated with regression, including normality, residual normality, and equal variances. Outliers among standardized effect sizes (that is, median effect $\pm$ interquartile range $\pm$ 1.5) were adjusted using upper/lower quartile replacement (Tukey, 1970). Categorical variables (e.g., placebo, cannabinoid, synthetic cannabinoid) were dummy coded to facilitate meta-regression assessment (Wolf & Cartwright, 1974).

Ethics and Open Science Practices

As is common with meta-analytic assessments, the current report did not involve human subjects and therefore did not require institutional review board approval (Sullivan, 2011). In line with current recommendations and open science best practices (Open Science Collaboration, 2015), we have made metadata and corresponding code associated with this work freely available on GitHub.

Results

Primary Meta-Analysis

Literature search and review results are depicted in Table 3.1 and Figure 3.1. The search produced 954 records which underwent screening. Using exclusion criteria described above, 899 records were removed during abstract review, and another 30 were removed during full-text review. The current meta-analysis included data from 25 records that met inclusion criteria, providing data from k = 65 individual pharmacologic manipulations (39 cannabinoid manipulations vs. 26 placebo manipulations), involving 2,248 participants. On average, studies reported that participants' mean age ranged from 43.50 to 62.80 years (M = 52.09). Included studies assessed drug-induced pain reductions associated with several cannabinoid administration conditions, including whole-plant cannabis (n = 5), whole-plant cannabis extract (n = 11), and synthetic cannabinoids (n = 9). Pain-related clinical samples (pain populations) considered were neuropathic pain (n = 7), cancer (n = 4) diabetes (n = 3), MS (n = 3), abdominal pain (n = 1), arthritis (n = 1), chronic pain (n = 1), fibromyalgia (n = 1), headache (n = 1), HIV (n = 1), postoperative pain (n = 1), and "various" (n = 1). Standardized effect sizes are organized according to pain population in Figure 3.1 in the online supplemental materials.

On average, studies reported that 51.57% of participants were women. Fifteen studies provided data from parallel-group designs and 10 provided data from crossover designs.

No.	Author	Year	Details Regarding Sampled Studies		
			Administration	Dose	Pain Population
1	Abrams et al.	2007	Whole Plant	3.56 % THC	HIV
2	Blake et al.	2006	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Arthritis
3	Buggy et al.	2003	Extract	5.0 mg THC	Post-Operation
4	Corey-Bloom et al.	2012	Whole Plant	4.0% THC	Multiple Sclerosis
5	De Vries et al.	2017	Synthetic (Dronabinol)	8 mg	Abdominal Pain
	De Vries et al.	2017	Synthetic (Dronabinol)	8 mg	Abdominal Pain
6	Fallon et al.	2017	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Cancer
7	Frank et al.	2008	Synthetic (Nabilone)	0.25 mg	Neuropathic Pain
8	Johnson et al.	2010	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Cancer
			Extract	2.7 mg THC	Cancer
9	Karst et al.	2003	Synthetic (CT-3)	10.0 mg	Neuropathic Pain
10	Langford et al.	2012	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Neuropathic Pain
11	Lichtman et al.	2017	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Cancer
12	Narang et al.	2008	Synthetic (Dronabinol)	20.0 mg	Chronic Pain
		2008	Synthetic (Dronabinol)	10.0 mg	Chronic Pain
13	Nurmikko et al.	2007	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Neuropathic Pain
14	Pini et al.	2012	Synthetic (Nabilone)	0.5 mg	Headache
15	Portenoy et al.	2012	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Cancer
			Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Cancer
			Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Cancer

16	Rog et al.	2007	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Neuropathic Pain
17	Schimrigk et al.	2017	Synthtic (Nabilone)	7.5 mg - 15.0 mg	Multiple Sclerosis
18	Selvarajah et al.	2010	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Diabetes
29	Skrabek et al.	2007	Synthetic (Nabilone)	0.5 mg	Fibromyalgia
20	Svedson et al.	2004	Synthetic (Dronabinol)	2.5 mg – 10.0 mg	Multiple Sclerosis
		2004	Synthetic (Dronabinol)	2.5 mg – 10.0 mg	Multiple Sclerosis
21	Toth et al.	2012	Synthetic (Nabilone)	2.0 mg – 4.0 mg	Diabetes
22	Wade et al.	2003	Extract	2.5 mg THC / 2.5 mg CBD	Various
			Extract	2.5 mg THC	Various
			Extract	2.5 mg CBD	Various
23	Wallace et al.	2015	Whole Plant	7% THC	Diabetes
			Whole Plant	4% THC	Diabetes
			Whole Plant	1% THC	Diabetes
24	Ware et al.	2010	Whole Plant	9.4 % THC	Neuropathic Pain
			Whole Plant	6.0 % THC	Neuropathic Pain
			Whole Plant	2.5 % THC	Neuropathic Pain
25	Wisley et al.	2008	Whole Plant	7.0 % THC	Neuropathic Pain
			Whole Plant	3.5 % THC	Neuropathic Pain

Table 3.1. Studies Meeting Inclusion Criteria. Numbering corresponds to studies meeting inclusion criteria. Extracted variables were administration condition (administration), including cannabis whole plant, cannabis extract, synthetic cannabinoid, and placebo, administration dose (dose), administration route (route), population with

pain-related clinical condition (pain population), subjective pain outcome measure (pain measure), and associated scale (scale).

THC, delta-9-tetrahydrocannabinol; CBD, cannabidiol; CT3, dimethylheptyl-delta-8-tetrahydrocannabinol-11-Oic acid.

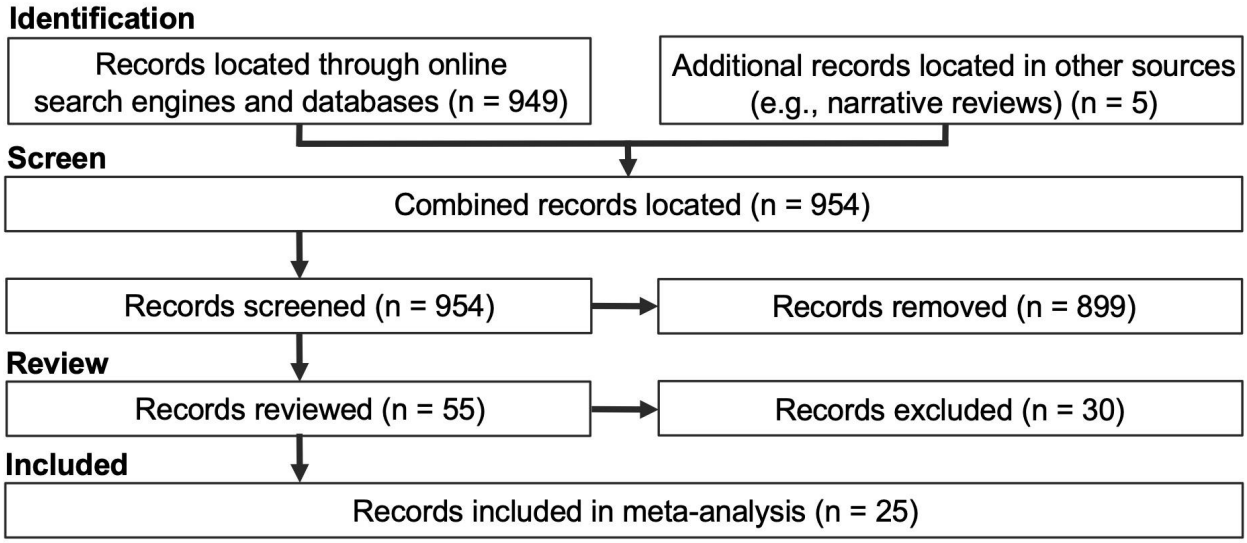

Figure 3.1. Literature Search and Review Pipeline. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (i.e., PRISMA) pipeline diagram showing search and review results. A preliminary search produced 949 records, with an additional five assembled from additional resources (e.g., narrative reviews), totaling 954 records overall. During abstract review, 899 records were removed from the meta-analysis pipeline. During complete article review, an additional 30 records were discarded based on study exclusion criteria. Finally, the 25 remaining records underwent data extraction and subsequent meta-analytic assessment.

Inverse-variance weighting and pooling across cannabinoid standardized effect sizes revealed that cannabinoid administration was associated with a medium-to-large effect, Cohen's d = -0.58, 95% CI (-0.74, -0.43) (see Figure 3.2). An assessment of variation revealed considerable heterogeneity among cannabinoid effect sizes, I^2 = 91.47%, 95% CI (87.93, 92.37). On the other hand, inverse-variance weighting and pooling across placebo standardized effect sizes revealed that placebo administration was associated with a small-to-medium effect, Cohen's d = -0.39, 95% CI (-0.52, -0.26) (see Figure 3.3). An assessment of variation revealed considerable heterogeneity among placebo effect sizes, I^2 = 92.66%, 95% CI (89.18, 93.70). Overall, cannabinoid administration was associated with greater pain reduction compared to placebo administration, $t(64) = -4.06$, $p < 0.05$. Visual inspection revealed some overlap between drug administration condition CIs.

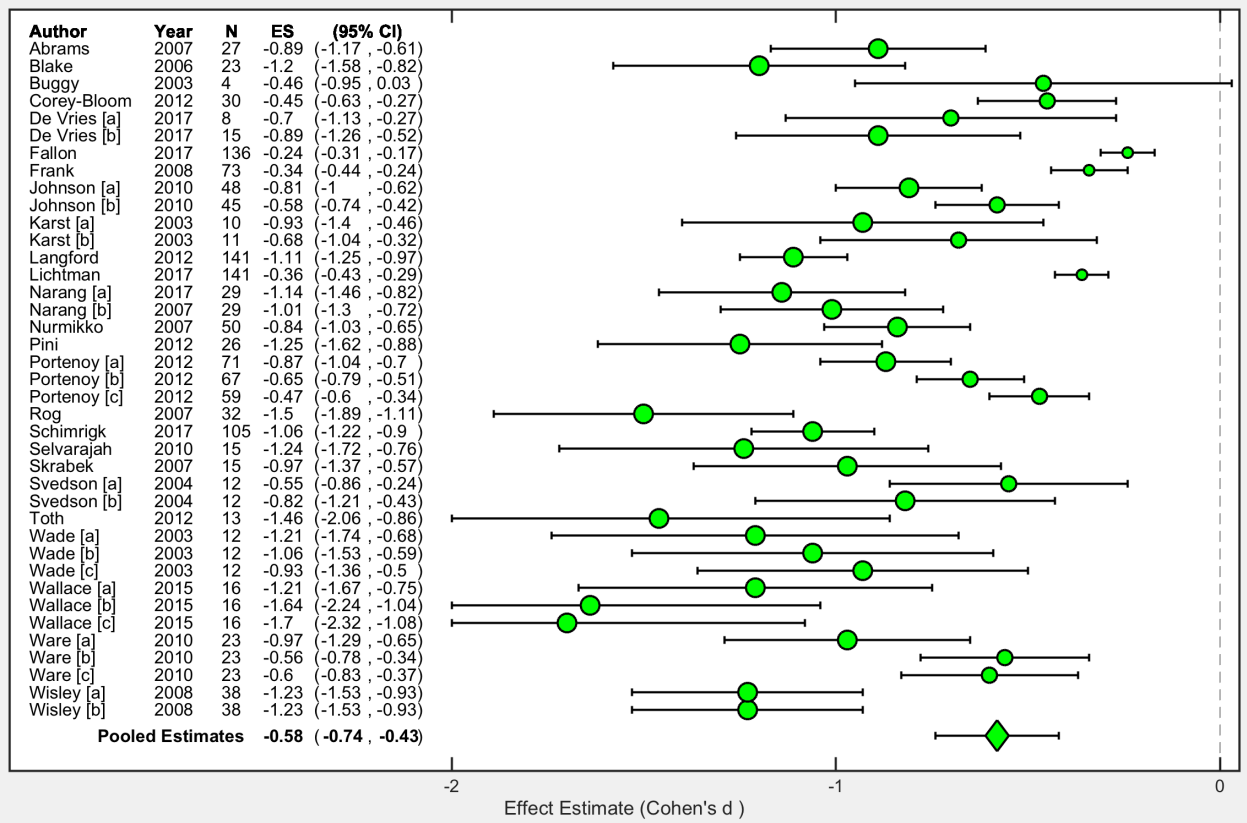

Figure 3.2. Pooled Cannabinoid Administration Effect. Study-level standardized effect size estimates (Cohen's d) were computed for each cannabinoid administration across included studies. Circle sizes are proportional to small, medium, and large effect size estimate interpretations (J. Cohen, 1988). Study-level estimates were inverse variance weighted and pooled to determine a representative estimate. When considering overall pain reduction effects, cannabinoid administration was associated with a medium-to-large effect across studies, Cohen's d = -0.58, 95% CI (-0.74, -0.43).

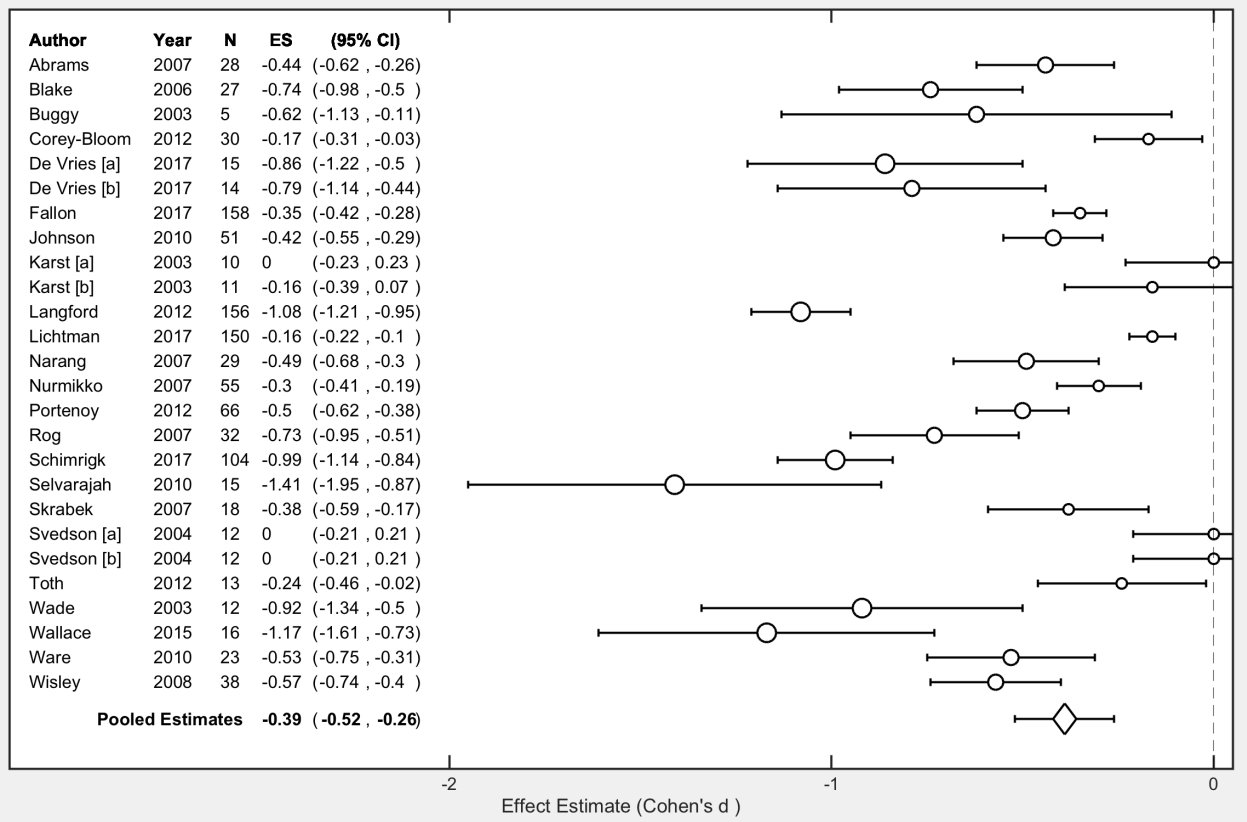

Figure 3.3. Pooled Placebo Administration Effect. Study-level standardized effect size estimates (Cohen's d) were computed for each placebo administration across included studies. Circle sizes are proportional to small, medium, and large effect size estimate interpretations (J. Cohen, 1988). Study-level estimates were inverse- variance weighted and pooled to determine a representative estimate. When considering overall pain reduction effects, placebo administration was associated with a small-to-medium effect across studies, Cohen's d = -0.39, 95% CI (-0.52, -0.26).

Exploratory Multiple Linear Regression (Meta-Regression)

Overall, the meta-regression model explained a moderate proportion of variance among individual studies, $R^2 = 0.37$ (adjusted $R^2 = 0.30$), $F(6, 48) = 4.62$, $p < 0.05$. Reported p values are associated with corresponding coefficient hypothesis tests. Meta-regression results revealed that, when controlling for other explanatory variables, drug administration conditions were linked with pain reduction among included studies, such that cannabinoids (whole-plant cannabis and whole-cannabis extracts) $B = -0.43$, 95% CI (-0.62, -0.24), $p < 0.05$ (Figure 3.4), and synthetic cannabinoids (Dronabinol, Nabilone, and CT3) $B = -0.39$, 95% CI (-0.65, -0.14), $p < 0.05$ (Figure 3.4), performed better than placebo. Furthermore, meta-regression results showed that, when controlling for other explanatory variables, sample size was linked with pain reduction, $B = 0.01$, 95% CI (0.00, 0.01), $p < 0.05$, such that studies involving smaller samples tended to report greater pain reduction effects (Figure 3.4). There were no observed interactions between drug administration conditions and sample size. Finally, meta-regression results showed that, when controlling for other explanatory variables, sample sex composition was linked with a modest, however nonsignificant, effect, $B = -0.64$, 95% CI(-1.37, 0.09), $p = 0.09$, such that studies including more female participants tended to report greater pain reductions (Figure 3.5).

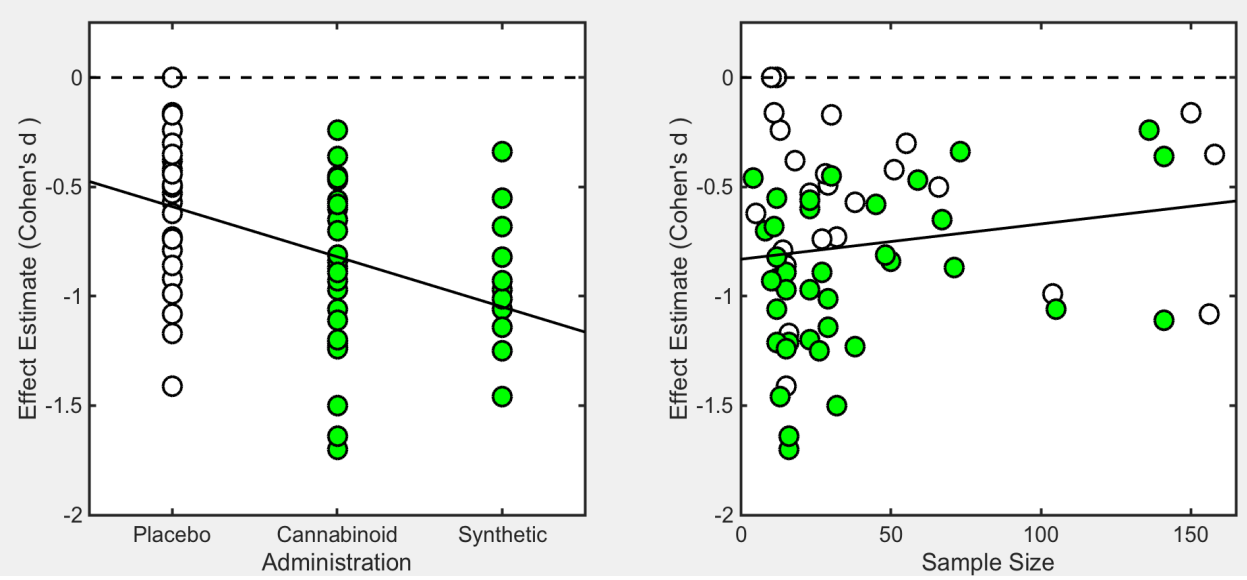

Figure 3.4. Bivariate Relationship Between Effect Size Estimates and Significant Predictors. Meta-regression results revealed that, when controlling for other explanatory variables, drug administration conditions were linked with pain reduction among included studies, such that cannabinoids (whole-plant cannabis and whole-plant cannabis extracts) B = -0.43, 95% CI (-0.62, -0.24), $p < 0.05$, and synthetic cannabinoids (Dronabinol, Nabilone, and CT3) B = -0.39, 95% CI (-0.62, -0.24), $p < 0.05$, performed better than placebo. Furthermore, meta-regression results showed that, when controlling for other explanatory variables, sample size was linked with pain reduction, B = 0.01, 95% CI (0.00, 0.01), $p < 0.05$, such that studies involving smaller samples tended to report greater pain reduction.

Cannabinoids, shaded (green) circles; placebo, unshaded circles.

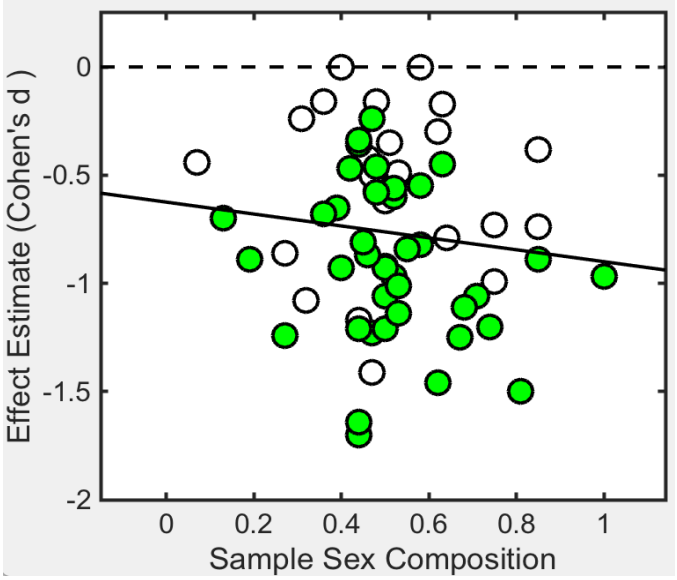

Figure 3.5. Bivariate Relationship Between Effect Size Estimates and Sample Sex Composition (Sex Ratio). Meta-regression results showed that, when controlling for other explanatory variables, sample sex composition was linked with a modest, albeit nonsignificant, effect, B = -0.64, 95% CI (-1.37, 0.09), p = 0.09, such that studies including more female participants tended to report greater pain reductions.

Cannabinoids, shaded (green) circles; placebo, unshaded circles.

Discussion

In this meta-analytic study, we coalesced results from peer-reviewed primary research articles that characterized cannabinoid and placebo-induced reductions of subjective pain ratings across medical conditions. Our findings extend current understanding about cannabinoids and pain, taking a meta-regression approach to examine relationships between various study-level characteristics and drug-induced pain reductions. When considering reductions in self-reported pain, we observed that cannabinoid administration was associated with a medium-to-large (Cohen, 1988) pooled effect size across included studies. Importantly, cannabinoid administration was

associated with statistically significant greater pain reduction than placebo administration, which yielded a small-to-medium (Cohen, 1988) pooled effect size. Indeed, placebo administration has been shown to enhance expectations about pain reduction (Bushe et al., 2016), potentially assuaging negative emotional/motivational aspects about pain experiences. Finally, results from our meta-regression analysis suggested that, when controlling for other explanatory variables, drug administration conditions and sample size predicted observed pain reduction. Taken together, these meta-analytic outcomes provide some evidence that cannabinoids, relative to placebo, might mitigate subjective pain reporting among those experiencing chronic pain tied to various medical conditions. However, more research is needed to understand nuances in cannabinoid-induced pain reduction, including outcome differences between single-dose versus long-term cannabinoid treatments, complex interactions with concurrent analgesic pharmacotherapies, and changes in cannabis conditional dependence rates as a function of increased access.

Neuropsychological Impact of Cannabinoid-Based Administrations

When considering cannabis's effect on pain, our primary meta-analysis outcomes suggest that cannabinoids may represent a viable option regarding pain management and treatment, outperforming corresponding placebo conditions across included studies. That cannabinoids were associated with pain reduction is not surprising, given that the most common medicinal cannabis applications throughout documented human history involve administration for pain (Parker, 2017). Indeed, early evidence suggests that medicinal cannabis may have been used to relieve pain around 400 C.E. (Zias et al., 1993). However, it was just in the 1990s that several reports described an endogenous

cannabinoid framework embedded within the central nervous system (William A. Devane et al., 1992) and peripheral nervous system (Munro et al., 1993), which interacts with exogenous cannabinoids to modulate pain.

Processing pain signals starts with nociceptive sensation signal transduction throughout the peripheral nervous system and terminates with subjective pain perception within the central nervous system (for an extended review, see (Millan, 1999)). First, peripheral sensory neurons detect noxious stimulation, which is then communicated to neuronal bodies around the spinal column. Next, sensory neurons synapse onto central dorsal horn neurons within the spinal cord, where pain signals are integrated across pathways. Finally, central dorsal horn neurons forward pain signals via ascending pathways to the brainstem, thalamus, and cortical brain regions, which process higher order pain behavior. Notably, cannabinoid receptors are densely concentrated in the frontal and limbic cortices; brain regions also associated with processing pain, including the anterior cingulate cortex (ACC) (M. Glass et al., 1997). As such, cannabinoid receptor agonists may work to mitigate subjective pain experiences via interactions with brain regions responsible for processing more complex mental operations, such as pain-related affective and motivational dimensions. Consistent with such an interpretation, recent reports have examined the relationship between cannabis and pain-related brain function. For example, (M. C. Lee et al., 2013) used functional MRI to investigate cannabis's impact on blood–oxygen-level- dependent signal fluctuations in response to experimental chemical pain (i.e., capsaicin) among normal participants. 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 may

modulate pain perception (unpleasantness) without affecting pain sensation (intenseness), a position supported by a recent meta-analysis of cannabinoid-induced modulations in experimental pain (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), perceived threat from noxious stimulation (Foltz & White, 1962), and monitoring survival-relevant goals (Lieberman & Eisenberger, 2015). Although acute cannabinoid receptor agonism dampens ACC responding to pain, effectively reducing pain-related negative affect, whether these effects endure beyond acute administration remains unclear. In a recent neuroimaging meta-analysis, Yanes and colleagues (2018) examined neurofunctional alterations associated with chronic cannabis use. When considering cannabis's impact across various mental tasks, those researchers observed that chronic cannabis was linked with, among other changes, decreased ACC activation. Furthermore, ancillary assessments revealed that activity within the ACC has been consistently linked with pain-related taxonomic descriptors (i.e., pain, pain monitor/discrimination) across the functional neuroimaging literature. To summarize, the neurobiological outcomes discussed here may represent potential higher order, brain-level mechanisms that support demonstrated cannabis-induced pain reduction.

Outcomes from Meta-Regression

Meta-regression results showed that sample size was associated with pain reduction standardized effect sizes across studies, such that studies involving smaller samples reported greater pain reduction. Moreover, there was no interaction between

reported sample size and drug administration conditions (i.e., cannabinoid, synthetic cannabinoid, and placebo), suggesting that this was the case across pharmacologic manipulations considered. Sample size represents an important determinant regarding how generalizable research results are to target populations (Wiedermann & Wiedermann, 2015). Often, studies with smaller samples have reported better therapeutic outcomes (Sterne & Egger, 2001). This phenomenon has been linked to outcome reporting biases (Chan & Altman, 2005), such as data omission when results lack statistical significance, poorer methodological parameters (Kjaergard et al., 2001), and increased between-study heterogeneity among studies with small samples (IntHout et al., 2015). Moving forward, it is important that researchers, health care providers, and lawmakers consider outcomes from studies on cannabinoid-induced pain reductions within the context of the sample sizes that derived them.

When considering sex-dependent effects in cannabinoid-induced pain reduction, meta-regression results suggested that among included studies, those studies that recruited more female participants reported greater, although nonsignificant, standardized effect sizes across drug administration conditions. It is worth noting that meta-regression outcomes derived using summary statistics (e.g., sample sex composition) may exhibit ecological confounding (Morgenstern, 1982) compared to using patient-level data (Thompson & Higgins, 2002). As such, the relationship between biological sex and cannabinoid analgesia should become clearer as new studies emerge that provide within-sample comparisons. Accumulating preclinical evidence suggests that females may be more sensitive to cannabis's pain-reducing effects. Indeed, greater pain reduction among females following cannabinoid receptor agonism has been shown in

acute pain and non-acute pain animal models (Craft et al., 2012, 2013; Tseng & Craft, 2001). However, whether these sex-dependent effects extend to humans remains unclear.

One recent report from Cooper and Haney (2016) examined pain reduction among male and female cannabis users following active cannabis consumption (3.65–5.60% THC) and placebo consumption (0.00% THC) (Z. D. Cooper & Haney, 2016). Among male cannabis users, those researchers found that cannabis consumption increased pain-onset latency compared to placebo, presumably by reducing pain sensitivity. Among female cannabis users, however, no differences were observed between active cannabis and placebo conditions. These discordant outcomes may highlight important nuances about cannabinoid-related reductions in reported pain. Specifically, findings from the current meta-analysis represent data from participants with various clinical conditions. Growing evidence suggests that women experience greater clinical pain (Rosseland & Stubhaug, 2004; Unruh, 1996), often endorsing increased pain-related distress (Paller et al., 2009). It is then possible that reported sex-differences in cannabinoid-induced pain reduction stem from differences in pain reporting, not pain sensation and/or perception. With this in mind, one important question facing subsequent research involves our current understanding of sex-dependent effects in cannabinoid-induced pain reduction. Moreover, subsequent research may consider sex differences across complimentary pain outcomes, such as pain tolerance, pain ratings, and pain questionnaires/scales.

Limitations

Findings presented here should be considered in the context of several methodological limitations. First, as is common with meta-analyses, our outcomes and

associated interpretations are constrained by the state of the current literature. Accordingly, results obtained here should be considered preliminary given the modest sample size (i.e., 25 papers). Moreover, recommendations regarding subgroup analyses and meta-analytic modeling prevented more refined assessments, such as estimating standardized effect sizes as a function of cannabinoid subclassifications (e.g., whole-plant cannabis, whole-plant cannabis extract, synthetic cannabinoid, THC, CBD, THC/CBD), dose (e.g., 2.5 mg THC, 5 mg THC), administration route (e.g., smoke, oromucosal spray, capsule), and pain population (e.g., central/peripheral neuropathic pain, cancer pain, multiple sclerosis pain). The inclusion of studies that involved several drug conditions and clinical samples into the same meta-analysis presumably contributed to observed between-study heterogeneity. More granular meta-analytic approaches should become possible as additional relevant studies are made available.

Second, even though included studies involved comparable endpoint measures (i.e., numeric rating scale, visual analog scale), these studies may contain confounds and/or biases that have not been addressed, such as temporal variation in societal attitudes toward cannabis, regional policies that promote medicinal cannabis, and interindividual differences regarding cannabis's expected effectiveness. With this in mind, we used fixed-effects multiple linear regression (meta-regression) to control confounding effects where possible (e.g., experimental design) (T. D. Stanley & Jarrell, 1989). Also, moving forward, researchers may consider systematically collecting/reporting concomitant endpoint measures (e.g., McGill Pain Questionnaire) (R. Melzack, 1975), to provide more complete characterizations of cannabis-related analgesic effects.

Third, despite rigorous review methods, several records were excluded from the current meta-analysis due to missing data. According to the Open Science Collaboration (2015), problematic practices within psychological science include selective reporting, omitting analyses, and insufficient specification regarding experimental parameters. Moreover, the current meta-analysis cannot consider studies that were conducted but never reported (i.e., “the file drawer problem”) (Rosenthal, 1979). Thus, improved reporting practices should enable enhanced meta-analysis assessments in general, and regarding cannabinoids in particular.

Finally, despite showing that cannabinoid administration was associated with pain reduction, many studies included in this meta-analysis did not give full consideration to neurocognitive side effects linked with cannabis (for an extended review, see (Crane, Schuster, Fusar-Poli, et al., 2013)). Future investigations should systematically examine cannabis’s therapeutic properties in the context of co-occurring undesired neurocognitive effects.

Conclusions

Our meta-analysis outcomes show that cannabinoid administration was associated with reductions in subjective pain across included studies, making them viable candidates for pain management and treatment. Moreover, meta-regression results suggested that drug administration condition and sample size predicted pain reduction effects. Finally, we observed that sample sex composition was associated (although, not statistically significant) with observed pain reduction, suggesting that this may be an important biological variable when considering cannabis-induced pain reduction. As social, societal, and political attitudes toward cannabis evolve, it is becoming increasingly

important to provide enhanced scientific understanding regarding risks and potential therapeutic applications. Such understanding should lead to more informed decision-making regarding cannabis among patients, care providers, and lawmakers.

Chapter 4

7T Functional MRS/MRI Assessment of Pain in Cannabis Users

An estimated 40 million Americans experience chronic pain, or pain lasting more than several months, costing the U.S. $635 billion every year. Such prevalence has contributed to a problematic dependence on opioid analgesics with nearly 50,000 people dying from opioid-related overdoses in 2017 alone. Moreover, negative affect and stress associated with chronic pain can have downstream effects on brain networks implicated in reward and punishment (Koob & Le Moal, 2008), rendering patients on opioid-based treatments more susceptible to medication misuse, dependence, and addiction. Indeed, opioid misuse estimates among chronic pain patients range from approximately 20% to 30% across studies (Vowles et al., 2015). This elevated health-economic burden stems from poor understanding about neurobiological mechanisms supporting the transition from normal pain to pathologically persistent pain (Ingvar, 2015), including influences from cortical-limbic neural circuits, which has hindered development of complementary pain treatments.

From a psychological science perspective, pain is considered a subjective experience with sensory, affective/motivational, and cognitive dimensions. Although the focus in pain medicine has long been centered around using first-line analgesic pharmacotherapies (i.e., opioids, non-steroidal anti-inflammatory drugs) to mitigate sensory pain dimensions such as stimulus discrimination, intensity, and source, approaches that target affective/motivational pain dimensions are lacking. Emerging clinical evidence suggests that neural networks that drive such affective/motivational features are important in the transition from acute, homeostatic-maintaining pain to

chronic pain (Navratilova & Porreca, 2014). As such, brain regions within cortical-limbic networks, including the anterior cingulate cortex (ACC), are of particular interest regarding pain treatment.

Converging evidence across domains implicates the ACC in affective/motivational aspects of the pain experience, namely, pain aversiveness (Cottam et al., 2016; Johansen et al., 2001; LaGraize et al., 2006; Navratilova et al., 2015; Navratilova & Porreca, 2014; Qu et al., 2011; Yan et al., 2012). Pain aversiveness contributes to the homeostatic nature of pain signals via interactions with learning systems to shape subsequent behavior. Such influence is important for avoiding subsequent harm. In one seminal example, Johansen and colleagues (2001) used place conditioning, a Pavlovian conditioning paradigm that measures context preference/avoidance, to examine pain aversiveness in rats with lesions to the rostral ACC. During pre-conditioning, animals were allowed to move freely between two chambers. However, during conditioning, one chamber was paired with sham treatment while the other chamber was paired with formalin treatment, a known acute pain model. Those researchers observed reduced place avoidance during post-conditioning among lesioned rats, providing causal evidence that the rostral ACC is needed to process aversive signals. In another example, Qu et al. (2011) extended these outcomes in an experimental neuropathic pain model, demonstrating that lesions to the rostral ACC block reward signals following lidocaine-induced pain reduction. It is worth noting that place preference was indeed observed in lesioned rats following appetitive stimulation (i.e., cocaine). Thus, rather than having broad effects on reward processing per se, the rostral ACC seems selectively involved in processing aversive (or lack thereof) signals. These outcomes are supported by recent

results from human neuroimaging studies. In 2016, Cottam and colleagues examined cerebral blood flow, an indirect measure of cortical activation, while patients with osteoarthritis pain made subjective pain evaluations. Cortical activation in middle cingulate, subgenual ACC, and others correlated with pain evaluations. Surprisingly, accounting for trait anxiety restricted this effect exclusively to the cingulate, underscoring that this region might be particularly tuned to aversive (and just aversive) pain aspects.

In recent years, the view that singular brain regions drive behavior has come into question (Mišić & Sporns, 2016). More contemporary theories in cognitive neuroscience posit that structural and functional connections between distributed neural networks drive brain-behavior relationships (Bressler & Menon, 2010; McIntosh, 1999), including pain behavior (Jones et al., 1991; Treede et al., 1999). This thinking has shaped current understanding about ACC contributions to pain. For example, results from a large-scale data-driven assessment examined which psychological processes were linked with dorsal ACC (dACC) activation across more than 10,000 functional neuroimaging studies (Wager et al., 2013) (Lieberman & Eisenberger, 2015). This assessment considered both pain and non-pain constructs. When considering mental processes that were said to be concurrent with dACC activation (i.e., an approach known as reverse inference (Poldrack, 2006; Poldrack et al., 2011), the conclusion reached was that this region was “selective for pain.” That is, that activation within the dACC was better explained via involvement in pain processing versus executive functions, conflict monitoring, or more-general salience processes. However, challenges to that assertion have stressed that this is problematic. Specifically, recent work from Wager and colleagues stressed that although the dACC serves survival-relevant functions, similar data-driven techniques demonstrate that this

region is equally important in language, memory, attention, and emotion (2016). Moreover, those authors underscore the need to consider information from distributed neural networks to achieve accurate brain-behavior relationships. An example comes from Wager and colleagues (Wager et al., 2013), who used functional magnetic resonance imaging (fMRI) and machine learning techniques to predict subjective pain ratings from brain activation data, revealing a “neurologic signature” that is both sensitive and specific to experimental pain. When working in concert, brain regions that predicted pain responses include the dACC, dorsal posterior insular cortex, anterior insular cortex, secondary somatosensory cortex, ventrolateral/medial thalamus, and hypothalamus. Subsequent experiments showed that pattern-level activation within the dACC correctly differentiated between (1) pain and non-pain thermal stimulation and between (2) social pain and social non-pain, but not between (3) two non-pain conditions. This is consistent with earlier evidence that the dACC contains both pain-responsive and non-pain-responsive neuron populations (Sikes & Vogt, 1992). When taken together, these outcomes support the supposition that the dACC is needed to process some pain signal aspects, but that this region also works in tandem with a distributed neurologic signature to shape pain behavior. As such, pain treatments that target affective/motivational pain dimensions related to dACC function represent promising therapeutic targets.

Pain and Cannabinoids

For thousands of years, whole-plant cannabis and its derivatives have been used in medicinal applications throughout the world (Parker, 2017). However, just relatively recently has biomedical science started to understand the mechanisms that support cannabis’s therapeutic effects. In 1964, chemists Yehiel Gaoni and Raphael Mechoulam

isolated and characterized what would soon be known as delta-9-tetrahyndracanninol (THC) (Parker, 2017) (Raphael Mechoulam & Gaoni, 1967), the main psychoactive constituent compound in cannabis. This led to the detection of receptors distributed throughout the central nervous system, dubbed cannabinoid type 1 (CB1) receptors, which were localized to brain regions consistent with cannabis's diverse pharmacologic effects on behavior (W. A. Devane et al., 1988). Subsequent discoveries would include (1) isolation and characterization of cannabidiol (CBD) (R. Mechoulam & Shvo, 1963), the main non-psychoactive constituent compound in cannabis, (2) endogenous cannabinoids anandamide (AEA) (William A. Devane et al., 1992) and 2-arachidonyl glycerol (2-AG) (Raphael Mechoulam et al., 1995), and (3) a second receptor type, cannabinoid type 2 (CB2) receptors, with concentrations in the immune system (Munro et al., 1993). With these breakthroughs, scientists had tools to conduct systematic investigations centered around both adverse consequences and therapeutic benefits associated with endogenous cannabinoid system signaling.

The most common applications of medicinal cannabis involve pain reduction (Parker, 2017). Accordingly, decades of preclinical research have been centered around examining effects of endogenous cannabinoid system signaling on pain outcomes (for reviews, please see (Burns & Ineck, 2006; Castaneto et al., 2014; Masocha, 2018; O'Hearn et al., 2017; Rahn & Hohmann, 2009). En masse, these studies provide extensive evidence that cannabinoids might represent promising analgesic agents (Soliman et al., 2019). For instance, in one report involving an established neuropathic pain model, male Sprague-Dawley rats were exposed to chronic constriction nerve injury via sciatic nerve ligation. Following surgical injury, rats completed thermal pain testing

using radiant heat, and the time to withdraw paws was recorded (i.e., paw-withdraw latency). Importantly, THC treatment was associated with increased paw-withdraw latencies during thermal pain compared to vehicle (Mao et al., 2000). Moreover, increased latencies tracked treatment with THC in a dose-dependent fashion. Furthermore, subsequent cannabinoid receptor antagonism blocked THC-related antinociceptive effects, suggesting that exogenous cannabinoids such as THC modulate pain signals. With regard to stimulus aversiveness, interactions between THC and CBD have received considerable attention. In one example involving place conditioning, researchers used elevated THC administrations (10 mg/kg) to induce conditioned place avoidance among rats (Vann et al., 2008). Following conditioning involving THC and non-THC contexts, animals received CBD administrations (1, 10, and 30 mg/kg) and time spent in apparatus arms was recorded. Those researchers found that small-to-moderate CBD doses, but not large CBD doses, reversed conditioned place avoidance associated with elevated THC. Therefore, it is possible that cannabis, and specifically interactions between constituent cannabinoids, reduces perceived aversiveness associated with contexts or stimulation, which could have implications for treating affective/motivational pain dimensions.

Despite growing evidence that cannabinoids are associated with pain reduction in animal models (Woodhams et al., 2015), findings from human studies have been mixed. For example, (Libman & Stern, 1985) found that moderate doses of oral THC (i.e., 20 mg) had no effect on experimental mechanical pain tolerance outcomes. On the other hand, more recent work from (Walter et al., 2015) involving experimental electrical pain demonstrates that comparable doses of oral THC (i.e., 15 mg) increases pain sensitivities. Importantly, that these (and many) studies reached conflicting conclusions

may stem from several study-level characteristics, such as chosen pain modalities, previous experience with cannabis, interindividual differences in pain perception unrelated to pharmacologic interventions (Nielsen et al., 2008), and even preconceived attitudes about cannabis-related analgesia (Sznitman & Bretteville-Jensen, 2015; Sznitman & Zolotov, 2015). To provide clarification, a recent meta-analysis considered cannabinoid effects on experimental pain outcomes in participants without pain pathologies (Vita et al., 2018). When considering results from 18 randomized placebo-controlled trials, cannabis preparations (i.e., whole-plant cannabis and derivatives, extracts, and synthetic cannabinoids) were associated with increased pain tolerance and thresholds and decreased pain-related unpleasantness. Indeed, these findings were consistent with a recent meta-analysis (Yanes et al., 2019), which showed enhanced cannabinoid-related pain reductions versus placebo across 25 studies involving various pain populations (e.g., chronic low-back pain, neuropathic pain, fibromyalgia).

Despite increasing evidence that the endogenous cannabinoid system modulates pain experiences, several open questions remain. For example, what are the neurobiological mechanisms that support cannabis-related pain modulation? Moreover, is repeated exposure to exogenous cannabinoid receptor agonists (e.g., THC) associated with long-term alterations to these mechanisms? Furthermore, how can empirical evidence about such mechanisms inform subsequent pain pharmacotherapy development? Indeed, these topics have received considerable attention in recent years (Baron, 2018; G. Campbell et al., 2019; Khan et al., 2019; G. Lee et al., 2018; Lossignol, 2019; Madden et al., 2018; O'Brien & McDougall, 2018; Shin et al., 2019; Stockings et al., 2018; Urits, Adamian, et al., 2019; Urits, Borchart, et al., 2019).

Cannabinoid Pharmacodynamics

Although the endogenous cannabinoid system has been implicated in several physiological processes (for a review, see Katona & Freund, 2012), the underlying mechanism of action operates in stark contrast to conventional neurotransmission. That is, endogenous cannabinoids are produced within post-synaptic neurons and interact with presynaptic neurons via retrograde neurotransmission (Egertová & Elphick, 2000; Katona et al., 1999). Presynaptic cannabinoid receptor binding then results in reduced calcium intake and reduced neurotransmitter release (Freund, Katona, & Piomelli, 2003). In this way, endogenous cannabinoid signals are considered important control signals, providing necessary feedback to modulate classical (anterograde) neurotransmitter systems (e.g., dopamine, serotonin, glutamate) (Südhof & Malenka, 2008). For example, in rats, treatment with the cannabinoid receptor agonist WIN55,212-2 diminished glutamate levels (Godino, Torres, & Sanchez-Prieto, 2007). More recently, co-administration of WIN55,212-2 and D-amphetamine produced dampened glutamate and dopamine release in rats versus D-amphetamine alone (Polissidis et al., 2014). WIN55,212-2 also diminished D-amphetamine-related behavior (e.g., hyperlocomotion). Given evidence that glutamate levels correlate with pain-related ACC activation (Cass et al., 2014; Cleve, Gussew, Wagner, Bär, & Reichenbach, 2017), and given evidence that ACC activation is reduced among cannabis users (Yanes et al., 2018), it is possible that cannabis-related differences in ACC activation stem from differences in ACC glutamate levels. Moreover, given evidence that cannabis treatments are associated with reductions in pain aversiveness (Yanes et al., 2019), it is then possible that reduced ACC glutamate levels are associated with pain reduction among users. Despite evidence that this (and other)

neurotransmitter system(s) may be involved in the effects of long-term, frequent cannabis use on pain processing, human neuroimaging studies exploring these effects are lacking. Providing enhanced understanding about cannabinoid-related changes in neurotransmitter systems implicated in pain processing is an important step toward developing effective pain management strategies as access to medicinal and recreational cannabis continue to expand.

Objectives and Hypotheses

To provide clarification regarding cannabis-related pain reduction, functional magnetic resonance spectroscopy (fMRS) was combined with fMRI to examine pain-related changes in neurotransmitter systems, including glutamate, among cannabis users and cannabis non-users. Unlike static spectroscopy, which involves data acquisition during rest conditions, fMRS capitalizes on demands associated with task-positive conditions. In this way, metabolite levels can be compared within subjects (e.g., pain versus baseline) and between groups (e.g., cannabis users versus non-users). Regarding the current work, the between-subject outcomes of interest were: differences in glutamate-related metabolite levels between cannabis users and cannabis non-users. Specifically, we hypothesized that (Hypothesis 1): dACC metabolite levels would be lesser among cannabis users versus cannabis non-users across nociceptive stimulation conditions regarding the following metabolites: (1A) glutamate, (1B), glutamine, and (1C) glutamate + glutamine (often referred to as Glx). Second, the within-subjects outcomes of interest were changes in glutamate-related metabolite across nociceptive stimulation conditions. Specifically, we hypothesized that (Hypothesis 2): nociceptive stimulation, including moderate, low, and baseline (none) stimulation, would be associated with

changes in: (2A) glutamate, (2B), glutamine, and (2C) glutamate + glutamine. Third, we hypothesized that (Hypothesis 3): dACC functional responses would correlate with dACC glutamate-related metabolite levels across groups and across nociceptive stimulation conditions. These hypotheses were tested using linear mixed-effects models, including both fixed (cannabis use group, nociceptive stimulation condition) and random effects (individual), to predict dACC metabolite levels.

Methods

Cannabis users and non-users were recruited to this ex post facto (quasi-experimental) cross-sectional protocol to determine associations between cannabis use and pain processing neurobiological correlates. First, participants completed online assessments relating to demographics, general mental health, general physical health, and substance use histories. Online assessment responses were used to determine participant eligibility. Second, those participants who met inclusion/exclusion criteria were invited to complete neuroimaging data collection. During neuroimaging data collection, participants completed combined fMRS and fMRI protocols involving low-to-moderate nociceptive stimulation. fMRS and fMRI outcomes were used to determine associations between cannabis use and dACC metabolite level changes and dACC functional responses, respectively. Specifically, dACC metabolite levels were used to test Hypotheses 1 and 2 and dACC functional responses were used to test Hypothesis 3.

Ethics and Open Science Practices

To protect participant privacy, a Certificate of Confidentiality was secured 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 (19-293 MR 1908). In line with current recommendations and open science best practices (Magezi, 2015; Meteyard & Davies, 2020), this protocol was preregistered and made available on Open Science Framework (https://osf.io/t2nb9). The preregistered protocol included (1) statistical hypotheses to be tested, (2) associated dependent/independent variables and operational definitions, (3) outcomes from a prospective power analysis and target sample size calculation, and (4) data handling and analysis plan.

Participants

Participants were men and women and needed to be between ages 19 and 24. Promotional materials, including advertisements with links to online assessments, were located online and on the Auburn University main campus and surrounding areas. Participants came from both university and non-university (i.e., surrounding community) settings. Those participants currently enrolled in undergraduate psychology courses at Auburn University received 3 research participation hours. Additionally, all participants received up to $20 for complete participation before June 1, 2020 and up to $40 for complete participation after June 1, 2020. The difference in compensation was meant to enhance recruitment efforts following public health restrictions on human subjects research following COVID-19. Prior to completing fMRS/fMRI data collection, participants completed online assessments relating to demographics, general mental health, general physical health, and substance use histories. For complete assessment record, please see Appendix A: Online Recruitment Materials. Specifically, participants completed the following assessments: a demographics questionnaire, Warwick-Edinburgh Well-Being

Scale (Tennant et al., 2007), Perceived Stress Scale – 4 (Bushe et al., 2016), Generalized Anxiety Disorder 7 (GAD7) (Spitzer et al., 2006), Patient Health Questionnaire 9/15 (PHQ9/15) (Kroenke et al., 2001), Prodromal Questionnaire - Brief Version (PQB) (Loewy et al., 2011; L. Xu et al., 2016), Graded Chronic Pain Scale (GCPS) (Von Korff et al., 1992), Neuropathic Pain Scale (NPS) (Galer & Jensen, 1997), Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al., 1991), Rutgers Alcohol Problem (RAPI) (White & Labouvie, 1989), Marijuana Smoking History Questionnaire (MSHQ) (Bonn-Miller & Zvolensky, 2009), Marijuana Motives Measure (Simons et al., 1998), and the Severity of Dependence Scale (Gossop et al., 1995) to determine dependence on several substances, including cannabis, opioids, cocaine, amphetamine, and prescription psychomotor stimulants (e.g., Adderall). Specifically, the following empirically informed assessment score values were used as inclusion cutoffs, such that those participants not meeting these criteria were excluded from further participation: anxiety (as indicated by the Generalized Anxiety Disorder 7 (GAD7), score > 15, (Spitzer et al., 2006), depression (as indicated by the Patient Health Questionnaire 9 (PHQ9), score $\geq$ 15, (Kroenke et al., 2001) and psychosis (as indicated by the Prodromal Questionnaire - Brief Version, general score $\geq$ 6, (Loewy et al., 2011; L. Xu et al., 2016). Additionally, the following dependence severity cutoff scores were used to determine substance use dependence: amphetamine $\geq$ 4, cocaine $\geq$ 15, heroin/opioids $\geq$ 7, and psychomotor stimulants $\geq$ 4. Following neuroimaging data collection, participants completed a post-scan questionnaire (e.g., “Please indicate the extent to which each of the following statements characterized your thoughts and feelings during the scans,” “During the short tasks that involved some pain, please describe in a few words any

strategies used to deal with the pain") and a shortened St. Mary's Hospital Sleep Questionnaire (Ellis et al., 1981) to assess sleep the previous night, which has been shown to impact neuroimaging outcomes. Please see Appendix B: Online Post-Scan Materials.

To be considered current cannabis users, participants needed to have consumed cannabis (e.g., smoked whole-plant cannabis) one-or-more times per week, on average, during the preceding 30 day period, as indicated by the Marijuana Smoking History Questionnaire (Bonn-Miller & Zvolensky, 2009). This was consistent with previous work conducted at Auburn University.

Of note, only participants who met the following criteria were allowed to complete fMRS/fMRI: (1) were not taking any over-the-counter or prescription medication that may cause or increase bleeding, (2) had no history of seizure, (3) were not taking medication to treat seizure, (4) had not consumed drugs (including alcohol) in the 24-hour period prior to the research study session, (5) had not consumed pain relievers in the 8-hour period prior to the research study session, (6) had not consumed food, drinks (except water), caffeine, and/or nicotine in the 30-minute period prior to the research study session, and (7) had not exercised in the 30-minute period prior to the research study session. In addition to exclusion criteria above, participants were excluded using standard MR contraindications as determined general protocol at the Auburn University MRI Research Center. Examples included, but were not limited to: implanted cardiac pacemakers, embedded metal objects/fragments, and claustrophobia. Although MR is not associated with harmful effects on pregnant women, we will exclude pregnant women as a precaution.

Apparatus

Those participants who met assessment score inclusion criteria as described above were invited to complete neuroimaging data collection. Importantly, the time between online assessment completion and fMRI/fMRS data collection varied between participants. To account for this, participants were asked whether their substance use patterns had changed since completing online assessments. Those participants who indicated that their substance use patterns changed (e.g., started using cannabis, started using amphetamine) were asked to complete online assessments again or excluded as appropriate.

fMRS/fMRI data collection was completed using a Siemens 7T MAGNETOM system at the Auburn University MRI Research Center. The scanner was outfitted with a 32-channel head coil provided by Nova Medical (Wilmington, MA).

During fMRS/fMRI data collection, participants received experimental nociceptive stimulation, involving an MR compatible pressure-based (mechanical) pain apparatus (Davis et al., 2016). Specifically, nociceptive stimulation involved securing a modified sphygmomanometer to the dorsal surface of participants' non-dominant hand. Then, pressure was increased inside the armband to the target pressure.

Procedure

Pain Stimulation

During fMRS/fMRI data acquisition, participants received nociceptive stimulation across three conditions: moderate, low, and baseline (none) nociceptive stimulation. For the current study, the operational definitions regarding nociceptive stimulation levels were as follows: *moderate* nociceptive stimulation level = 100 mmHg, *low* nociceptive

stimulation level = 50 mmHg, and *baseline* (no) nociceptive stimulation level = 0 mmHg. Importantly, nociceptive stimulation levels were informed by previous work involving the MR compatible pressure-based pain apparatus. Specifically, Davis and colleagues (2016) demonstrated that college-aged young-adult participants reported an average maximum nociceptive stimulation tolerance M = 193.79 ± 86.48 mmHg (range: 69.00 - 267.60). Because there was substantial variation in individual stimulation tolerance, and because participants would need to withstand longer stimulation periods during fMRS (i.e., 230 sec; please see Figure 4.1 Graphical Depiction of fMRS Scan Run Time Course), the decision was made to take 50% of the reported average maximum nociceptive stimulation tolerance as the moderate nociceptive stimulation level in the current study (i.e., 96.89 mmHg, rounded to 100 mmHg to promote accurate operation across participants). Accordingly, 50% moderate nociceptive stimulation was considered low nociceptive stimulation (i.e., 50 mmHg) and no stimulation was used during baseline measurements (i.e., 0 mmHg). Across conditions, if participants indicated that nociceptive stimulation had become “too uncomfortable to continue,” the given scan run was aborted and participants were given the option to withdraw from the study without penalty.

fMRS Data Collection

MRS enables the detection of small neurochemical (metabolite) concentrations in the presence of comparatively very large water concentrations in small volumes over narrow frequency ranges (Salibi & Brown, 1998). MRS produces spectra rather than images (e.g., MRI, CT), which plot signal frequencies (x axis) versus signal intensities (y axis). Protons that compose specific metabolites resonate at specific frequencies (i.e., points along the x axis; also called chemical shift), and peaks above points represent

metabolite concentrations. Importantly, the difference between peak points differentiates metabolites, and spectral resolution – the degree to which metabolite-specific peaks can be differentiated from each other – is enhanced with increasing magnetic field strengths (Westbrook & Talbot, 2018). Moreover, advances in MR instrumentation, including scanner, gradient, and radiofrequency systems, have increased spectral resolution substantially, providing better signal-to-noise (SNR) ratios, and permitting shorter scan times (e.g., < 10 minutes for complete MRS protocols in clinical settings) (Salibi & Brown, 1998). Perhaps as a result, MRS applications have expanded in recent years, including metabolite-centered sequences to enable smaller signal detection (also called editing (e.g., “GABA editing”)), integration into clinical settings/practice to examine pathology-related changes in metabolite levels (e.g., N-acetylaspartic acid (NAA) as a measure of tumor spread), and combination with task challenges to assess contributions from excitatory/inhibitory signals during psychological processes (for reviews, please see (Jelen et al., 2018; Mullins, 2018; J. A. Stanley & Raz, 2018). In this way, task-based MRS (fMRS) can be leveraged to understand how changes across various metabolite levels work in concert to support cognitive and behavioral phenomena.

To characterize pain-related metabolite level changes, fMRS data were collected during three scan runs (conditions): moderate, low, and baseline stimulation (Figure 4.1). Scan runs were approximately 5 min each, and included an instructions phase, preparation/dummy scans, an on-ramp phase (6 sec), a fixed stimulation phase (230 sec), an off-ramp phase (6 sec), and a visual analog scale (VAS) phase (10 sec). During the on-ramp phase, apparatus pressure was increased from 0 mmHg to 100 or 50 mmHg, depending on scan run condition. During the fixed stimulation phase, apparatus pressure

was held constant. During the off-ramp phase, apparatus pressure was decreased to 0 mmHg. During the VAS phase, participants provided one subjective pain rating (anchors: 0 = “no pain”, 10 = “most pain possible”) regarding the immediately preceding nociceptive stimulation period. Importantly, to permit pain responses to normalize between conditions, scan run order was fixed across participants: (1) low, (2) baseline, and (3) moderate stimulation. Also, two reference scans were collected between baseline and moderate stimulation scan runs to be used during fMRS data preprocessing.

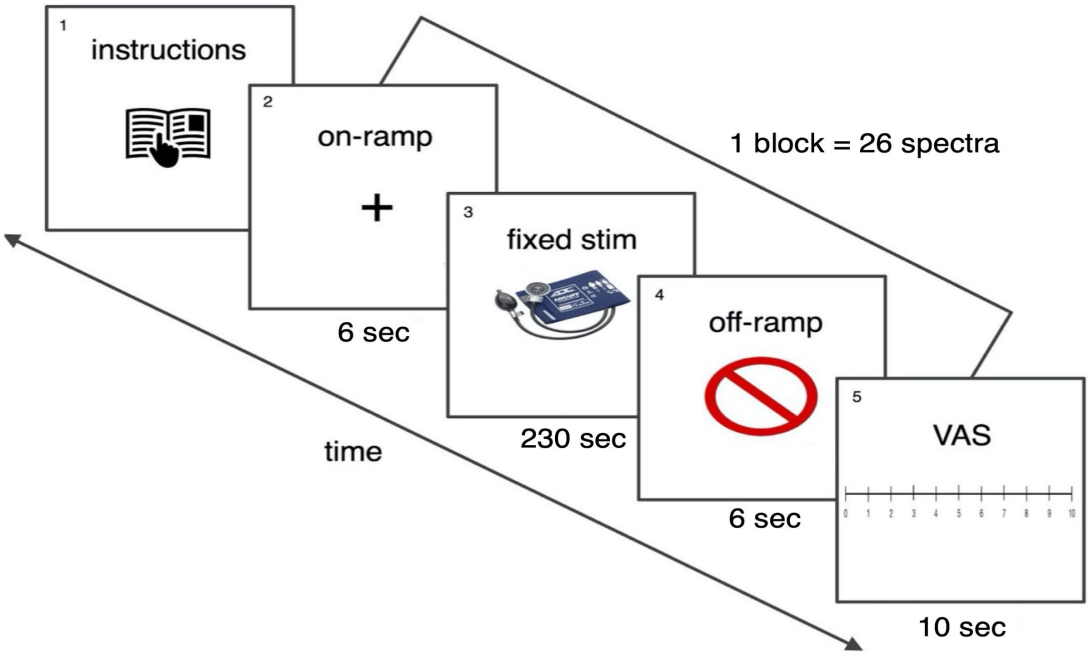

Figure 4.1. Graphical Depiction of fMRS Scan Run Time Course. Participants completed fMRS data collection across three nociceptive stimulation conditions: moderate, low, and baseline stimulation.

fMRS data was collected from one voxel (40 [A>>P] × 25 [R>>L] × 15 [F>>H] mm), centered around the dACC, using a standard STEAM sequence (TR/TE = 10000/5 ms) consisting of three slice-selective 90° pulses (Zhu & Barker, 2011) (Figure 4.2). Following standard data collection procedures, including participant positioning, global (whole-brain) shimming, anatomy-guided voxel placement, localized (voxel) shimming, and water suppression, single spectra acquisitions were measured once every 10 seconds, resulting in 26 single spectra acquisitions per scan run. This process was repeated three times, once per nociceptive stimulation condition. Please see Appendix C: 7T Scanner Protocol.

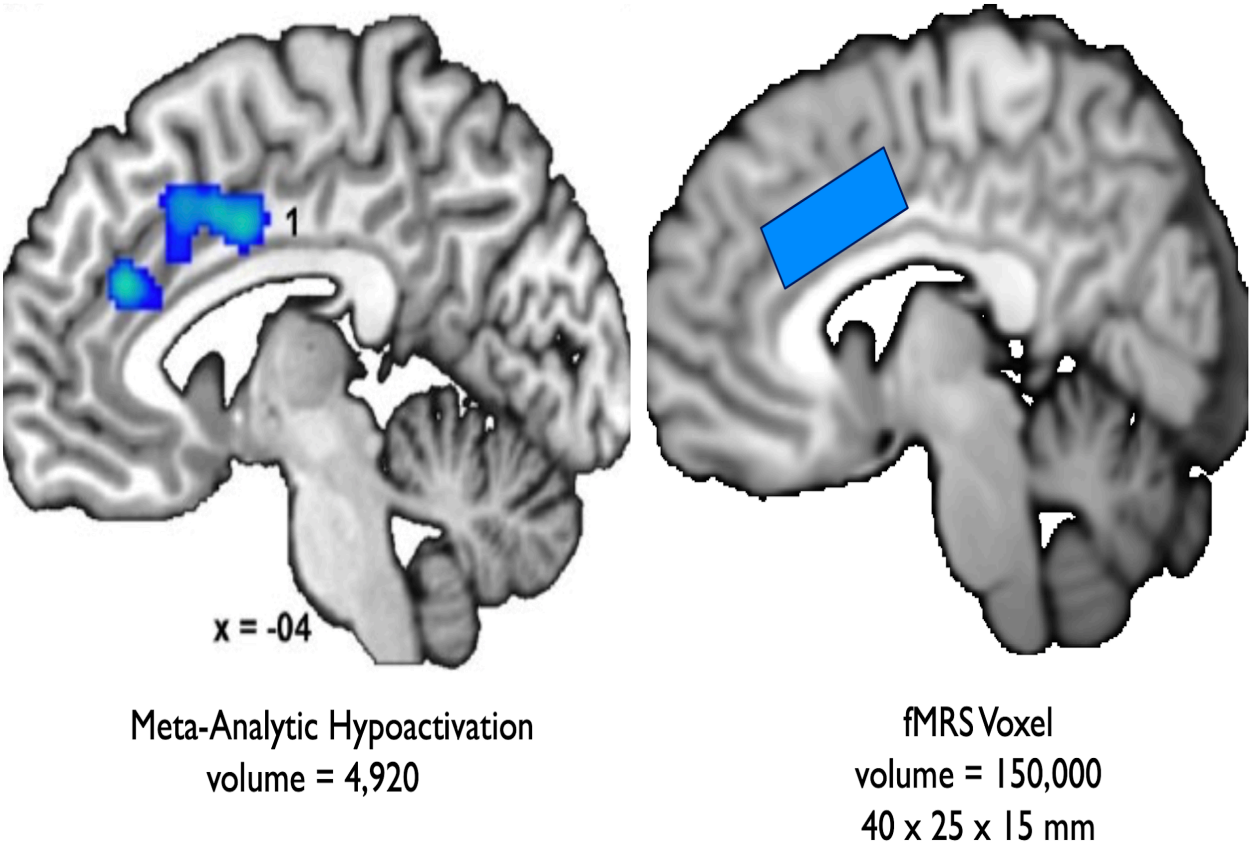

Figure 4.2. Meta-Analytically and Anatomically Informed fMRS Voxel Placement. Results from a recent meta-analysis of functional neuroimaging studies involve comparisons between cannabis uses and cannabis non-users (Yanes et al., 2018) were

used to inform fMRS voxel parameters and placement. The fMRS voxel (right) was larger (3:1) than the meta-analytic cluster (left) to account for spatial uncertainties associated with meta-analysis outcomes. During each data collection session, one participant-level high-resolution structural image was used to guide fMRS voxel placement and ensure that it encompassed the bilateral dACC.

fMRI Data Collection

High-resolution fMRI data were acquired using a whole-brain multiband sequence (80 slices acquired parallel to the AC-PC line, 1.5 mm isotropic voxels, TR/TE: 1000/24.4 ms, flip angle: 45°, base/phase resolution: 136/100, multi-band acceleration factor: 5) optimized in-house. To examine associations between pain-related changes in dACC metabolite levels and pain-related changes in dACC activation, fMRI data were collected during two scan runs, each consisting of alternating nociceptive stimulation conditions: moderate nociceptive stimulation, low nociceptive stimulation, and baseline (no) stimulation (Figure 4.3). Scan runs were approximately 5.5 min each, and included an instructions phase, preparation/dummy scans, and 10 back-to-back nociceptive stimulation trials, each involving: an on-ramp phase (6 sec), a fixed stimulation phase (8 sec), an off-ramp phase (6 sec), and a VAS phase (10 sec). During the on-ramp phase, apparatus pressure was increased from 0 mmHg to either 100 or 50 mmHg, depending on trial condition. During the fixed stimulation phase, apparatus pressure was held constant. During the off-ramp phase, apparatus pressure was decreased to 0 mmHg. During the VAS phase, participants provided one subjective pain rating (anchors: 0 = “no pain”, 10 = “most pain possible”) regarding the immediately preceding nociceptive stimulation trial. Importantly, nociceptive stimulation order was fixed across participants,

and alternated between low stimulation and moderate stimulation within scan runs. There was also one baseline period toward the start of each scan run. Please see Appendix C: 7T Scanner Protocol.

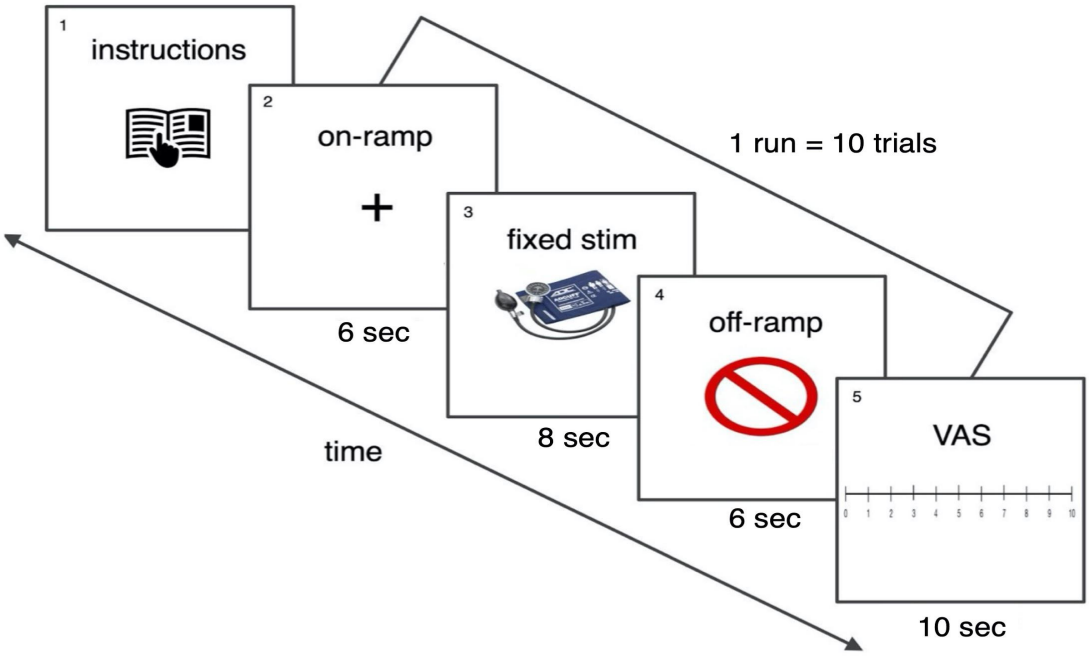

Figure 4.3. Graphical Depiction of fMRI Scan Run Time Course. Participants completed fMRI data collection across three nociceptive stimulation conditions: moderate, low, and baseline stimulation.

fMRS Data Preprocessing

fMRS data were preprocessed using LCModel, a proprietary software used for *in vivo* proton MR spectra quantification (Provencher, 2001). LCModel estimates spectra as linear combinations of model spectra from simulations or aqueous metabolite solutions (e.g., phantom solutions with known metabolite levels). A representative LCModel analysis output is provided in Figure 4.4. The current work leveraged existing basis sets from the Auburn University MRI Research Center for the following metabolites: alanine,

aspartate, creatine, phosphocreatine, GABA, glucose, glutamine, glutamate, glutamine + glutamate (Glx), glutathione, glycerophosphocholine, phosphocholine, myo-inositol, lactate, *N*-acetylaspartate (NAA), *N*-acetylaspartylglutamate (NAAG), scyllo-inositol, taurine, glycine, and phenylalanine. Although spectroscopic studies routinely consider baseline metabolite levels, the current work examined task-based changes in glutamate-related metabolite levels across nociceptive stimulation conditions. Specifically, single spectra acquisitions were averaged across each run to compute one participant-level time-resolved spectra per nociceptive stimulation condition. Then, preprocessed metabolite levels were examined using linear mixed-effects models (please see Modeling and Statistical Analyses).

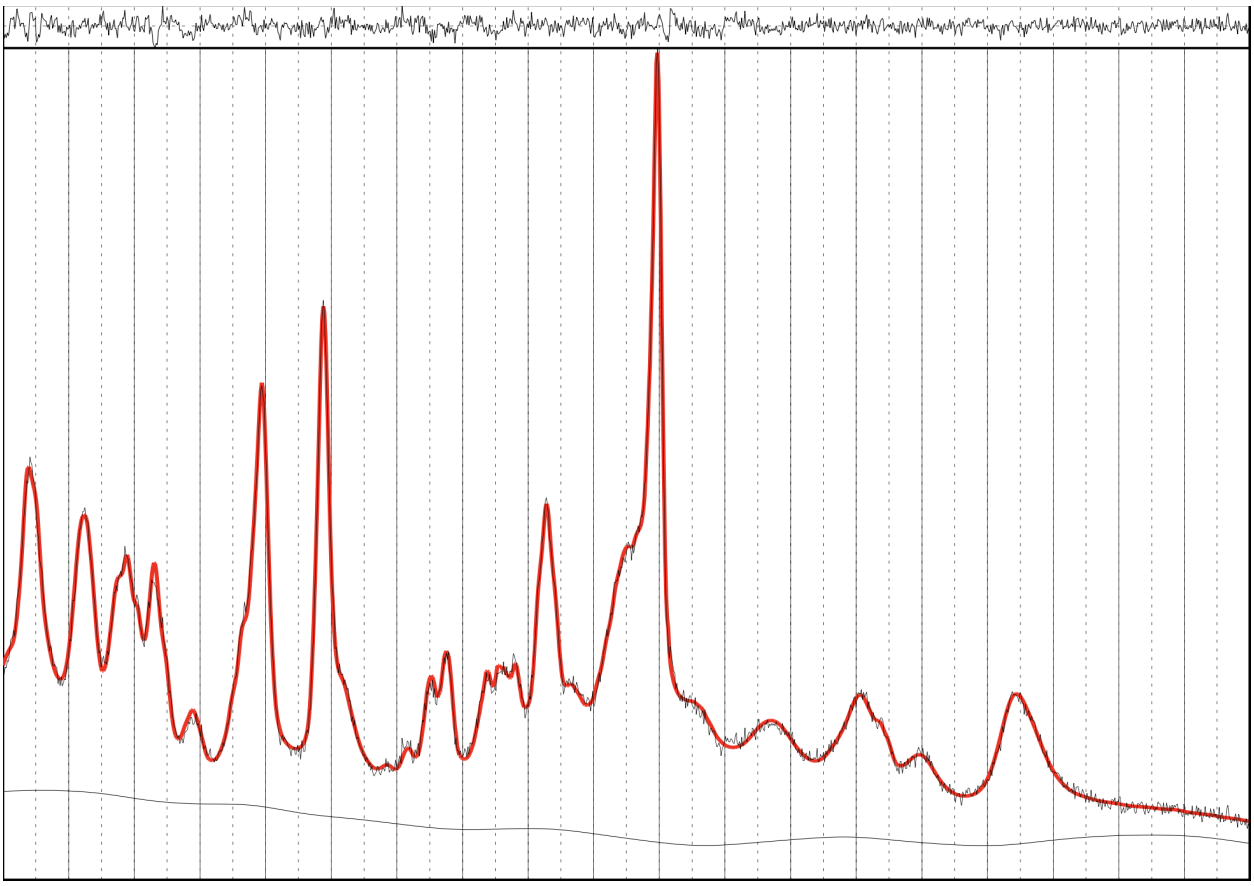

Figure 4.4. Representative fMRS Analysis Output from LCModel. The 1H-MRS chemical shift range and metabolite peaks of a cannabis non-users adult dACC at 7T. The y-axis represents detected concentration of the given metabolite. The x-axis is the frequency chemical shift in parts per million (ppm).

fMRI Data Preprocessing

fMRI data were preprocessed using the Analysis of Functional Neuroimages (AFNI) package (https://afni.nimh.nih.gov/). Importantly, the following preprocessing steps were completed at the subject level. Then, resultant subject-level statistical maps were combined to draw group-level inferences. First, structural data were skull-stripped and warped to a standard space (Montreal Neurological Institute (MNI) 152) using linear

and nonlinear transformations. Second, functional data were slice-time corrected to account for temporal differences across acquisitions. Third, linear and nonlinear transformations from structural data registration were used to warm associated functional data. Fourth, functional data were masked using tissue segmentations from subject-specific volumes, such that only gray matter functional data were retained. Fifth, functional data were smoothed using a 3 mm FWHM kernel. Sixth, six motion parameters (yaw°, pitch°, roll°, delta A>>P, delta R>>L, and delta I>>S) were regressed onto functional data to correct for substantial movement during scan runs. Finally, using a standard gamma function to deconvolve functional data with the hemodynamic response, mass voxelwise testing was conducted to locate those voxels across the whole brain where blood-oxygenation level-dependent (BOLD) signal fluctuations demonstrated statistically significant associations with nociceptive stimulation event time courses. Resultant voxelwise beta coefficients, representing the association between various stimulus classes and a given voxel, were used in subsequent analyses. Please see Appendix D: AFNI Preprocessing Pipeline (afniproc.py).

To examine associations between dACC metabolite levels and dACC functional responses, voxelwise values representing the contrast between the main effects of moderate nociceptive stimulation and baseline (no) nociceptive stimulation (i.e., moderate > baseline) were extracted and averaged from the bilateral (combined left, right hemispheres) middle anterior cingulate cortex region from the AFNI-provided Desai probabilistic atlas, including gyri and sulci and based on a typical AFNI processing pipeline using FreeSurfer (Destrieux et al., 2010). Pearson's correlation coefficients were

then used to describe associations between various dACC metabolite levels and dACC functional responses during moderate nociceptive stimulation.

Modeling and Statistical Analyses

Linear mixed-effects models were used to account for non-independence in the hierarchical/nested data structure due to the repeated-measures approach taken. Linear mixed-effects models estimate fixed and random effects simultaneously within the same model (Baayen et al., 2008). Importantly, random effects estimates describe variation in intercepts and/or slopes associated with each observational "unit" (i.e., participant) (Snijders & Bosker, 2011). In this way, individual differences in baseline metabolite levels (intercepts) and metabolite level changes in response to nociceptive stimulation (slopes) can be modeled alongside fixed effects (Meteyard & Davies, 2020). To concurrently estimate random and fixed effects, mixed-effects models were fit using the `lmer` "Fit Linear Mixed-Effects Models" R package, version 1.1.23, (https://CRAN.R-project.org/package=lme4), using restricted maximum likelihood (REML). Results were reported using field-specific best practice guidelines for linear mixed-effects models (Meteyard & Davies, 2020).

Linear mixed-effects models were used to test Hypothesis 1 (i.e., dACC glutamate-related metabolite levels are associated with cannabis use (factor: level 0 = level 1 = non-user)) and Hypothesis 2 (i.e., dACC glutamate-related metabolite levels are associated with nociceptive stimulation condition (moderate, low, and baseline (none))). Specifically, mixed-effects models involved two fixed effects (i.e., group, condition) to estimate (1) the effect of cannabis on dACC metabolite levels and (2) the effect of nociceptive stimulation on dACC metabolite levels. Additionally, mixed-effects models

also included one random effect (i.e., individual (intercept)) to model variance between participants' baseline dACC metabolite levels. Three model variants were tested as specified below (i.e., one predicting dACC glutamate, one predicting dACC glutamine, and one predicting dACC glutamate + glutamine (often referred to as Glx)). Across all hypotheses tested, statistical significance was determined using a = 0.05.

Model 1:

$dACC_{Glutamate} \sim B_0 + B_1 * Group + B_2 * Condition + (B_0|Participant) + e$

Model 2:

$dACC_{Glutamine} \sim B_0 + B_1 * Group + B_2 * Condition + (B_0|Participant) + e$

Model 3:

$dACC_{Glx} + Glutamine \sim B_0 + B_1 * Group + B_2 * Condition + (B_0|Participant) + e$

Online assessment and fMRS data were inspected using standard linear model assumptions. Univariate outliers, or those observations that were greater/less than the median observation + two interquartile ranges (IQR), were replaced using upper limits (i.e., median + 2IQR) and lower limits (i.e., median - 2IQR) (Tukey, 1970).

Prospective Power Analysis

Preliminary data were used to compute a prospective power curve and to determine the target sample size needed to obtain adequate power. Specifically, metabolite levels were measured across three nociceptive stimulation conditions as described above in 10 participants (n_{users} = 5, $n_{non\text{-}users}$ = 5) and assessed using linear mixed-effects models as described above (i.e., $dACC_{Glutamate} \sim B_0 + B_1 * Group + B_2 * Condition + (B_0|Participant) + e$). Interpolated data ($N_{interpolated}$ = 50) were generated from preliminary data ($N_{preliminary}$ = 10) using the above-mentioned model and the `extend`

function in R (https://CRAN.R-project.org/package=extend). Then, the `powerSim` and `powerCurve` functions in R (https://CRAN.R-project.org/package=powerSim), which compute prospective power for a mixed-effects model across sample sizes using 1,000 Monte Carlo simulations were used to generate the curve shown above. Curve values, including observed power at various sample sizes (green line) and associated 95% confidence interval (green shading), were plotted in Python. Based on the observed power curve, it was determined that 30 participants were needed to achieve 80% power and 40 participants were needed to achieve approximately 90% power (Figure 4.5). The target sample size was determined to be 40 participants.

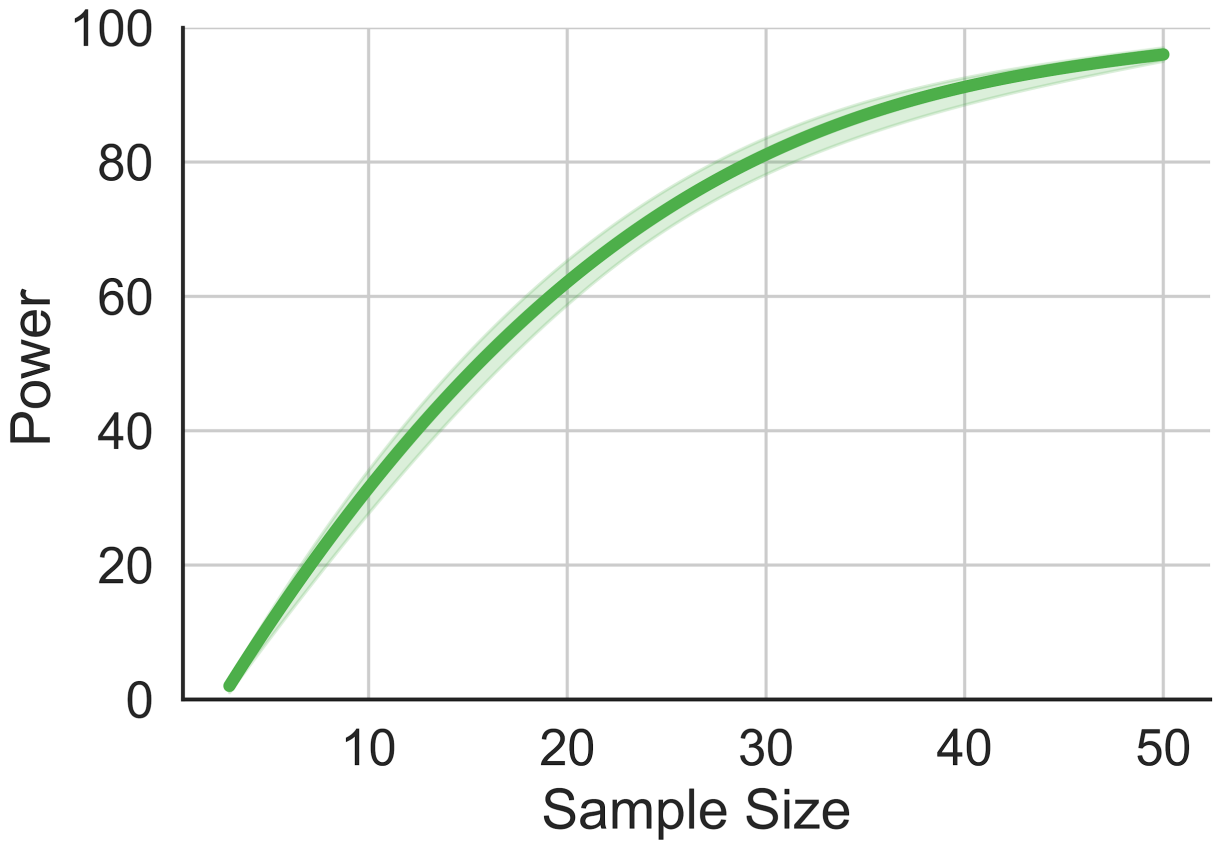

Figure 4.5. Prospective Power Curve. Created using the `simr`: Power Analysis for Generalised Linear Mixed Models by Simulation R package, version 1.0.5, (https://cran.r-project.org/web/packages/simr/).

Results

Participants

During recruitment, 1,127 respondents completed online screening materials. Of those respondents, those meeting inclusion/exclusion criteria as described above were invited to complete fMRS/fMRI data collection. Overall, 41 participants were enrolled (17 cannabis users, 24 cannabis non-users), of which none were excluded using predetermined exclusion criteria and MR contraindications. During data collection, one

non-user expressed discomfort associated with nociceptive stimulation and asked to be withdrawn from the protocol prior to fMRS and fMRI data collection. Therefore, the linear mixed-effects model outcomes (e.g., fMRS outcomes) presented represent a total sample of N = 40 participants (n_{users} = 17 cannabis users, $n_{non\text{-}users}$ = 23). Additionally, three participants (two users, one non-user) expressed discomfort associated with nociceptive stimulation and asked to be withdrawn from the protocol beteen fMRS and fMRI data collection. Therefore, the correlation outcomes (e.g., fMRS + fMRI outcomes) presented represent a total sample of N = 37 participants (n_{users} = 15 cannabis users, $n_{non\text{-}users}$ = 22). Data are presented as mean (M) $\pm$ standard deviations (SD), or variance (S^2), or appropriate statistical test coefficients unless stated otherwise (e.g., B, CI, r, t, p).

Participant demographic, mental health, and physical health data are presented in Table 4.1 and Figures 4.6 and 4.7. Other than one statistically significant difference regarding total number of prodromal symptoms endorsed (PQB, p = 0.027), no between group differences were observed. Participant substance use data are presented in Table 3.2. Other than one statistically significant difference regarding problematic alcohol consumption (RAPI, p = 0.002), no between group differences were observed.

As shown in Figure 4.6, several associations were observed between demographic, mental/physical health, and substance use variables among cannabis users. Specifically, recent cannabis use (i.e., cannabis use episode in preceding 30-day period) was associated with anxiety symptoms (r = 0.79, p < 0.001), depression symptoms (r = 0.63, p < 0.001), prodromal symptoms (r = 0.52, p < 0.01), and somatic symptoms (r = 0.43, p < 0.05). Moreover, problem alcohol use was inversely associated

with neuropathic pain ($r = -0.57$, $p < 0.01$). Among non-users (Figure 4.7), an association was observed between problem alcohol use and prodromal symptoms ($r = 0.42$, < 0.01).

Variable	Users	Non-Users	*p*
Participants	17	23	
Men (% Men)	7 (41%)	6 (26%)	
Women (% Women)	10 (59%)	17 (74%)	
Age (yrs)	19.94 ± 1.73	20.3 ± 2.49	0.591
Height (in)	64.93 ± 4.17	63.88 ± 4.18	0.437
Weight (lb)	158 ± 26.14	147.1 ± 42.73	0.358
% Race (A/B/H/I/W)	0/9/0/0/91	6/18/0/6/70	
% Hispanic	12	0	
% Left Handed	13	6	
Health			
GAD-7	6.38 ± 5.39	3.61 ± 3.07	0.077
PHQ-9	7.75 ± 6.16	4.96 ± 3.94	0.123
PHQ-15	6.69 ± 5.16	5.3 ± 3.66	0.365
PQB	3.19 ± 3.17	1.04 ± 1.58	0.021
PSS	6.81 ± 2.93	6.22 ± 2.37	0.506
WBS	48.81 ± 9.82	51.78 ± 5.77	0.289
Pain			
GCPS	2.75 ± 1.87	2.33 ± 1.6	0.473
NPS	1.8 ± 1.53	1 ± 1.21	0.091

Table 4.1. Summary of Demographic, Mental Health, and Physical Health Characteristics. Data are presented as mean ± SD unless otherwise stated. N = 40 participants were completed online assessments ($n = 17_{users}$, $n = 23_{non\text{-}users}$). With one exception (prodromal symptom severity; PQB), there were no statistically significant differences between users and non-users regarding demographic, mental/physical health, and pain variables. Regarding prodromal symptoms, more symptoms were endorsed by users versus non-users ($p < 0.05$). Additionally, there was a trend toward

statistical significance regarding anxiety symptoms (GAD7), such that users experience more anxiety than non-users.

GAD, Generalized Anxiety Disorder; PHQ, Patient Health Questionnaire; PSS, Perceived Stress Scale; WBS, Well Being Scale; GCPS, Generalized Chronic Pain Scale; NPS, Neuropathic Pain Scale.

Statistical significance determined using a = 0.05.

Variable	Users			Non-Users			p
Cannabis Use							
Onset Age (yrs)	16.56	±	1.97	18.5	±	0.7	
Regular Use (yrs)	1	±	0.97	.	±	.	
Past-Month Use (eps)	15.19	±	10.39	.	±	.	
Recent Use (hrs)	73.83	±	67.99	3,960	±	2,545.58	<0.001
Other Use							
Alcohol	8	±	5.06	2.78	±	3.88	0.002
Nicotine	.	±	.	.	±	.	
Dependence							
Amphetamine	.	±	.	.	±	.	
Cocaine	.	±	.	.	±		
Opioid	.	±	.	.	±	.	
Other Stimulants	0.12	±	0.34	0.04	±	0.21	0.404

Table 4.2. Summary of Cannabis and Other Use Characteristics Among Cannabis Users. Data are presented as mean ± SD unless otherwise stated. Importantly, because non-users were excluded if/when they endorsed > 3 lifetime cannabis use episodes, approximately $n = 2/23_{\text{non-users}}$ were included who endorsed some lifetime cannabis use. With one exception (alcohol), there were no statistically significant differences between users and non-users regarding substance use characteristics other than cannabis. Regarding alcohol, users reported more alcohol than non-users ($p < 0.01$). Regarding cannabis, use onset age was greater among two non-users who endorsed some lifetime cannabis use versus users.

Alcohol = RAPI (Rutgers Alcohols Problems Index); Other Stimulants = prescription/nonprescription psychomotor stimulant use.

Statistical significance determined using a = 0.05; .indicates no observations recorded.

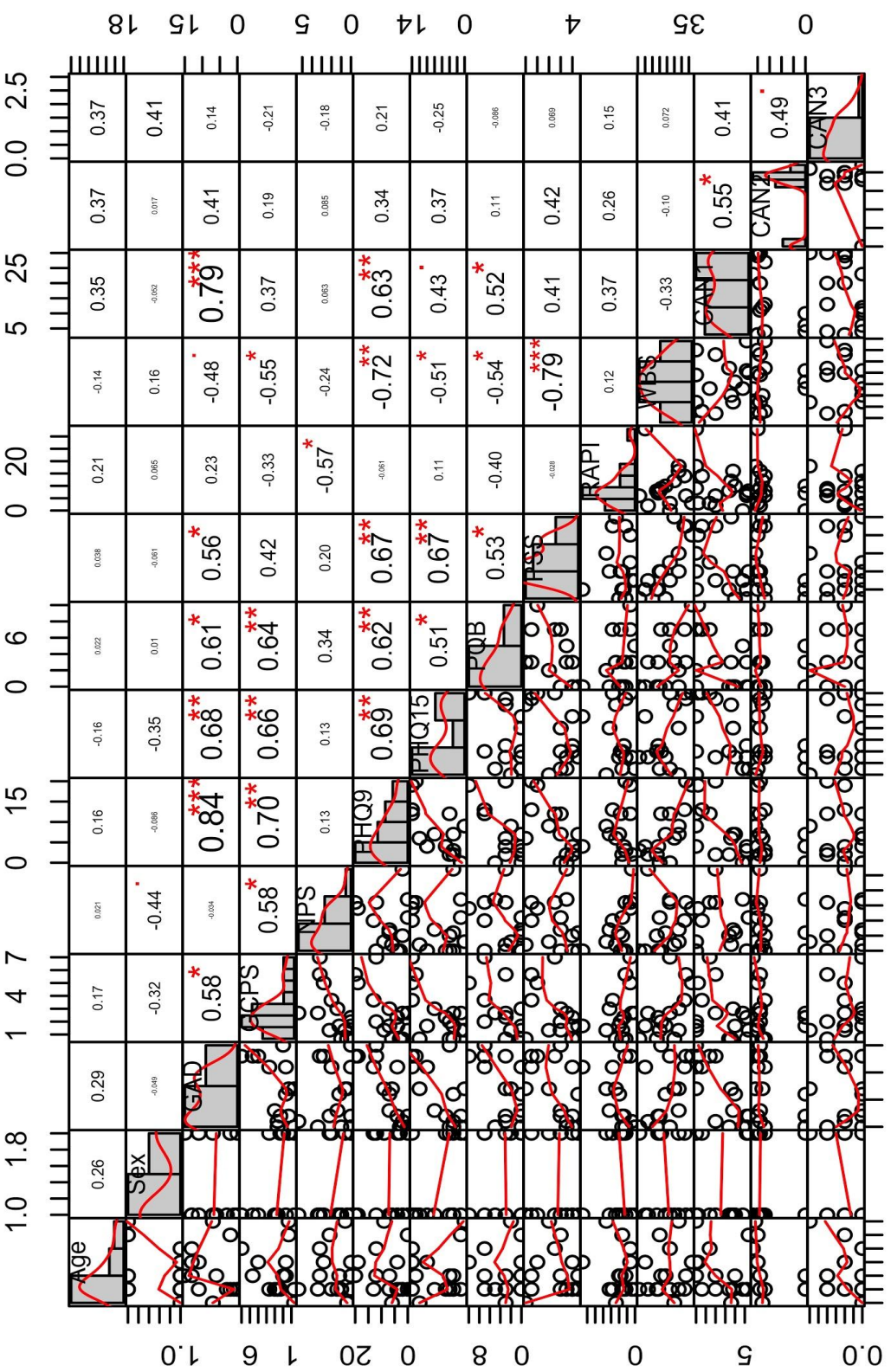
Age
Sex
GAD
GGPS
NPS
PHQ9
PHQ15
PQB
PSS
RAPI
WBS
CAN1
CAN2
CAN3

Figure 4.6. Correlation Plot Depicting Bivariate Correlations Between Considered Variables Among Cannabis Users. Names for each variable are shown in the diagonal. Response distributions for each variable are also shown on the diagonal. Beneath the diagonal, bivariate scatter plots are shown with a fitted line. Above the diagonal, Peason's correlation coefficients are shown. Correlation coefficient text size corresponds to relationship strength. Created using the `PerformanceAnalytics`: Econometric Tools for Performance and Risk Analysis R package, version 2.0.4,(https://cran.r-project.org/web/packages/PerformanceAnalytics/).

GAD, Generalized Anxiety Disorder 7; GCPS, Generalized Chronic Pain Scale; NPS, Neuropathic Pain Scale; PHQ, Patient Health Questionnaire; PQB, Prodromal Questionnaire Brief Version; PSS, Perceived Stress Scale; RAPI, Rutgers Alcohol Problem Index; WBS, Well Being Scale; CAN1, Past-Month Use; CAN2, Onset Age; CAN3, Regular Use Years.

Significance codes: 0 "***", 0.001 "**", 0.01 "*", 0.05 ".", 0.1 " "

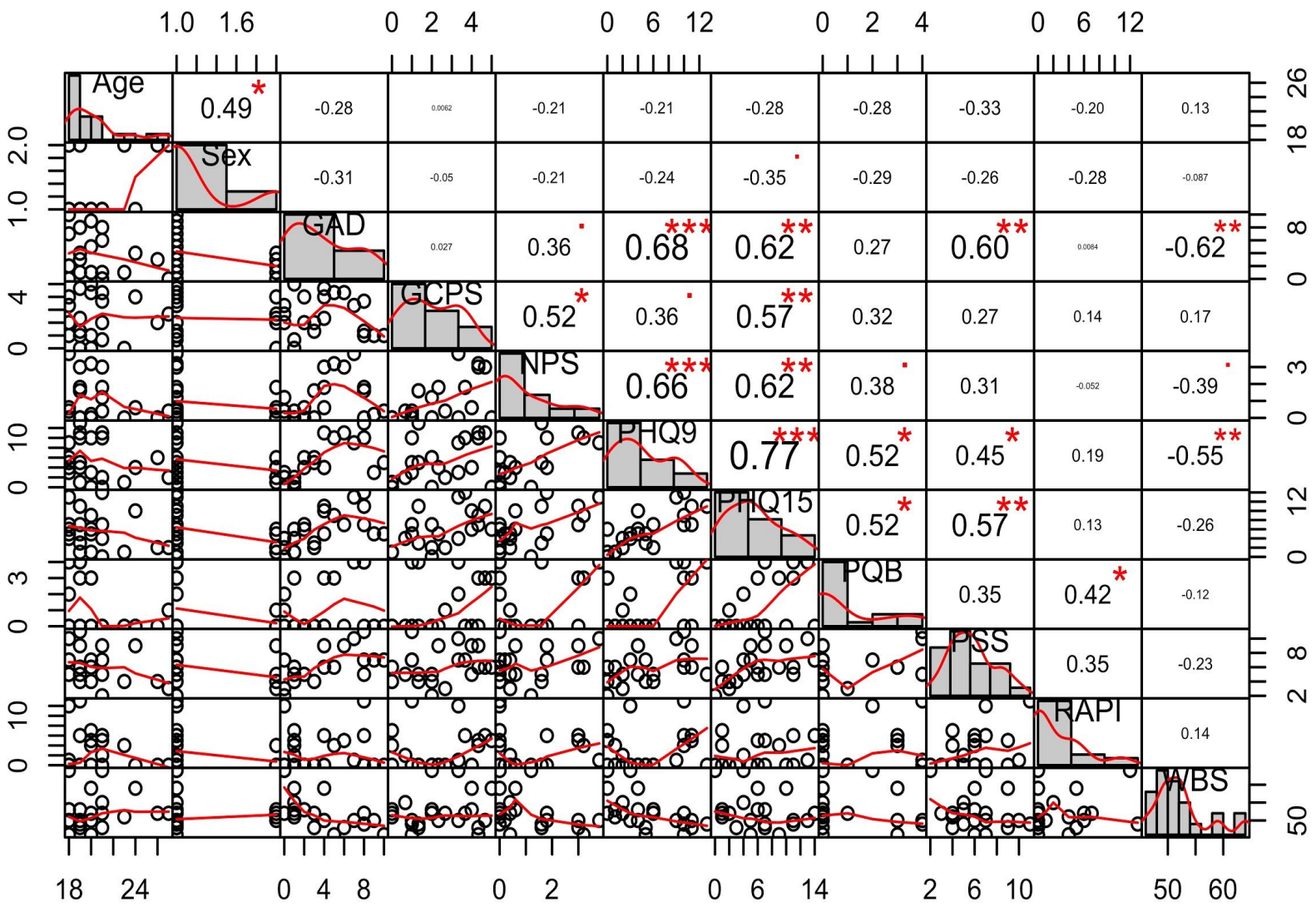
Age
Sex
GAD
GCPS
NPS
PHQ9
PHQ15
PQB
PSS
RAPI
WBS
0.49 *
-0.28
0.0062
-0.21
-0.21
-0.28
-0.28
-0.33
-0.20
0.13
-0.31
-0.05
-0.21
-0.24
-0.35 .
-0.29
-0.26
-0.28
-0.087
0.027
0.36 .
0.68 ***
0.62 **
0.27
0.60 **
0.0084
-0.62 **
0.52 *
0.36 .
0.57 **
0.32
0.27
0.14
0.17
0.66 ***
0.62 **
0.38 .
0.31
-0.052
-0.39 .
0.77 ***
0.52 *
0.45 *
0.19
-0.55 **
0.52 *
0.57 **
0.13
-0.26
0.35
0.42 *
-0.12
0.35
-0.23
0.14

Figure 4.7. Correlation Plot Depicting Bivariate Correlations Between Considered Variables Among Cannabis Non-Users. Names for each variable are shown in the diagonal. Response distributions for each variable are also shown on the diagonal. Beneath the diagonal, bivariate scatter plots are shown with a fitted line. Above the diagonal, Peason's correlation coefficients are shown. Correlation coefficient text size corresponds to relationship strength. Created using the PerformanceAnalytics: Econometric Tools for Performance and Risk Analysis R package, version 2.0.4,(https://cran.r-project.org/web/packages/PerformanceAnalytics/).

GAD, Generalized Anxiety Disorder 7; GCPS, Generalized Chronic Pain Scale; NPS, Neuropathic Pain Scale; PHQ, Patient Health Questionnaire; PQB, Prodromal Questionnaire Brief Version; PSS, Perceived Stress Scale; RAPI, Rutgers Alcohol Problem Index; WBS, Well Being Scale.

Significance codes: 0 "***", 0.001 "**", 0.01 "*", 0.05 ".", 0.1 " "

Metabolite	Users				Non-Users				p
Ala	0.05	± 0.03	289	%	0.07	± 0.05	233	%	0.274
Asp	1.28	± 0.25	9	%	1.46	± 0.19	8	%	0.02
Cr	1.43	± 0.44	11	%	1.47	± 0.44	10	%	0.762
GABA	0.64	± 0.13	7	%	0.66	± 0.12	7	%	0.611
Gln	1.15	± 0.17	4	%	1.23	± 0.16	4	%	0.167
Glu	4.9	± 0.31	1	%	5.03	± 0.22	1	%	0.17
Glx	5.92	± 0.76	1		6.24	± 0.31	1		0.008
GPC	0.77	± 0.1	4	%	0.79	± 0.11	4	%	0.601
GSH	0.53	± 0.09	6	%	0.55	± 0.06	6	%	0.454
Ins	3.47	± 0.26	2	%	3.48	± 0.25	2	%	0.872
Lac	0.33	± 0.05	11	%	0.33	± 0.05	11	%	0.801
NAA	4.82	± 0.36	1	%	4.91	± 0.29	1	%	0.433
PCr	2.93	± 0.55	4	%	2.89	± 0.5	5	%	0.828
PCh	0.16	± 0.09	82	%	0.14	± 0.06	27	%	0.531
PE	0.99	± 0.25	15	%	1.09	± 0.26	12	%	0.255
Tau	1.01	± 0.15	5	%	1.04	± 0.16	6	%	0.531

Table 4.3. Summary of Baseline dACC Metabolite Levels in Cannabis Users and Non-Users. Metabolite levels were calculated in LCModel. Data are presented as mean ± SD and CRLB (Cramer-Rao lower bounds).

Ala, alanine; Asp, aspartate; Cr, creatine; GABA, gamma-aminobutyric acid; Gln, glutamine; Glu, glutamate; GPC, glycerophosphocholine; GSH, glutathione; Ins, *myo*-inositol; Lac, lactate; NAA, *N*-acetylaspartate; PCr, phosphocreatine; PCh, phosphocholine; PE, phosphoethanolamine; Tau, taurine.

Statistical significance determined using a = 0.05; All metabolite levels are in institutional units (IU).

Baseline dACC Metabolite Levels

Baseline dACC metabolite levels are reported in Table 3.3.

Glutamate-Related Differences Between Cannabis Users and Non-Users

Regarding glutamate levels, metabolite quantitation revealed that mean dACC glutamate across nociceptive stimulation conditions was M_{users} = 4.78 $\pm$ 0.61 versus $M_{non\text{-}users}$ = 5.01 $\pm$ 0.24. This corresponded to 4.49% less dACC glutamate among users on average. When considering coefficients associated with Model 1 (Table 4.4), linear mixed-effects modeling demonstrated that dACC glutamate levels were lesser in cannabis users (B = -0.23 (95% CI: -0.01, <0.00) IU). This effect reached marginal statistical significance (t(38) = -2.09, p = 0.043). However, the effect was no longer statistically significant after adjusting univariate outliers as described above (B = 0.12 (95% CI: -0.02, 0.26) IU, t(38) = -1.62, p = 0.113). Also, there was a negative association between nociceptive stimulation and dACC glutamate metabolite levels (B = -0.07 (95% CI: -0.15, <0.00) IU). This effect was marginally non statistically significant (t(80) = -1.96, p = 0.053). However, the effect became statistically significant after adjusting univariate outliers (B = -0.03 (95% CI: -0.05, -0.01) IU, t(80) = -2.72, p = 0.008). Examining random effects revealed minimal variation between participant intercepts (S^2 = 0.07, SD = 0.27). Group-specific trends are shown in Figure 4.8.

Fixed Effect	Estimate	SE	95% CI		p
			LL	UL	
Intercept	4.86	0.09	4.68	<0.00	<0.001
Group	-0.23	0.11	-0.01	<0.00	0.043
Condition	-0.07	0.04	-0.15	<0.00	0.053
Random Effect	Variance	SD			
Intercept	0.07	0.27			

Table 4.4. Linear Mixed-Effects Model Coefficients: Glutamate. N = 40 participants (n_{users} = 17, $n_{non\text{-}users}$ = 23) completed fMRS data collection. Reported estimates are unstandardized beta coefficients.

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

[a] 0 = non-user, 1 = user; [b] nociceptive stimulation condition (moderate pain (100 mmHg), low (50 mmHg), baseline (none)); [c] between-participant variance (participant number).

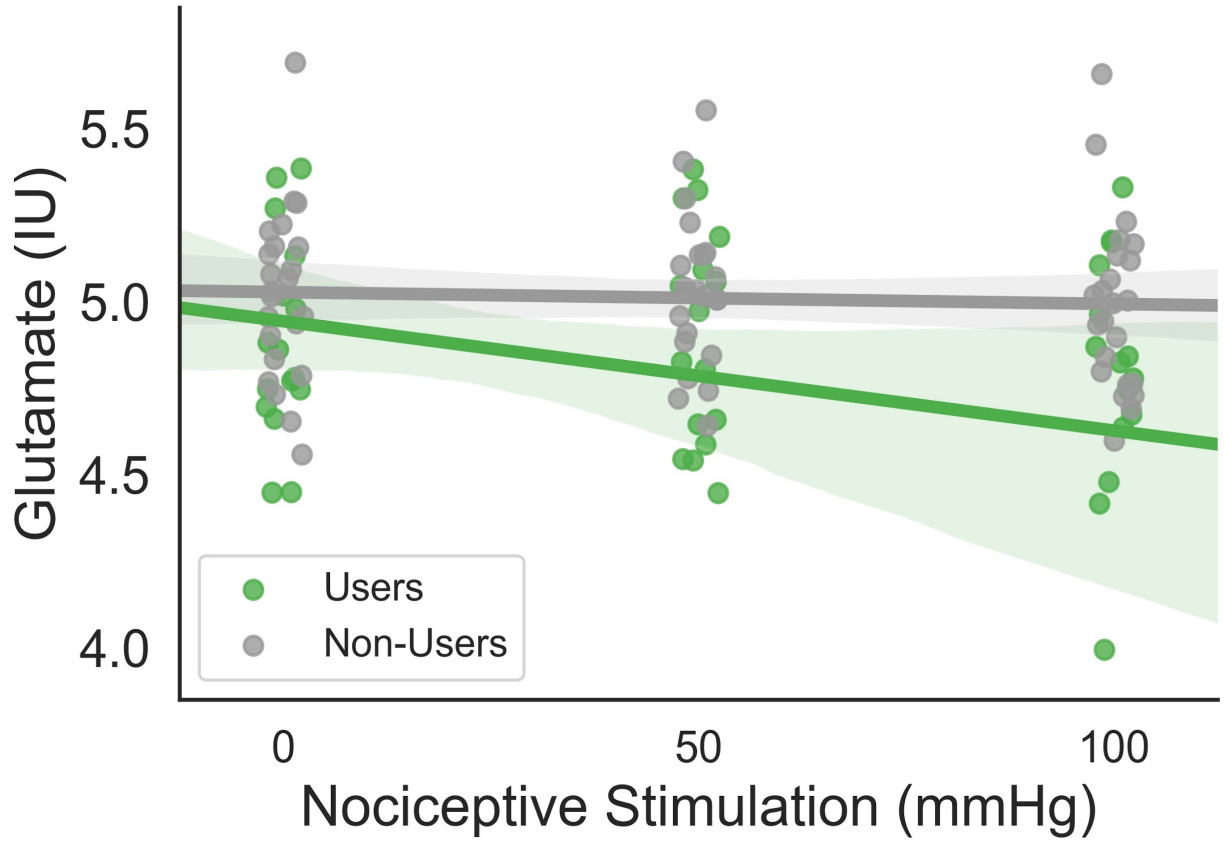

Figure 4.8. Between-Group Differences in dACC Glutamate Across Nociceptive Stimulation Conditions. N = 40 participants (n_{users} = 17, $n_{non\text{-}users}$ = 23) completed fMRS data collection.

IU, institutional units; mmHG, millimeters of Mercury.

Regarding glutamine levels (data shown below), metabolite quantitation revealed that mean dACC glutamine across nociceptive stimulation conditions was M_{users} = 1.13 $\pm$ 0.20 versus $M_{non\text{-}users}$ = 1.23 $\pm$ 0.17. This corresponded to 7.68% less dACC glutamine among users on average. When considering coefficients associated with Model 2 (Table 4.5), linear mixed-effects modeling demonstrated that dACC glutamine levels were lesser in cannabis users (B = -0.09 (95% CI: -0.02, 0.21) IU). This effect failed to reach statistical significance (t(38) = -1.65, p = 0.107). Moreover, the effect remained non statistically significant after adjusting univariate outliers as described above (B = 0.07 (95% CI: -0.02, 0.17) IU, t(38) = -1.48, p = 0.146). Also, there was a negative association between nociceptive stimulation and dACC glutamine metabolite levels (B = -0.02 (95% CI: -0.03, <0.01) IU). This effect failed to reach statistical significance (t(80) = -1.68, p = 0.097). Moreover, the effect remained non statistically significant after adjusting univariate outliers (B = -0.01 (95% CI: -0.02, <0.01) IU, t(80) = -1.11, p = 0.270). Examining random effects revealed minimal variation between participant intercepts (S^2 = <0.01, SD = 0.08). Group-specific trends are shown in Figure 4.9.

Fixed Effect	Estimate	SE	95% CI		p
			LL	UL	
Intercept	1.15	0.04	1.06	1.23	<0.001
Group	-0.09	0.06	-0.02	0.21	0.107
Condition	-0.02	0.01	-0.03	<0.01	0.097
Random Effect	Variance	SD			
Intercept	<0.01	0.08			

Table 4.5. Linear Mixed-Effects Model Coefficients: Glutamine. N = 40 participants (n_{users} = 17, $n_{non\text{-}users}$ = 23) completed fMRS data collection. Reported estimates are unstandardized beta coefficients.

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

[a] 0 = non-user, 1 = user; [b] nociceptive stimulation condition (moderate pain (100 mmHg), low (50 mmHg), baseline (none)); [c] between-participant variance (participant number).

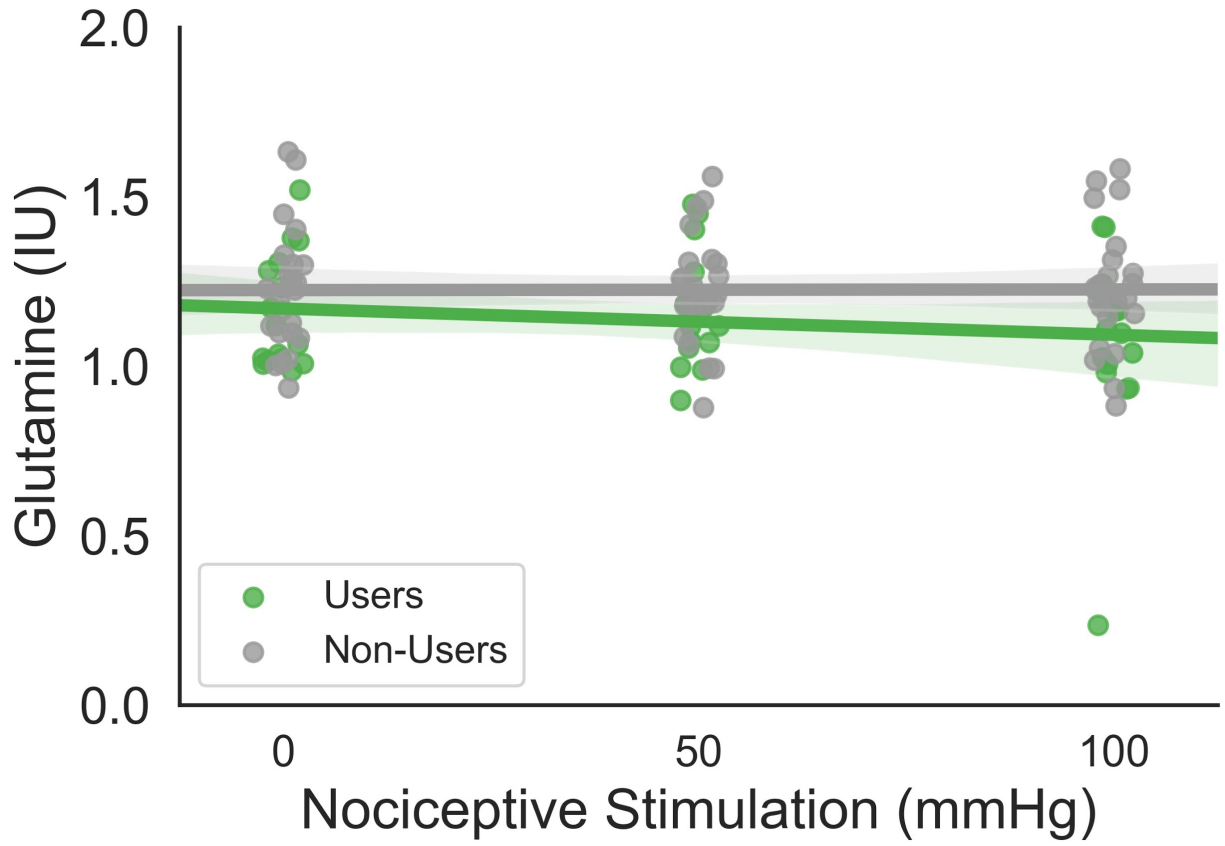

Figure 4.9. Between-Group Differences in dACC Glutamine Levels Across Nociceptive Stimulation Conditions. N = 40 participants (n_{users} = 17, $n_{non\text{-}users}$ = 23) completed fMRS data collection.

IU, institutional units; mmHG, millimeters of Mercury.

Regarding glutamate + glutamine (commonly referred to as Glx) levels (data shown below), metabolite quantitation revealed that mean dACC Glx across nociceptive stimulation conditions was M_{users} = 5.91 $\pm$ 0.76 versus $M_{non\text{-}users}$ = 6.23 $\pm$ 0.31. This corresponded to 5.12% less dACC Glx among users on average. When considering coefficients associated with Model 3 (Table 4.6), linear mixed-effects modeling demonstrated that dACC Glx levels were lesser in cannabis users (B = -0.32 (95% CI: -0.59, -0.05,) IU). This effect reached statistical significance (t(38) = -2.29, p = 0.028). However, the effect was no longer statistically significant after adjusting univariate outliers as described above (B = -0.17 (95% CI: <0.01, 0.33) IU, t(38) = -2.00, p = 0.053). Also, there was a negative association between nociceptive stimulation and dACC Glx levels (B = -0.09 (95% CI: -0.18, <0.01) IU). This effect was marginally non statistically significant (t(80) = -1.95, p = 0.055). However, the effect became statistically significant after adjusting univariate outliers (B = -0.03 (95% CI: -0.05, -0.01) IU, t(80) = -2.58, p = 0.012). Examining random effects revealed minimal variation between participant intercepts (V = 0.01, SD = 0.11). Group-specific trends are shown in Figure 4.10.

Fixed Effect	Estimate	SE	95% CI		p
			LL	UL	
Intercept	6.01	0.12	5.78	6.24	<0.001
Group	-0.32	0.14	-0.59	-0.05	0.028
Condition	-0.09	0.05	-0.18	<0.01	0.055
Random Effect	Variance	SD			
Intercept	0.01	0.11			

Table 3.6. Linear Mixed-Effects Model Coefficients: Glutamate + Glutamine (Glx). N = 40 participants (n_{users} = 17, $n_{non\text{-}users}$ = 23) completed fMRS data collection. Reported estimates are unstandardized beta coefficients.

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

[a] 0 = non-user, 1 = user; [b] nociceptive stimulation condition (moderate pain (100 mmHg), low (50 mmHg), baseline (none)); [c] between-participant variance (participant number).

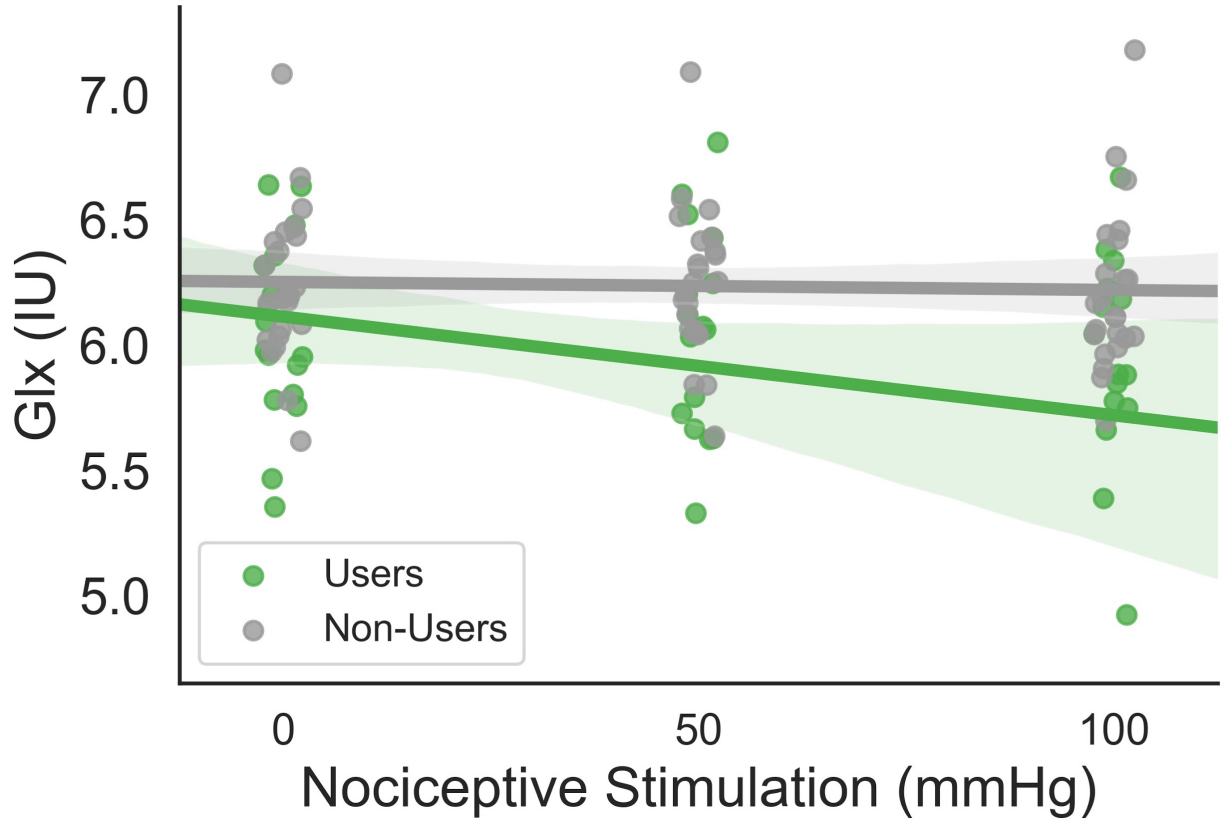

Figure 4.10. Between-Group Differences in dACC Glutamate + Glutamine (Glx) Across Nociceptive Stimulation Conditions. N = 40 participants (n_{users} = 17, $n_{non\text{-}users}$ = 23) completed fMRS data collection.

IU, institutional units; mmHG, millimeters of Mercury.

Exploratory Assessment

Because differences were observed between users and non-users regarding baseline dACC aspartate levels ($p = 0.020$), task-based changes in dACC aspartate levels were considered in exploratory assessments. Regarding aspartate levels, metabolite quantitation revealed that mean dACC aspartate across nociceptive stimulation conditions was $M_{users} = 1.25 \pm 0.27$ versus $M_{non\text{-}users} = 1.42 \pm 0.17$. This corresponded to 11.69% less dACC aspartate among users on average. When considering coefficients associated with this exploratory assessment (Table 4.7), linear mixed-effects modeling demonstrated that dACC aspartate levels were lesser in cannabis users (B = -0.17 (95% CI: -0.28, -0.06) IU). This effect reached statistical significance ($t(38) = -2.98$, $p = 0.005$). Moreover, the effect remained statistically significant after adjusting univariate outliers as described above (B = -0.14 (95% CI: -0.24, -0.04) IU, $t(38) = -2.81$, $p = 0.008$). Also, there was a negative association between nociceptive stimulation and dACC aspartate levels (B = -0.03 (95% CI: -0.06, <0.01) IU). This effect failed to reach statistical significance ($t(80) = -1.45$, $p = 0.151$). Moreover, the effect remained non statistically significant after adjusting univariate outliers (B = -0.02 (95% CI: -0.05, <0.01) IU, $t(80) = -1.36$, $p = 0.177$). Examining random effects revealed minimal variation between participant intercepts (V = 0.02, SD = 0.14). Group-specific trends are shown in Figure 4.11.

Fixed Effect	Estimate	SE	95% CI		p
			LL	UL	
Intercept	1.28	0.05	1.19	1.37	<0.001
Group	-0.17	0.06	-0.28	-0.06	0.005
Condition	-0.03	0.02	-0.06	<0.01	0.151
Random Effect	Variance	SD			
Intercept	0.02	0.14			

Table 4.7. Linear Mixed-Effects Model Coefficients: Aspartate. N = 40 participants (n_{users} = 17, $n_{non\text{-}users}$ = 23) completed fMRS data collection. Reported estimates are unstandardized beta coefficients.

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

[a] 0 = non-user, 1 = user; [b] nociceptive stimulation condition (moderate pain (100 mmHg), low (50 mmHg), baseline (none)); [c] between-participant variance (participant number).

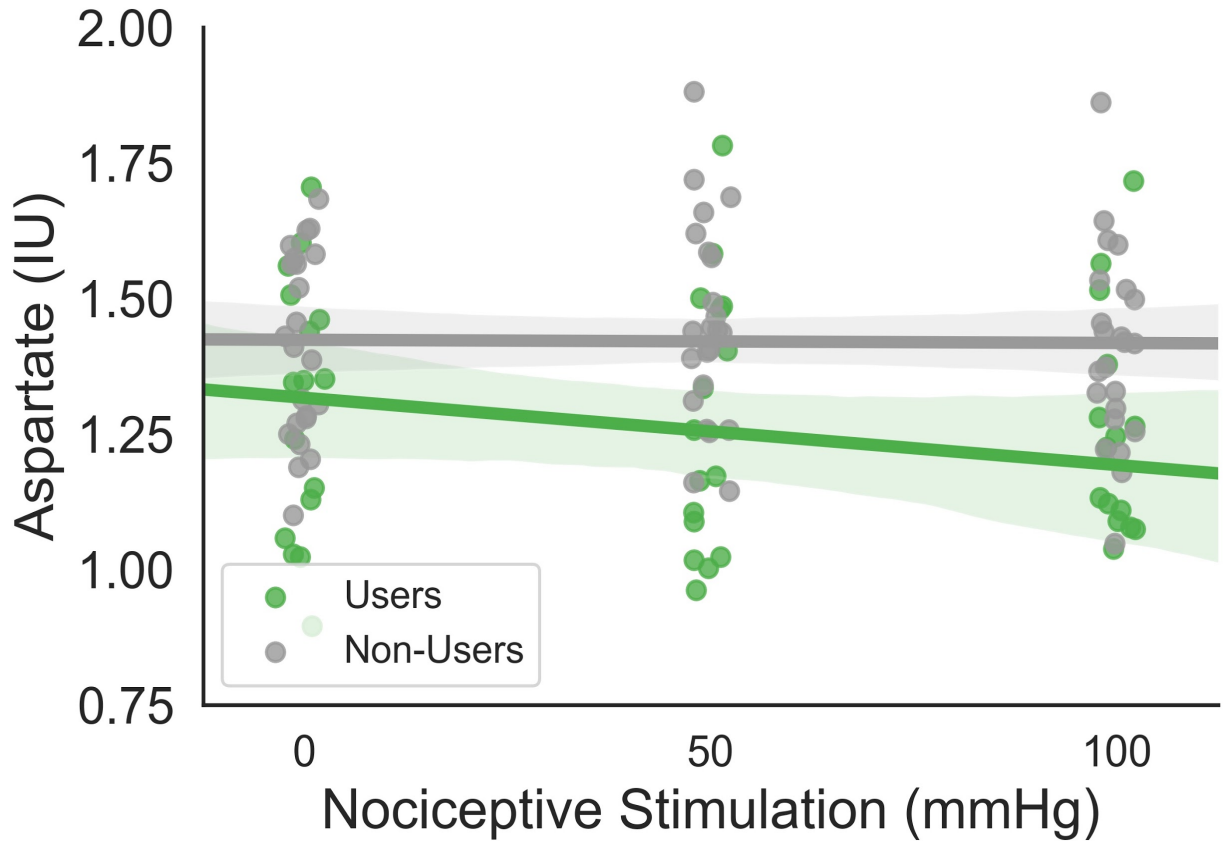

Figure 4.11. Between-Group Differences in dACC Aspartate Across Nociceptive Stimulation Conditions. N = 40 participants (n_{users} = 17, $n_{non\text{-}users}$ = 23) completed fMRS data collection.

IU, institutional units; mmHG, millimeters of Mercury.

Associations Between dACC Responses and dACC Metabolite Levels

Regarding Hypothesis 3 (i.e., dACC responses are associated with dACC glutamate-related metabolite levels), combined assessment of fMRI and fMRS measures revealed no associated between measures during moderate nociceptive stimulation (Figure 4.12). Specifically, voxelwise beta coefficients, which represent the main effect of moderate nociceptive stimulation, were averaged across dACC voxels, and Pearson's correlations coefficients were computed between spatially-resolved response values and (1) glutamate ($r = 0.11$, $t(34) = 0.65$, $p = 0.520$), (2) glutamine ($r = 0.16$, $t(34) = 0.96$, $p = 0.345$), and (3) glutamate + glutamine (Glx) ($r = 0.16$, $t(34) = 0.93$, $p = 0.361$). Additionally, one exploratory assessment was conducted to examine associations between dACC responses and aspartate levels, which were found to be different between users and non-users. No associations were observed between dACC responses and aspartate ($r = 0.004$, $t(34) = 0.02$, $p = 0.980$). Importantly, because Hypothesis 3 involved understanding task-based associations between dACC functional responses and dACC metabolite levels, analyses focused on the moderate nociceptive stimulation condition, where task effects were expected to be greatest.

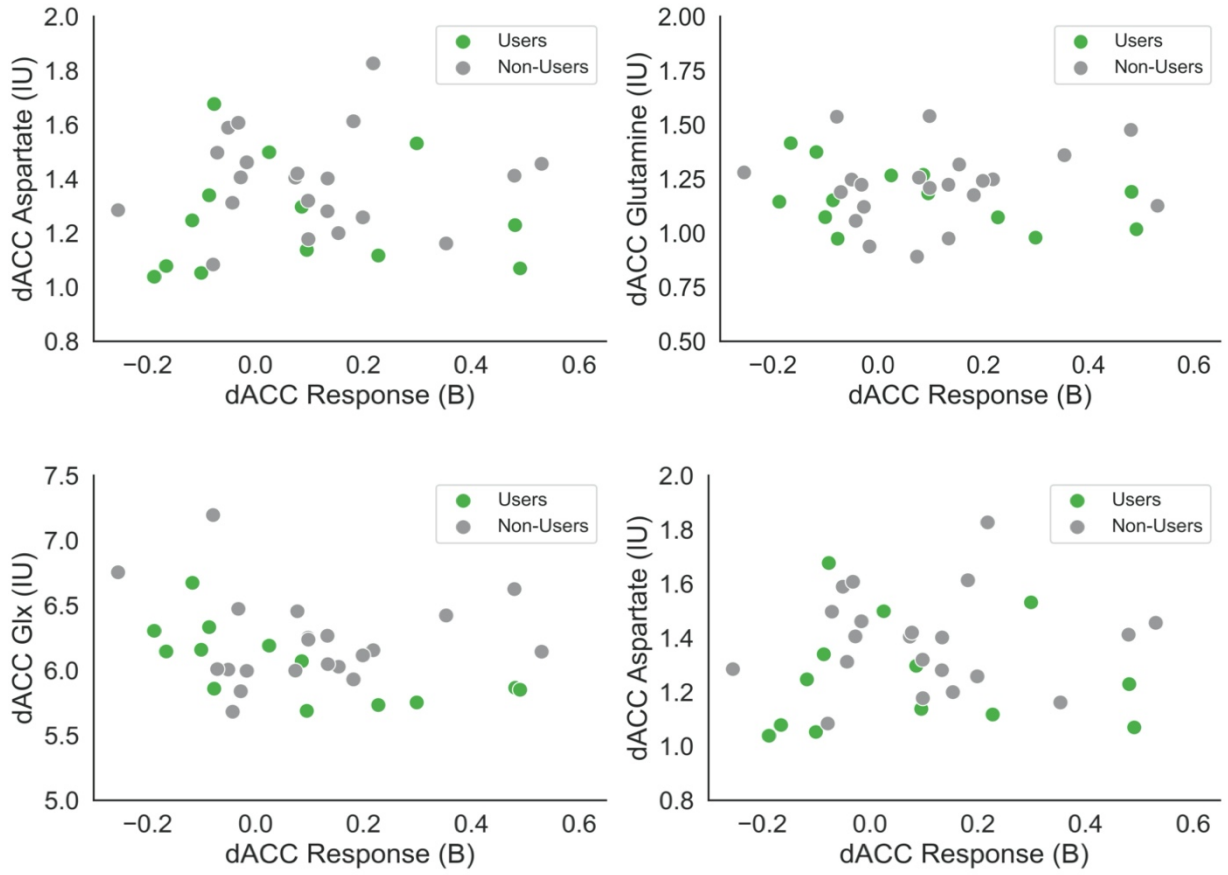

Figure 4.12. Bivariate Correlations Between dACC Functional Responses and dACC Metabolite Levels Under Moderate Pain. No associations were observed between beta coefficients from a bilateral dACC ROI, representing the main effect of moderate nociceptive stimulation, and glutamate-related metabolite levels, including glutamate, glutamine, and glutamate + glutamine (Glx). Importantly, an exploratory assessment found no associations between dACC responding and aspartate during moderate nociceptive stimulation.

B, beta coefficient; dACC, dorsal anterior cingulate cortex; Glx, glutamate + glutamine; IU, institutional units; ROI, region of interest.

Discussion

To better understand the impact of cannabis use on pain processing, 7T fMRS and fMRI were combined to examine associations between dACC glutamate-related metabolite level changes (fMRS) and dACC functional responses (fMRI) during acute nociceptive stimulation in cannabis users and non-users. Regarding Hypothesis 1, modest associations were observed between cannabis use and various metabolite levels, such that cannabis users demonstrated lower dACC glutamate and glutamate + glutamine (Glx), but no difference in glutamine. Regarding Hypothesis 2, no associations were observed between nociceptive stimulation and dACC metabolite levels. Finally, regarding Hypothesis 3, no associations were observed between dACC functional responses and metabolite levels during nociceptive stimulation. In addition, in an exploratory assessment, an association was observed between cannabis use and dACC aspartate, such that users demonstrated lesser aspartate. No associations were observed between functional responses and aspartate.

The Glutamate-Glutamine Cycle

Glutamate-related metabolites, including glutamate and glutamine, are among the most abundant amino acid neurotransmitters in the mammalian central nervous system (Govindaraju et al., 2000). Glutamate metabolites interact with GABA via a glutamate-glutamine cycle that maintains brain homeostasis between excitation and inhibition signals (Bak et al., 2006; Rubenstein & Merzenich, 2003; Walls et al., 2015).

Glutamate, among the primary excitatory neurotransmitters, is predominantly localized to presynaptic neurons, and can be released into the synapse via calcium-dependent and calcium-independent (spontaneous) mechanisms (Suryanarayanan &

Slaughter, 2006; Vyleta & Smith, 2011). Once in the synapse, glutamate can (1) return to the presynaptic glutamate neuron, (2) bind to postsynaptic glutamate receptors, including ionotropic and metabotropic glutamate receptors (Niciu et al., 2012), or (3) be passed into neighboring glial cells via various excitatory amino acid transporters (EAATs), including EAAT1 (GLAST in rodents), EAAT2 (GL-1 in rodents), EAAT3, EAAT4, and EAAT5 (O'shea, 2002), which vary in abundance and importance across brain areas (Bak et al., 2006; Niciu et al., 2012). Importantly, disruptions in extracellular glutamate concentration control systems, especially those that increase glutamate levels, can have deleterious effects on neuronal structure and function, such as cell damage and death (Choi, 1994; Doble, 1999). Moreover, such disruptions have been linked to various psychological and neurological conditions (Beart & O'shea, 2007).

Once extracellular glutamate has been passed into neighboring glial cells (astrocytes, oligodendrocytes), glutamate is converted to glutamine via glutamine synthetase, a glia-specific enzyme, in a metabolic process that requires ammonia (Bak et al., 2006; Niciu et al., 2012; Ramadan et al., 2013; Walls et al., 2015). Following conversion, glial as well as neuronal glutamine transporters move glutamine back into neighboring neurons (Niciu et al., 2012), where glutaminase, a neuron-specific phosphate-activated enzyme, converts glutamine to glutamate (Bak et al., 2006; Niciu et al., 2012; Ramadan et al., 2013). Importantly, along with *de novo* production from glucose and amino acids, the glutamate-glutamine cycle is an essential pathway in neuronal glutamate production (Erecińska & Silver, 1990). As such, it has been suggested that associations between glutamate and glutamine represent promising avenues regarding drug discovery and development (Banasr et al., 2010).

Historically, glutamate, glutamine, and other, similar metabolites have been difficult to dissociate due to similarities in chemical and electromagnetic properties (Rae, 2014). For example, glutamate and glutamine have similar resonant frequencies (otherwise known as chemical shift), and notwithstanding that they have distinct absolute brain concentrations (12mM and 1-4mM respectively), isolating these metabolite concentrations using MRS can be challenging, especially with lower magnetic field strengths (e.g., 1.5 T)(Ford & Crewther, 2016). As such, a composite signal, Glx, is often the focus of investigation. Glx can be measured using several standard MRS sequences (Baeshen et al., 2020) and, perhaps stemming from evidence that Glx levels are not influenced by glutamine levels, can be taken to represent glutamate levels and neurotransmission (Ford & Crewther, 2016). Regarding results presented here, associations were observed between experimental variables and glutamate but not glutamine. Moreover, somewhat stronger associations were observed with Glx. Taken together, these outcomes suggest that glutamate levels are impacted in long-term, frequent cannabis users without concomitant changes in glutamine, pointing toward glutamate-specific interpretations, which are described below.

Cannabis Use is Associated with Lesser Glutamate-Related Metabolite Levels

Exposure to cannabinoid receptor agonists, including THC, is associated with lesser glutamate levels across cortical and subcortical areas. Regarding short-term cannabis, a substantial experimental corpus involving animal models demonstrates that cannabinoid acute administration is associated with reduced glutamate function, however, the exact cellular and molecular mechanisms remain the focus on ongoing research (for recent reviews, please see (K. Cohen et al., 2019; Colizzi et al., 2016)).

First, CB1 agonists reduce glutamate release. In one seminal study, rat hippocampal neurons in magnesium solution were exposed to delta-9-THC and intracellular calcium concentration spikes and associated postsynaptic excitatory signaling were reduced in dose dependent manner (Shen & Thayer, 1999). Second, CB1 agonists reduce glutamate reuptake and subsequent glutamate release. In another study, rat striatal neurons were incubated with delta-9-THC and extracellular glutamate reuptake and release were examined (Brown et al., 2003). Interestingly, THC exposure was associated with decreased glutamate reuptake but no concomitant changes in basal glutamate release, suggesting that CB1 activation reduces downstream glutamate release via indirect effects on upstream glutamate reuptake. Said another way, it is possible that reduced glutamate reuptake into presynaptic terminals causes increased extracellular glutamate concentrations in the synapse, activating presynaptic metabotropic glutamate receptors (mGluRs), which act as autoreceptors, reducing subsequent glutamate release. Interestingly, presynaptic mGluR activation has been linked with analgesic effects (Dolan et al., 2003; Goudet et al., 2009; W. Li & Neugebauer, 2006; Yang & Gereau IV, 2003; Zhu et al., 2005). For example, group II mGluR agonists (including mGluR2 and mGluR3) reduce inflammation-induced sensitivity to noxious stimulation (Sharpe et al., 2002; Simmons et al., 2002). Similarly, group III mGluRs are also presynaptic autoreceptors that control glutamate release, however, their involvement in nociceptive processing remains the focus of ongoing investigation (Goudet et al., 2009). As such, it is possible that pain-reduction effects associated with acute cannabis administration stem from complex associations between both CB1 and presynaptic metabotropic glutamate receptors, however, more research is needed to confirm precise mechanisms. Third,

sustained exposure to CB1 agonists results in CB1 desensitization. To illustrate, mice hippocampal (CA1-CA3) neurons were treated with delta-9-THC overnight (~18 hours), and excitatory postsynaptic currents were recorded (Straiker & Mackie, 2005). Importantly, sustained exposure to THC prevented subsequent CB1 responses to potent agonists WIN 55212-2 and HU-210, suggesting that long-term THC desensitizes CB1 receptors. Additionally, such associations were absent in CB1 knockout animals and reversed via CB1 antagonism, further supporting the importance of CB1 activation in glutamate neurotransmission. Given that the endogenous cannabinoid system is involved in a range of homeostatic processes (Finn, 2020; Parker, 2017), distributed glutamate receptor desensitization stemming from long-term cannabis use can have important behavioral, physiological, and neurobiological implications.

It is worth noting that the studies discussed here involved short and moderate term (e.g., ~18 hours) THC or other CB1 agonist administration. Because the current study involved long-term, frequent cannabis users, and because users were required to abstain from cannabis during the 24-hour period preceding neuroimaging data collection and were therefore likely experiencing acute withdrawal effects, extrapolations should be considered with caution. Indeed, a recent meta-analysis of studies involving regular cannabis users and users with cannabis use disorder found that 47% of users experience withdrawal symptoms upon cessation (e.g., anxiety, depression) (Bahji et al., 2020). As such, it becomes important to consider that neurobiological differences during pain processing between users and non-users stem from acute withdrawal from cannabis imposed by the current study protocol. Moving forward, well-controlled studies are

needed involving long-term, repeated CB1 agonism are needed to determine exact effects of cannabis use on glutamate-related metabolite levels.

An increasing assemblance of human neuroimaging studies have examined cannabis-related changes in glutamate metabolite levels (for a recent review, please see (K. Cohen et al., 2019)). In a primary study (Chang et al., 2006), baseline (i.e., not task-related) metabolite quantitation was used to assess neurotransmitter levels in three groups: HIV+ cannabis users, HIV- cannabis users, and HIV- non-user controls. 4T MRS demonstrated that cannabis was associated with decreased glutamate throughout the right hemisphere basal ganglia, including the dorsal and ventral striatum, irrespective of HIV status. Moreover, glutamate levels were associated with cannabis use duration, albeit in frontal brain areas. Similar outcomes were observed in a more recent report involving young-adult daily cannabis users (Muetzel et al., 2013). Using 3T MRS, lesser baseline glutamate and glutamine (Glx) levels was evidenced in right hemisphere basal ganglia structures among women users but not men, suggesting that the specific nature of cannabis-related changes in baseline glutamate levels may be sex-dependent. This is in line with the results reported here, as the study sample was ~70% female, and differences in glutamate-related metabolites were observed. However, appropriately powered analyses are needed to accurately test possible sex effects. Importantly, two relevant investigations have measured ACC baseline glutamate levels in cannabis users If you would like to be reassigned as the Reviewer so that you can complete the Final Review step, please let us know (Prescot et al., 2011, 2013). In both studies, 3T MRS revealed 15% (N = 34) and 14% (N = 29), respectively, reductions in ACC glutamate among users. Results reported here are somewhat consistent with these outcomes as cannabis users

demonstrated 4.50% less dACC glutamate and 5.12% less dACC glutamate + glutamine (Glx) versus non-users. Moreover, this work extends earlier reports by (1) incorporating prospective power calculations to determine an approximate sample size needed to control Type II error rates (N = 40), which perhaps contributed to the more conservative effects estimates observed, (2) using high field strength (7T) MRI to derive glutamate-related metabolites, which provided enhanced signal-to-noise relative to lower magnetic field strengths, and (3) quantifying glutamate-related metabolites across experimentally manipulated levels of dACC-dependent task demands (i.e., fMRS) to examine patterns in dynamic glutamate level changes.

Nociceptive Stimulation and Glutamate Neurotransmission

Glutamate receptors, including ionotropic and metabotropic receptors, are expressed throughout the central and peripheral nervous systems and across levels of the pain neuraxis (Goudet et al., 2009). Indeed, glutamate neurotransmission is considered an essential component of pain processing and pain control. To date, several studies have considered the effects of acute nociceptive stimulation on MR detectable metabolites in humans (Archibald et al., 2020; Chiappelli et al., 2018; Cleve et al., 2015; De Matos et al., 2017; Gradinger et al., 2019; Gussew et al., 2010; Gutzeit et al., 2011; Hansen et al., 2014; Harris et al., 2013; Kupers et al., 2009; Mullins, 2018; Zunhammer et al., 2016). Across studies, brain areas examined have included the: ACC, dorsal ACC, anterior insula, posterior insula, occipital cortex, thalamus, and brainstem nuclear complex.

Results from a recent systematic review of pain-related fMRS studies suggest that glutamate-related metabolite levels increase across studied brain regions in response to

experimental pain (Archibald et al., 2020). Specifically, 50% of included studies reported region-specific pain-related increases in glutamate, glutamine, or Glx, while the remaining 50% reported no statistically significant changes. Regarding the ACC, three records examined metabolite levels in response to pain: (1) (Cleve et al., 2015) reported *increases* in Glx (22%), (2) (Mullins et al., 2005) reported *increases* in glutamate (9%), glutamine (11%), and Glx (16%), and (3) (Kupers et al., 2009) reported *no change* in glutamate and Glx.

Critically, an absence of task-related fluctuations in dACC glutamate levels observed in the current study may have several causes. First, the above-mentioned studies involved temperature-based nociceptive stimulation (heat, cold) which, in contrast to pressure-based stimulation used here, may be associated with distinct effects on glutamate levels. Second, fMRS voxel parameters and placement varied considerably between studies, which can make evaluating successful replication difficult. Third, the nature of nociceptive stimulation during fMRS data acquisition is important for interpretations about brain-behavior relationships. For example, (Cleve et al., 2015) alternated between pain and no-pain states during continuous fMRS data acquisition (44 heat stimuli per 1 fMRS run). In contrast, the current study involved sustained nociceptive stimulation, such that pressure was not increased/decreased at any time throughout scan runs (1 pressure stimulus per 1 fMRS run). As such, it is possible that glutamate-related metabolite levels increased following nociceptive stimulus onset and normalized over the course of fMRS runs (~5 m). Moreover, that no associations were observed between dACC metabolite levels and functional responses during pain may be due, at least in part, to the way fMRI measures were recorded. Indeed, nociceptive stimulation during fMRI

runs was administered in a pain on/off manner (10 pressure stimuli per 1 fMRI run). When taken together, despite several studies demonstrating ACC glutamate level increases during pain, methodological inconsistencies can make evaluating agreement with previous findings challenging.

Glutamatergic Function in Pain Conditions- Implications for Cannabis Users

Changes in excitatory and inhibitory neurotransmitter systems have been implicated in pain conditions (MacDermott, 2001). As such, there is increasing interest in the development of neurotransmitter-based biomarkers that can advance diagnostics and therapeutics associated with various pain profiles (e.g., headache, lower back pain, neuropathic pain). Using MRS, several studies have examined differences in glutamate-related metabolite levels between pain patients and controls, and a recent meta-analysis provided consensus regarding specific metabolites, brain areas, and pain conditions (Peek et al., 2020). Regarding ACC metabolite levels across pain conditions, included studies demonstrated *increased* ACC glutamate (Prescot et al., 2011) among migraine patients but *decreased* ACC glutamine among musculoskeletal pain patients (Gussew et al., 2010; Kameda et al., 2018). No statistically significant trends were observed regarding other ACC metabolites (GABA, Glx) or pain conditions (chronic pain syndromes, neuropathic pain, pelvic pain, urologic pain). When taken together, these results suggest that distinct trend-level changes in metabolite levels may represent important biomarkers associated with specific pain conditions.

Importantly, increased pain sensitivities have been reported in substance use populations. The *Integrated Reciprocal Model of Pain and Substance Use* (Ditre et al., 2019) posits that long-term use across several drug classes can contribute to the

development and progression of chronic pain (Ditre et al., 2019; Egli et al., 2012; Shi et al., 2010; Zale et al., 2015). Conversely, pain (acute, chronic) can motivate substance use onset/continuation (Dhingra et al., 2014; Ditre et al., 2010, 2015; Ditre & Brandon, 2008; Lawton & Simpson, 2009; Moskal et al., 2018) and act as a barrier to cessation. In this way, chronic substance use can exacerbate current pain conditions and current pain conditions can exacerbate chronic substance use. Regarding cannabis, an increasing assortment of studies have demonstrated worse pain outcomes among cannabis compared to non-users (G. Campbell et al., 2018; Degenhardt et al., 2015; Jamal et al., 2019; Liu et al., 2019; Salottolo et al., 2018; Sturgeon et al., 2020; Touil & Lavand'homme, 2019; Yanes et al., 2020).

In one seminal study (Jefferson et al., 2013), clinical endpoints were monitored in orthopedic operation candidates with and without cannabis use histories following scheduled surgeries. Researchers tracked (1) patient pain intensities during the six-hour period post operation, (2) need for rescue opioid analgesics to manage pain, (3) mood, and (4) a global assessment. In the first hour post operation, cannabis users ($n = 42$) reported greater pain intensities than non-users ($n = 31$) ($p < 0.001$). Cannabis users also required more rescue opioid analgesic doses during the first six hours post operation (pethidine (0.5 mg/kg I.V.)), which were administered when patients' reported pain intensities were ≥ 2 on a rating scale ($p = 0.003$). This association has had mixed replication outcomes in subsequent studies (G. Campbell et al., 2018; Jamal et al., 2019; Liu et al., 2019; Salottolo et al., 2018), and may depend on methodological considerations/choices across studies, including which relevant variables were/were not controlled in statistical models (e.g., patient baseline pain, reported pain efficacy, nicotine

co-use, alcohol co-use). Importantly, among users, participant characteristics, including estimated cannabis, nicotine, and alcohol use, were not associated with analgesic requirements. Importantly, despite no observed differences between users and non-users regarding mood and summed pain intensities across the six-hour period, users reported somewhat greater dissatisfaction with postoperative pain management ($p = 0.023$).

In a more recent study (Yanes et al., 2020), young adult cannabis users with comparatively short cannabis use histories (1-3 years) and non-users were compared across several laboratory and non-laboratory pain outcomes. In one experiment, users ($n = 31$) and age- and sex-matched non-users ($n = 33$) completed acute pain assessments in response to pressure-based nociceptive stimulation. No differences were observed between users and non-users regarding pain ratings following stimulation ($p = .801$), however, cannabis was marginally associated with lower pain tolerance after controlling for participant anxiety ($p = 0.046$). Critically, cannabis use characteristics, including past-month use, recent use (48 hours), and onset age, were not associated with pain ratings or pain tolerance. In a second experiment, cannabis users ($n = 185$) and non-users ($n = 586$) pain-related non-laboratory assessments. Although no differences were observed between users and non-users regarding most pain assessments, cannabis was associated with somewhat greater pain-related interference in day-to-day function, including occupational, recreational, and social activities ($p < 0.001$).

Lesser dACC Aspartate Linked with Cannabis Use

In addition to glutamate, there are several MRS detectable metabolites that are associated with excitatory neurotransmission, including aspartate, lactate, and glucose (Ballini et al., 2008; Dawson, 1999). To date, several studies have shown small

concentration changes in these metabolites during stimulation and task performance (Lin et al., 2012; Mangia et al., 2007; Schaller et al., 2013). In the current study, between-group differences were observed regarding dACC aspartate levels that were similar to differences seen in glutamate and Glx. This is perhaps not surprising given that aspartate and glutamate are closely linked. Specifically, aspartate is directly involved in the transamination processes that converts α-ketoglutarate into glutamate (Bednařík et al., 2015). Moreover, aspartic acid, and several of its derivatives, have demonstrated pharmacologic action at glutamatergic receptors. For example, N-methyl-d-aspartate, a synthetic analog, functions a potent agonist to N-methyl-d-aspartate (NMDA) receptors, although the exact physiological purpose remains unclear (E. C. Johnson, 2017). Given the known role of NMDA receptors in pain processing (Das, 2015), one open research question involves understanding how increased pain sensitivities seen in cannabis users relates to sustained changes in aspartate levels. For example, to what extent does lesser dACC aspartate levels predict pain sensitivity among users and, relatedly, could pharmacotherapies that target aspartic acid be viable treatment targets? Importantly, because this between-group difference was observed during an exploratory assessment, hypothesis driven replication studies are warranted.

Limitations

It is important to consider the results reported herein with respect to several methodological limitations. First, participants recruited to the current study represent a convenience sample, and therefore are not representative of the general population, or even subpopulations that are of research interest (e.g., pain patients, medical cannabis users, lifelong chronic cannabis users, etc.). Specifically, participants (1) were

predominantly secondary education students, (2) reported no current/previous chronic pain conditions, and (3) endorsed short cannabis use histories by comparison to previous studies. Moreover, it is unclear whether participants in the current study considered themselves recreational users, medicinal users, both, or something else (e.g., spiritual users). Indeed, collectively, cannabis users are not heterogenous, and it is likely that the impact of cannabis on pain neurobiology varies between cannabis use subpopulations, especially those with preexisting conditions (e.g., chronic pain), for which medicinal cannabis is being sought. Moreover, increasing evidence suggests that the effects of cannabis on pain neurobiology vary between male and female users (Z. D. Cooper & Craft, 2018; Z. D. Cooper & Haney, 2016), which was not considered in the current study due to low statistical power associated with the target sample size. As such, inferences drawn from reported outcomes should be constrained to similar cohorts. Nevertheless, given that previous reports have predominantly examined pain outcomes in *adult* and *older adult* cannabis users, with mean sample ages ranging from 28 to 57 years across studies, the findings presented here could potentially represent early onset of cannabis-related neurobiological changes that support the transition to pain sensitization seen in older cannabis users. Second, and related to the previous point, cannabis users and non-users were 91% and 70% white, respectively, which further restricts generalization. Indeed, previous reports have documented differences in pain neurobiology between socioeconomic and ethnic groups (C. M. Campbell & Edwards, 2012; Losin et al., 2020), which underscores the need to recruit diverse samples in human neuroscience research. Moreover, women users were overrepresented, which makes extrapolation to men users challenging (Z. D. Cooper & Craft, 2018; Z. D. Cooper & Haney, 2016). Third, the

pressure-based pain paradigm used in the current study may have constrained observed outcomes. For example, results from a recent meta-analysis of functional neuroimaging studies involving nociceptive stimulation suggest that the tasks used to probe pain brain responses are associated with convergent and divergent neurobiological correlates (A. Xu et al., 2020). As such, the results presented here may be relevant regarding acute mechanical pain but not other acute pain modalities, including chemical, electrical, or thermal, or even broader pain domains, such as chronic pain, inflammatory pain, or neuropathic pain. Additional considerations regarding pain research are discussed below (please see Additional Considerations: Pain Research). Fourth, as is common in cross-sectional studies involving illicit/controlled substance use populations, interpretations about causal associations were hampered due to the methodological approach taken, which did not involve the experimental manipulation of cannabis use. For example, given the current study experimental design, it is difficult to determine whether long-term, frequent cannabis use precedes dACC metabolite level changes, or whether preexisting baseline differences across dACC metabolite systems make can make someone more likely to consume cannabis. As such, longitudinal studies that consider temporal associations between cannabis use and neurobiological processes that drive pain experiences are necessary to provide additional clarification. Similarly, participants' cannabis use patterns were estimated from self-report measures and are as such narrowed by concerns regarding inaccurate/incomplete reporting in substance use populations (Harrison & Hughes, 1997; Rouse et al., 1985), especially cannabis use populations (Prince et al., 2018). Additional considerations about cannabis use assessments and research are discussed below (please see Additional Considerations:

Cannabis Use Measurement). Fifth, observed pain-related changes in dACC glutamate levels were inconsistent with previous reports (Archibald et al., 2020). One barrier to the continued growth of MRS/fMRS as a tool in translational and clinical research involves lacking standardized measurement methods, which are needed to (1) more accurately compare empirical evidence across studies and (2) integrate experimental findings with clinical care (Salibi & Brown, 1998). Accordingly, it is possible that the divergent outcomes regarding pain-related changes in dACC glutamate levels reported here stem from inconsistencies between MRS/fMRS studies, specifically pertaining to measurement parameters and techniques. For example, those fMRS studies that have reported the greatest glutamate-related metabolite level changes in response to task processing involved comparatively long echo times (long TE > 30 ms; current study TE = 5 ms) (Apšvalka et al., 2015; Cleve et al., 2015; Lally et al., 2014), and are therefore better able to detect glutamate compartmental changes (Jelen et al., 2018). Additional considerations about MRS/fMRS methodology are discussed below (please see Additional Considerations: MRS/fMRS Methodology).

Additional Considerations: Pain Research

Behavioral research has been “instrumental” to the development of a collective understanding about the neurobiological effects, both pain-related and non-pain-related, associated with various drug classes (Vierck et al., 2008; Withey et al., 2020). However, despite extensive preclinical and clinical research in recent decades, we have only limited understanding about distributed central and peripheral mechanisms that underpin nociceptive processing (Coghill, 2020), and as a result, advancements regarding novel (non-opioid) pain treatments have been slow (Corbett et al., 2006; Kissin, 2016).

Regarding pain research involving animals, perhaps one reason for such shortcomings involves known limitations associated with common preclinical models of nociception and pain (for a review, please see (Withey et al., 2020)). Critically, while much preclinical pain work has involved assessment of reflexive responses (e.g., paw withdrawal, licking, guarding, etc.), it has become increasingly clear that the pain experience involves more complex (central) processes that serve as links between sensory inputs and motor outputs. For those reasons, contemporary models of nociception have expanded on traditional pain assays to assess CNS-dependent processes, including operant behavior (Kangas & Bergman, 2014; Withey et al., 2018), restoration of function (Neubert et al., 2005; Ramirez et al., 2015; Rohrs et al., 2015), and naturalistic assessment with ecological validity (Negus et al., 2015). Moving forward, the inclusion of such CNS-dependent assessments in classical pain assays should improve translation between preclinical and clinical work (Withey et al., 2020).

Similarly, pain research involving humans, specifically neuroimaging research, predominantly has involved measuring neurobiological processes (e.g., changes in metabolism, cerebral blood flow, blood oxygenation, metabolites) in response to acute nociceptive stimulation (e.g., heat (thermal), electrical, mechanical, but less so cold (thermal) and chemical) that takes place inside the scanning environment (for a primer, please see (Moayedi et al., 2018). Importantly, these biological-based approaches may not capture important psychological, social, and/or environmental (contextual) processes that modulate pain experiences, which can be desirable in some instances (e.g., (Summers et al., 2010)) or undesirable in other instances (e.g., (Jensen et al., 2014)), depending on the given research question. It is worth noting that the pressure-based pain

apparatus used in the current study administered acute mechanical nociceptive stimulation to participants' non-dominant hand for extended periods of time (i.e., 230 sec). Participants were then asked to provide pain ratings. Therefore, the metabolite level changes reported here are likely not representative of the multifaceted nature of pain processing, which includes sensory/discriminative, emotional/motivational, and cognitive aspects (Ronald Melzack, 1999; Ronald Melzack & Casey, 1968), but rather a specific neurobiological response to sustained painful stimulation (and possibly habituation) with limited generalizability. Importantly, recent work involving a similar approach (Yanes et al., 2020) demonstrated that recreational cannabis users experience more pain-related interference in day-to-day activities, however, associations with observed neurobiological effects remain unclear. Subsequent research endeavors may consider incorporating assessments with such ecological relevance to more accurately model cannabis-related influences across several pain experience aspects.

Additional Considerations: Cannabis Use Measurement

One common limitation in studies involving cannabis use measurement, and controlled substance use measurement in general, involves inconsistent reporting regarding use patterns among users, which perhaps stems from possible consequences associated with endorsing illicit activities (Finn, 2020). Much of what is known about cannabis use national trends comes from three self-report measures: the National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration, 2016), the Monitor the Future (National Institute on Drug Abuse, 2020) survey, and Youth Risk Behavior Survey (Reising & Cygan, 2020) . Importantly, although these assessments provide some clarification regarding cannabis use incidence, prevalence, and possible

changes in both, they are not considered objective evidence of exposure (Finn, 2020) (Finn, 2020). That is, these measures do not involve the direct observation, and therefore objective quantitation, of substance use biomarkers, such as the presence of cannabinoids and/or associated metabolites in blood, hair, saliva, and/or urine. Similarly, other self-report measures, such as the MSHQ (Bonn-Miller & Zvolensky, 2009) and MMM (Simons et al., 1998), which were used in the current study, can be problematic for several reasons.

First, users are more likely to overestimate how much cannabis is prepared/consumed in a given use episode. For example, one recent study demonstrated regular-to-heavy users can overestimate how much cannabis is in a bowl, cannabis cigarette (joint), or concentrate preparation by 168%, 137%, and 213%, respectively (Prince et al., 2018). Importantly, studies that exclusively examine cannabis use frequencies (e.g., past-month use episodes, lifetime use episodes) may overlook important heterogeneities regarding cannabis use quantities among users. Moreover, those studies that do consider cannabis use quantities may record overestimated (biased) measures, which makes drawing inferences about drug-brain-behavior correlations difficult.

Second, cannabis formulations have evolved dramatically in recent decades (Spindle et al., 2019). For example, examining Drug Enforcement Administration (DEA) cannabis confiscations from 1995 - 2015 revealed that THC content has increased from 4% to 12% during that time frame, while CBD content has decreased from 0.28% to 0.15% (ElSohly et al., 2016). Moreover, newer products can report as much as 60%-90% THC (Finn, 2020). This suggests that much more potent cannabis forms are increasingly

being consumed. It is worth noting that the MSHQ (Bonn-Miller & Zvolensky, 2009), the main measure used to estimate cannabis use characteristics in the current study, does not include items that pertain to cannabis source, strain, or even potency.

Third, experimentation with different cannabis preparations has become much more common in recent decades. Recent studies suggest that approximately 30%-50% of adult users (Steigerwald et al., 2018) and approximately 60% of adolescent users (Knapp et al., 2019) endorse some form of non-smoked cannabis consumption (e.g., edibles, vaping, concentrates). In the current study, participants were asked about their "typical means" of cannabis consumption. No participants endorsed "ingestion," two participants endorsed "one hitter," three participants endorsed "bong," four participants endorsed "joint," and seven participants endorsed "bowl." Importantly, the MSHQ does not ask about (or provide the option to endorse) electronic cigarettes and/or vaping. Indeed, sharp rises in such methods, particularly among adolescents, have prompted national research responses (Civiletto & Hutchison, 2020). Moving forward, the development of new measurement tools (e.g., for an example, albeit about electronic cigarettes broadly, please see (Cristello et al., 2020)) that accurately assessing cannabis use patterns will be important to advancing cannabis and cannabinoid research.

Additional Considerations: MRS/fMRS Methodology

A well-known limitation of MRS research in that intracellular glutamate contained in vesicles, which represents an 20-25% of overall cerebral cortex glutamate (Fonnum, 1984; Risto A. Kauppinen & Williams, 1991), cannot be detected with current methods due to microenvironmental factors that impact T2 relaxation times and/or resonant frequencies (Jelen et al., 2018; R. A. Kauppinen et al., 1994). For example, under severe

metabolic deficient (anoxia) conditions, which causes increased vesicular glutamate release, 1H MRS detects ~100% of absolute glutamate concentration in tissue samples as confirmed using biochemical analysis (high performance liquid chromatography) (Risto A. Kauppinen & Williams, 1991). However, under metabolic normal (normoxia) conditions, 1H MRS detects ~80% of absolute glutamate concentration, suggesting that MRS undetectable glutamate pools exist under normal conditions, which are likely bound in presynaptic vesicles. As such, it is assumed that MRS methods measure glutamate movement from intracellular to extracellular compartments associated with neuronal activity rather than absolute concentration (Jelen et al., 2018).

MRS measurements are sensitive to local changes in magnetic field local homogeneities (Salibi & Brown, 1998), and regional changes in blood oxygenation/deoxygenation associated with brain activation (i.e., BOLD effects) are known to cause such changes (Bednařík et al., 2015, 2018; Mangia et al., 2007). As such, spectral resolution can diminish as the hemodynamic response develops (Jelen et al., 2018), as is common with block design approaches where stimulation can last > 60 sec. Moreover, repetitive stimulus presentation can make glutamate changes even more challenging to detect (Mullins, 2018). In the current study, a comparatively long block design (i..e, 230 sec) was used to address uncertainties about interindividual differences in pain responses. Moreover, nociceptive stimulation levels were not changed within scan runs (50 mmHg, 230 sec; 100 mmHg 230 sec). Indeed, while one earlier fMRS study involving visual stimulation demonstrated *no change* in occipital glutamate following repetitive visual stimulus presentation despite showing task-related activation (Apšvalka et al., 2015), yet another fMRS study demonstrated *less* occipital glutamate following

repetitive visual stimulus presentation (Ip et al., 2017), which has been attributed to adaptation effects (Mullins, 2018). It is worth noting that this effect would generalize across metabolite signals, such that comparisons between metabolites (and between participants) would continue to be reasonable. Nevertheless, subsequent investigations regarding pain-related metabolite level changes in cannabis users may consider event-related designs, where spectra are acquired following short nociceptive stimulation (i.e., < 2 sec) several times throughout scan runs to prevent BOLD-like effects in metabolite measures.

Future Directions

Opioidergic Function in Cannabis Users

Despite analgesic efficacy reported by medicinal and recreational cannabis users, mounting empirical evidence suggests that long-term cannabis use is associated with worse pain outcomes. For example, cannabis using pain patients require larger opioidergic drug doses to manage pain than cannabis non-using patients (Jamal et al., 2019; Jefferson et al., 2013; Liu et al., 2019; Salottolo et al., 2018). Moreover, cannabis users are at increased risk for misusing opioids, developing opioid use disorder, and relapsing following opioid use disorder treatment (Khan et al., 2019). Despite mounting behavioral and epidemiological evidence pointing toward cannabis-related effects on mu opioid system function, mechanistic studies are lacking. Specifically, it is unknown whether long-term cannabis impacts mu opioid system function in (i) pain network brain regions that mediate opioidergic drug analgesic effects (anterior cingulate) and/or (ii) expectancy network brain regions that mediate placebo analgesic effects (caudate, putamen). Additionally, contributions from related neurotransmitter systems in brain

regions rich in cannabinoid and opioid receptors have not been explored in humans. For example, chronic cannabinoid exposure impacts glutamatergic and GABAergic responses to opioid drugs in the rat nucleus accumbens (Hoffman et al., 2003); whether this translates to humans remains unclear. Given problematic overreliance on opioid medicines in the US, one important challenge facing biomedical research involves characterizing neurobiological consequences of long-term cannabis on (i) pain brain regions, (ii) placebo brain regions, and (iii) related neurotransmitter systems. Therefore, examining mu opioid system function in cannabis users addresses a critical need to develop systems-level understandings about pain neurobiology, particularly as access to medicinal and recreational cannabis continues to expand and opioid medicines continue to be the standard of care in pain medicine. Specifically, subsequent studies should aim to: (1) establish influences of cannabis use on opioid and placebo analgesia neurobiology and (2) determine relationships with related neurotransmitter systems, including glutamate and GABA.

Conclusions

To provide clarification regarding the neurobiological impact of cannabis use on neurochemical and neurobiological correlates of pain processes, fMRS and fMRI were combined to examine associations between dACC glutamate-related metabolite levels and dACC functional responses during nociceptive stimulation. First, there was some evidence to suggest that cannabis use impacts dACC glutamate and Glx levels but not glutamine. Second, perhaps due to methodological considerations and limitations, there was limited evidence that nociceptive stimulation condition impacts dACC metabolite levels. Third, and related to the previous point, there were associations observed between

dACC functional responses during pain and dACC metabolite levels. Additionally, in an exploratory assessment, an association was observed between cannabis use and aspartate, such that users demonstrated lower dACC aspartate versus non-users. Indeed, this was the most meaningful effect observed. Given increasing evidence that long-term cannabis can have deleterious effects on pain processing, there is a critical need to develop systems-level understandings regarding cannabinoid pain modulation, particularly as access to medicinal and recreational cannabis continues to expand and opioid medicines continue to be the standard of care in pain medicine.

Chapter 5

General Discussion

The research program presented herein sought to provide enhanced understanding regarding cannabis-related pain modulation. Specifically, the three chapters discussed had distinct, but complementary, aims: (1) determine those brain regions that show consistent cannabis-related functional changes among users versus non-users, (2) describe the overall impact of acute cannabis administration on objective pain outcomes across patient populations that experience pain, and (3) use these related pieces of information to inform the current study, which examined cannabis-related neurobiological differences between cannabis users and non-users during pain processing. Specifically, combined fMRS and fMRI were used to assess dACC glutamate-related metabolite level changes and dACC functional responses during acute nociceptive stimulation. Three hypotheses were tested: (1) dACC glutamate-related metabolite levels are lesser among cannabis users, (2) dACC glutamate-related metabolite levels track nociceptive stimulation, and (3) dACC glutamate-related metabolite levels are associated with dACC functional responses. These hypotheses were tested using linear mixed-effects models across three metabolites: glutamate, glutamine, and glutamate + glutamine (referred to as Glx).

First, there was modest evidence that cannabis use was associated with differences in dACC glutamate and Glx but not glutamine. Visual inspection revealed that this effect was stronger during moderate nociceptive stimulation versus low or baseline (no) stimulation. This outcome was consistent with previous reports demonstrating lesser excitatory metabolite levels in cannabis users. It is worth noting that fMRS detects

extracellular glutamate – that is, glutamate that has been released from presynaptic vesicles into the synaptic cleft – before being cleared by various glutamate transporters. As such, it is likely that task-related changes in glutamate and Glx observed using fMRS represent increases/decreases in glutamate release rather than increases/decreases in glutamate synthesis per se (and therefore total glutamate). Regarding the current research program, it is possible that the fMRS evidence presented in Chapter 4 represents a metabolite-based mechanism that explains meta-analytic evidence discussed in Chapter 2, namely, lesser ACC activation across neuroimaging task ontologies (albeit, not including pain) seen in cannabis users versus non-users. Moving forward, there is one important research question related to the fMRI data that was also collected in the current study: are there differences between cannabis users and non-users regarding dACC functional responses during acute nociceptive stimulation and, perhaps more importantly, how are these differences related to evidenced metabolite differences?

Second, there was weak evidence that dACC glutamate-related metabolite levels were associated with nociceptive stimulation. Specifically, there was some evidence that glutamate and Glx levels were *negatively* associated with nociceptive stimulation, such that increased stimulus intensities produced decreased metabolite levels. Visual inspection revealed that this effect was stronger in cannabis users. There was no effect on glutamine levels. This outcome was inconsistent with previous reports, which suggest excitatory metabolite levels are *positively* associated with stimulus intensities in several domains, including motor, vision, and pain. Critically, that a negative association was observed likely stems from the specific analysis approach taken, which involved

averaging fMRS measurements within each nociceptive stimulation block. That is, it is possible that dACC glutamate-related metabolite levels *increased* with stimulus onset but then *decreased* as painful stimulation endured (and perhaps even undershot following prolonged stimulation), which would lower block mean metabolite levels. Moreover, because this trend was observed in cannabis users but not in non-users, negative associations between pain stimulation and excitatory metabolite levels on the block-level may represent a metabolite-based biomarker that explains increased pain sensitivity sometimes seen in users (Ditre et al., 2019; Yanes et al., 2020). In Chapter 3, meta-analytic evidence was presented that suggests cannabinoid treatments are associated with pain reduction in pain populations. Importantly, the included studies represented cannabis-naïve participants, with relatively little-to-no cannabis use histories. As such, it is possible that repeat cannabis exposure leads to changes in pain-related excitatory metabolite levels, which could explain pain differences between cannabis-naïve and cannabis-using participants, that is, short-term pain reduction and long-term pain sensitization, respectively. To provide clarification, subsequent studies may consider examining pain-related metabolite levels in new cannabis users across several timepoints using longitudinal methods.

Third, there was no evidence that dACC glutamate-related metabolite levels correlate with dACC functional responses during nociceptive stimulation. This was somewhat inconsistent with relevant literature. In general, it is accepted that regional increases in excitatory metabolite levels as measured by fMRS correlate with brain activation as measured by fMRI (Betina Ip et al., 2017). Despite this, several studies have shown no association between these measures. One important consideration in

combined fMRS/fMRI studies is the time course by which experimental stimulation impacts fMRS signals and fMRI signals. Regarding fMRS signals, the current study involved averaging spectra measurements within each nociceptive stimulation block, such that each time-resolved spectrum represented 230 seconds. However, fMRI signals were measured several times within each block, such that each functional response represented 8 seconds. Thus, it is possible that these two measures represent different, yet complementary, neurobiological aspects of pain processing that cannot be assessed using correlation analyses. Moving forward, a similar approach would involve examining associations between fMRS signals that represent within-block timesteps (i.e., spectra 1-5, 6-10, etc.) and fMRI signals to better characterize such associations.

When taken together, the three studies presented herein advance our understanding about the effect(s) of repeat cannabis exposure on neurobiological mechanisms that support pain processing. Specifically, outcomes presented in Chapter 2 outline neurobiological changes associated with chronic cannabis use, including changes in known pain brain regions. However, whether these changes translate to observable differences in pain sensitivity remained unclear. To provide clarification regarding cannabis-related pain modulation, Chapter 3 describes meta-analytic evidence showing that acute cannabinoid administrations are associated with pain reduction. However, whether repeat cannabis exposure, as in the case of recreational cannabis users, is associated with neurobiological changes that support differential pain sensitivity was an open research question. Finally, the current study is described in Chapter 4, which examined dACC metabolite level changes and functional responses during acute

nociceptive stimulation in cannabis users and non-users to understand neurobiological mechanisms that might support cannabis-related pain modulation.

An increasing assemblance of empirical evidence suggests that cannabis use is associated with increased pain sensitivity. However, whether pain represents a cause, a consequence, or both, of cannabis use is the focus of ongoing investigation. That the preponderance of evidence regarding cannabis-related pain modulation constitutes cross-sectional research – including the studies reported herein – represents a significant barrier. Nevertheless, naturalistic and longitudinal studies are providing some clarification. In one recent report, medical cannabis users provided cannabis characteristics (e.g., strain, dose, route) and general characteristics (e.g., current pain, mood, side effects) during repeat cannabis use episodes via smartphone application technology (Cuttler et al., 2020). Critically, across pain symptoms, it was shown that cannabis dose increased over time, suggesting that users experience diminishing returns regarding cannabis-related pain reduction. On the other hand, it is possible that increased doses were necessary to counteract pain condition progression. Despite these lingering questions, these outcomes stress the need to consider implications of expanding access to medical and recreational cannabis. That is, notwithstanding considerable evidence demonstrating short-term cannabis-related analgesic effects, long-term cannabis use could worsen pain sensitivity.

According to the International Association for the Study of Pain, pain is “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.” From a neurobiological perspective, pain experiences represent collective contributions from central and peripheral

mechanisms working in concert to produce private and public pain behavior, which have become more clear in recent decades with advances in neuroimaging technologies. Importantly, given problematic overreliance on opioid pain treatment, there is a critical to develop programmatic research regarding pain modulation by non-opioid pharmacologic agents, including cannabinoids, entheogen, and others. Conversely, it is of equal importance to consider long-term consequences associated with repeat exposure to these drug classes. In general, the long-term goals of this emerging research program are to delineate the neurobiological, psychological, and social factors that underpin pain modulations and develop unifying frameworks regarding drug and placebo analgesia. Understanding how drug and placebo (belief) effects interact to control pain across individuals and populations represents an important step toward developing effective pain management strategies. Moreover, comprehensive studies that examine distinct and combined influences from pharmacologic and non-pharmacologic (expectancy) effects across drug classes (cannabinoid, opioids, entheogens) should provide a more thorough characterization of neural processes that subserve the pain experience.

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Information Letter

You are invited to participate in a research study examining the effects of cannabis on pain processing. This research study is being conducted by Julio A. Yanes, MS, Graduate Research Assistant at Auburn University, and Dr. Jennifer L. Robinson, Associate Professor at Auburn University. You were selected as a possible participant because you expressed interest via email or Sona Systems.

What will be involved if you participate? If you decide to participate in Part 1 of this research study, you will be asked to complete online questionnaires. The questionnaires will relate to mental health, physical health, and substance use. Completing these questionnaires should take 30 minutes. Based on their responses to specific questions, some participants may be eligible to participate in Phase 2 of this research study, which involves an MRI scanning session.

Are there risks or discomforts? The risks associated with participating in Phase 1 of this research study are that you experience emotional distress that could result from thinking about certain topics (e.g., mental health, pain). If you find yourself experiencing distress, you may discontinue participation at any time. Should you decide to discontinue, you would receive research hours via Sona Systems that correspond to time spent completing the questionnaires. If you wish to speak with someone about your distress, a reference list of resources in the Auburn-Opelika area will be available following the questionnaires. Also, you can request of copy of the reference list by contacting the investigators listed on this letter.

There are also risks associated with confidentiality breaches. To minimize this risk, only investigators have access to data obtained in connection with the research study that can be identified as belonging to you. If you decide to withdraw, you may withdraw any data that has been collected as long as it is identifiable. You will be assigned a participant number so that your name and other pieces of identifying information are not directly associated with data collected. All data, including your responses to these questionnaires, will be associated with that participant number. Following data collection completing, any/all links to identifiable information will be destroyed. The results of this study may be presented in a professional venue, such as a journal of conference. In such an event, group data will be presented.

The research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example if there was a court subpoena. Information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except if there is a federal, state, or local law that requires disclosure (such as to report child abuse, see below); if you have consented to the disclosure; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information that is needed for auditing or program evaluation by the National Institutes of Health, which is funding this project, or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information to be released to any other person not connected with this research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of harm to self or others or of the abuse or neglect of a child or elderly or disabled adult.

Are there benefits to yourself or others? If you participate in Phase 1 of this research study, you can expect to receive no direct personal benefits.

Will you receive compensation? During Phase 1, you will be compensated for participation with one research hour via Sona Systems. Your instructors should assign specific values of course credit to these hours. Please check with your instructors for more information. During Phase 2, you will be compensated for participation with three research hours via Sona Systems. Moreover, during Phase 2, you will be compensated $5 for showing up to your MRI scanning session. Furthermore, you will receive $5 for every 30-minute block you are inside the scanner. The total compensation will be $10 for 0-30 minutes of scanning, $15 for 30-60 minutes of scanning, and $20 for 60-90 minutes of scanning. If you volunteered through Sona Systems, you will be compensated for participating with three research hours.

Are there costs? If you decide to participate in this research study, you will not incur any costs. If you require medical attention, you will be responsible for all costs for medical attention/treatment.

If you change your mind about participating, you can withdraw from the research study at any time. Your participation is completely voluntary. If you choose to withdraw, your data can be withdrawn as long as it is identifiable. Your decision about whether or not to participate will not jeopardize your relationship with Auburn University, or any associated/affiliated department, center, or office.

If you have questions about this research study, please ask them now. Alternatively, you can contact Julio A. Yanes, MS, at yanes@auburn.edu, or Dr. Jennifer L. Robinson, jrobinson@auburn.edu, who are the research study investigators. A copy of this document will be given to you for your records at your request.

If you have questions about your rights as a research participant, you may contact the Auburn University Office of Human Subjects Research or the Institutional Review Board by phone (334)844-5966 or email at hsubjec@auburn.edu or IRBchair@auburn.edu.

HAVING READ THE INFORMATION PROVIDED, YOU MUST DECIDE WHETHER OR NOT YOU WISH TO PARTICIPATE IN THIS RESEARCH STUDY.

You may print a copy of this information letter to keep for your records.

○ I have reviewed the information letter and would like to continue with Phase 1.

Email

Again, your privacy will be protected. Before completing Phase 1, you will be asked to provide your email address. We will use provided email addresses to contact participants about Phase 2. Investigators that oversee this project have been granted a "Certificate of Confidentiality" from the government. Certificates like these permit the research team to refuse to disclose names, email addresses, and other pieces of "identifiable information" from participants in response to legal demands. This protects you, as well as the investigators, from legal action(s) that could be associated with reporting illicit activities (e.g., cannabis).

For more information about Certificates of Confidentiality, please visit https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-109.html.

Please provide your email address in the space below so that we may contact you about Phase 2.

Demographics

How old are you? Use the slider below to indicate your age.

0 10 20 30 40 50 60 70 80 90 100

Age

Which of the following best describes your sex?

- Male
- Female

Which of the following best describes your gender?

- Male
- Female
- Non-Binary
- Non-Conforming

How would you describe yourself? Please select one that best describes you.

- ○ American Indian or Alaska Native
- ○ Asian or Asian American
- ○ Black or African American
- ○ Hawaiian or Pacific Islander
- ○ White

How would you describe yourself? Please select one that best describes you.

- ○ Hispanic or Latino
- ○ Non-Hispanic or Non-Latino

How would you describe yourself? Please select one that best describes you.

- ○ Student
- ○ Full-time employed
- ○ Part-time employed
- ○ Out of work for more than one (1) year
- ○ Out of work for less than one (1) year
- ○ Retired
- ○ Unable to work

What is the highest education level that you've achieved?

- Never attended school or only attended kindergarten
- 1st - 8th grade (i.e., elementary school)
- 9th - 11th grade (i.e., some high school)
- 12th grade of GED (i.e., high school graduate)
- Currently enrolled in undergraduate program
- Completed undergraduate program
- Currently enrolled in graduate program
- Completed graduate program

What is the primary language you speak at home?

- English
- Spanish
- Other

Are you currently taking medication for psychological/psychiatric conditions (e.g., Xanax, Adderall, etc.)?

- Yes
- No

Do you have a current diagnosis of a psychological/psychiatric condition (e.g., Anxiety, ADHD, etc.)

- Definitely yes
- Probably yes
- Might or might not
- Probably not
- Definitely not

Have you previously received counseling or psychotherapy?

- Yes
- No

Have you ever been hospitalized for psychological/psychiatric reasons?

- Yes
- No

Has someone from your family (i.e., parents, grandparents, siblings, other relatives) been diagnosed and/or treated for psychological/psychiatric conditions?

- ○ Yes
- ○ No

Please indicate your preferences in the use of hands in the following activities or objects

	Always left	Usually Left	Both Equally	Usually Right	Always Right
Writing	○	○	○	○	○
Throwing	○	○	○	○	○
Toothbrush	○	○	○	○	○
Spoon	○	○	○	○	○

Well-Being Scale

The following questions relate to your sense of well-being. Please select the response that best describes your experience in the last two weeks.

I've been feeling optimistic about the future.

- ○ None of the time
- ○ Rarely

- ○ Some of the time
- ○ Often
- ○ All of the time

I've been feeling useful.

- ○ None of the time
- ○ Rarely
- ○ Some of the time
- ○ Often
- ○ All of the time

I've been feeling relaxed.

- ○ None of the time
- ○ Rarely
- ○ Some of the time
- ○ Often
- ○ All of the time

I've been feeling interested in other people.

- ○ None of the time
- ○ Rarely
- ○ Some of the time

- ○ Often
- ○ All of the time

I've had energy to spare.

- ○ None of the time
- ○ Rarely
- ○ Some of the time
- ○ Often
- ○ All of the time

I've been dealing with problems well.

- ○ None of the time
- ○ Rarely
- ○ Some of the time
- ○ Often
- ○ All of the time

I've been thinking clearly.

- ○ None of the time
- ○ Rarely
- ○ Some of the time
- ○ Often

- ○ All of the time

I've been feeling good about myself.

- ○ None of the time
- ○ Rarely
- ○ Some of the time
- ○ Often
- ○ All of the time

I've been feeling close to other people.

- ○ None of the time
- ○ Rarely
- ○ Some of the time
- ○ Often
- ○ All of the time

I've been feeling confident.

- ○ None of the time
- ○ Rarely
- ○ Some of the time
- ○ Often
- ○ All of the time

I've been able to make up my own mind about things.

- None of the time
- Rarely
- Some of the time
- Often
- All of the time

I've been feeling loved.

- None of the time
- Rarely
- Some of the time
- Often
- All of the time

I've been I've been interested in new things.

- None of the time
- Rarely
- Some of the time
- Often
- All of the time

I've been feeling cheerful.

- None of the time
- Rarely
- Some of the time
- Often
- All of the time

Perceived Stress Scale (PSS) 4

The following questions ask about your thoughts/feelings. In each case, please select the answer that best describes how you've felt during the last month (i.e., approximately the last 30 days).

In the last month, how often have you felt that you were unable to control the important things in your life?

- Never
- Almost Never
- Sometimes
- Fairly Often
- Very Often

In the last month, how often have you felt confident about your ability to handle your personal problems?

- Never
- Almost Never
- Sometimes
- Fairly Often
- Very Often

In the last month, how often have you felt that things were going your way?

- Never
- Almost Never
- Sometimes
- Fairly Often
- Very Often

In the last month, how often have you felt that difficulties were piling up so high that you could not overcome them?

- Never
- Almost Never
- Sometimes
- Fairly Often

○ Very Often

PHQ-SADS

Your answers to the questions below will help the research understand any health-related problems you may have. Please answer each question to the best of your abilities.

During the last four (4) weeks, how much have you been bothered by any of the following problems?

	Not bothered	Bothered a little	Bothered a lot
Stomach pain	○	○	○
Back pain	○	○	○
Pain in your arms, legs, or joints (knees, hips, etc.)...	○	○	○
Feeling tired or having little energy	○	○	○
Trouble falling or staying asleep, or sleeping too much	○	○	○
Menstrual cramps or other problems with your period	○	○	○

	Not bothered	Bothered a little	Bothered a lot
Pain or problems during sexual intercourse	○	○	○
Headaches	○	○	○
Chest pain	○	○	○
Dizziness	○	○	○
Fainting spells	○	○	○
Feeling your heart pound or race	○	○	○
Shortness of breath	○	○	○
Constipation, loose bowels, or diarrhea	○	○	○
Nausea, gas, or indigestion	○	○	○

Over the last two (2) weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
Feeling nervous, anxiety, or on edge	○	○	○	○
Not being able to stop or control worrying	○	○	○	○
Worrying too much about different things	○	○	○	○
Trouble relaxing	○	○	○	○

	Not at all	Several days	More than half the days	Nearly every day
Bring so restless that it is hard to sit still	○	○	○	○
Becoming easily annoyed or irritable	○	○	○	○
Feeling afraid as if something awful might happen	○	○	○	○

Questions about anxiety attacks. If you've never had anxiety attacks, you should select "no" for every answer.

	No	Yes
A. In the last four (4) weeks, have you had an anxiety attack - suddenly feeling fear or panic?	○	○
Has this ever happened before.	○	○
Do some of these attacks come suddenly out of the blue - that is, is situations where you don't expect to be nervous or uncomfortable.	○	○
Do these attacks bother you a lot or are you worried about having another attack.	○	○

	No	Yes
During your last bad anxiety attack, did you have symptoms like shortness of breath, sweating, or your heart racing, pounding, or skipping?	○	○

Over the last two (2) weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things.	○	○	○	○
Feeling down, depressed, or hopeless.	○	○	○	○
Trouble falling or staying asleep, or sleeping too much.	○	○	○	○
Feeling tired or having little energy.	○	○	○	○
Poor appetite or overeating.	○	○	○	○
Feeling bad about yourself - or that you are a failure or have let yourself or your family down.	○	○	○	○

	Not at all	Several days	More than half the days	Nearly every day
Trouble concentrating on things, such as reading the newspaper or watching television.	○	○	○	○
Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.	○	○	○	○
Thoughts that you would be better off dead a lot more than usual.	○	○	○	○

If you said that you've experienced any of the problems in this questionnaire, describe how difficult these problems have made it for you to do your work, take care of things at home, or get along with other people.

- ○ Not difficult at all
- ○ Somewhat difficult
- ○ Very difficult
- ○ Extremely difficult
- ○ I haven't experienced any of the problems in this questionnaire

Prodromal Questionnaire Brief Version (PQB)

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.

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

- ○ Yes
- ○ No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- ○ Strongly disagree
- ○ Disagree
- ○ Neutral
- ○ Agree
- ○ Strongly agree

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

- Yes
- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

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

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

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

- Yes
- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

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

- Yes
- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

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

- Yes
- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- ○ Strongly disagree
- ○ Disagree
- ○ Neutral
- ○ Agree
- ○ Strongly agree

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

- ○ Yes
- ○ No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- ○ Strongly disagree
- ○ Disagree
- ○ Neutral
- ○ Agree
- ○ Strongly agree

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

- ○ Yes

- ○ No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- ○ Strongly disagree
- ○ Disagree
- ○ Neutral
- ○ Agree
- ○ Strongly agree

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

- ○ Yes
- ○ No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- ○ Strongly disagree
- ○ Disagree
- ○ Neutral
- ○ Agree
- ○ Strongly agree

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

- Yes
- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

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

- Yes
- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

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

- Yes
- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

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

- Yes
- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

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

- Yes
- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- ○ Strongly disagree
- ○ Disagree
- ○ Neutral
- ○ Agree
- ○ Strongly agree

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

- ○ Yes
- ○ No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- ○ Strongly disagree
- ○ Disagree
- ○ Neutral
- ○ Agree
- ○ Strongly agree

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

- ○ Yes

- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

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

- Yes
- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

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

- Yes
- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

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

- Yes
- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

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

- Yes
- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

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

- Yes
- No

Regarding the previous question, when this happens, I feel frightened, concerned, or it causes problems for me.

- Strongly disagree
- Disagree
- Neutral
- Agree
- Strongly agree

Graded Chronic Pain Scale (GCPS)

Throughout our lives, most of us experience pain from time-to-time (e.g., such as minor headaches, sprains, and toothaches). Have you experienced pain other than these time-to-time pains? If so, the following questions pertain to that pain.

How would you rate your pain on a 0-10 scale at the present time, that is right now, where 0 is "no pain" and 10 is "pain as bad as can be?"

0 1 2 3 4 5 6 7 8 9 10

Use the slider to provide your answer

In the past six months, how intense was your worst pain, rated on a 0-10 scale, where 0 is "no pain" and 10 is "pain as bad as can be?"

0 1 2 3 4 5 6 7 8 9 10

Use the slider to provide your answer

In the past six months, on the average, how intense was your pain rated on a 0-10 scale, where 0 is "no pain" and 10 is "pain as bad as can be?" (That is, what was your usual pain at times when you were experiencing pain?)

0 1 2 3 4 5 6 7 8 9 10

0 1 2 3 4 5 6 7 8 9 10

Use the slider to provide your answer

In the past six months, how much has pain interfered with your daily activities rated on a 0-10 scale, where 0 is "no interference" and 10 is "unable to carry out daily activities?"

0 1 2 3 4 5 6 7 8 9 10

Use the slider to provide your answer

In the past six months, how much has pain changed your ability to take part in recreational, social and family activities rated on a 0-10 scale, where 0 is “no change” and 10 is “extreme change?”

0 1 2 3 4 5 6 7 8 9 10

Use the slider to provide your answer

In the past six months, how much has pain changed your ability to do housework rated on a 0-10 scale, where 0 is “no change” and 10 is “extreme change?”

0 1 2 3 4 5 6 7 8 9 10

Use the slider to provide your answer

About how many days in the last six months have you been kept from your usual activities (work, school or housework) because of pain?

Neuropathic Pain Scale (NPS)

Throughout our lives, most of us experience pain from time-to-time (e.g., such as minor headaches, sprains, and toothaches). Have you experienced pain other than these time-to-time pains? If so, the following questions pertain to that pain.

Please tell us how intense your pain feels. Using the slider below, please choose the number that best describes the intensity of your pain.

0 1 2 3 4 5 6 7 8 9 10

Use the slider to provide your answer

Tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing," or "like jolts."

0 1 2 3 4 5 6 7 8 9 10

Use the slider to provide your answer

Please tell us how hot your pain feels. Words used to describe very hot pain include "burning" and "on fire."

0 1 2 3 4 5 6 7 8 9 10

Use the slider to provide your answer

Please tell us how dull your pain feels. Words used to describe very dull pain include "like a dull toothache," "dull pain," "aching," and "like a bruise."

0 1 2 3 4 5 6 7 8 9 10

Use the slider to provide your answer

Please tell us how cold your pain feels. Words used to describe very cold pain include "like ice" and "freezing."

0 1 2 3 4 5 6 7 8 9 10

Like a great deal

Fagerstrom Test for Nicotine Dependence (FND)

The following questions relate smoking cigarettes. For each question, enter the answer choice which best describes your response. Note, we're referring to tobacco cigarettes not referring to cannabis cigarettes (aka "joints").

Do you smoke cigarettes?

- Yes
- No

How soon after you wake up do you smoke your first cigarette?

- Within 5 minutes
- Between 5 minutes and 30 minutes
- Between 30 minutes and 60 minutes
- After 60 minutes
- I don't smoke regularly (I only smoke socially, I only smoke when I'm drinking)

Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in the cinema)?

- Yes
- No
- I don't smoke regularly (I only smoke socially, I only smoke when I'm drinking)

Which cigarette would you hate most to give up?

- The first in the morning

- Any other cigarette
- I don't smoke regularly (I only smoke socially, I only smoke when I'm drinking)

How many cigarettes per day do you smoke?

- 10 or less
- Between 11 and 20
- Between 20 and 30
- More than 30
- I don't smoke regularly (I only smoke socially, I only smoke when I'm drinking)

Do you smoke more frequently during the first hours after waking than during the rest of the day?

- Yes
- No
- I don't smoke regularly (I only smoke socially, I only smoke when I'm drinking)

Do you smoke when you are so ill that you are in bed most of the day?

- Yes
- No
- I don't smoke regularly (I only smoke socially, I only smoke when I'm drinking)

Rutgers Alcohol Problem Index (RAPI)

The following questions relate to alcohol. For each question, as yourself the following: how many times did the following things happen while you were drinking alcohol or because of your alcohol use during the last 3 years?

Got into fights, acted bad, or did mean things.

- Never
- 1-2 times
- 3-5 times
- 6-10 times
- More than 10 times

Went to work or school high or drunk.

- Never
- 1-2 times
- 3-5 times
- 6-10 times
- More than 10 times

Caused shame or embarrassment to someone.

- Never
- 1-2 times
- 3-5 times
- 6-10 times
- More than 10 times

Neglected your responsibilities.

- Never
- 1-2 times
- 3-5 times
- 6-10 times
- More than 10 times

Relatives avoided you.

- Never
- 1-2 times
- 3-5 times
- 6-10 times
- More than 10 times

Felt that you needed more alcohol than you used to use in order to get the same effect.

- ○ Never
- ○ 1-2 times
- ○ 3-5 times
- ○ 6-10 times
- ○ More than 10 times

Tried to control your drinking by trying to drink only at certain times of day or certain places.

- ○ Never
- ○ 1-2 times
- ○ 3-5 times
- ○ 6-10 times
- ○ More than 10 times

Had withdrawal symptoms, that is, felt sick because you stopped or cut down on drinking.

- ○ Never
- ○ 1-2 times
- ○ 3-5 times
- ○ 6-10 times
- ○ More than 10 times

Noticed a change in your personality.

- Never
- 1-2 times
- 3-5 times
- 6-10 times
- More than 10 times

Felt that you had a problem with school.

- Never
- 1-2 times
- 3-5 times
- 6-10 times
- More than 10 times

Tried to cut down on drinking.

- Never
- 1-2 times
- 3-5 times
- 6-10 times
- More than 10 times

Suddenly found yourself in a place that you could not remember getting to.

- Never
- 1-2 times
- 3-5 times
- 6-10 times
- More than 10 times

Passed out or fainted suddenly.

- Never
- 1-2 times
- 3-5 times
- 6-10 times
- More than 10 times

Had a fight, argument, or bad feelings with a friend.

- Never
- 1-2 times
- 3-5 times
- 6-10 times
- More than 10 times

Kept drinking when you promised yourself not to.

- Never
- 1-2 times
- 3-5 times
- 6-10 times
- More than 10 times

Felt you were going crazy.

- Never
- 1-2 times
- 3-5 times
- 6-10 times
- More than 10 times

Felt physically or physiologically dependent on alcohol.

- Never
- 1-2 times
- 3-5 times
- 6-10 times
- More than 10 times

Was told by a friend or neighbor to stop or cut down drinking.

- ○ Never
- ○ 1-2 times
- ○ 3-5 times
- ○ 6-10 times
- ○ More than 10 times

Marijuana Smoking Histories Questionnaire (MSHQ)

The following questions relate to marijuana/cannabis. For each question, enter the answer choice which best describes your response.

Do you currently smoke marijuana, or have your ever smoked marijuana?

- ○ Yes
- ○ No

Please move the slider to the space that best describes your marijuana use in the last 30 days, where 0 = "I have smoked

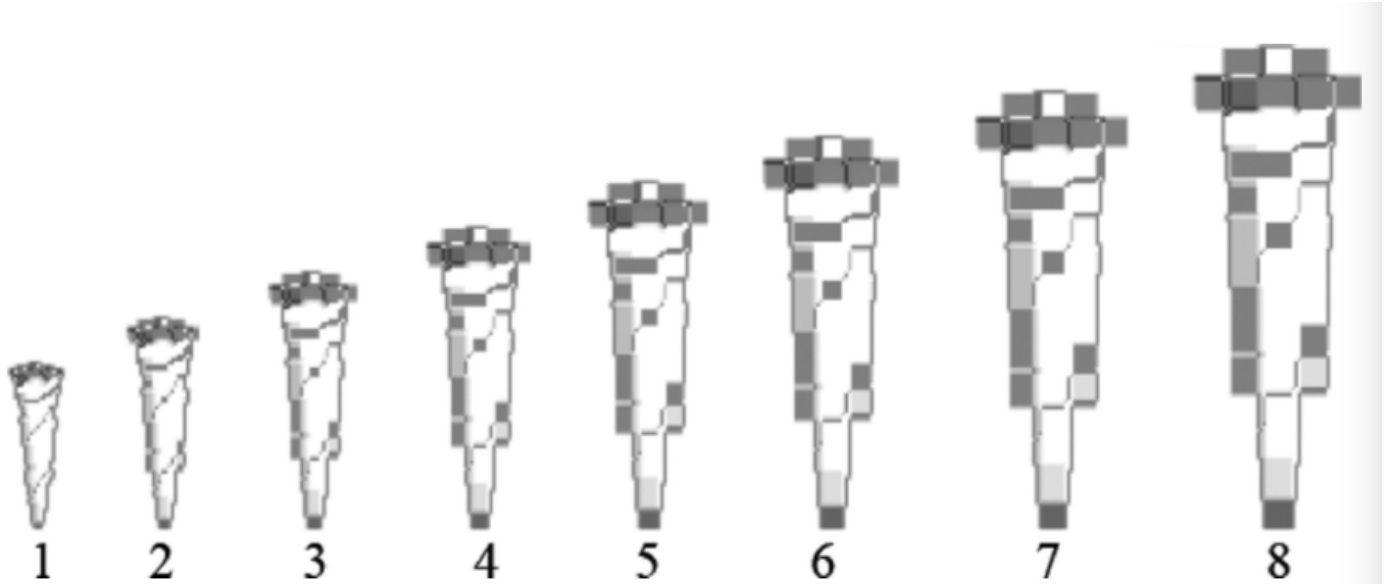
marijuana 0 times in the last 30 days," and 30 = "I have smoked marijuana 30, or more, times in the last 30 days."

0 4 8 11 15 19 23 26 30

Use the slider to provide your answer

Regarding the previous question, have your marijuana-use patterns been consistent over the last six months?

- Yes, my marijuana-use patterns have been mostly consistent for the last six months.
- No, I was consuming much MORE marijuana six months ago.
- No, I was consuming much LESS marijuana six months ago.
- No, I wasn't consuming marijuana AT ALL six months ago.



Please move the slider to the space that best describes how much marijuana you smoke per occasion.

0 1 2 2 3 4 5 6 6 7 8

Use the slider to provide your answer

What is the typical means by which you consume marijuana?

- Joint
- Bowl
- Bong
- One-hitter
- Ingestion

In which of the following situations you typically smoke marijuana?

- Alone
- With two or three people
- With more than three people

How old were you when you first smoked marijuana?

0 3 6 9 12 15 18 21 24 27 30

Use the slider to provide your answer

How old were you when you started regular daily marijuana smoking?

0 3 6 9 12 15 18 21 24 27 30

Use the slider to provide your answer

For how many years, altogether, have you been a regular daily marijuana smoker?

0 3 6 9 12 15 18 21 24 27 30

Use the slider to provide your answer

Think about your smoking during the last week. How many times were you smoking, on average, each day? For example, "I smoked _ _ _ _ _ times each day."

0 1 2 2 3 4 5 6 6 7 8

Use the slider to provide your answer

When were you smoking the heaviest? Please answer in years. For example, "I was smoking heaviest about _ _ _ _ _ years ago."

0 3 6 9 12 15 18 21 24 27 30

Use the slider to provide your answer

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

Day

Hours

Have you in the past had a disease or illness you believe was caused or aggravated by your smoking marijuana?

- Yes
- No

Do you have any symptoms now that you believe are caused by your smoking marijuana?

- Yes
- No

Do you have a disease or illness now that you believe is caused by, or aggravated by, your smoking marijuana?

- Yes
- No

Marijuana Motives Measure (MMM)

The following questions relate to reasons why people smoke marijuana/cannabis. For each question, enter the answer choice which best describes how often you've used marijuana/cannabis for that given reason.

To forget my worries.

- Never
- Almost never
- About half of the time
- Almost always
- Always

Because my friends pressure me to use marijuana/cannabis.

- Never
- Almost never
- About half of the time
- Almost always
- Always

Because marijuana/cannabis helps me enjoy a party.

- Never
- Almost never
- About half of the time
- Almost always
- Always

Because marijuana/cannabis helps me when I feel depressed or nervous.

- Never
- Almost never
- About half of the time
- Almost always
- Always

To be sociable.

- Never
- Almost never
- About half of the time
- Almost always
- Always

To cheer me up when I am in a bad mood.

- Never
- Almost never
- About half of the time
- Almost always
- Always

Because I like the feeling.

- Never
- Almost never
- About half of the time
- Almost always
- Always

So that others won't kid me about not using marijuana/cannabis.

- Never
- Almost never
- About half of the time
- Almost always
- Always

Because it's exciting.

- Never
- Almost never
- About half of the time
- Almost always
- Always

To get high.

- Never
- Almost never
- About half of the time
- Almost always
- Always

Because it makes social gatherings more fun.

- Never
- Almost never
- About half of the time
- Almost always
- Always

To fit in with the group I like.

- Never
- Almost never
- About half of the time
- Almost always
- Always

Because it gives me a pleasant feeling.

- Never
- Almost never
- About half of the time
- Almost always
- Always

Because it improves parties/celebrations.

- Never
- Almost never
- About half of the time
- Almost always
- Always

Because I feel more self-confident/sure of myself.

- Never
- Almost never
- About half of the time
- Almost always
- Always

To celebrate a special occasion with friends.

- Never
- Almost never
- About half of the time
- Almost always
- Always

To forget about my problems.

- Never
- Almost never
- About half of the time
- Almost always
- Always

So I won't feel left out.

- Never
- Almost never
- About half of the time
- Almost always
- Always

To know myself better.

- Never
- Almost never
- About half of the time
- Almost always
- Always

Because it helps me be more creative/original.

- Never
- Almost never
- About half of the time
- Almost always
- Always

To understand things differently.

- Never
- Almost never
- About half of the time
- Almost always
- Always

To expand my awareness.

- Never
- Almost never
- About half of the time
- Almost always
- Always

To be more open to experiences.

- Never
- Almost never
- About half of the time
- Almost always
- Always

Because it treats my symptoms.

- Never
- Almost never
- About half of the time
- Almost always
- Always

Severity of Dependence Scale (SDS) - Cannabis

The following questions relate to marijuana/cannabis. For each question, enter the answer choice which best describes your marijuana/cannabis use over the last 12 months.

Have you consumed marijuana/cannabis more than three times in the last 12 months?

- Yes
- No

Did you ever think your use of marijuana/cannabis was out of control?

- Never or almost never
- Sometimes
- Often
- Always

Did the prospect of missing out on using marijuana/cannabis make you very anxious or worried?

- Never or almost never
- Sometimes
- Often
- Always

How much did you worry about your use of marijuana/cannabis?

- ○ Not at all
- ○ A little
- ○ Often
- ○ Always or almost always

Did you wish you could stop using marijuana/cannabis ?

- ○ Never or almost never
- ○ Sometimes
- ○ Often
- ○ Always

How difficult would you find it to stop or go without marijuana/cannabis?

- ○ Not difficult at all
- ○ Quite difficult
- ○ Very difficult
- ○ Impossible

Severity of Dependence Scale (SDS) - Opioids

The following questions relate to opioids, including prescription and non-prescription treatments (e.g., heroin).

For each question, enter the answer choice which best describes your opioids sue over the last 12 months.

Have you consumed opioids, including prescription and non-prescription treatments (e.g., heroin) more than three times in the last 12 months?

- Yes
- No

Did you ever think your use of opioids was out of control?

- Never or almost never
- Sometimes
- Often
- Always

Did the prospect of missing out on opioids make you very anxious or worried?

- Never or almost never
- Sometimes
- Often
- Always

How much did you worry about your use of opioids?

- Not at all
- A little
- Often
- Always or almost always

Did you wish you could stop?

- Never or almost never
- Sometimes
- Often
- Always

How difficult would you find it to stop or go without opioids?

- Not difficult at all
- Quite difficult
- Very difficult
- Impossible

Severity of Dependence Scale (SDS) - Cocaine

The following questions relate to cocaine. For each question, enter the answer choice which best describes your cocaine use over the last 12 months.

Have you consumed cocaine more than three times in the last 12 months?

- Yes
- No

Did you ever think your use of cocaine was out of control?

- Never or almost never
- Sometimes
- Often
- Always

Did the prospect of missing out on cocaine make you very anxious or worried?

- Never or almost never
- Sometimes
- Often

- Always

How much did you worry about your use of cocaine?

- Not at all
- A little
- Often
- Always or almost always

Did you wish you could stop using cocaine?

- Never or almost never
- Sometimes
- Often
- Always

How difficult would you find it to stop or go without cocaine?

- Not difficult at all
- Quite difficult
- Very difficult
- Impossible

Severity of Dependence Scale (SDS) - Amphetamines

The following questions relate to amphetamines. For each question, enter the answer choice which best describes your amphetamines use over the last 12 months.

Have you consumed amphetamines more than three times in the last 12 months?

- Yes
- No

Did you ever think your use of amphetamines was out of control?

- Never or almost never
- Sometimes
- Often
- Always

Did the prospect of missing out on amphetamines make you very anxious or worried?

- Never or almost never

- Sometimes
- Often
- Always

How much did you worry about your use of amphetamines?

- Not at all
- A little
- Often
- Always or almost always

Did you wish you could stop using amphetamines?

- Never or almost never
- Sometimes
- Often
- Always

How difficult would you find it to stop or go without amphetamines?

- Not difficult at all
- Quite difficult
- Very difficult
- Impossible

Block - Severity of Dependence Scale (SDS) - Psychomotor Stimulant

The following questions relate to psychomotor stimulants commonly used to treat ADHD (e.g., Adderall, Vyvanse). For each question, enter the answer choice which best describes your psychomotor stimulant use over the last 12 months. Note, this includes prescription and non-prescription (e.g., recreational) use.

Have you consumed psychomotor stimulants more than three times in the last 12 months?

- ○ Yes
- ○ No

Did you ever think your use of psychomotor stimulants was out of control?

- ○ Never or almost never
- ○ Sometimes
- ○ Often

- Always

Did the prospect of missing out on psychomotor stimulants make you very anxious or worried?

- Never or almost never
- Sometimes
- Often
- Always

How much did you worry about your use of psychomotor stimulants?

- Not at all
- A little
- Often
- Always or almost always

Did you wish you could stop using psychomotor stimulants?

- Never or almost never
- Sometimes
- Often
- Always

How difficult would you find it to stop or go without psychomotor stimulants?

- ○ Not difficult at all
- ○ Quite difficult
- ○ Very difficult
- ○ Impossible

Thanks

Thanks for completing the Neuroimaging and Cannabis Project. These are some post-scan questions to help us better understand your data. Please answer them to the best of your abilities.

To begin, please provide your participant number.

Cannabis Questions

Remember that your privacy is protected by our confidentiality certificate. For those participants who endorsed cannabis use during Phase 1, how long has it been since your last use episode? Please respond in hours. If you did not endorse cannabis use during Phase 1, respond "NA."

Remember that your privacy is protected by our confidentiality certificate. Using the slider below, please indicate how confident you are that cannabis reduces pain.

"I strongly believe that cannabis DOES NOT reduce pain." "I strongly believe that cannabis DOES reduce pain."

0 10 20 30 40 50 60 70 80 90 100

Click to write Choice 1

Remember that your privacy is protected by our confidentiality certificate. In the space below, please indicate how long it's been (in hours) since you've used cannabis. For example, if it's been 1 day, enter 24 hours, if it's been 2 days, enter 48 hours, etc.

Post-Scan Survey

Women: please enter the date of your last menstrual period. If you do not know the exact date, please provide your best estimate. Use the format mm/dd/yy.

☐ mm

☐ dd

☐ yy

During the short tasks that involved some pain, please describe in a few words any strategies used to deal with the pain.

We are interested in the thoughts and feelings that you experienced during the scans, particularly when you weren't engaged in a task (e.g., structural scans, pain-task scans). Please indicate the extent to which each of the following statements characterized your thoughts and feelings during the scans.

	Strongly Disagree	Disagree	Undecided	Agree	Strongly Agree
I thought about my feelings.	○	○	○	○	○
I felt restless.	○	○	○	○	○
I felt anxious.	○	○	○	○	○
I felt tired.	○	○	○	○	○
I felt sleepy.	○	○	○	○	○
I felt comfortable.	○	○	○	○	○
I felt relaxed.	○	○	○	○	○

	Strongly Disagree	Disagree	Undecided	Agree	Strongly Agree
I felt happy.	○	○	○	○	○
I enjoyed the session.	○	○	○	○	○

St. Mary's Sleep Questionnaire

This questionnaire refers to your sleep over the past 24 hours. Please try to answer each question to the best of your abilities.

Last night, at what time did you settle down?

☐ hours

☐ minutes

Last night, at what time did you finally fall asleep?

☐ hours

☐ minutes

This morning, at what time did you wake up?

☐ hours

☐ minutes

This morning, at what time did finally get out of bed?

☐ hours

☐ minutes

Please use the slider to describe how light/deep your sleep was , where 0 = "very light" and 10 = "very deep."

0 1 2 3 4 5 6 7 8 9 10

Please use the slider to describe how badly/well you slept , where 0 = "very badly" and 10 = "very well."

0 1 2 3 4 5 6 7 8 9 10

Please use the slider to describe how unsatisfied/satisfied you were with your sleep , where 0 = "very unsatisfied" and 10 = "very satisfied."

0 1 2 3 4 5 6 7 8 9 10

Please use the slider below to indicate how many times you woke up, where 0 = "zero times" and 10 = "ten times or more."

0 1 2 3 4 5 6 7 8 9 10

SIEMENS MAGNETOM Investigational_Device_7T syngo MR B17

\\USER\Yanes\F31\fMRS/fMRI_PAIN\localizer_250V

TA: 0:14 PAT: 2 Voxel size: 1.2×1.1×3.0 mm Rel. SNR: 1.00 SIEMENS: gre

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	5
Dist. factor	20 %
Position	Isocenter
Orientation	Sagittal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Slice group 2	
Slices	5
Dist. factor	20 %
Position	Isocenter
Orientation	Coronal
Phase enc. dir.	R >> L
Rotation	0.00 deg
Slice group 3	
Slices	5
Dist. factor	20 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	280 mm
FoV phase	100.0 %
Slice thickness	3.0 mm
TR	8.6 ms
TE	3.00 ms
Averages	1
Concatenations	15
Filter	None
Coil elements	A32

Contrast

TD	0 ms
MTC	Off
Magn. preparation	None
Flip angle	20 deg
Fat suppr.	None
Water suppr.	None
SWI	Off
Averaging mode	Short term
Reconstruction	Magnitude
Measurements	1
Multiple series	Each measurement

Resolution

Base resolution	256
Phase resolution	90 %
Phase partial Fourier	6/8
Interpolation	On
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	24
Reference scan mode	Integrated
Image Filter	Off
Distortion Corr.	Off
Prescan Normalize	Off
Normalize	Off
B1 filter	Off
Raw filter	Off
Elliptical filter	Off

Geometry

Multi-slice mode	Sequential
Series	Interleaved
Saturation mode	Standard
Special sat.	None
Table position	H
Table position	0 mm
Inline Composing	Off
Tim CT mode	Off

System

V32	Off
A32	On
Positioning mode	REF
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
AutoAlign	---
Auto Coil Select	Off
Shim mode	Tune up
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
! Ref. amplitude 1H	250.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	350 mm
A >> P	263 mm
F >> H	350 mm

Physio

1st Signal/Mode	None
Segments	1
Tagging	None
Dark blood	Off
Resp. control	Off

Inline

Subtract	Off

Liver registration	Off
Std-Dev-Sag	Off
Std-Dev-Cor	Off
Std-Dev-Tra	Off
Std-Dev-Time	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On
Wash - In	Off
Wash - Out	Off
TTP	Off
PEI	Off
MIP - time	Off
MapIt	None
Contrasts	1

Sequence

Introduction	On
Dimension	2D
Phase stabilisation	Off
Asymmetric echo	Allowed
Bandwidth	320 Hz/Px
Flow comp.	No
RF pulse type	Normal
Gradient mode	Normal
Excitation	Slice-sel.
RF spoiling	On

\\USER\Yanes\F31\fMRS/fMRI_PAIN\b1map_250V

TA: 0:57 Voxel size: 3.9×3.9×5.0 mm Rel. SNR: 1.00 USER: b1map_658

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	1
Dist. factor	150 %
Position	L0.0 A8.8 H18.9
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
FoV read	250 mm
FoV phase	100.0 %
Slice thickness	5 mm
TR	800 ms
TE 1	14 ms
TE 2	14 ms
Averages	1
Filter	None
Coil elements	A32

Contrast

Flip angle 1	90 deg
Flip angle 2	120 deg
Flip angle 3	60 deg
Flip angle 4	135 deg
Flip angle 5	45 deg
Measurements	1

Resolution

Base resolution	64
Phase resolution	100 %
Raw filter	Off

Geometry

Series	Interleaved
Navigator 1	
Position	L4.1 A10.4 H18.9
Orientation	Transversal
Rotation	0.00 deg
Base size phase	50 mm
Base size read	50 mm
Thickness	50 mm
Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	REF
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
AutoAlign	---
Auto Coil Select	Default
Shim mode	Tune up
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
! Ref. amplitude 1H	250.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	350 mm
A >> P	263 mm
F >> H	350 mm

Composing

Sequence

Contrasts	2
Bandwidth	260.416667 Hz/Px
T1 Compensation	Mean T1
Mean T1	500.0 ms
Angles	1
Amplitude Weighting	Linear
Scale Bar	Enabled
Raw Data	Disabled

\\USER\Yanes\F31\fMRS/fMRI_PAIN\AAHScout

TA: 2:50 PAT: Off Voxel size: 1.6×1.6×1.6 mm Rel. SNR: 1.00 SIEMENS: AALScout

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	On
Load images to graphic segments	On
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slab group 1	
Slabs	1
Dist. factor	20 %
Position	L0.0 A16.9 F22.9
Orientation	Sagittal
Phase enc. dir.	A >> P
Rotation	0 deg
AutoAlign	Head
Phase oversampling	0 %
Slice oversampling	0.0 %
Slices per slab	128
FoV read	260 mm
FoV phase	100.0 %
Slice thickness	1.6 mm
TR	20.00 ms
TE	5.00 ms
Averages	1
Concatenations	1
Filter	None
Coil elements	A32

Contrast

Flip angle	25.0 deg
Averaging mode	Short term
Reconstruction	Magnitude
Measurements	1

Resolution

Base resolution	160
Phase resolution	100 %
Slice resolution	69 %
Phase partial Fourier	6/8
Slice partial Fourier	6/8
PAT mode	None
Image Filter	Off
Distortion Corr.	Off
Prescan Normalize	Off
Normalize	Off
B1 filter	Off
Raw filter	Off
Elliptical filter	Off

Geometry

Multi-slice mode	Sequential
Series	Ascending
Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	REF
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Off
Shim mode	Tune up
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	350 mm
A >> P	263 mm
F >> H	350 mm

Inline

Time to center	64.7 s
MapIt	None
Contrasts	1

Sequence

Introduction	On
Dimension	3D
Asymmetric echo	Weak
Bandwidth	550 Hz/Px
RF pulse type	Fast
Gradient mode	Normal
Excitation	Non-sel.
RF spoiling	On

\\USER\Yanes\F31\fMRS/fMRI_PAIN\t1_mprage_1iso_sag_p2_AA

TA: 5:25 PAT: 2 Voxel size: 1.0×1.0×1.0 mm Rel. SNR: 1.00 SIEMENS: tfl

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slab group 1	
Slabs	1
Dist. factor	50 %
Position	L0.0 P3.0 H1.4
Orientation	Sagittal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
Slice oversampling	0.0 %
Slices per slab	192
FoV read	256 mm
FoV phase	100.0 %
Slice thickness	1.00 mm
TR	2200 ms
TE	2.82 ms
Averages	1
Concatenations	1
Filter	None
Coil elements	A32

Contrast

Magn. preparation	Non-sel. IR
TI	1050 ms
Flip angle	7 deg
Fat suppr.	Water excit. fast
Water suppr.	None
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	1
Multiple series	Each measurement

Resolution

Base resolution	256
Phase resolution	100 %
Slice resolution	100 %
Phase partial Fourier	Off
Slice partial Fourier	Off
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	40
Accel. factor 3D	1
Reference scan mode	Integrated
Image Filter	Off
Distortion Corr.	Off
Prescan Normalize	Off
Normalize	Off
B1 filter	Off
Raw filter	Off
Elliptical filter	Off

Geometry

Multi-slice mode	Single shot
Series	Ascending
Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	FIX
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
AutoAlign	Head > Basis
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	On
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	L0.0 P3.0 H1.4
Orientation	Sagittal
Rotation	0.00 deg
F >> H	256 mm
A >> P	256 mm
R >> L	192 mm

Physio

1st Signal/Mode	None
Dark blood	Off
Resp. control	Off

Inline

Subtract	Off
Std-Dev-Sag	Off
Std-Dev-Cor	Off
Std-Dev-Tra	Off
Std-Dev-Time	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Save original images	On

Sequence

Introduction	On
Dimension	3D
Elliptical scanning	Off
Asymmetric echo	Off
Bandwidth	240 Hz/Px
Flow comp.	No

Echo spacing	6.9 ms
RF pulse type	Normal
Gradient mode	Fast
Excitation	Non-sel.
RF spoiling	On

\\USER\Yanes\F31\fMRS/fMRI_PAIN\fastestmap_577

TA: 0:12 Vol: 40 ×25 ×15 mm Rel. SNR: 1.00 USER: fastestmap_577

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Position	R1.0 A14.8 H54.3
Orientation	T > C10.2
Rotation	-0.01 deg
Vol A >> P	40 mm
Vol R >> L	25 mm
Vol F >> H	15 mm
TR	4154 ms
TE	36.80 ms
Averages	1
Filter	None
Coil elements	A32

Contrast

Tau	2.00 ms
Excite flip angle	90 deg
Refocus flip angle	180 deg
Measurements	1

Resolution

Vector size	256

Geometry

Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	FIX
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
AutoAlign	Head > Basis
Auto Coil Select	Default
Shim mode	Tune up
Adj. water suppr.	Off
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	R1.0 A14.8 H54.3
Orientation	T > C10.2
Rotation	89.99 deg
A >> P	40 mm
R >> L	25 mm
F >> H	15 mm

Physio

1st Signal/Mode	None

Composing

Sequence

Phase cycling	None
Bandwidth	294120 Hz
Acquisition duration	0 ms
Type of fit	Linear 3-bar
Vol fit factor	150 %
Refocus pulses	Normal
Excitation pulse duration	5760 ms
Refocus pulse duration	5120 ms
Bar FoV	384 mm
Bar thickness	5.0 mm
Multi-echo acquisition	On
Number of echoes	10
Inversion pulse	Off

\\USER\Yanes\F31\fMRS/fMRI_PAIN\svs_st_vapor_643_LW

TA: 0:20 Vol: 40 ×25 ×15 mm Rel. SNR: 1.00 USER: svs_st_vapor_643

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Position	R1.0 A14.8 H54.3
Orientation	T > C10.2
Rotation	-0.01 deg
Vol A >> P	40 mm
Vol R >> L	25 mm
Vol F >> H	15 mm
TR	10000 ms
TE	5.00 ms
Averages	1
Filter	None
Coil elements	A32

Contrast

TM	45.00 ms
Flip angle	90 deg
VAPOR	None
VAPOR suppr.	Water suppr.
Water s. BW	135 Hz
Water s. delta pos.	0.00 ppm
Measurements	1

Resolution

Vector size	2048

Geometry

Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	FIX
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
AutoAlign	Head > Basis
Auto Coil Select	Default
Shim mode	Advanced
Adj. water suppr.	Off
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto

Adjust volume

Position	R1.0 A14.8 H54.3
Orientation	T > C10.2
Rotation	89.99 deg
A >> P	40 mm
R >> L	25 mm
F >> H	15 mm

Physio

1st Signal/Mode	None

Composing

Sequence

Preparation scans	1
Delta frequency	0.0 ppm
Phase cycling	Auto
Bandwidth	4000 Hz
Acquisition duration	512 ms
Remove oversampling	On
TX/RX Nucleus	1H
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
RF pulse duration	3200 us
Spoiler max. amplitude	20.0 mT/m
Spoiler duration	500 us
Acq. window shift	200 us
Min. settling delay	300 us
Gradient ramp time	200 us
VAPOR flip angle	60 deg
VAPOR delay 8	28 ms
VAPOR delay 7	76 ms
VAPOR delay 6	68 ms
VAPOR delay 5	102 ms
VAPOR delay 4	105 ms
VAPOR delay 3	122 ms
VAPOR delay 2	100 ms
VAPOR delay 1	150 ms
Enable OVS	On
Resolve averages	Off
Inversion pulse	Off
Symmetric RF pulses	Off
Invert SS grad. pol.	Off
Shift RO frequency	Off
Debug loop type	None

\\USER\Yanes\F31\fMRS/fMRI_PAIN\svs_st_vapor_643_FA_CAL

TA: 0:16 Vol: 40 ×25 ×15 mm Rel. SNR: 1.00 USER: svs_st_vapor_643

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Position	R1.0 A14.8 H54.3
Orientation	T > C10.2
Rotation	-0.01 deg
Vol A >> P	40 mm
Vol R >> L	25 mm
Vol F >> H	15 mm
TR	8000 ms
TE	5.00 ms
Averages	1
Filter	None
Coil elements	A32

Contrast

TM	45.00 ms
Flip angle	70 deg
VAPOR	None
VAPOR suppr.	Water suppr.
Water s. BW	135 Hz
Water s. delta pos.	0.00 ppm
Measurements	10

Resolution

Vector size	2048

Geometry

Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	FIX
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
AutoAlign	Head > Basis
Auto Coil Select	Default
Shim mode	Advanced
Adj. water suppr.	Off
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto

Adjust volume

Position	R1.0 A14.8 H54.3
Orientation	T > C10.2
Rotation	89.99 deg
A >> P	40 mm
R >> L	25 mm
F >> H	15 mm

Physio

1st Signal/Mode	None

Composing

Sequence

Preparation scans	1
Delta frequency	-2.0 ppm
Phase cycling	Auto
Bandwidth	4000 Hz
Acquisition duration	512 ms
Remove oversampling	On
TX/RX Nucleus	1H
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
RF pulse duration	3200 us
Spoiler max. amplitude	20.0 mT/m
Spoiler duration	500 us
Acq. window shift	200 us
Min. settling delay	300 us
Gradient ramp time	200 us
VAPOR flip angle	60 deg
VAPOR delay 8	28 ms
VAPOR delay 7	76 ms
VAPOR delay 6	68 ms
VAPOR delay 5	102 ms
VAPOR delay 4	105 ms
VAPOR delay 3	122 ms
VAPOR delay 2	100 ms
VAPOR delay 1	150 ms
Enable OVS	On
Resolve averages	Off
Inversion pulse	Off
Symmetric RF pulses	Off
Invert SS grad. pol.	Off
Shift RO frequency	Off
Debug loop type	Flip angle
Flip angle inc.	10 deg
Measurements	10 ms

\\USER\Yanes\F31\fMRS/fMRI_PAIN\svs_st_vapor_643_CHECK_WS

TA: 0:40 Vol: 40 ×25 ×15 mm Rel. SNR: 1.00 USER: svs_st_vapor_643

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Position	R1.0 A14.8 H54.3
Orientation	T > C10.2
Rotation	-0.01 deg
Vol A >> P	40 mm
Vol R >> L	25 mm
Vol F >> H	15 mm
TR	10000 ms
TE	5.00 ms
Averages	2
Filter	None
Coil elements	A32

Contrast

TM	45.00 ms
Flip angle	90 deg
VAPOR	Enabled
VAPOR suppr.	Water suppr.
Water s. BW	135 Hz
Water s. delta pos.	0.00 ppm
Measurements	1

Resolution

Vector size	2048

Geometry

Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	FIX
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
AutoAlign	Head > Basis
Auto Coil Select	Default
Shim mode	Advanced
Adj. water suppr.	Off
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto

Adjust volume

Position	R1.0 A14.8 H54.3
Orientation	T > C10.2
Rotation	89.99 deg
A >> P	40 mm
R >> L	25 mm
F >> H	15 mm

Physio

1st Signal/Mode	None

Composing

Sequence

Preparation scans	2
Delta frequency	-2.0 ppm
Phase cycling	Auto
Bandwidth	4000 Hz
Acquisition duration	512 ms
Remove oversampling	On
TX/RX Nucleus	1H
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
RF pulse duration	3200 us
Spoiler max. amplitude	20.0 mT/m
Spoiler duration	500 us
Acq. window shift	200 us
Min. settling delay	300 us
Gradient ramp time	200 us
VAPOR flip angle	60 deg
VAPOR delay 8	28 ms
VAPOR delay 7	76 ms
OVS pulse duration	5120 us
OVS flip angle RO	90 deg
OVS flip angle PH	90 deg
OVS flip angle SL	90 deg
VAPOR delay 6	68 ms
VAPOR delay 5	102 ms
VAPOR delay 4	105 ms
VAPOR delay 3	122 ms
VAPOR delay 2	100 ms
VAPOR delay 1	150 ms
Enable OVS	On
Resolve averages	Off
Inversion pulse	Off
Symmetric RF pulses	Off
Invert SS grad. pol.	Off
Shift RO frequency	Off
Debug loop type	None

\\USER\Yanes\F31\fMRS/fMRI_PAIN\svs_st_vapor_643_WS_CAL

TA: 0:16 Vol: 40 ×25 ×15 mm Rel. SNR: 1.00 USER: svs_st_vapor_643

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Position	R1.0 A14.8 H54.3
Orientation	T > C10.2
Rotation	-0.01 deg
Vol A >> P	40 mm
Vol R >> L	25 mm
Vol F >> H	15 mm
TR	8000 ms
TE	5.00 ms
Averages	1
Filter	None
Coil elements	A32

Contrast

TM	45.00 ms
Flip angle	90 deg
VAPOR	Enabled
VAPOR suppr.	Water suppr.
Water s. BW	135 Hz
Water s. delta pos.	0.00 ppm
Measurements	10

Resolution

Vector size	2048

Geometry

Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	FIX
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
AutoAlign	Head > Basis
Auto Coil Select	Default
Shim mode	Advanced
Adj. water suppr.	Off
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto

Adjust volume

Position	R1.0 A14.8 H54.3
Orientation	T > C10.2
Rotation	89.99 deg
A >> P	40 mm
R >> L	25 mm
F >> H	15 mm

Physio

1st Signal/Mode	None

Composing

Sequence

Preparation scans	1
Delta frequency	-2.0 ppm
Phase cycling	Auto
Bandwidth	4000 Hz
Acquisition duration	512 ms
Remove oversampling	On
TX/RX Nucleus	1H
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
RF pulse duration	3200 us
Spoiler max. amplitude	20.0 mT/m
Spoiler duration	500 us
Acq. window shift	200 us
Min. settling delay	300 us
Gradient ramp time	200 us
VAPOR flip angle	45 deg
VAPOR delay 8	28 ms
VAPOR delay 7	76 ms
OVS pulse duration	5120 us
OVS flip angle RO	90 deg
OVS flip angle PH	90 deg
OVS flip angle SL	90 deg
VAPOR delay 6	68 ms
VAPOR delay 5	102 ms
VAPOR delay 4	105 ms
VAPOR delay 3	122 ms
VAPOR delay 2	100 ms
VAPOR delay 1	150 ms
Enable OVS	Off
Resolve averages	Off
Inversion pulse	Off
Symmetric RF pulses	Off
Invert SS grad. pol.	Off
Shift RO frequency	Off
Debug loop type	VAP FA
VAP FA inc.	5 deg
Measurements	10 ms

\\USER\Yanes\F31\fMRS/fMRI_PAIN\svs_st_vapor_643_50PAIN_26AVG

TA: 5:00 Vol: 40 ×25 ×15 mm Rel. SNR: 1.00 USER: svs_st_vapor_643

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Position	R1.0 P3.7 H56.7
Orientation	T > C-0.1
Rotation	-0.01 deg
Vol A >> P	40 mm
Vol R >> L	25 mm
Vol F >> H	15 mm
TR	10000 ms
TE	5.00 ms
Averages	26
Filter	None
Coil elements	A32

Contrast

TM	45.00 ms
Flip angle	90 deg
VAPOR	Enabled
VAPOR suppr.	Water suppr.
Water s. BW	135 Hz
Water s. delta pos.	0.00 ppm
Measurements	1

Resolution

Vector size	2048

Geometry

Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	FIX
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
AutoAlign	Head > Basis
Auto Coil Select	Default
Shim mode	Advanced
Adj. water suppr.	Off
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto

Adjust volume

Position	R1.0 P3.7 H56.7
Orientation	T > C-0.1
Rotation	89.99 deg
A >> P	40 mm
R >> L	25 mm
F >> H	15 mm

Physio

1st Signal/Mode	None

Composing

Sequence

Preparation scans	4
Delta frequency	-2.0 ppm
Phase cycling	Auto
Bandwidth	4000 Hz
Acquisition duration	512 ms
Remove oversampling	On
TX/RX Nucleus	1H
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
RF pulse duration	3200 us
Spoiler max. amplitude	20.0 mT/m
Spoiler duration	500 us
Acq. window shift	200 us
Min. settling delay	300 us
Gradient ramp time	200 us
VAPOR flip angle	60 deg
VAPOR delay 8	28 ms
VAPOR delay 7	76 ms
OVS pulse duration	5120 us
OVS flip angle RO	90 deg
OVS flip angle PH	90 deg
OVS flip angle SL	90 deg
VAPOR delay 6	68 ms
VAPOR delay 5	102 ms
VAPOR delay 4	105 ms
VAPOR delay 3	122 ms
VAPOR delay 2	100 ms
VAPOR delay 1	150 ms
Enable OVS	On
Resolve averages	On
Inversion pulse	Off
Symmetric RF pulses	Off
Invert SS grad. pol.	Off
Shift RO frequency	Off
Debug loop type	None

\\USER\Yanes\F31\fMRS/fMRI_PAIN\svs_st_vapor_643_BASELINE_26AVG

TA: 5:00 Vol: 40 ×25 ×15 mm Rel. SNR: 1.00 USER: svs_st_vapor_643

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Position	R1.0 P3.7 H56.7
Orientation	T > C-0.1
Rotation	-0.01 deg
Vol A >> P	40 mm
Vol R >> L	25 mm
Vol F >> H	15 mm
TR	10000 ms
TE	5.00 ms
Averages	26
Filter	None
Coil elements	A32

Contrast

TM	45.00 ms
Flip angle	90 deg
VAPOR	Enabled
VAPOR suppr.	Water suppr.
Water s. BW	135 Hz
Water s. delta pos.	0.00 ppm
Measurements	1

Resolution

Vector size	2048

Geometry

Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	FIX
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
AutoAlign	Head > Basis
Auto Coil Select	Default
Shim mode	Advanced
Adj. water suppr.	Off
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto

Adjust volume

Position	R1.0 P3.7 H56.7
Orientation	T > C-0.1
Rotation	89.99 deg
A >> P	40 mm
R >> L	25 mm
F >> H	15 mm

Physio

1st Signal/Mode	None

Composing

Sequence

Preparation scans	4
Delta frequency	-2.0 ppm
Phase cycling	Auto
Bandwidth	4000 Hz
Acquisition duration	512 ms
Remove oversampling	On
TX/RX Nucleus	1H
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
RF pulse duration	3200 us
Spoiler max. amplitude	20.0 mT/m
Spoiler duration	500 us
Acq. window shift	200 us
Min. settling delay	300 us
Gradient ramp time	200 us
VAPOR flip angle	60 deg
VAPOR delay 8	28 ms
VAPOR delay 7	76 ms
OVS pulse duration	5120 us
OVS flip angle RO	90 deg
OVS flip angle PH	90 deg
OVS flip angle SL	90 deg
VAPOR delay 6	68 ms
VAPOR delay 5	102 ms
VAPOR delay 4	105 ms
VAPOR delay 3	122 ms
VAPOR delay 2	100 ms
VAPOR delay 1	150 ms
Enable OVS	On
Resolve averages	On
Inversion pulse	Off
Symmetric RF pulses	Off
Invert SS grad. pol.	Off
Shift RO frequency	Off
Debug loop type	None

\\USER\Yanes\F31\fMRS/fMRI_PAIN\svs_st_vapor_643_BASELINE_RFOFF

TA: 1:00 Vol: 25 ×25 ×25 mm Rel. SNR: 1.00 USER: svs_st_vapor_643

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Position	Isocenter
Orientation	Coronal
Rotation	0.00 deg
Vol R >> L	25 mm
Vol F >> H	25 mm
Vol A >> P	25 mm
TR	10000 ms
TE	5.00 ms
Averages	4
Filter	None
Coil elements	A32

Contrast

TM	45.00 ms
Flip angle	90 deg
VAPOR	Only RF off
VAPOR suppr.	Water suppr.
Water s. BW	135 Hz
Water s. delta pos.	0.00 ppm
Measurements	1

Resolution

Vector size	2048

Geometry

Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	REF
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
AutoAlign	Head > Basis
Auto Coil Select	Default
Shim mode	Advanced
Adj. water suppr.	Off
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto

Adjust volume

Position	Isocenter
Orientation	Coronal
Rotation	0.00 deg
F >> H	25 mm
R >> L	25 mm
A >> P	25 mm

Physio

1st Signal/Mode	None

Composing

Sequence

Preparation scans	2
Delta frequency	0.0 ppm
Phase cycling	Auto
Bandwidth	4000 Hz
Acquisition duration	512 ms
Remove oversampling	On
TX/RX Nucleus	1H
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
RF pulse duration	3200 us
Spoiler max. amplitude	20.0 mT/m
Spoiler duration	500 us
Acq. window shift	200 us
Min. settling delay	300 us
Gradient ramp time	200 us
VAPOR flip angle	60 deg
VAPOR delay 8	28 ms
VAPOR delay 7	76 ms
OVS pulse duration	5120 us
OVS flip angle RO	90 deg
OVS flip angle PH	90 deg
OVS flip angle SL	90 deg
VAPOR delay 6	68 ms
VAPOR delay 5	102 ms
VAPOR delay 4	105 ms
VAPOR delay 3	122 ms
VAPOR delay 2	100 ms
VAPOR delay 1	150 ms
Enable OVS	Off
Resolve averages	Off
Inversion pulse	Off
Symmetric RF pulses	Off
Invert SS grad. pol.	Off
Shift RO frequency	Off
Debug loop type	None

\\USER\Yanes\F31\fMRS/fMRI_PAIN\svs_st_vapor_643_BASELINE_NONE

TA: 1:00 Vol: 25 ×25 ×25 mm Rel. SNR: 1.00 USER: svs_st_vapor_643

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Position	Isocenter
Orientation	Coronal
Rotation	0.00 deg
Vol R >> L	25 mm
Vol F >> H	25 mm
Vol A >> P	25 mm
TR	10000 ms
TE	5.00 ms
Averages	4
Filter	None
Coil elements	A32

Contrast

TM	45.00 ms
Flip angle	90 deg
VAPOR	None
VAPOR suppr.	Water suppr.
Water s. BW	135 Hz
Water s. delta pos.	0.00 ppm
Measurements	1

Resolution

Vector size	2048

Geometry

Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	REF
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
AutoAlign	Head > Basis
Auto Coil Select	Default
Shim mode	Advanced
Adj. water suppr.	Off
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto

Adjust volume

Position	Isocenter
Orientation	Coronal
Rotation	0.00 deg
F >> H	25 mm
R >> L	25 mm
A >> P	25 mm

Physio

1st Signal/Mode	None

Composing

Sequence

Preparation scans	2
Delta frequency	0.0 ppm
Phase cycling	Auto
Bandwidth	4000 Hz
Acquisition duration	512 ms
Remove oversampling	On
TX/RX Nucleus	1H
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
RF pulse duration	3200 us
Spoiler max. amplitude	20.0 mT/m
Spoiler duration	500 us
Acq. window shift	200 us
Min. settling delay	300 us
Gradient ramp time	200 us
VAPOR flip angle	60 deg
VAPOR delay 8	28 ms
VAPOR delay 7	76 ms
VAPOR delay 6	68 ms
VAPOR delay 5	102 ms
VAPOR delay 4	105 ms
VAPOR delay 3	122 ms
VAPOR delay 2	100 ms
VAPOR delay 1	150 ms
Enable OVS	Off
Resolve averages	Off
Inversion pulse	Off
Symmetric RF pulses	Off
Invert SS grad. pol.	Off
Shift RO frequency	Off
Debug loop type	None

\\USER\Yanes\F31\fMRS/fMRI_PAIN\svs_st_vapor_643_100PAIN_26AVG

TA: 5:00 Vol: 40 ×25 ×15 mm Rel. SNR: 1.00 USER: svs_st_vapor_643

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Position	R1.0 P3.7 H56.7
Orientation	T > C-0.1
Rotation	-0.01 deg
Vol A >> P	40 mm
Vol R >> L	25 mm
Vol F >> H	15 mm
TR	10000 ms
TE	5.00 ms
Averages	26
Filter	None
Coil elements	A32

Contrast

TM	45.00 ms
Flip angle	90 deg
VAPOR	Enabled
VAPOR suppr.	Water suppr.
Water s. BW	135 Hz
Water s. delta pos.	0.00 ppm
Measurements	1

Resolution

Vector size	2048

Geometry

Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	FIX
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
AutoAlign	Head > Basis
Auto Coil Select	Default
Shim mode	Advanced
Adj. water suppr.	Off
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto

Adjust volume

Position	R1.0 P3.7 H56.7
Orientation	T > C-0.1
Rotation	89.99 deg
A >> P	40 mm
R >> L	25 mm
F >> H	15 mm

Physio

1st Signal/Mode	None

Composing

Sequence

Preparation scans	4
Delta frequency	-2.0 ppm
Phase cycling	Auto
Bandwidth	4000 Hz
Acquisition duration	512 ms
Remove oversampling	On
TX/RX Nucleus	1H
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
RF pulse duration	3200 us
Spoiler max. amplitude	20.0 mT/m
Spoiler duration	500 us
Acq. window shift	200 us
Min. settling delay	300 us
Gradient ramp time	200 us
VAPOR flip angle	60 deg
VAPOR delay 8	28 ms
VAPOR delay 7	76 ms
OVS pulse duration	5120 us
OVS flip angle RO	90 deg
OVS flip angle PH	90 deg
OVS flip angle SL	90 deg
VAPOR delay 6	68 ms
VAPOR delay 5	102 ms
VAPOR delay 4	105 ms
VAPOR delay 3	122 ms
VAPOR delay 2	100 ms
VAPOR delay 1	150 ms
Enable OVS	On
Resolve averages	On
Inversion pulse	Off
Symmetric RF pulses	Off
Invert SS grad. pol.	Off
Shift RO frequency	Off
Debug loop type	None

\\USER\Yanes\F31\fMRS/fMRI_PAIN\gre_field_mapping

TA: 1:02 Voxel size: 2.5×2.5×2.5 mm Rel. SNR: 1.00 SIEMENS: gre_field_mapping

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	56
Dist. factor	0 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	210 mm
FoV phase	100.0 %
Slice thickness	2.5 mm
TR	475.0 ms
TE 1	4.08 ms
TE 2	5.1 ms
Averages	1
Concatenations	1
Filter	None
Coil elements	A32

Contrast

MTC	Off
Flip angle	35 deg
Fat suppr.	None
Averaging mode	Short term
Reconstruction	Magn./Phase
Measurements	1
Multiple series	Off

Resolution

Base resolution	84
Phase resolution	100 %
Phase partial Fourier	6/8
Interpolation	Off
Image Filter	Off
Distortion Corr.	Off
Prescan Normalize	Off
Normalize	Off
B1 filter	Off
Raw filter	Off
Elliptical filter	Off

Geometry

Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None
Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	FIX
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
AutoAlign	Head > Brain
Auto Coil Select	Default
Shim mode	Advanced
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
! Position	Isocenter
! Orientation	Transversal
! Rotation	0.00 deg
! R >> L	130 mm
! A >> P	170 mm
! F >> H	120 mm

Composing

Sequence

Introduction	On
Dimension	2D
Asymmetric echo	Off
Contrasts	2
Bandwidth	607 Hz/Px
Flow comp.	Yes
RF pulse type	Normal
Gradient mode	Normal
RF spoiling	On

\\USER\Yanes\F31\fMRS/fMRI_PAIN\cmrr_mbep2d_1TR_1P5ISO_REST_w_MOVIE

TA: 5:17 PAT: 2 Voxel size: 1.5×1.5×1.5 mm Rel. SNR: 1.00 USER: cmrr_mbep2d_bold

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	80
Dist. factor	0 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	204 mm
FoV phase	100.0 %
Slice thickness	1.50 mm
TR	1000 ms
TE	24.4 ms
Multi-band accel. factor	5
Filter	Raw filter
Coil elements	A32

Contrast

MTC	Off
Magn. preparation	None
Flip angle	45 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	300
Delay in TR	0 ms
Multiple series	Off

Resolution

Base resolution	136
Phase resolution	100 %
Phase partial Fourier	7/8
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	12
Reference scan mode	GRE
Distortion Corr.	Off
Prescan Normalize	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off
Hamming	Off

Geometry

Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None
Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	REF
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Sum of Squares
AutoAlign	Head > Brain
Auto Coil Select	Default
Shim mode	Advanced
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
! Position	Isocenter
! Orientation	Transversal
! Rotation	0.00 deg
! R >> L	130 mm
! A >> P	170 mm
! F >> H	120 mm

Physio

1st Signal/Mode	None

BOLD

GLM Statistics	Off
Dynamic t-maps	Off
Starting ignore meas	0
Ignore after transition	0
Model transition states	On
Temp. highpass filter	On
Threshold	4.00
Paradigm size	20
Meas[1]	Baseline
Meas[2]	Baseline
Meas[3]	Baseline
Meas[4]	Baseline
Meas[5]	Baseline
Meas[6]	Baseline
Meas[7]	Baseline
Meas[8]	Baseline
Meas[9]	Baseline
Meas[10]	Baseline
Meas[11]	Active
Meas[12]	Active
Meas[13]	Active
Meas[14]	Active
Meas[15]	Active
Meas[16]	Active
Meas[17]	Active
Meas[18]	Active
Meas[19]	Active
Meas[20]	Active

Motion correction	Off
Spatial filter	Off

Sequence

Introduction	Off
Contrasts	1
Bandwidth	1934 Hz/Px
Flow comp.	No
Free echo spacing	Off
Echo spacing	0.66 ms
EPI factor	136
Gradient mode	Normal
RF spoiling	Off
Excite pulse duration	5760 us
Single-band images	Off
MB LeakBlock kernel	Off
MB dual kernel	Off
MB RF phase scramble	On
SENSE1 coil combine	Off
Invert RO/PE polarity	Off
PF omits higher k-space	Off
Force equal slice timing	Off
Online multi-band recon.	Online
FFT scale factor	0.60
GRE iPAT ref. FA	12.0 deg
Physio recording	Off
Triggering scheme	Standard

\\USER\Yanes\F31\fMRS/fMRI_PAIN\cmrr_mbep2d_1TR_1P5ISO_PAIN1

TA: 5:27 PAT: 2 Voxel size: 1.5×1.5×1.5 mm Rel. SNR: 1.00 USER: cmrr_mbep2d_bold

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	80
Dist. factor	0 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	204 mm
FoV phase	100.0 %
Slice thickness	1.50 mm
TR	1000 ms
TE	24.4 ms
Multi-band accel. factor	5
Filter	Raw filter
Coil elements	A32

Contrast

MTC	Off
Magn. preparation	None
Flip angle	45 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	310
Delay in TR	0 ms
Multiple series	Off

Resolution

Base resolution	136
Phase resolution	100 %
Phase partial Fourier	7/8
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	12
Reference scan mode	GRE
Distortion Corr.	Off
Prescan Normalize	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off
Hamming	Off

Geometry

Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None
Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	REF
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Sum of Squares
AutoAlign	Head > Brain
Auto Coil Select	Default
Shim mode	Advanced
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
! Position	Isocenter
! Orientation	Transversal
! Rotation	0.00 deg
! R >> L	130 mm
! A >> P	170 mm
! F >> H	120 mm

Physio

1st Signal/Mode	None

BOLD

GLM Statistics	Off
Dynamic t-maps	Off
Starting ignore meas	0
Ignore after transition	0
Model transition states	On
Temp. highpass filter	On
Threshold	4.00
Paradigm size	20
Meas[1]	Baseline
Meas[2]	Baseline
Meas[3]	Baseline
Meas[4]	Baseline
Meas[5]	Baseline
Meas[6]	Baseline
Meas[7]	Baseline
Meas[8]	Baseline
Meas[9]	Baseline
Meas[10]	Baseline
Meas[11]	Active
Meas[12]	Active
Meas[13]	Active
Meas[14]	Active
Meas[15]	Active
Meas[16]	Active
Meas[17]	Active
Meas[18]	Active
Meas[19]	Active
Meas[20]	Active

Motion correction	Off
Spatial filter	Off

Sequence

Introduction	Off
Contrasts	1
Bandwidth	1934 Hz/Px
Flow comp.	No
Free echo spacing	Off
Echo spacing	0.66 ms
EPI factor	136
Gradient mode	Normal
RF spoiling	Off
Excite pulse duration	5760 us
Single-band images	Off
MB LeakBlock kernel	Off
MB dual kernel	Off
MB RF phase scramble	On
SENSE1 coil combine	Off
Invert RO/PE polarity	Off
PF omits higher k-space	Off
Force equal slice timing	Off
Online multi-band recon.	Online
FFT scale factor	0.60
GRE iPAT ref. FA	12.0 deg
Physio recording	Off
Triggering scheme	Standard

\\USER\Yanes\F31\fMRS/fMRI_PAIN\cmrr_mbep2d_1TR_1P5ISO_REST

TA: 5:17 PAT: 2 Voxel size: 1.5×1.5×1.5 mm Rel. SNR: 1.00 USER: cmrr_mbep2d_bold

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	80
Dist. factor	0 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	204 mm
FoV phase	100.0 %
Slice thickness	1.50 mm
TR	1000 ms
TE	24.4 ms
Multi-band accel. factor	5
Filter	Raw filter
Coil elements	A32

Contrast

MTC	Off
Magn. preparation	None
Flip angle	45 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	300
Delay in TR	0 ms
Multiple series	Off

Resolution

Base resolution	136
Phase resolution	100 %
Phase partial Fourier	7/8
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	12
Reference scan mode	GRE
Distortion Corr.	Off
Prescan Normalize	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off
Hamming	Off

Geometry

Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None
Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	REF
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Sum of Squares
AutoAlign	Head > Brain
Auto Coil Select	Default
Shim mode	Advanced
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
! Position	Isocenter
! Orientation	Transversal
! Rotation	0.00 deg
! R >> L	130 mm
! A >> P	170 mm
! F >> H	120 mm

Physio

1st Signal/Mode	None

BOLD

GLM Statistics	Off
Dynamic t-maps	Off
Starting ignore meas	0
Ignore after transition	0
Model transition states	On
Temp. highpass filter	On
Threshold	4.00
Paradigm size	20
Meas[1]	Baseline
Meas[2]	Baseline
Meas[3]	Baseline
Meas[4]	Baseline
Meas[5]	Baseline
Meas[6]	Baseline
Meas[7]	Baseline
Meas[8]	Baseline
Meas[9]	Baseline
Meas[10]	Baseline
Meas[11]	Active
Meas[12]	Active
Meas[13]	Active
Meas[14]	Active
Meas[15]	Active
Meas[16]	Active
Meas[17]	Active
Meas[18]	Active
Meas[19]	Active
Meas[20]	Active

Motion correction	Off
Spatial filter	Off

Sequence

Introduction	Off
Contrasts	1
Bandwidth	1934 Hz/Px
Flow comp.	No
Free echo spacing	Off
Echo spacing	0.66 ms
EPI factor	136
Gradient mode	Normal
RF spoiling	Off
Excite pulse duration	5760 us
Single-band images	Off
MB LeakBlock kernel	Off
MB dual kernel	Off
MB RF phase scramble	On
SENSE1 coil combine	Off
Invert RO/PE polarity	Off
PF omits higher k-space	Off
Force equal slice timing	Off
Online multi-band recon.	Online
FFT scale factor	0.60
GRE iPAT ref. FA	12.0 deg
Physio recording	Off
Triggering scheme	Standard

\\USER\Yanes\F31\fMRS/fMRI_PAIN\cmrr_mbep2d_1TR_1P5ISO_PAIN2

TA: 5:27 PAT: 2 Voxel size: 1.5×1.5×1.5 mm Rel. SNR: 1.00 USER: cmrr_mbep2d_bold

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	80
Dist. factor	0 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	204 mm
FoV phase	100.0 %
Slice thickness	1.50 mm
TR	1000 ms
TE	24.4 ms
Multi-band accel. factor	5
Filter	Raw filter
Coil elements	A32

Contrast

MTC	Off
Magn. preparation	None
Flip angle	45 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	310
Delay in TR	0 ms
Multiple series	Off

Resolution

Base resolution	136
Phase resolution	100 %
Phase partial Fourier	7/8
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	12
Reference scan mode	GRE
Distortion Corr.	Off
Prescan Normalize	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off
Hamming	Off

Geometry

Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None
Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	REF
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Sum of Squares
AutoAlign	Head > Brain
Auto Coil Select	Default
Shim mode	Advanced
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
! Position	Isocenter
! Orientation	Transversal
! Rotation	0.00 deg
! R >> L	130 mm
! A >> P	170 mm
! F >> H	120 mm

Physio

1st Signal/Mode	None

BOLD

GLM Statistics	Off
Dynamic t-maps	Off
Starting ignore meas	0
Ignore after transition	0
Model transition states	On
Temp. highpass filter	On
Threshold	4.00
Paradigm size	20
Meas[1]	Baseline
Meas[2]	Baseline
Meas[3]	Baseline
Meas[4]	Baseline
Meas[5]	Baseline
Meas[6]	Baseline
Meas[7]	Baseline
Meas[8]	Baseline
Meas[9]	Baseline
Meas[10]	Baseline
Meas[11]	Active
Meas[12]	Active
Meas[13]	Active
Meas[14]	Active
Meas[15]	Active
Meas[16]	Active
Meas[17]	Active
Meas[18]	Active
Meas[19]	Active
Meas[20]	Active

Motion correction	Off
Spatial filter	Off

Sequence

Introduction	Off
Contrasts	1
Bandwidth	1934 Hz/Px
Flow comp.	No
Free echo spacing	Off
Echo spacing	0.66 ms
EPI factor	136
Gradient mode	Normal
RF spoiling	Off
Excite pulse duration	5760 us
Single-band images	Off
MB LeakBlock kernel	Off
MB dual kernel	Off
MB RF phase scramble	On
SENSE1 coil combine	Off
Invert RO/PE polarity	Off
PF omits higher k-space	Off
Force equal slice timing	Off
Online multi-band recon.	Online
FFT scale factor	0.60
GRE iPAT ref. FA	12.0 deg
Physio recording	Off
Triggering scheme	Standard

\\USER\Yanes\F31\fMRS/fMRI_PAIN\cmrr_mbep2d_1TR_1P5ISO_LEARN

TA: 8:22 PAT: 2 Voxel size: 1.5×1.5×1.5 mm Rel. SNR: 1.00 USER: cmrr_mbep2d_bold

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	Off
Start measurements	single

Routine

Slice group 1	
Slices	80
Dist. factor	0 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	204 mm
FoV phase	100.0 %
Slice thickness	1.50 mm
TR	1000 ms
TE	24.4 ms
Multi-band accel. factor	5
Filter	Raw filter
Coil elements	A32

Contrast

MTC	Off
Magn. preparation	None
Flip angle	45 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	485
Delay in TR	0 ms
Multiple series	Off

Resolution

Base resolution	136
Phase resolution	100 %
Phase partial Fourier	7/8
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	12
Reference scan mode	GRE
Distortion Corr.	Off
Prescan Normalize	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off
Hamming	Off

Geometry

Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None
Table position	H
Table position	0 mm
Inline Composing	Off

System

V32	Off
A32	On
Positioning mode	REF
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Sum of Squares
AutoAlign	Head > Brain
Auto Coil Select	Default
Shim mode	Advanced
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
! Position	Isocenter
! Orientation	Transversal
! Rotation	0.00 deg
! R >> L	130 mm
! A >> P	170 mm
! F >> H	120 mm

Physio

1st Signal/Mode	None

BOLD

GLM Statistics	Off
Dynamic t-maps	Off
Starting ignore meas	0
Ignore after transition	0
Model transition states	On
Temp. highpass filter	On
Threshold	4.00
Paradigm size	20
Meas[1]	Baseline
Meas[2]	Baseline
Meas[3]	Baseline
Meas[4]	Baseline
Meas[5]	Baseline
Meas[6]	Baseline
Meas[7]	Baseline
Meas[8]	Baseline
Meas[9]	Baseline
Meas[10]	Baseline
Meas[11]	Active
Meas[12]	Active
Meas[13]	Active
Meas[14]	Active
Meas[15]	Active
Meas[16]	Active
Meas[17]	Active
Meas[18]	Active
Meas[19]	Active
Meas[20]	Active

Motion correction	Off
Spatial filter	Off

Sequence

Introduction	Off
Contrasts	1
Bandwidth	1934 Hz/Px
Flow comp.	No
Free echo spacing	Off
Echo spacing	0.66 ms
EPI factor	136
Gradient mode	Normal
RF spoiling	Off
Excite pulse duration	5760 us
Single-band images	Off
MB LeakBlock kernel	Off
MB dual kernel	Off
MB RF phase scramble	On
SENSE1 coil combine	Off
Invert RO/PE polarity	Off
PF omits higher k-space	Off
Force equal slice timing	Off
Online multi-band recon.	Online
FFT scale factor	0.60
GRE iPAT ref. FA	12.0 deg
Physio recording	Off
Triggering scheme	Standard

Table of contents

```
#!/bin/tcsh -xef

echo "auto-generated by afni_proc.py, Sun Oct 25 10:23:46 2020"
echo "(version 7.12, April 14, 2020)"
echo "execution started: `date`"

# to execute via tcsh:
#   tcsh -xef proc.${subj} |& tee output.proc.${subj}
# to execute via bash:
#   tcsh -xef proc.${subj} 2>&1 | tee output.proc.${subj}

# ========================== auto block: setup ============================
# script setup

# take note of the AFNI version
afni -ver

# check that the current AFNI version is recent enough
afni_history -check_date 27 Jun 2019
if ( $status ) then
    echo "** this script requires newer AFNI binaries (than 27 Jun 2019)"
    echo "   (consider: @update.afni.binaries -defaults)"
    exit
endif

# the user may specify a single subject to run with
if ( $#argv > 0 ) then
    set subj = $argv[1]
else
    set subj = ${subj}
endif

# assign output directory name
set output_dir = $subj.results

# verify that the results directory does not yet exist
if ( -d $output_dir ) then
    echo output dir "$subj.results" already exists
    exit
endif

# set list of runs
set runs = (`count -digits 2 1 2`)

# create results and stimuli directories
mkdir $output_dir
mkdir $output_dir/stimuli

# copy stim files into stimulus directory
cp ${PWD}/stim/base.txt       \
    ${PWD}/stim/ramp_on.txt   \
```

```
    ${PWD}/stim/pain_low.txt  \
    ${PWD}/stim/ramp_off.txt  \
    ${PWD}/stim/rate.txt      \
    ${PWD}/stim/pain_high.txt \
    $output_dir/stimuli

# copy anatomy to results dir
3dcopy
                              \
    ${PWD}/${subj}/ses-mri01/anat/${subj}_ses-mri01_acq-mprage_T1w.nii \
    $output_dir/${subj}_ses-mri01_acq-mprage_T1w

# ========================== auto block: tcat ==========================
# apply 3dTcat to copy input dsets to results dir,
# while removing the first 0 TRs
3dTcat -prefix $output_dir/pb00.$subj.r01.tcat                    \
    ${PWD}/${subj}/ses-mri01/func/${subj}_ses-mri01_task-pain_run-1_bold.nii'
     [0..$]'
3dTcat -prefix $output_dir/pb00.$subj.r02.tcat                    \
    ${PWD}/${subj}/ses-mri01/func/${subj}_ses-mri01_task-pain_run-2_bold.nii'
     [0..$]'

# and make note of repetitions (TRs) per run
set tr_counts = ( 310 310 )

# -------------------------------------------------------
# enter the results directory (can begin processing data)
cd $output_dir


# --------------------------------------------------------
# data check: compute correlations with spherical ~averages
@radial_correlate -nfirst 0 -do_clean yes -rdir radcor.pb00.tcat \
                  pb00.$subj.r*.tcat+orig.HEAD

# ========================== auto block: outcount ==========================
# data check: compute outlier fraction for each volume
touch out.pre_ss_warn.txt
foreach run ( $runs )
    3dToutcount -automask -fraction -polort 3 -legendre                     \
                pb00.$subj.r$run.tcat+orig > outcount.r$run.1D

    # outliers at TR 0 might suggest pre-steady state TRs
    if ( `1deval -a outcount.r$run.1D"{0}" -expr "step(a-0.4)"` ) then
        echo "** TR #0 outliers: possible pre-steady state TRs in run $run" \
            >> out.pre_ss_warn.txt
    endif
end

# catenate outlier counts into a single time series
cat outcount.r*.1D > outcount_rall.1D
```

```
# get run number and TR index for minimum outlier volume
set minindex = `3dTstat -argmin -prefix - outcount_rall.1D\'`
set ovals = ( `1d_tool.py -set_run_lengths $tr_counts                        \
                          -index_to_run_tr $minindex` )
# save run and TR indices for extraction of vr_base_min_outlier
set minoutrun = $ovals[1]
set minouttr  = $ovals[2]
echo "min outlier: run $minoutrun, TR $minouttr" | tee out.min_outlier.txt

# ================================== tshift ==================================
# time shift data so all slice timing is the same
foreach run ( $runs )
    3dTshift -tzero 0 -quintic -prefix pb01.$subj.r$run.tshift \
             pb00.$subj.r$run.tcat+orig
end

# --------------------------------
# extract volreg registration base
3dbucket -prefix vr_base_min_outlier                                 \
    pb01.$subj.r$minoutrun.tshift+orig"[$minouttr]"

# ================================== align ==================================
# for e2a: compute anat alignment transformation to EPI registration base
# (new anat will be intermediate, stripped,                                  \
#     ${subj}_ses-mri01_acq-mprage_T1w_ns+orig)
align_epi_anat.py -anat2epi -anat ${subj}_ses-mri01_acq-mprage_T1w+orig \
       -save_skullstrip -suffix _al_junk                                   \
       -epi vr_base_min_outlier+orig -epi_base 0                           \
       -epi_strip 3dAutomask                                               \
       -giant_move                                                         \
       -volreg off -tshift off

# ================================== tlrc ==================================
# warp anatomy to standard space
@auto_tlrc -base MNI_avg152T1+tlrc -input                              \
    ${subj}_ses-mri01_acq-mprage_T1w_ns+orig -no_ss

# store forward transformation matrix in a text file
cat_matvec ${subj}_ses-mri01_acq-mprage_T1w_ns+tlrc::WARP_DATA -I > \
    warp.anat.Xat.1D

# ================================== volreg ==================================
# align each dset to base volume, to anat, warp to tlrc space

# verify that we have a +tlrc warp dataset
if ( ! -f ${subj}_ses-mri01_acq-mprage_T1w_ns+tlrc.HEAD ) then
    echo "** missing +tlrc warp dataset:                                  \
        ${subj}_ses-mri01_acq-mprage_T1w_ns+tlrc.HEAD"
    exit
endif
```

```
# register and warp
foreach run ( $runs )
    # register each volume to the base image
    3dvolreg -verbose -zpad 1 -base vr_base_min_outlier+orig             \
             -1Dfile dfile.r$run.1D -prefix rm.epi.volreg.r$run          \
             -cubic                                                      \
             -1Dmatrix_save mat.r$run.vr.aff12.1D                        \
             pb01.$subj.r$run.tshift+orig

    # create an all-1 dataset to mask the extents of the warp
    3dcalc -overwrite -a pb01.$subj.r$run.tshift+orig -expr 1            \
           -prefix rm.epi.all1

    # catenate volreg/epi2anat/tlrc xforms
    cat_matvec -ONELINE                                                  \
               ${subj}_ses-mri01_acq-mprage_T1w_ns+tlrc::WARP_DATA -I    \
               ${subj}_ses-mri01_acq-mprage_T1w_al_junk_mat.aff12.1D -I  \
               mat.r$run.vr.aff12.1D > mat.r$run.warp.aff12.1D

    # apply catenated xform: volreg/epi2anat/tlrc
    3dAllineate -base ${subj}_ses-mri01_acq-mprage_T1w_ns+tlrc           \
                -input pb01.$subj.r$run.tshift+orig                      \
                -1Dmatrix_apply mat.r$run.warp.aff12.1D                  \
                -mast_dxyz 1.5                                           \
                -prefix rm.epi.nomask.r$run

    # warp the all-1 dataset for extents masking
    3dAllineate -base ${subj}_ses-mri01_acq-mprage_T1w_ns+tlrc           \
                -input rm.epi.all1+orig                                  \
                -1Dmatrix_apply mat.r$run.warp.aff12.1D                  \
                -mast_dxyz 1.5 -final NN -quiet                          \
                -prefix rm.epi.1.r$run

    # make an extents intersection mask of this run
    3dTstat -min -prefix rm.epi.min.r$run rm.epi.1.r$run+tlrc
end

# make a single file of registration params
cat dfile.r*.1D > dfile_rall.1D

# ----------------------------------------
# create the extents mask: mask_epi_extents+tlrc
# (this is a mask of voxels that have valid data at every TR)
3dMean -datum short -prefix rm.epi.mean rm.epi.min.r*.HEAD
3dcalc -a rm.epi.mean+tlrc -expr 'step(a-0.999)' -prefix mask_epi_extents

# and apply the extents mask to the EPI data
# (delete any time series with missing data)
foreach run ( $runs )
    3dcalc -a rm.epi.nomask.r$run+tlrc -b mask_epi_extents+tlrc          \
```

```
           -expr 'a*b' -prefix pb02.$subj.r$run.volreg
end

# warp the volreg base EPI dataset to make a final version
cat_matvec -ONELINE                                                    \
           ${subj}_ses-mri01_acq-mprage_T1w_ns+tlrc::WARP_DATA -I      \
           ${subj}_ses-mri01_acq-mprage_T1w_al_junk_mat.aff12.1D -I  >   \
           mat.basewarp.aff12.1D

3dAllineate -base ${subj}_ses-mri01_acq-mprage_T1w_ns+tlrc             \
            -input vr_base_min_outlier+orig                            \
            -1Dmatrix_apply mat.basewarp.aff12.1D                      \
            -mast_dxyz 1.5                                             \
            -prefix final_epi_vr_base_min_outlier

# create an anat_final dataset, aligned with stats
3dcopy ${subj}_ses-mri01_acq-mprage_T1w_ns+tlrc anat_final.$subj

# record final registration costs
3dAllineate -base final_epi_vr_base_min_outlier+tlrc -allcostX         \
            -input anat_final.$subj+tlrc |& tee out.allcostX.txt

# ----------------------------------------
# warp anat follower datasets (affine)
3dAllineate -source ${subj}_ses-mri01_acq-mprage_T1w+orig              \
            -master anat_final.$subj+tlrc                              \
            -final wsinc5 -1Dmatrix_apply warp.anat.Xat.1D             \
            -prefix anat_w_skull_warped

# ----------------------------------------------------------
# data check: compute correlations with spherical ~averages
@radial_correlate -nfirst 0 -do_clean yes -rdir radcor.pb02.volreg      \
                  pb02.$subj.r*.volreg+tlrc.HEAD

# ================================= blur ==================================
# blur each volume of each run
foreach run ( $runs )
    3dmerge -1blur_fwhm 3.0 -doall -prefix pb03.$subj.r$run.blur \
            pb02.$subj.r$run.volreg+tlrc
end

# ================================= mask ==================================
# create 'full_mask' dataset (union mask)
foreach run ( $runs )
    3dAutomask -prefix rm.mask_r$run pb03.$subj.r$run.blur+tlrc
end

# create union of inputs, output type is byte
3dmask_tool -inputs rm.mask_r*+tlrc.HEAD -union -prefix full_mask.$subj

# ---- create subject anatomy mask, mask_anat.$subj+tlrc ----
```

```
#      (resampled from tlrc anat)
3dresample -master full_mask.$subj+tlrc -input                          \
           ${subj}_ses-mri01_acq-mprage_T1w_ns+tlrc                     \
           -prefix rm.resam.anat

# convert to binary anat mask; fill gaps and holes
3dmask_tool -dilate_input 5 -5 -fill_holes -input rm.resam.anat+tlrc  \
            -prefix mask_anat.$subj

# compute tighter EPI mask by intersecting with anat mask
3dmask_tool -input full_mask.$subj+tlrc mask_anat.$subj+tlrc          \
            -inter -prefix mask_epi_anat.$subj

# compute overlaps between anat and EPI masks
3dABoverlap -no_automask full_mask.$subj+tlrc mask_anat.$subj+tlrc    \
            |& tee out.mask_ae_overlap.txt

# note Dice coefficient of masks, as well
3ddot -dodice full_mask.$subj+tlrc mask_anat.$subj+tlrc               \
      |& tee out.mask_ae_dice.txt

# ---- create group anatomy mask, mask_group+tlrc ----
#      (resampled from tlrc base anat, MNI_avg152T1+tlrc)
3dresample -master full_mask.$subj+tlrc -prefix ./rm.resam.group      \
           -input ~/abin/MNI_avg152T1+tlrc

# convert to binary group mask; fill gaps and holes
3dmask_tool -dilate_input 5 -5 -fill_holes -input rm.resam.group+tlrc \
            -prefix mask_group

# note Dice coefficient of anat and template masks
3ddot -dodice mask_anat.$subj+tlrc mask_group+tlrc                    \
      |& tee out.mask_at_dice.txt

# ================================== scale ==================================
# scale each voxel time series to have a mean of 100
# (be sure no negatives creep in)
# (subject to a range of [0,200])
foreach run ( $runs )
    3dTstat -prefix rm.mean_r$run pb03.$subj.r$run.blur+tlrc
    3dcalc -a pb03.$subj.r$run.blur+tlrc -b rm.mean_r$run+tlrc \
           -c mask_epi_extents+tlrc                            \
           -expr 'c * min(200, a/b*100)*step(a)*step(b)'       \
           -prefix pb04.$subj.r$run.scale
end

# ================================ regress ==================================

# compute de-meaned motion parameters (for use in regression)
1d_tool.py -infile dfile_rall.1D -set_nruns 2                           \
           -demean -write motion_demean.1D
```

```
# compute motion parameter derivatives (just to have)
1d_tool.py -infile dfile_rall.1D -set_nruns 2                                \
           -derivative -demean -write motion_deriv.1D

# convert motion parameters for per-run regression
1d_tool.py -infile motion_demean.1D -set_nruns 2                             \
           -split_into_pad_runs mot_demean

# create censor file motion_${subj}_censor.1D, for censoring motion
1d_tool.py -infile dfile_rall.1D -set_nruns 2                                \
    -show_censor_count -censor_prev_TR                                       \
    -censor_motion 0.3 motion_${subj}

# note TRs that were not censored
set ktrs = `1d_tool.py -infile motion_${subj}_censor.1D                      \
                       -show_trs_uncensored encoded`

# ----------------------------
# run the regression analysis
3dDeconvolve -input pb04.$subj.r*.scale+tlrc.HEAD                            \
    -censor motion_${subj}_censor.1D                                         \
    -ortvec mot_demean.r01.1D mot_demean_r01                                 \
    -ortvec mot_demean.r02.1D mot_demean_r02                                 \
    -polort 3                                                                \
    -num_stimts 6                                                            \
    -stim_times 1 stimuli/base.txt 'BLOCK(10)'                               \
    -stim_label 1 base                                                       \
    -stim_times 2 stimuli/ramp_on.txt 'BLOCK(6)'                             \
    -stim_label 2 ramp_on                                                    \
    -stim_times 3 stimuli/pain_low.txt 'BLOCK(6)'                            \
    -stim_label 3 pain_low                                                   \
    -stim_times 4 stimuli/ramp_off.txt 'BLOCK(6)'                            \
    -stim_label 4 ramp_off                                                   \
    -stim_times 5 stimuli/rate.txt 'BLOCK(12)'                               \
    -stim_label 5 rate                                                       \
    -stim_times 6 stimuli/pain_high.txt 'BLOCK(6)'                           \
    -stim_label 6 pain_high                                                  \
    -jobs 12                                                                 \
    -gltsym 'SYM: pain_low -base'                                            \
    -glt_label 1 pain_low-base                                               \
    -gltsym 'SYM: pain_high -base'                                           \
    -glt_label 2 pain_high-base                                              \
    -gltsym 'SYM: pain_high -pain_low'                                       \
    -glt_label 3 pain_high-pain_low                                          \
    -gltsym 'SYM: base -pain_high'                                           \
    -glt_label 4 base-pain_high                                              \
    -gltsym 'SYM: rate -base'                                                \
    -glt_label 5 rate-base                                                   \
    -fout -tout -x1D X.xmat.1D -xjpeg X.jpg                                  \
    -x1D_uncensored X.nocensor.xmat.1D                                       \
```

```
    -fitts fitts.$subj                                                  \
    -errts errts.${subj}                                                \
    -bucket stats.$subj


# if 3dDeconvolve fails, terminate the script
if ( $status != 0 ) then
    echo '---------------------------------------'
    echo '** 3dDeconvolve error, failing...'
    echo '   (consider the file 3dDeconvolve.err)'
    exit
endif


# display any large pairwise correlations from the X-matrix
1d_tool.py -show_cormat_warnings -infile X.xmat.1D |& tee out.cormat_warn.txt

# display degrees of freedom info from X-matrix
1d_tool.py -show_df_info -infile X.xmat.1D |& tee out.df_info.txt

# -- execute the 3dREMLfit script, written by 3dDeconvolve --
tcsh -x stats.REML_cmd

# if 3dREMLfit fails, terminate the script
if ( $status != 0 ) then
    echo '---------------------------------------'
    echo '** 3dREMLfit error, failing...'
    exit
endif


# create an all_runs dataset to match the fitts, errts, etc.
3dTcat -prefix all_runs.$subj pb04.$subj.r*.scale+tlrc.HEAD

# --------------------------------------------------
# create a temporal signal to noise ratio dataset
#    signal: if 'scale' block, mean should be 100
#    noise : compute standard deviation of errts
3dTstat -mean -prefix rm.signal.all all_runs.$subj+tlrc"[$ktrs]"
3dTstat -stdev -prefix rm.noise.all errts.${subj}_REML+tlrc"[$ktrs]"
3dcalc -a rm.signal.all+tlrc                                        \
       -b rm.noise.all+tlrc                                         \
       -c mask_epi_anat.$subj+tlrc                                  \
       -expr 'c*a/b' -prefix TSNR.$subj

# --------------------------------------------------
# compute and store GCOR (global correlation average)
# (sum of squares of global mean of unit errts)
3dTnorm -norm2 -prefix rm.errts.unit errts.${subj}_REML+tlrc
3dmaskave -quiet -mask full_mask.$subj+tlrc rm.errts.unit+tlrc      \
          > mean.errts.unit.1D
```

```
3dTstat -sos -prefix - mean.errts.unit.1D\' > out.gcor.1D
echo "-- GCOR = `cat out.gcor.1D`"

# ---------------------------------------------------
# compute correlation volume
# (per voxel: correlation with masked brain average)
3dmaskave -quiet -mask full_mask.$subj+tlrc errts.${subj}_REML+tlrc      \
          > mean.errts.1D
3dTcorr1D -prefix corr_brain errts.${subj}_REML+tlrc mean.errts.1D

# create ideal files for fixed response stim types
1dcat X.nocensor.xmat.1D'[8]' > ideal_base.1D
1dcat X.nocensor.xmat.1D'[9]' > ideal_ramp_on.1D
1dcat X.nocensor.xmat.1D'[10]' > ideal_pain_low.1D
1dcat X.nocensor.xmat.1D'[11]' > ideal_ramp_off.1D
1dcat X.nocensor.xmat.1D'[12]' > ideal_rate.1D
1dcat X.nocensor.xmat.1D'[13]' > ideal_pain_high.1D

# ---------------------------------------------------
# extract non-baseline regressors from the X-matrix,
# then compute their sum
1d_tool.py -infile X.nocensor.xmat.1D -write_xstim X.stim.xmat.1D
3dTstat -sum -prefix sum_ideal.1D X.stim.xmat.1D

# ============================ blur estimation ==============================
# compute blur estimates
touch blur_est.$subj.1D   # start with empty file

# create directory for ACF curve files
mkdir files_ACF

# -- estimate blur for each run in epits --
touch blur.epits.1D

# restrict to uncensored TRs, per run
foreach run ( $runs )
    set trs = `1d_tool.py -infile X.xmat.1D -show_trs_uncensored encoded \
                          -show_trs_run $run`
    if ( $trs == "" ) continue
    3dFWHMx -detrend -mask mask_epi_anat.$subj+tlrc                      \
            -ACF files_ACF/out.3dFWHMx.ACF.epits.r$run.1D                \
            all_runs.$subj+tlrc"[$trs]" >> blur.epits.1D
end

# compute average FWHM blur (from every other row) and append
set blurs = ( `3dTstat -mean -prefix - blur.epits.1D'{0..$(2)}'\'` )
echo average epits FWHM blurs: $blurs
echo "$blurs   # epits FWHM blur estimates" >> blur_est.$subj.1D

# compute average ACF blur (from every other row) and append
set blurs = ( `3dTstat -mean -prefix - blur.epits.1D'{1..$(2)}'\'` )
```

```
echo average epits ACF blurs: $blurs
echo "$blurs   # epits ACF blur estimates" >> blur_est.$subj.1D

# -- estimate blur for each run in errts --
touch blur.errts.1D

# restrict to uncensored TRs, per run
foreach run ( $runs )
    set trs = `1d_tool.py -infile X.xmat.1D -show_trs_uncensored encoded \
                          -show_trs_run $run`
    if ( $trs == "" ) continue
    3dFWHMx -detrend -mask mask_epi_anat.$subj+tlrc                    \
            -ACF files_ACF/out.3dFWHMx.ACF.errts.r$run.1D              \
            errts.${subj}+tlrc"[$trs]" >> blur.errts.1D
end

# compute average FWHM blur (from every other row) and append
set blurs = ( `3dTstat -mean -prefix - blur.errts.1D'{0..$(2)}'\'` )
echo average errts FWHM blurs: $blurs
echo "$blurs   # errts FWHM blur estimates" >> blur_est.$subj.1D

# compute average ACF blur (from every other row) and append
set blurs = ( `3dTstat -mean -prefix - blur.errts.1D'{1..$(2)}'\'` )
echo average errts ACF blurs: $blurs
echo "$blurs   # errts ACF blur estimates" >> blur_est.$subj.1D

# -- estimate blur for each run in err_reml --
touch blur.err_reml.1D

# restrict to uncensored TRs, per run
foreach run ( $runs )
    set trs = `1d_tool.py -infile X.xmat.1D -show_trs_uncensored encoded \
                          -show_trs_run $run`
    if ( $trs == "" ) continue
    3dFWHMx -detrend -mask mask_epi_anat.$subj+tlrc                    \
            -ACF files_ACF/out.3dFWHMx.ACF.err_reml.r$run.1D           \
            errts.${subj}_REML+tlrc"[$trs]" >> blur.err_reml.1D
end

# compute average FWHM blur (from every other row) and append
set blurs = ( `3dTstat -mean -prefix - blur.err_reml.1D'{0..$(2)}'\'` )
echo average err_reml FWHM blurs: $blurs
echo "$blurs   # err_reml FWHM blur estimates" >> blur_est.$subj.1D

# compute average ACF blur (from every other row) and append
set blurs = ( `3dTstat -mean -prefix - blur.err_reml.1D'{1..$(2)}'\'` )
echo average err_reml ACF blurs: $blurs
echo "$blurs   # err_reml ACF blur estimates" >> blur_est.$subj.1D


# ================== auto block: generate review scripts ===================
```

```
# generate a review script for the unprocessed EPI data
gen_epi_review.py -script @epi_review.$subj    \
    -dsets pb00.$subj.r*.tcat+orig.HEAD

# generate scripts to review single subject results
# (try with defaults, but do not allow bad exit status)
gen_ss_review_scripts.py -mot_limit 0.3 -exit0 \
    -ss_review_dset out.ss_review.$subj.txt    \
    -write_uvars_json out.ss_review_uvars.json

# ========================== auto block: finalize ==========================

# remove temporary files
\rm -f rm.*

# if the basic subject review script is here, run it
# (want this to be the last text output)
if ( -e @ss_review_basic ) then
    ./@ss_review_basic |& tee out.ss_review.$subj.txt

    # generate html ss review pages
    # (akin to static images from running @ss_review_driver)
    apqc_make_tcsh.py -review_style basic -subj_dir . \
        -uvar_json out.ss_review_uvars.json
    tcsh @ss_review_html |& tee out.review_html
    apqc_make_html.py -qc_dir QC_$subj

    echo "\nconsider running: \n\n    afni_open -b
     $subj.results/QC_$subj/index.html\n"
endif

# return to parent directory (just in case...)
cd ..

echo "execution finished: `date`"




# ========================================================================
# script generated by the command:
#
# afni_proc.py -subj_id ${subj} -blocks tshift align tlrc volreg blur mask
                                        \
#     scale regress -radial_correlate_blocks tcat volreg -copy_anat
                                        \
#     ${PWD}/${subj}/ses-mri01/anat/${subj}_ses-mri01_acq-mprage_T1w.nii
 \
#     -dsets
                                        \
```

```
#     ${PWD}/${subj}/ses-mri01/func/${subj}_ses-mri01_task-pain_run-1_bold.nii
 \
#     ${PWD}/${subj}/ses-mri01/func/${subj}_ses-mri01_task-pain_run-2_bold.nii
 \
#     -tcat_remove_first_trs 0 -align_opts_aea -giant_move -tlrc_base
                                        \
#     MNI_avg152T1+tlrc -volreg_align_to MIN_OUTLIER -volreg_align_e2a
                                        \
#     -volreg_tlrc_warp -mask_epi_anat yes -blur_size 3.0 -regress_stim_times
                                        \
#     ${PWD}/stim/base.txt
 \
#     ${PWD}/stim/ramp_on.txt
 \
#     ${PWD}/stim/pain_low.txt
 \
#     ${PWD}/stim/ramp_off.txt
 \
#     ${PWD}/stim/rate.txt
 \
#     ${PWD}/stim/pain_high.txt
 \
#     -regress_stim_types times times times times times times
                                        \
#     -regress_stim_labels base ramp_on pain_low ramp_off rate pain_high
                                        \
#     -regress_basis_multi 'BLOCK(10)' 'BLOCK(6)' 'BLOCK(6)' 'BLOCK(6)'
                                        \
#     'BLOCK(12)' 'BLOCK(6)' -regress_censor_motion 0.3
                                        \
#     -regress_motion_per_run -regress_opts_3dD -jobs 12 -gltsym 'SYM:
                                        \
#     pain_low -base' -glt_label 1 pain_low-base -gltsym 'SYM: pain_high
                                        \
#     -base' -glt_label 2 pain_high-base -gltsym 'SYM: pain_high -pain_low'
                                        \
#     -glt_label 3 pain_high-pain_low -gltsym 'SYM: base -pain_high'
                                        \
#     -glt_label 4 base-pain_high -gltsym 'SYM: rate -base' -glt_label 5
                                        \
#     rate-base -regress_reml_exec -regress_make_ideal_sum sum_ideal.1D
                                        \
#     -regress_est_blur_epits -regress_est_blur_errts -regress_run_clustsim
                                        \
#     no -html_review_style basic -execute
```