THE POWER OF PLACEBO: EVALUATING CANNABINOID-RELATED BELIEFS AND THE ROLE OF CANNABIDIOL (CBD) EXPECTANCY ON ACUTE STRESS AND ANXIETY

by

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Dalhousie University is located in Mi'kma'ki,
the ancestral and unceded territory of the Mi'kmaq.
We are all Treaty people.

DEDICATION

I would like to dedicate this work to my late research supervisor, Dr. Sean Barrett. Sean has given me the gift of opportunity to pursue the research and career path that had only existed in my dreams. It is my hope that this dissertation represents at least a small piece of the wisdom and knowledge he has instilled in me throughout this journey. Thank you, Sean, for everything.

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ABSTRACT

Cannabis is associated with several therapeutic and non-therapeutic effects, which may partly be related to varying ratios of cannabinoids like Δ-9-tetrahydrocannabidol (THC) and cannabidiol (CBD), each with unique effects, uses, and mechanisms of action. Expectations or beliefs about substances influence substance-related outcomes and are central to the "placebo effect". While various reports indicate that CBD is utilized and perceived as beneficial for stress- and anxiety-related processes, findings from experimental and clinical investigations are equivocal. The extent to which CBD-related expectancy factors contribute to these purported stress and anxiety dampening effects is unclear. My dissertation aims to gain insight into the expectancy-related influences of well-recognized cannabinoids (THC, CBD), broadly, and as they relate to placebo CBD. Study 1 evaluated the extent to which a community sample of Canadian adults (n=345) endorsed various beliefs about THC and CBD using a cross-sectional survey. Participants tended to endorse beliefs that CBD-containing products (vs. THC) possessed more therapeutic effects (e.g., anxiolysis), and those with prior cannabis use experience (vs. no prior experience) endorsed higher positive beliefs regarding cannabinoid effects. Utilizing a community-recruited sample of healthy adults (n=43), Study 2a and 2b evaluated the extent to which CBD-related expectation (i.e., the placebo effect) influenced various subjective-emotional and psychophysiological indices of acute stress and anxiety using an experimental crossover half-balanced-placebo design. Study 2a findings indicated that those with the strongest beliefs about CBD's anxiety-dampening effects self-reported less anxiety when they thought they received CBD (vs. CBD-free oil). Heart rate variability (HRV) also appeared to be influenced by CBD expectancy within the context of a stressor. Study 2b revealed that CBD expectancy blunted cortisol reactivity; however, this was specific to the anticipation of stress and was predominantly observed among males. Taken together, my research suggests that people tend to have different expectancies regarding the effects of THC and CBD. Further, a placebo effect was identified for CBD in the context of stress and anxiety. This was pronounced among those who endorse strong beliefs about its helpfulness and occurs during the *anticipation* of a stressor, which could reflect the mechanism through which CBD influences future-oriented cognitive processes related to anxiety.

LIST OF ABBREVIATIONS USED

CBD	Cannabidiol
THC	Δ9-Tetrahydrocannabinol
CBN	Cannabinol
CBG	Cannabigerol
PTSD	Posttraumatic stress disorder
GAD	Generalized anxiety disorder
SAD	Social anxiety disorder
LMM	Linear mixed models
GEE	Generalized estimating equations
HPA	Hypothalamic pituitary adrenal
ANS	Autonomic nervous system
SNS	Sympathetic nervous system
PNS	Parasympathetic nervous system
STAI-S-SF	State-Trait Anxiety Inventory-State version-Short Form
I-PANAS-SF	International-Positive and Negative Affect Schedule-Short Form
NRS	Numeric Rating Scale
VAS	Visual Analogue Scale
B-BAES	Brief-Biphasic Alcohol Effect Scale
CU	Any prior cannabis use
NCU	No prior cannabis use
CPT	Cold Pressor Task
MAST	Maastricht Acute Stress Test
HRV	Heart rate variability

HR	Heart rate
RMSSD	Root mean square of successive differences
QIC	Quasi-likelihood under the independence model criterion
BIC	Bayesian Information Criterion
EDR	ECG-derived respiration rate
FDR	False discovery rate
ECG	Electrocardiogram
EMM	Estimated Marginal Mean
SE	Standard Error
ELISA	Enzyme-linked immunosorbent assay
CV	Coefficient of variation
fMRI	functional Magnetic Resonance Imaging
SSRI	Selective serotonin reuptake inhibitor
SEM	Sensor Electronic Module
ADI	AD Instruments
SPSS	Statistical Package for the Social Sciences
N	Total sample size
n	Subsample of total sample size
RCT	Randomized control trial

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I have spent the last five years of my Ph.D. learning, growing, adapting, succeeding, and of course, failing. This completed dissertation reflects my journey, which would not have been possible without the tireless and unwavering support and encouragement of my supervisors, committee members, mentors, family, and friends. The following brief section is but a small note of appreciation for the community that has helped me along the way.

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CHAPTER 1. GENERAL INTRODUCTION

My dissertation aims to examine expectancies related to cannabinoids found in cannabis and evaluate the impact of cannabidiol (CBD)-specific expectation (i.e., the placebo effect) on subjective and physiological responses to acute stress. It consists of three publication style manuscripts. The first manuscript evaluates various therapeutic and non-therapeutic expectancies regarding two of the most widely known cannabinoids (CBD and Δ9-tetrahydrocannabinol [THC]) among a community sample of Canadian adults with or without prior cannabis use experience. The second manuscript examines the extent to which CBD expectancy alone influences subjective and physiological indices of stress, anxiety, and mood in response to an acute laboratory stressor among a sample of healthy adults. The third manuscript is an extension of the analyses presented in the second manuscript and focuses on evaluating the extent to which CBD expectancy impacts cortisol responsivity in the context of acute stress and the role of biological sex in these processes. Before presenting these findings, I will introduce and discuss the following topics: the mechanisms involved in producing drug effects including pharmacological and non-pharmacological factors, the placebo effect and associated influence of expectancies, research design considerations for evaluating drug effects, an overview of cannabis and specific cannabinoids (i.e., THC, CBD), a review of the stress response system, a summary of the current literature evaluating the impact of CBD on indices of stress and anxiety, and finally, the objectives of my research.

Drug Effects

Drug effects are the widespread subjective (e.g., mood, behaviour, thoughts, perceptual experiences) and physiological (e.g., neurochemical, biological) changes that occur following the use of a substance. These drug effects can be specific to the

substance, in that they are directly related to their pharmacological properties, or they can be non-specific to the substance and related to factors that are non-pharmacological (e.g., sensorimotor characteristics, expectations/beliefs about a substance; for a review, see Meyer et al., 2022). Oftentimes, drug effects tend to be driven by a combination of both pharmacological and non-pharmacological factors.

Pharmacological Factors

Specific drug or pharmacological factors are related to the complex physical and biochemical interactions that occur between a pharmacologically active substance (i.e., a drug) and a target site in living tissue. Pharmacokinetic and pharmacodynamic processes are key in understanding how the body interacts with a drug (i.e., what the body does to the drug) and how a drug interacts with the body (i.e., what the drug does to the body), respectively. Briefly, pharmacokinetic components of drug action include the route of administration, how it is absorbed and distributed throughout the body (e.g., bioavailability), metabolic processes associated with inactivation, and excretion. Pharmacodynamic components of drug action include processes that are ultimately responsible for producing the downstream effects and interactions associated with a given drug. These predominantly include the strength, extent, and type of receptor binding (e.g., affinity, full or partial agonist or antagonist) and the cascade of post-receptor biobehavioural effects (e.g., receptor up- or down- regulation, tolerance, sensitization, dependence, withdrawal).

Although is it well established that drug-related effects are directly associated with these intricate biochemical processes, they can only account for some, but not all variability in drug responses. For instance, drug-related effects do not fully explain how the same drug taken at the same dose produces distinct effects in two different people, or

even within the same person on two different occasions. Additionally, pharmacological factors cannot explain observed changes in subjective and physiological state following the administration of a pharmacologically inert compound, more colloquially known as a "placebo" (e.g., Wampold et al., 2005).

Non-pharmacological Factors

In contrast to specific drug factors, non-specific drug factors are not associated with the pharmacological properties of a substance (i.e., they are non-pharmacological). Various individual characteristics as well as contextual influences, such as an individual's prior drug-taking experience, expectations about the effects of a drug, current mood state, sensorimotor characteristics of the substance (e.g., ritual, method of administration), psychosocial contextual factors (e.g., the presence of others), and the environment/ location have all been shown to impact the subjective, behavioural, and physiological outcomes associated with drug use (Amanzio et al., 2001; Kirsch, 1985; Ulrich, 1984; Uthaug et al., 2021; Volkow et al., 2003).

Historically, decades of research on "set and setting" have emphasized the influence of non-pharmacological factors in shaping drug effects (Zinberg, 1984). "Set" refers to the mindset of the individual using a substance (e.g., expectation, mood state, intention), whereas "setting" emphasizes factors related to the external environment where substance use is taking place (e.g., physical and social environment). Indeed, these factors have been used to explain the significant variability in experiences following psychedelic use, from anxiety and psychosis-inducing to creative, spiritual, and therapeutic (for a review, see Hartogsohn, 2016). For example, findings from a systematic review on psychedelic drugs revealed that those who were in a state of surrender and high in trait openness were most likely to have positive experiences, whereas those who were

low in openness and in a preoccupied, apprehensive, or confused state were more likely to experience adverse reactions (Aday et al., 2021). Although set and setting theory was developed to better understand psychedelic experiences, its emphasis on non-pharmacological factors is also relevant to other substances (Dwyer & Moore, 2013; Zinberg, 1984).

The "placebo effect" is another well-studied phenomenon that seeks to explain drug effects driven by non-pharmacological factors. Although a placebo is a pharmacologically inert compound, the placebo effect is a well-documented psychobiological phenomenon. For example, in a meta-analysis of clinical trials for anti-depressant medication, the true drug effect (i.e., the effect directly related to pharmacological factors) was responsible for 25.16% of the overall effect on subjective symptoms of depression, whereas the placebo effect explained 50.97% of the observed outcome (Kirsch & Sapirstein, 1998)[1]. In 2013, however, Kirsch noted that this "placebo effect" was likely over-estimated as it did not consider the often overlooked methodological artifact of regression towards the mean. This will be discussed in more detail in the proceeding subsection: Evaluating Drug Effects in Research. Moreover, many studies have reported evidence that placebo-induced analgesic responses can be reduced or reversed by an opioid antagonist (i.e., naloxone), which implicates biological changes in facilitating placebo responses (e.g., Benedetti, 1996; Benedetti et al., 1999; Levine & Gordon, 1984). Mechanistically, there is not one single placebo effect but many, depending on the disease, illness, or state being targeted. For example, μ-opioid receptors activation has been associated with opioid-related placebo analgesia (Wager et

[1] The remaining 23.87% was estimated to be explained by natural history factors.

al., 2007) whereas cannabinoid receptor (i.e., CB1) activation has been implicated in mediating non-opioid-related (i.e., nonsteroidal anti-inflammatory) placebo analgesia (Benedetti, Amanzio, et al., 2011). Studies involving pain and Parkinson's disease have also implicated the dopaminergic system and associated reward pathways (i.e., expectation of improvement) in the placebo effect (de la Fuente-Fernández et al., 2001, 2002; Scott et al., 2007). Additionally, similar changes in amygdala activation and amygdala-frontal connectivity have been observed in individuals with social anxiety disorder following 6-8 weeks of treatment with placebo or a selective-serotonin reuptake inhibitor (SSRI). These changes only occurred in individuals who experienced decreased subjective anxiety, suggesting that both the placebo and SSRI acted on similar neural pathways among responders (Faria et al., 2012, 2014).

Synthesizing mechanistic and clinical placebo theories with applied set and setting research may facilitate a more comprehensive understanding the role of non-pharmacological factors in drug outcomes as well as implications for research and practice, which will be discussed in Chapter 7. Through ontological integration of these theories, "set and setting" may be best understood as the *components* that underlie placebo effects (Hartogsohn, 2016; Pronovost-Morgan et al., 2023). Indeed, it is not the placebo itself that creates a cascade of biophysiological, behavioural, and subjective changes, but the context and meaning one associates with a given placebo (e.g., meaning we attach to certain substances, pills, medical treatment) that informs our expectations and produces a placebo effect (Moerman & Jonas, 2002).

Expectancies and the placebo effect

Researchers have proposed integrative models to attempt to explain placebo effects (e.g., Benedetti, Carlino, et al., 2011; Colloca & Miller, 2011; Kirsch, 2018).

Within these explanatory models, expectation and learning mechanisms appear to be crucial. Although they could be considered technically distinct processes, their influences are interacting and arguably inseparable in the context of placebo effects (i.e., expectation informed by learning).

In earlier work, Kirsch (1985) describes the concept of "response expectancy" to describe an individual's prediction of their automatic reaction (e.g., emotional, physiological) to a given situation or stimuli.[2] Broadly speaking, our ability to expect and anticipate outcomes (i.e., proactive processing vs. reactive processing) is evolutionarily advantageous as it has allowed us to quickly interpret and respond to our environment, thereby minimizing computational demands (Ingvar, 1985). For example, anticipating how we will respond emotionally and physiologically in the presence of a threat allows us to be able to act more quickly when that threatening stimulus is present (i.e., experience fear, sympathetic arousal, and urges to escape). Placebo effects are hypothesized to be largely mediated by response expectancies (e.g., Kirsch, 2018; Montgomery & Kirsch, 1997). Specifically, there is evidence to suggest that expectancies are cultivated by several factors, including verbal information, conditioning, and observational social learning, which in turn facilitate placebo effects (Kirsch, 2018).

Verbal information includes the information or instructions provided to the individual about the content of the substance they receive. Of relevance to placebo theory, researchers have used the term "stimulus expectancy" to describe an individual's beliefs about the substance they are receiving (i.e., active or inactive; Kirsch, 1999). Stimulus

[2] Throughout this dissertation, the terms "a priori beliefs", "expectations", and "expectancies" are used interchangeably to describe response expectancies, as defined herein.

expectancies can be influenced through verbal information or instructions about the substance the individual is receiving. For example, individuals who were deceptively told that they received a potent analgesic (relative to when they were deceptively informed they received an antibiotic), experienced increased pain tolerance associated with activation of the endogenous opioid system (Amanzio & Benedetti, 1999). Similarly, when individuals who regularly smoke cigarettes were deceptively told they received a nicotine-containing inhaler (relative to when they were correctly informed they received a nicotine-free inhaler), they reported lower levels of withdrawal-related craving and engaged in less smoking behaviour (Copp et al., 2015). Even in the absence of any verbal information, applying a placebo ointment led to a hypoalgesia effect in response to painful stimuli relative to a control group (Bieniek & Bąbel, 2022). Participants in this study likely interpreted the ointment as pharmacologically active and having analgesic properties. Taken together, stimulus expectancies are important in the facilitation of placebo effects as it provides the individual with information (e.g., verbal, visual) to mobilize their expectations about the consequences or outcomes associated with a given stimuli (i.e., response expectancies).

Classical conditioning broadly refers to the unconscious learning processes through which stimuli become associated with certain effects or outcomes over time. For example, the shape or colour of a pill (conditioned/neutral stimulus) in the absence of any pharmacologically active ingredient can effectively reduce symptoms, like pain, if similar pills with active ingredients (unconditioned stimulus) have reduced symptoms in the past (unconditioned response). This occurs through repeated pairings of unconditioned stimulus (i.e., active ingredients) with the conditioned stimulus (e.g., vesicle the active ingredient is in, like a pill), ultimately facilitating a conditioned response (e.g., symptom

reduction) that occurs with placebo administration/in absence of any pharmacologically active ingredient. Research has demonstrated that placebos tend to have more substantial effects when they are administered following conditioning periods where pharmacologically active substances have been administered, compared to when placebos are given for the first time (Amanzio & Benedetti, 1999; Laska & Sunshine, 1973), supporting the role of classical conditioning in the development of placebo effects. In the context of placebo-induced analgesia, other conditioning procedures involve lowering the intensity of a stimulus after a placebo has been applied or administered during a conditioning phase (Voudouris et al., 1985). Similar conditioning trials have been shown to enhance placebo analgesia via explicit response expectancies (Montgomery & Kirsch, 1997). Thus, it appears that classical conditioning procedures (i.e., unconscious learning) enhance positive response expectancies (i.e., conscious cognitive process), which, in turn, elicit larger placebo responses.

In addition to learning that takes place through classical conditioning mechanisms, observational learning has been implicated in facilitating placebo effects (Meeuwis et al., 2023). Social learning theory refers to the process through which one's behaviour or reactions are influenced by observing another person's reactions or behaviour (Bandura, 1969, 1976; Galef Jr., 1988). Indeed, other people's actions and associated outcomes can offer important information about the possible reinforcing or harmful consequences of a given behaviour. This, in turn, may influence the observer's actions and the consequences in a similar way to the model (i.e., the person/people they are observing). Notably, social learning can occur through behavioural modeling (e.g., direct observation of specific behaviour), symbolic modeling (e.g., indirect observation; videos), and verbal modeling (e.g., verbal descriptions of behaviour) (Bandura, 1976), all of which have been shown to

induce placebo effects (for a review, see Bajcar & Bąbel, 2018). For example, Colloca and Benedetti (2009) tested the effect of social learning on placebo analgesia using a laboratory-based experiment. They found that the group of participants who directly observed analgesic effects in another person experienced placebo analgesia that was similar in strength to the group of participants who were exposed to a conditioning procedure. Researchers have demonstrated that the effect of social learning on placebo effects appears to be mediated by acquired expectancies (Bajcar et al., 2022; Bajcar & Bąbel, 2018; Kirsch, 2018; Meeuwis et al., 2023).

Taken together, response expectancies, or beliefs that we have about how we will respond to stimuli in our environment (e.g., a pill), are thought to be informed by our learning history (i.e., personal conditioning history, social observation) and verbal and/or visual information provided to us about the stimuli (i.e., stimulus expectancy) by significant others or society more generally. These response expectancies are then, in turn, crucial in facilitating placebo effects. Sex differences have also been observed in the context of placebo responding. Relative to women, men have consistently been found to be more sensitive to placebo effects for a range of symptoms and conditions (e.g., Abrams & Kushner, 2004; Butcher & Carmody, 2012). The available research highlighting these sex differences will be reviewed in detail in Chapter 5.

It is important to note that not all conditions are equally amenable to being influenced by placebo effects (Hróbjartsson & Gøtzsche, 2010). For example, symptoms or conditions that involve perceived subjective, behavioural, and/or psychological outcomes, like pain, nausea, and anxiety, appear more likely to be impacted by placebos than those that involve acute illness, or chronic hereditary or degenerative diseases (e.g., heart attack, anemia, bacterial infection) (Wampold et al., 2005). Further, a meta-analysis

of placebo treatments for peripheral diseases found that placebos improved physical parameters (e.g., hypertension, asthma) by approximately 33% on average, whereas biochemical parameters (e.g., diabetes, hypercholesterolemia, anemia) were relatively unaffected (Meissner et al., 2007). Importantly, however, the studies included in this meta-analysis did not have a no-treatment control, thus extra-placebo factors like natural course and regression to the mean likely contributed to these improvements.

Although most placebo research focuses on pain and placebo analgesia, other reports have identified similar mediating relationships between response expectancies and placebo effects for symptoms like itch and dyspnea (for a review, see Wolters et al., 2019). Relatedly, another experimental study induced expectancies about participant's ability to cope with stressors following the completion of a questionnaire that assessed these capabilities (Pulopulos et al., 2020). Regardless of their actual abilities, researchers randomly informed participants that they either had or did not have strong abilities to cope with stressful situations (i.e., high and low expectancies, respectively). Following exposure to a laboratory stressor, participants in the high expectancy group experienced the stressor as less threatening and challenging, and had a lower cortisol response to stress, compared to the low expectancy group. Although no active or inert substance was administered during this study, it is nonetheless relevant to placebo theory, highlighting the key role of expectancy in dictating subjective and physiological responses.

It has been hypothesized that expectation may promote a cascade of psychophysiological actions through at least two pathways: anxiety modulation and reward modulation (for a review, see Benedetti et al., 2011). First, anxiety modulation (i.e., decrease of anxiety) has been implicated in placebo effects. It seems intuitive that anxiety would decrease if a distressing symptom, such as pain, is expected to diminish. In

a study examining placebo analgesia in response to rectal stimulation among participants with irritable bowel syndrome, participants experienced a significant placebo analgesic response that appeared to be at least partly mediated by changes in their emotional state (Vase et al., 2005). Indeed, expected pain relief was strongly correlated with anxiety in that higher expected pain relief tended to coincide with lower anxiety levels, which then facilitated a placebo analgesic response. Other studies providing evidence for the involvement of anxiety modulation in placebo effects have evaluated nocebo effects (i.e., negative outcomes or adverse effects prompted by beliefs that an intervention will cause these adverse outcomes). For example, Benedetti et al. (2006) induced nocebo hyperalgesia via verbal suggestion following administration of an inert compound. They found that in addition to inducing hyperalgesia, a significant hypothalamic-pituitary-adrenal (HPA) axis response was also induced. Further, both responses were blocked by a benzodiazepine, suggesting that anxiety is implicated in both these responses.

In addition to the ability for expectations to modulate anxiety, they are also thought to influence reward mechanisms. For example, in a sample of participants with Parkinson's disease, researchers identified a relationship between dopamine release in reward-related brain regions and a placebo effect (de la Fuente-Fernández et al., 2002). Specifically, they found that placebo administration increased dopamine in the ventral striatum (nucleus accumbens; implicated in reward), as well as a relationship between increased dopamine in the dorsal striatum (implicated in motor control) and actual placebo-induced clinical benefit (i.e., placebo effect). Researchers hypothesized that the *expectation* of symptom improvement may be considered rewarding and occurs regardless of actual symptom improvement. Additionally, another study evaluated the effects of 6 weeks of placebo treatment (versus fluoxetine) on brain glucose metabolism

in participants with depression (Mayberg et al., 2002). One of the key findings highlighted significant ventral striatal (nucleus accumbens) and orbital frontal changes at one week of treatment among those who eventually experienced clinical benefit in placebo and active drug conditions. Importantly, one week of treatment is not sufficient to induce a clinical response; thus, the observed brain metabolic changes in reward areas likely illustrate the *expectation* or *anticipation* of clinical benefit. Other investigations have demonstrated dopamine and opioid activity in reward and motivation neural circuits associated with both the anticipation and actual perceived efficacy of placebo-related analgesia (Scott et al., 2008).

Anxiety and reward modulation processes implicate a third type of learning involved in the induction of placebo effects. In addition to classical conditioning and social learning, operant conditioning also involves learning through direct or indirect pairing of stimuli, behaviour, and outcomes. In operant conditioning, the consequences of a given behaviour are fundamental in shaping the behaviour. Specifically, a behaviour that is immediately followed by a reinforcer (positive or negative) increases the likelihood of the behaviour reoccurring, whereas a behaviour followed by a punisher (positive or negative) tends to decrease the behaviour (Skinner, 1965). In the context of placebo effects, the repeated pairings of taking a drug (behaviour) and experiencing symptom reduction (consequence: negative reinforcement) and increased ability to engage in daily activities (consequence: positive reinforcement), would theoretically increase the likelihood of taking a drug or placebo in the guise of an active drug in the future (for a review, see Bąbel, 2020). Although there have been fewer studies evaluating the role of operant conditioning (vs. classical conditioning) in placebo effects, there is some experimental evidence that placebo hypoalgesia can be induced via operant conditioning

paradigms (Adamczyk et al., 2019; Bieniek & Bąbel, 2022). Similar to classical conditioning and social learning, learned expectations via operant conditioning appear to be key mediators of placebo effects (Bieniek & Bąbel, 2022).

Finally, it is worth noting that response expectancies tend to be self-confirming (Kirsch, 1985). In other words, because placebos can mimic the effect of drugs through these learning processes, the consequences following their administration (e.g., decreased symptoms/negative experiences and/or increased reward/positive experiences) provides positive feedback to the individual that confirms and reinforces the expectancy of their occurrence. As a result, these response expectancies and associated placebo responses tend to be highly resistant to extinction (Colloca & Benedetti, 2006; Montgomery & Kirsch, 1997). Taken together, this emphasizes the importance of considering non-pharmacological factors, like expectancy, in research evaluating drug-related outcomes.

Evaluating Drug Effects in Research

The gold standard for assessing drug-specific therapeutic effects in humans are double-blind randomized controlled trials (RCTs; Sackett et al., 1996), wherein participants are informed they have an equal chance of being assigned to an active drug or inert placebo condition. In this design, the assumption of additivity (i.e., additive model) is relied upon as a basis to determine the "true" drug effect, by subtracting the response in the placebo condition (i.e., placebo response) from the drug condition (i.e., drug effect). Notably, a placebo *response*, as referred to in RCTs, is comprised of the expectancy-mediated outcomes defined previously (i.e., placebo *effect*), as well as 'extra-placebo factors', such as improvement in symptoms due to spontaneous remission/natural history (i.e., course of disease), and regression to the mean (Benedetti, Carlino, et al., 2011; Kirsch, 2013).

Regression to the mean is a statistical artifact wherein extreme or elevated scores on a given outcome tend to regress to the population mean over time. Some researchers argue that this artifact explains a significant portion of the improvement in response to placebo treatment (Hengartner, 2020; Senn, 2011). Not surprisingly, regression to the mean tends to be particularly pronounced among clinical samples who were included in a study based on their elevated scores on a given outcome measurement (e.g., depression symptoms) (Barnett et al., 2005). In comparing short-term remission rates among individuals with moderate depression, Hengartner (2020) noted that those receiving placebo antidepressant treatment experienced similar symptom remission rates to untreated participants (26% and 23%, respectively; Jakobsen et al., 2017; Whiteford et al., 2013). The author therefore concludes that the genuine placebo effect as it relates to treatment expectancy is likely smaller than what has been reported in many previous investigations.

Despite the ubiquity of this additive model in clinical research, its validity has been questioned. Critics of the additive model highlight difficulties with complete blinding of drug conditions such that participants are able to guess the group they have been assigned to (e.g., Wampold et al., 2005). For example, participants may experience side effects or other observed changes in subjective or physiological state, which they are provided information about during the consent process and make guesses about their drug or placebo assignment accordingly. It is therefore possible that placebo effects in the drug and placebo conditions are amplified and reduced, respectively, due to the impact of response expectancies (Fisher & Greenberg, 1997; Kirsch & Sapirstein, 1998). If this were true, it would violate the core assumption of the additive model, which is that the magnitude of the placebo effect is equal in both the active drug and placebo conditions.

Determining the mechanisms through which drugs exert their effects is not only relevant from an academic standpoint, but it also has important clinical and policy implications. If, for example, a 'true' drug response cannot be correctly determined using existing research designs and models (i.e., additive model), then they cannot accurately inform clinicians, patients, and policy decision-makers about which novel medications to invest further resources into. Additionally, the RCT design is poorly suited to providing precise estimates about the magnitude of true placebo effects (vs. placebo responses) since extra-placebo variables (i.e., regression to the mean, spontaneous remission, natural history) are often not controlled for (i.e., not including a 'no treatment' control condition). While RCTs can still provide key insight into the efficacy of drug treatments for various clinical purposes, its limitations provide rationale for the use of other research designs to supplement and provide specificity to the information gleaned from RCTs.

In fact, the balanced-placebo design was initially developed to test expectancy effects or true placebo effects associated with various drugs used for non-clinical purposes (e.g., nicotine, alcohol, caffeine; Rohsenow & Marlatt, 1981). In the traditional balanced-placebo design, participants are randomly assigned to receive either the active drug or inert placebo, but the information provided to them about their drug condition is either accurate or inaccurate/deceptive. This yields four experimental conditions: (a) expect active drug, receive active drug (pharmacology + expectancy), (b) expect active drug, receive placebo (expectancy only), (c) expect placebo, receive active drug (pharmacology only), and (d) expect placebo, receive placebo (no pharmacology, no expectancy/control). In addition to being able to evaluate the additivity model (Kirsch, 2000), this design allows for the direct assessment of the independent and combined effects of a drug's pharmacological properties and its expectancy-driven placebo effects

(Sutton, 1991a). A variation of this design (i.e., half-balanced-placebo design) has also been used to evaluate placebo effects in research wherein an inert placebo is administered to all participants while still providing deceptive information to half of the participants about the drug content (e.g., Kirsch & Weixel, 1988; Wager et al., 2007). Other modifications, like using a cross-over versus between-subjects design can decrease inter-individual variation in drug and/or placebo responsiveness (e.g., Hammami et al., 2010).

A recent systematic review of 30 studies using balanced-placebo designs (Boussageon et al., 2022) found that only four studies supported the additivity assumption, whereas 16 found evidence of interactions between pharmacology and expectancy. These interactions were either sub-additive/antagonistic (i.e., total treatment effect was less than drug + placebo effect; e.g., Lund et al., 2014) or supra-additive/synergistic (i.e., total treatment effect was greater than drug + placebo effect; e.g., Hammami et al., 2016). Taken together, findings from these studies suggest that congenitally estimated drug effects may be biased due to interaction effects that are not accounted for in RCTs. As a result, pharmacological drug effects derived from RCTs may be over- or under-estimated. Understanding the role of expectancies and associated placebo effects are critical for contextualizing drug-related outcomes, particularly when evaluating the efficacy of novel therapeutic agents.

Cannabis

There has been growing interest in the use of cannabis and its chemical components for a range of therapeutic purposes and conditions (Khan et al., 2020; Legare et al., 2022). Cannabis, although a singular term, refers to the various preparations of the *Cannabis sativa* plant. While the chemical composition of cannabis is constantly evolving, it's resin is known to contain at least 500 unique chemical compounds, of which

125 are cannabinoids and 120 are terpenes (Radwan et al., 2021). Cannabinoids are the compounds found in cannabis that tend to have a characteristic chemical structure, some of which exert their action on cannabinoid receptors located throughout the brain and body. Among the most abundant cannabinoids, THC is known for its psychoactive and intoxicating effects (e.g., 'high' feeling), whereas CBD is non-intoxicating, though has gained more interest for its therapeutic potential (e.g., WHO, 2018). Moreover, terpenes, such as myrcene and limonene, are the second largest class of chemical compounds found in cannabis and are responsible for generating aroma. Research has suggested that cannabinoids and terpenes are largely responsible for producing effects associated with cannabis (McPartland & Russo, 2001; Russo, 2011). The prevalence and ratio of these cannabinoids and terpenes can vary widely depending on the species or variety of cannabis (for a review, see Booth & Bohlmann, 2019). Notably, interactions between different cannabinoids and/or terpenes can result in variable biopsychological effects compared to single isolated cannabinoids (i.e., synergistic and/or antagonistic effects; Christensen et al., 2023; McPartland & Russo, 2001; Russo, 2011), making cannabis a uniquely complex drug.

To add to its complexity, multiple preparations of cannabis exist, including dried herbal product and extracted oil of specific cannabinoid and terpenes that can be used in various oral, inhaled, or topical formulations. Common methods and routes of administration include smoked dried flower (e.g., joints, bongs, pipes, vaporizers), vaporized concentrates or oil (e.g., dabs, vape pens), oral consumption (e.g., edibles, oils), oromucosal sublingual (oils, sprays), and topical/transdermal (creams) (Russell et al., 2018; Stella et al., 2021). Additionally, there is a dearth of well-validated and utilized standardized assessments to determine use patterns that account for the different

pharmacokinetic profiles associated with different methods of administration, as well as differences in cannabinoid composition and potency. As a result, consensus regarding a "standard dose" of cannabis, as has been developed for other substances (e.g., alcohol) has not been achieved (Temple et al., 2011), though some attempts at standardization have been proposed (e.g., Freeman & Lorenzetti, 2020). Some measures and guidelines have been developed in effort to resolve inconsistencies related to cannabis assessment and dosing (e.g., Cuttler & Spradlin, 2017; Freeman & Lorenzetti, 2020); however, such research is still in its infancy. Taken together, these factors unsurprisingly contribute to the difficulties conducting and making inferences about existing cannabis research, which is important given how increasingly accessible cannabis has become in recent decades due to policy changes (e.g., legalization; Hall et al., 2019).

In terms of prevalence, cannabis is one of the most widely used substances world-wide, with recent 2020 estimates suggesting that approximately 4% of the global adult population used cannabis at least once in the last year (United Nations Office on Drugs and Crime (UNODC), 2022). More recent Canadian data from 2023 show that past-year non-medical use rates among those 16 years and older was much higher than the global average at 26% (Health Canada, 2024). People have reported using cannabis for different reasons, some of which have been identified through literature on motives. For example, among participants engaging in frequent, recreational cannabis use, motives tended to involve coping, social, conformity, expansion, and routine (Benschop et al., 2015). It appears that one of the most common reasons for cannabis use among regular users is to relieve tension and stress and promote relaxation (i.e., coping; Copeland et al., 2001; Green et al., 2003; Hyman & Sinha, 2009).

Despite the variability of cannabis with regards to cannabinoid composition and potency and the distinct pharmacodynamic profiles associated with different cannabinoids, many studies have treated cannabis as a singular, constant entity. Moreover, the potency of THC in cannabis has drastically increased over the last few decades (ElSohly et al., 2016; Freeman et al., 2019). Conjectures based on these studies are therefore at risk of being overly reductionistic. As such, disentangling effects and outcomes as they relate to different cannabinoids (i.e., THC, CBD) may be of benefit, especially in the context of informing policy and potential therapeutic applications.

Cannabinoids: THC and CBD

THC, the primary psychoactive cannabinoid identified in most varieties of cannabis, has been associated with a range of psychological and behavioural effects. For example, acute THC administration has been associated with feelings of euphoria/"high", numbness or tingling of extremities, light-headedness/dizziness, floating sensations, difficulties paying attention, memory disruptions, increased heart rate, sweating, time dilation, fatigue, increased introspection, increased appetite, and anxiety (for a review, see Stella, 2023). THC has been implicated in various therapeutic effects. For example, among a convenience sample of primary care patients, the majority (>50%) who used THC reported that it was "very helpful" in improving pain, depression, sleep, arthritis, and migraine (Wershoven et al., 2020). However, a recent systematic review and meta-analysis concluded that there is the moderate evidence for THC and its' synthetic analogues (i.e., dronabinol, nabilone) for only a subset of symptoms and conditions: chronic pain, appetite stimulation, and Tourette (Bilbao & Spanagel, 2022). Evidence for other therapeutic effects were graded at low, very low, or no evidence based on available RCTs.

The pharmacokinetics and pharmacodynamics of THC have been described in detail elsewhere (Grotenhermen, 2003; Stella, 2023) and are largely beyond the scope of this dissertation. Briefly, in terms of pharmacodynamics, THC has been shown to primarily act on the endocannabinoid system, which is a complex whole-body system responsible for maintaining internal balance (i.e., homeostasis) in various psychobiological processes (e.g., emotion, digestion, respiration, reproduction) via downstream signalling processes (Battista et al., 2012; Lowe et al., 2021). Specifically, it binds to cannabinoid 1 (CB1) receptors located predominantly located throughout the brain and central nervous system as a partial agonist, producing a cascade of downstream actions. This is thought to mediate the psychoactive effects described previously. Additionally, THC has been shown to be a partial agonist of CB2 receptors, located primary on immune cells, which may in part facilitate anti-inflammatory actions and other potential therapeutic effects (Grotenhermen, 2003).

CBD is the second most abundant cannabinoid in cannabis. While it is devoid of reinforcing properties that are associated with euphoria and the subjective "high" related to THC, there has been a surge of interest in using CBD as a therapeutic agent. In fact, CBD use for therapeutic purposes over the last decade has grown considerably (WHO, 2018) as it has been claimed to produce a broad range of effects including anti-inflammatory, antiepileptic, sedative, anxiolytic, antipsychotic, antidepressant, and neuroprotective actions (Atalay et al., 2019; Bergamaschi, Queiroz, Chagas, et al., 2011; Campos et al., 2016; Khoury et al., 2017). Additionally, a cross-sectional survey of participants who had prior experience using CBD found that it was being used for a range of physical and mental health symptoms, of which anxiety, sleep, stress, and general health and wellbeing, and pain were most frequently endorsed (Moltke & Hindocha,

2021). Despite respondents self-reporting effectiveness for stress, sleep, and anxiety among those using for these purposes (Moltke & Hindocha, 2021), a recent meta-analysis highlighted that epilepsy and Parkinson's Disease are the only conditions and symptoms where there is moderate/high evidence to support the therapeutic efficacy of CBD. Of the existing research considered within this meta-analysis, other therapeutic effects associated with CBD have low, very low, or no graded evidence to support them (Bilbao & Spanagel, 2022).

While the pharmacokinetics and pharmacodynamics of CBD have been detailed in previous reports (Grotenhermen, 2003; Stella, 2023), it is notable that its mechanisms of action are complex and not yet fully understood. CBD's purported therapeutic effects are likely facilitated by multiple concurrent mechanisms, implicating the serotonin, opioid, and endocannabinoid systems (Stella, 2023). In addition to modulating targets not mediated by cannabinoid receptors, research has demonstrated that CBD is a negative allosteric modulator of CB1 receptors, thereby restraining CB1 signaling (Laprairie et al., 2015).

When administered together, THC and CBD appear to have interacting effects. For example, CBD has been shown to decrease the potency and efficacy of THC at CB1 receptors (Laprairie et al., 2015), which may in part explain the observed reduction of THC-associated adverse effects (e.g., memory/cognition effects) when co-administered with CBD (for a review, see Boggs et al., 2018). Pre-clinical studies have also supported the increased efficacy of CBD and THC combined or full-spectrum cannabis compared to THC or CBD alone for various conditions (Procaccia et al., 2022; Russo, 2019). It is important to note, however, that the complex combined psychopharmacological effects of THC and CBD are obscure (Morales et al., 2017). Indeed, critics have highlighted the

contradictory and equivocal findings of pre-clinical and clinical studies evaluating effects related to combined THC and CBD applications, noting difficulties drawing inferences from variable cannabinoid ratios and dosages (Christensen et al., 2023). At present, recent meta-analysis indicates that moderate grade evidence exists for synthetic THC and CBD combined (i.e., nabimols) in the treatment of spasticity associated with multiple sclerosis, chronic pain, sleep quality, and substance use disorders (Bilbao & Spanagel, 2022).

With regards to pharmacokinetics, it is worth noting that cannabinoids generally have poor bioavailability when administered orally. For example, the bioavailability of oral THC ranges from 4-12% and is approximately 6% for CBD (Chayasirisobhon, 2021). Given the high lipophilicity of cannabinoids, studies have found that CBD levels, for example, were higher when administered in a lipid-based solution (e.g., sesame or vegetable oil), compared to non-lipid solutions (Bergeria et al., 2022; Crippa et al., 2022), or when consumed with food, compared to a fasted state (Bergeria et al., 2022). In fact, one investigation found that when consumed with a high-fat meal, CBD's bioavailability had a four-to-five-fold increase relative to a fasted state (Taylor et al., 2018). Peak plasma concentrations of orally-administered cannabinoids occurs at approximately 2-4 hours for CBD (Bergeria et al., 2022; Crippa et al., 2022) and 2-3 hours for THC (Hansen et al., 2024). These pharmacokinetic profiles are important to consider when evaluating outcomes of pre-clinical and clinical studies, which commonly use oral routes of administration to evaluate the therapeutic efficacy of cannabinoids.

The Stress Response System

To critically evaluate the mechanisms through which CBD may be exerting therapeutic effects, it is important to review some of the key emotional and psychophysiological processes that may be implicated. The stress response system is

highly complex and involves multiple systems. Not only is it involved in mobilizing responses to minor and major stressors, but dysfunction within this system is also implicated in various mental and physical health conditions. The following subsection will provide a review of the stress response system.

During a stress response, the autonomic nervous system (ANS) and hypothalamic-pituitary adrenal (HPA) axis are activated within seconds of anticipating a perceived threat and can last up to 90 minutes following the termination of the stressor (Dickerson & Kemeny, 2004; Sapolsky et al., 2000). Briefly, opposing processes of the parasympathetic (i.e., PNS via acetylcholine) and sympathetic nervous systems (i.e., SNS via norepinephrine) within the ANS facilitate the first wave of acute stress responding and occur almost immediately. Physiological parameters implicated in stress responding, like heart rate (HR) and heart rate variability (HRV), are regulated by the ANS and help mobilize energy to cope with stressors. Notably, HR appears to be regulated by the dynamic relationship between both PNS and SNS influences, which act to slow and increase the heart rate, respectively (for a review, see Shaffer & Ginsberg, 2017). This relationship is complex such that the PNS and SNS can increase and decrease together or separately to produce changes in HR (e.g., HR recovery following exercise involves continual elevation of SNS activity combined with PNS re-activation; Pierpont et al., 2013). The PNS has been shown to contribute the majority of the influence to HR regulation at rest, until heart rate reaches ~140 beats per minute, at which point contributions from the PNS and SNS are approximately equal (White & Raven, 2014).

Relative to parasympathetic influences, which exert their effects very quickly (<1 second), sympathetic influences tend to exert their actions more slowly (>5 seconds) (Nunan et al., 2010). Given that commonly used metrics of HRV reflect measures related

to the precise beat-to-beat timing of the heart rhythm (i.e., Root Mean Square of Successive Differences; RMSSD), these outputs are thought to be dominated by vagal inputs and therefore provide information about PNS activation (Thayer et al., 2012).

During the second wave of the stress response, the HPA axis facilitates a cascade of actions that ultimately leads to the release of cortisol with a peak response occurring approximately 21-40 minutes following the onset of a stressor (Dickerson & Kemeny, 2004), with some evidence for a peak as early as 10 minutes post-stressor onset (Balters et al., 2020).

Although the link between the ANS and HPA axis is more difficult to elucidate due to the lag in responding between the two systems, research has demonstrated that a reciprocal association likely exists (e.g., Pulopulos et al., 2018; Stam et al., 2023). For example, vagal activity is thought to play a role in inhibiting the HPA axis (Thayer & Sternberg, 2006). Elevated vagal activity appears to increase activity in areas of the prefrontal cortex (PFC) (Thayer et al., 2012), which has inhibitory connections with the amygdala (Baeken et al., 2010). Given that the amygdala appears to play a potentiating role in HPA responsivity (Herman et al., 2005), the inhibition of the amygdala through vagal activity in the PFC could theoretically minimize the extent of cortisol release in response to a stressor. Although this would be suggestive of a strong relationship between cortisol and HRV, many studies have found non-significant or weak associations between changes in HRV and cortisol during stressful situations (e.g., Heilman et al., 2008; La Marca et al., 2011; Looser et al., 2010). One possibility is that these studies have not adequately considered the temporal synchronization of the stress response system, as the anticipation period prior to the onset of a stressor may be particularly relevant in the context of successful stress adaptation. Indeed, one study found that anticipation-induced,

but not stress-induced changes in HRV were associated with HPA axis reactivity (i.e., cortisol response; Pulopulos et al., 2018).

A key factor predicting an individual's response to a stressor is in their interpretation of the stressor (McEwen, 1998). If one interprets an event or situation as threatening, various biophysiological systems (e.g., ANS, HPA axis, immune system) become involved to mobilize the individual to cope with a perceived threat. A process called "allostasis" has been termed to describe the change in these biophysiological processes leading to adaptation (i.e., stability through change; Sterling & Eyer, 1988). In the short-term, allostasis helps to adapt and protect an organism. This process often begins in anticipation of an event or stressor (e.g., appraisal of a stressor and one's ability to cope), which can help the body prepare for change *before* the stressful situation or event takes place. Notably, prior knowledge and experience also plays a role in interpreting situations and facilitating anticipation-induced changes in bodily processes (Sterling, 2012). Emotions like anxiety, and their cognitive components, can indeed be useful during this process with the caveat that they occur in appropriate/relevant situations, and are not enduring or chronic (for a review, see Sylvers et al., 2011).

In terms of observable changes in physiological indicators of stress, there are a few possible scenarios that could represent allostasis. One possibility is that higher vagal tone, as measured through increased HRV, may act as an initial marker of successful emotional regulation that predicts dampened HPA axis responsivity (i.e., smaller cortisol increase) in response to a stressor (e.g., Pulopulos et al., 2018). On the other hand, it is possible that acute, reactive decreases in HRV and associated cortisol increases in response to a stressor is adaptive, so long as it only occurs in relevant contexts and is not enduring (Weber et al., 2010).

Unlike short-term allostasis, long-term allostasis, also known as "allostatic load" (i.e., imbalance of biophysiological systems that influence adaptation), is associated with various negative consequences, including enduring biophysiological changes leading to various negative physical health and mental health effects. Allostatic load can manifest as frequent biophysiological stress responses, lack of adaptation to stressors over time (i.e., habituation), an inability to shut down stress responses, or inadequate stress responses leading to hyperactivity of other systems (e.g., increased immune system and inflammatory activity) (McEwen & Gianaros, 2011).

It is worth noting that biological sex is implicated in various psychological and physiological processes, such as responses to and experiences of stress and other emotions. Literature evaluating these sex differences will be reviewed and summarized in more detail in Chapter 5. Briefly, women tend to be more likely to experience stress- and anxiety-related disorders (Altemus et al., 2014), a higher level of daily and chronic stressors (Matud, 2004), and perceive higher levels of stress (Graves et al., 2021), relative to men. Additionally, while women appear to respond more strongly to a stressor initially via changes in ANS (e.g., increased HR, decreased HRV) (Hamidovic et al., 2020), men tend to have a stronger HPA response to stressors (e.g., increased cortisol) (Gu et al., 2022; Liu et al., 2017). It is therefore possible that men and women may respond to stressors differently. This highlights the importance of considering potential sex differences in research evaluating the stress response system.

Overall, stressors are a normal part of daily life. The stress response system is fundamental in facilitating adaptive responding to stressors as well as contributing to overall health and the likelihood of experiencing various psychophysiological disorders. Thus, it is possible that the stress response system is implicated in facilitating at least

some of CBD's purported therapeutic effects as they directly relate to acute and/or chronic experiences of stress and anxiety.

The effects of CBD on stress and anxiety

Observational studies of non-medical/recreational cannabis users have highlighted that stress relief (Moltke & Hindocha, 2021) and anxiety reduction (Corroon & Phillips, 2018; Tran & Kavuluru, 2020) are among the most common self-reported reasons for using CBD. The majority of participants using CBD for these purposes also endorse a moderate-to-high degree of therapeutic efficacy (Corroon & Phillips, 2018; Moltke & Hindocha, 2021). Another observational study investigated real-world data from an application that supports medical cannabis users (Kalaba & Ware, 2022). Researchers found that individuals most frequently used medical cannabis to treat anxiety disorders and that CBD-dominant products were often selected for the management of mental health conditions in general. Individuals also endorsed significant therapeutic effects for all conditions being treated with medical cannabis, including anxiety (i.e., anxiety reduction) (Kalaba & Ware, 2022). Additionally, among patients presenting to a medical cannabis center for various conditions, daily CBD treatment (40-100mg/day) significantly improved self-reported symptoms of anxiety and depression after 3 weeks (regardless of which underlying condition they were being treated for) (Gulbransen et al., 2020). Taken together, these substantial claims have prompted researchers to further investigate the purported therapeutic effects of CBD for stress- and anxiety-related conditions using controlled, experimental study designs.

Experimental studies evaluating the impact of CBD on stress and anxiety in humans have either used non-clinical/healthy populations or clinical samples. There are notable differences between these two subgroups that are important to consider when

critically evaluating the literature on CBD, stress, and anxiety. First, studies using healthy participants experimentally induce acute stress and anxiety that may not necessarily represent pathological or disordered processes. Additionally, CBD tends to be administered as a one-time/single dose in these investigations; thus, the timing of stress- and anxiety-induction as well as outcome assessments are crucial to accurately capture the pharmacological effects of CBD. Given that the majority of people using cannabis do so on a non-daily basis (i.e., only 15% of those who use cannabis are daily users; Health Canada, 2024), examining the efficacy of CBD for acute stress and anxiety has relevant implications. On the other hand, clinical studies of participants with stress- or anxiety-related disorders (e.g., generalized anxiety disorder [GAD], social anxiety disorder [SAD], posttraumatic stress disorder [PTSD]) have distinct characteristics that differentiate them from non-clinical populations. Specifically, their experiences of anxiety and/or stress are more chronic and pathological and less adaptive, with notable differences in their appraisal of and responses to stressors. For example, relative to healthy controls, individuals with GAD showed greater amygdala activation in anticipation of negative stimuli (Nitschke et al., 2009). Core cognitive processes implicated in anxiety disorders, like worry, impact stress responsivity more than the stressor itself (Brosschot et al., 2007). In many studies with clinical populations, CBD also tends to be administered daily (vs. one time) with outcomes monitored over time.

It is common practice to test the effects of a novel substance or compound on healthy individuals prior to evaluating its efficacy in clinical populations. In fact, trials with healthy populations are key in determining whether to invest in and pursue research with specific clinical conditions. However, given the differences between sample subgroups with regards to psychophysiological responsivity to stressors, as well as

research design and methodology, it is unclear to what extent direct inferences can be made between populations (i.e., findings from healthy participants may not be fully translatable to clinical populations, and vice versa). It is possible that CBD influences stress and anxiety through different processes in healthy and clinical populations (Crippa et al., 2018). In addition to research with healthy individuals being a 'first step' in evaluating its efficacy for clinical conditions, it also has implications for those who use cannabis to cope with anxiety or stress. Indeed, observational studies of individuals who use CBD for stress and anxiety reduction are not limited to those with clinical syndromes (e.g., Corroon & Phillips, 2018; Moltke & Hindocha, 2021; Tran & Kavuluru, 2020).

Exposure to minor daily stressors (e.g., interpersonal difficulties, work- or school-related challenges) is relatively common among the general population, occurring on approximately 2-3 days per week (Almeida, 2005; Almeida et al., 2002). Chronic, high frequency, or high intensity stressors, as well as stressors perceived as being more threatening, tend to be associated with more negative outcomes, such as lower positive affect, higher negative affect, psychological distress, and physical symptoms (Almeida, 2005; Grzywacz et al., 2004). Combined, this also increases the risk of experiencing mental and physical health difficulties, particularly if these stressors are not being managed effectively (i.e., how they are being interpreted and responded to; Charles et al., 2013; Piazza et al., 2013). Importantly, it appears that the response or reaction to a stressor is more important than the stressor itself in predicting positive or negative outcomes (Charles et al., 2013). It is therefore understandable that people seek various pharmacological and nonpharmacological strategies to modulate the effect of stressors on their daily lives. This further highlights the utility of investigating the effects and actions of CBD in both healthy and clinical samples.

A literature review was conducted via PubMed to identify all published peer-reviewed experimental research to our knowledge that tests the effects of CBD on stress and/or anxiety up until March 2024. The identified research described below has been categorized and presented according to the population being studied. Investigations using clinical samples will be summarized first followed by studies using healthy participants. The latter will be outlined in more detail as it is most relevant to this dissertation.

CBD has been tested in clinical populations of individuals with stress- or anxiety-related disorders, including SAD and PTSD. First, there have been five clinical studies evaluating the efficacy of CBD among those with SAD. Four of the five studies found positive results, wherein 300mg-800mg of oral CBD administration was associated with subjective anxiety improvements (Bergamaschi et al., 2011; Berger et al., 2022; Crippa et al., 2011; Masataka, 2019). Among these studies with positive findings, three were placebo-controlled RCTs with relatively small sample sizes (Bergamaschi et al., 2011; Crippa et al., 2011; Masataka, 2019), whereas the other was an open-label, unblinded study without any control (Berger et al., 2022). Moreover, two of the positive studies evaluated the efficacy of CBD on anxiety outcomes after one dose and an experimental stressor (Bergamaschi et al., 2011; Crippa et al., 2011), whereas the other two employed a daily dosing regimen for four weeks (Masataka, 2019) or 12 weeks (Berger et al., 2022). The RCT that did not find any positive treatment outcomes administered 300mg of CBD (vs. placebo) prior to eight exposure-based treatment sessions (Kwee et al., 2022). They found that CBD did not improve treatment outcomes relative to placebo. Although their sample size appeared adequate, it is noteworthy that they did not administer CBD with food or within an oil vehicle, and only had a two-hour absorption period, which likely impacted the bioavailability and absorption rate of CBD. It is unclear to what extent these

factors impacted outcomes. Taken together, the evidence to support the efficacy of CBD for SAD appears to be limited by few placebo-controlled studies with relatively small sample sizes and is therefore inconclusive.

Second, there were three identified clinical studies evaluating the efficacy of CBD among those with PTSD. Two studies found at least some positive effects of 33.18mg-300mg oral CBD on subjective PTSD or anxiety symptom severity (Bolsoni et al., 2022b; Elms et al., 2019). One study with positive findings was an open-label, unblinded case series, wherein PTSD symptoms reduced across 8 weeks of daily CBD treatment (Elms et al., 2019). The other study was a single-dose placebo-controlled RCT and the effects of CBD were mixed depending on the type of trauma (Bolsoni et al., 2022b). Only participants who had nonsexual trauma showed lower levels of anxiety and cognitive impairment after listening to an audio recording of their trauma story (CBD vs. placebo), whereas no effects of CBD were found in those who had sexual trauma. Although highly speculative, the authors proposed that sexual assault survivors may need a higher dose of CBD (despite similar trauma severity scores between subgroups in their study). The authors of this report also assessed whether their single dose of CBD would influence participants' subjective anxiety post-trauma recall one week after CBD had been administered (Bolsoni et al., 2022a). They failed to find any significant differences between CBD and placebo. It is also worth noting that outcomes in these studies were assessed 90-minutes post-CBD administration. While CBD's absorption was facilitated by a corn oil vehicle, it is unclear whether peak plasma concentrations were achieved at 90 minutes. Taken together, the impact of CBD on PTSD and associated anxiety symptom severity is weak and remains inconclusive.

Third, there have been three studies evaluating the efficacy of CBD on individuals with sub-clinical traits, such as elevated baseline anxiety or trait worry. Each of these studies found at least one positive finding related to various CBD doses and administration parameters on subjective anxiety (Bidwell et al., 2024; Dahlgren et al., 2022; Gournay et al., 2023). One of the studies used a placebo-controlled RCT design and tested the effects of acute versus two weeks of oral CBD (300mg, 50mg) on individuals who were identified as high trait worriers (Gournay et al., 2023). They found that two weeks of 300mg CBD decreased anxiety relative to baseline; however, this group also had the highest baseline anxiety, and thus other factors may have influenced the results (e.g., regression to the mean). There were no other CBD-driven effects identified on anxiety or worry. The other two positive studies were open-label trials testing the effects of full-spectrum, high CBD product (sublingual, dried flower) among samples of individuals with mild-to-severe anxiety symptoms (Bidwell et al., 2024; Dahlgren et al., 2022). Both studies found that repeated CBD administration had positive effects on stress reduction and/or anxiety symptoms. Taken together, the effects of CBD on anxiety symptoms among those with generally elevated anxiety-related symptoms is largely limited to open-label studies wherein expectancies are not controlled for and results are, therefore, inconclusive.

Most of the experimental stress and anxiety research to date has been conducted on healthy adult populations. All 12 studies identified that evaluated the impact of CBD on stress and/or anxiety outcomes were double-blind placebo-controlled RCTs. Only five of the 12 studies found a positive effect of oral CBD dosages (300mg, 400mg, 1mg/kg) on subjective indices of anxiety relative to placebo (Crippa et al., 2004; Linares et al., 2018; Zuardi et al., 1982, 1993, 2017). Most of these investigations induced anxiety

through the use of a social stressor (simulated public speaking test; Linares et al., 2018; Zuardi et al., 1993, 2017), whereas the other studies provoked acute anxiety using neural imaging anticipation (SPECT; Crippa et al., 2004) and THC (Zuardi et al., 1982). Among all studies with healthy participants, four have evaluated the efficacy of multiple dosages relative to placebo. Two studies found that 300mg was effective at impacting subjective anxiety outcomes, while higher and lower dosages were not (Linares et al., 2018; Zuardi et al., 2017), the other two studies found no effect of 300mg, or any other dose tested (Leen-Feldner et al., 2022; Stanley et al., 2022). While these studies used similar administration parameters (i.e., oral CBD administered within an oil vehicle to promote absorption, 1.5-2.5-hour absorption periods), they differed in the stressor used. Only the studies with positive findings tended to use social/public speaking stressors, whereas the other two investigations used academic testing (Stanley et al., 2022) and a carbon dioxide challenge (Leen-Feldner et al., 2022). It is therefore possible that 300mg of single-dosed CBD is only effective at attenuating socially related anxiety. Despite the subjective anxiolytic effects of CBD observed in these studies, they tend to occur in absence of associated physiological changes that often coincide with anxiety or stress reduction (i.e., heart rate, blood pressure, skin conductance, cortisol). One exception is a study by Fusar-Poli et al. (2009) which found that, relative to placebo, CBD was associated with a reduced electrodermal skin conductance response (SCR; i.e., number of SCR fluctuations) during the processing of intensely fearful faces. Notably, the threshold of detection for these SCRs was set at .01 microSiemens, which is considerably lower than thresholds used in other studies (e.g., .05, .2; Graham et al., 2005; Shiota et al., 2011; Williams et al., 2001). It is unclear whether this finding would be replicated at different thresholds.

Other RCTs have observed a positive effect of CBD on fear-related learning mechanisms and neurobiological processes. For example, using a laboratory-based fear conditioning and extinction procedure, Das et al. (2013) found that vaporized CBD (vs placebo) led to enhanced consolidation of extinction learning processes. This effect was only observed when CBD was administered *after* extinction learning, suggesting that timing is key. Two other studies that used fMRI data from the same sample of 15 men were interested in evaluating the effects of oral CBD (600mg), THC (10mg), and placebo on brain functioning during emotional processing. Although the subjective anxiolytic effects of CBD were inconclusive (i.e., $p>.05$), there were observed functional neural differences in CBD and THC administration, relative to placebo. The results as they pertain to CBD will be discussed in detail as they are most relevant to this dissertation. CBD was associated with decreased signalling in the amygdala as well as the anterior cingulate cortex in response to fearful faces (Fusar-Poli et al., 2009). Their second study demonstrated that these changes were mediated by decreased connectivity *between* these brain regions (Fusar-Poli et al., 2010); this connectivity has been implicated in attention to threat and emotional processing (Bishop, 2007) and may be implicated in anxiety disorders (Berkowitz et al., 2007).

Finally, four RCTs had negative/null findings in that oral CBD (150mg-600mg) did not significantly impact any self-reported, behavioural, biophysiological, or neural outcomes relative to placebo (Bloomfield et al., 2022; Leen-Feldner et al., 2022; Rossi et al., 2023; Stanley et al., 2022). In addition to numerous dosages tested between studies, various administration parameters were used, including variable absorption periods (1.5-3 hours) and unstandardized food and CBD preparations (administration with and without

food, dissolved in oil and without any oil), making it difficult to ascertain whether a true null effect of CBD exists.

Taken together, there is some evidence to suggest that acute/single dose CBD administration influences stress- and anxiety-related indices in healthy populations; however, research findings are largely mixed. The positive effects tend to be specific to self-report anxiety reductions following a social stressor (i.e., public speaking). While physiological indices of stress and anxiety (e.g., heart rate, blood pressure, skin conductance) have largely been unaffected by CBD administration, there have been reports of CBD-related neural changes that could explain some of the positive anxiolytic findings (Crippa et al., 2004; Fusar-Poli et al., 2009, 2010). Overall, the variability in CBD dosages and administration parameters that impact absorption and bioavailability, as well as other study limitations such as small sample sizes and non-replicated findings, all lend to the difficulties in making conjectures about the efficacy of CBD for stress and anxiety among both clinical and non-clinical populations. Importantly, these RCTs have not considered potential expectancy and placebo-driven influences.

CBD-related expectancies

The significance of evaluating and considering CBD-related expectancies in experimental and clinical research is underscored by the known influence of non-pharmacological factors in facilitating drug outcomes and the well-studied placebo effect, which appears to be at least in part mediated by expectation. This is particularly relevant in the context of CBD, a substance that, despite our not fully knowing its mechanisms of action, is often used for and perceived as efficacious for therapeutic purposes (e.g., stress and anxiety) among medical and non-medical and/or recreational users. One could argue that the potential for response expectancies associated with CBD is limited due to

minimal overt changes to physiological markers such as heart rate or body temperature (e.g., Iffland & Grotenhermen, 2017), and few subjective and behavioral effects (e.g. Haney et al., 2016). As such, participants in double-blind placebo-controlled CBD trials may not be able to guess their assigned drug condition. On the other hand, several studies have reported reliable differences between CBD and an inert placebo on subjective feelings of sedation and anxiety (Bergamaschi et al., 2011a; 2011b; Crippa et al., 2004; 2011; Zuardi et al., 1993), but the extent to which such differences impact participants perceptions about their drug assignment is not known. Indeed, since expectations tend to activate in the context of ambiguity, and since our internal or interoceptive signals tend to serve as highly ambiguous cues (e.g., racing heart), interoceptive signals can be attributed to a placebo, thereby reinforcing the initial response expectancy.

Summary

Drug effects are comprised of pharmacological and non-pharmacological factors (Meyer et al., 2022). The placebo effect is an example of a non-pharmacological factor that has often been ignored in clinical and experimental cannabis research, despite having 'real' subjective, behavioural, and physiological effects. Theories have suggested that the placebo effect is mediated by individual expectancies, which can be informed by various processes including classical, operant, and social learning mechanisms (e.g., Kirsch, 2013). Although placebo-controlled, double-blind RCTs are considered the gold standard design to assess the efficacy of a drug, they are unable to provide precise estimates of drug and placebo effects, which may lead to biased conclusions (Wampold et al., 2005). Supplementing these studies with balanced-placebo designs can be helpful in the context of understanding mechanisms through which drugs exert their effects.

Cannabis is a highly complex plant with hundreds of unique chemical compounds (Radwan et al., 2021) that vary according to the preparation, making it a particularly challenging drug to study. Among its most abundant cannabinoids, THC has been associated with various psychoactive and positively reinforcing properties, whereas CBD has gained significant interest as a potential therapeutic agent (WHO, 2018). CBD has been claimed to have anxiolytic and stress-dampening effects in clinical populations (Gulbransen et al., 2020; Kalaba & Ware, 2022) and non-clinical healthy individuals (Corroon & Phillips, 2018; Moltke & Hindocha, 2021); however, consistent evidence supported by RCTs for these claims is lacking (Dammann et al., 2024). It is unclear to what extent these effects are attributable to non-pharmacological expectancy-based factors.

Dissertation Aims

The primary aims of my dissertation are to (i) gain insight into cannabinoid-related response expectancies (i.e., THC, CBD), and (ii) evaluate the extent to which CBD-related expectation alone (stimulus and response expectancies) contribute to the purported stress- and anxiety-dampening effects associated with CBD in healthy adults (i.e., the placebo effect). Overall, my dissertation aims to offer preliminary insights into the non-pharmacological, expectancy-based components of cannabinoid effects. This is also a fundamental step in better understanding CBD's mechanism of action for acute stress and anxiety processes, which has important research, clinical, and policy implications for adults using cannabis non-medicinally and/or recreationally as well as potential downstream effects for clinical populations.

It is worth noting that the COVID-19 pandemic and cannabis-related research policies impacted my original dissertation plan. Specifically, I had initially planned to

conduct a full cross-over balanced-placebo design using hempseed oil and a low dose of sublingual CBD oil (.3mg/kg) to evaluate the extent to which expectancy and pharmacology alone and in combination contributed to CBDs purported stress and anxiety dampening effects in a sample of healthy adult participants. Unfortunately, new government restrictions on cannabis-related research had prevented our group from obtaining CBD oil for research purposes, despite REB approval. We decided to proceed with recruitment for the placebo/hempseed oil drug condition; however, after 43 participants had engaged in the in-person study procedures, the COVID-19 pandemic required us to indefinitely pause data collection at which time we decided to conclude the study and disseminate the placebo arm of this research (Study 2a). Given the virtual environment mandated by the pandemic, we decided to conduct a survey-based study to broadly evaluate expectancies about the effects of CBD and THC (Study 1). Further, given the restrictions on in-person work, our group was unable to access and analyze some of the physiological data we had collected (i.e., salivary cortisol). As a result, we were required to wait to analyze cortisol data, at which time we decided to extend Study 2a by evaluating the role of biological sex and CBD-related expectation on cortisol in the context of an acute stressor (Study 2b).

Although all three studies included at least one within subject nested factor, different analytic approaches were selected to in attempt to optimize interpretability and minimize bias from the limitations presenting within each dataset. Additionally, across all studies, the data remained untransformed (i.e., no log transformations were applied prior to analysis), as these kinds of data transformations have been shown to add to interpretation challenges (e.g., changing the mean values) and rarely improves model fit (Feng et al., 2014). Different decisions were also made regarding the retention of extreme

multivariate outliers across studies. The rationale for these decisions and the selected statistical approaches will be provided below.

Study 1

Entitled "*Perceptions about THC and CBD effects among adults with and without prior cannabis experience*", Study 1 (Spinella, Bartholomeusz, et al., 2023) investigated the extent to which people have various response expectancies about the effects of CBD, THC, and THC & CBD combined. Prior research has largely focused on evaluating expectancies for cannabis, without considering individual cannabinoids (Buckner et al., 2013; Hayaki et al., 2010; Skenderian et al., 2008; Torrealday et al., 2008; Waddell et al., 2021). To our knowledge, only one study has been interested in evaluating expectancies related to CBD (Walukevich-Dienst et al., 2022). This is important given that most experimental and clinical research is interested in testing the effects of specific cannabinoids, like THC and CBD. Study 1 provides insight into the extent to which people's expectancies differ between cannabinoids and/or based on prior cannabis use experience (i.e., prior use versus no prior use).

Using a cross-sectional survey-based design, we sampled adults across Canada and included responses of those who self-reported having at least some knowledge of CBD and THC (n = 345). We hypothesized that (i) CBD-containing products would be associated with the highest expectancies for various therapeutic effects, (ii) THC-containing products would be associated with the highest expectancies for positive and negative non-therapeutic effects, and (iii) individuals who reported prior cannabis use experience would have the highest expectancies for therapeutic and positive non-therapeutic effects. These hypotheses were derived from literature highlighting the increased interest and use of CBD for therapeutic purposes (Hurd, 2017; Khoury et al.,

2017; Revol et al., 2024), as well as expectancy research associating positive expectancies with the use of a substance (Jones et al., 2014; Skenderian et al., 2008). To evaluate hypotheses, linear mixed models (LMM) were used as they can account for clustering of cannabinoid within each participant. Notably, some of the model residuals were identified to be kurtotic and contained up to 18 multivariate outliers, which appears to violate distributional assumptions of LMM. However, given that distributional assumption violations tend to be most influential in smaller samples (Knief & Forstmeier, 2021), and our sample contained a large number of observations, it was decided that LMM remained the optimal analytic strategy for this data. Additionally, multivariate outliers were removed to improve model fit.

Study 2a

Entitled "*Evaluating cannabidiol (CBD) expectancy effects on acute stress and anxiety in healthy adults: A randomized crossover study*", Study 2a (Spinella et al., 2021) investigated the extent to which CBD expectancy alone (i.e., stimulus expectancy) influenced acute stress, anxiety, and mood in healthy adults, and whether CBD response expectancies predicted outcomes. Prior research has focused on evaluating the pharmacologically driven effects of CBD for stress- and/or anxiety-related processes; however, these investigations have not tested the contribution of expectancy-based placebo mechanisms in these outcomes. This study is the first to our knowledge that fills this research gap, providing preliminary insight into the relative contribution of expectancies.

Using a randomized, crossover, half-balanced-placebo design, we sampled healthy adults (n = 43) across two experimental laboratory sessions. Participants self-administered the same CBD-free hempseed oil sublingually during both sessions, though

were provided with different information about the contents of the oil (contains CBD, contains hempseed oil) prior to participating in a laboratory stress-induction task. We hypothesized that (i) the CBD expectancy condition would be associated with distinct patterns of subjective and physiological responses to stress relative to the CBD-free expectancy condition (i.e., lower stress, anxiety, negative affect), and (ii) stronger response expectancies would predict larger subjective benefits in the CBD expectancy condition. These hypotheses were derived from prior expectancy research (e.g., Kirsch, 1985; Laferton et al., 2018). To test these hypotheses, population-averaged models (i.e., Generalized Estimating Equations [GEE]) were selected as they can account for the clustering of expectancy and time within each participant. Some of the model residuals were identified as non-normal (e.g., kurtotic, skewed) and four models contained a few extreme multivariate outliers. Given the smaller sample size, influences of violations of normality are more likely to lead to biased results. Therefore, GEE was selected as the analytic approach for this study as it tends to be more robust to violations of normality (Hubbard et al., 2010) and outliers were retained. Unlike marginal or mixed model approaches, however, GEE uses listwise deletion of cases with missing values. We decided to prioritize violations of normality in this study given the increased potential for biased results among this sample.

Study 2b

Entitled "*The impact of cannabidiol expectancy on cortisol responsivity in the context of acute stress: Associations with biological sex*", Study 2b (Spinella, Burdeyny, et al., 2023) is an extension of Study 2a that aimed to explore the extent to which CBD expectancy alone impacts cortisol in the context of a laboratory stressor. To our knowledge, no other research had evaluated the impacts of CBD expectancy on subjective

and physiological indices of stress and anxiety. As such, we wanted to extend the results of Study 2a and provide insight into the pattern of HRV that had been observed by evaluating cortisol responsivity, which had not been possible initially due to COVID-19 restrictions. Further, we were interested in evaluating the extent to which sex differences impact physiological stress responsivity in the context of CBD expectancy.

We hypothesized that (i) cortisol would be lower during anticipation of a stressor in the CBD expectancy condition, (ii) males would have higher cortisol than females in response to acute stress, and (iii) males would be more responsive to placebo/expectancy influences than females. These hypotheses were developed based on our previous findings (Spinella et al., 2021), as well as literature on sex differences in HPA axis responsivity (Liu et al., 2017) and placebo effects (Vambheim & Flaten, 2017). Population-averaged models (i.e., marginal models) were selected as the analytic approach to test these hypotheses given that it can account for clustering of expectancy and time within each participant. There were similar challenges with slightly kurtotic residuals and identified multivariate outliers. However, we conducted analyses on subsamples of participants (<40 participants) to control for the known influences of hormonal contraceptives. Given that GEE can yield biased results with less than 40 clusters (Kauermann & Carroll, 2001), we opted to use an analytically comparable approach (i.e., marginal models) while similarly retaining outliers in analyses given the smaller sample size.

Outline

Each of the above manuscripts are presented in the upcoming chapters: Study 1 can be found in Chapter 2, Study 2a in Chapter 4, and Study 2b in Chapter 6. Chapters 3

and 5 provide transitions between studies and Chapter 7 is an integrative discussion of all three manuscripts, including relevant theoretical, practical, and clinical implications.

CHAPTER 2. STUDY 1: PERCEPTIONS ABOUT THC AND CBD EFFECTS AMONG ADULTS WITH AND WITHOUT PRIOR CANNABIS EXPERIENCE

This study is included in the manuscript presented below. Under the supervision of Dr. Sean Barrett, I was directly involved in developing the research questions and hypotheses, coordinating online data collection, preparing the dataset for analysis, conducting the analyses, and interpreting the study findings. I wrote the initial draft of the manuscript, incorporated feedback from co-authors, submitted the original investigation to a peer-reviewed journal and subsequently led each round of revisions. This manuscript was published as an Open Access article in *Addictive Behaviors* (2023) under a Creative Commons license (CC BY-NC-ND). See Appendix A for copyright details under this license. Please note that the manuscript included in this dissertation has been slightly modified from the final published version. The full reference is as follows:

Spinella, T. C., Bartholomeusz, J., Stewart, S. H., & Barrett, S. P. (2023). Perceptions about THC and CBD effects among adults with and without prior cannabis experience. *Addictive Behaviors*, *137*, 107508. https://doi.org/10.1016/j.addbeh.2022.107508

Abstract

Background. Cannabis is associated with a range of therapeutic and non-therapeutic, positive and negative effects. While some benefits and harms may be specific to individual cannabinoid constituents (THC, CBD), individual expectancies may also play a role.

Objectives. Evaluate the extent to which individuals hold expectancies about the effects of CBD, THC, and THC & CBD combined, and whether this differs with prior cannabis experience.

Methods. Canadian adults (*N*=345; *n*=58 cannabis use naïve, *n*=287 prior cannabis use) completed a Qualtrics survey. Participants provided information regarding their expectancies about the effects of cannabinoids (THC, CBD, THC & CBD combined) via a 15-item questionnaire, which included various therapeutic (e.g., helps with pain),non-therapeutic positive (e.g., enhances positive feelings), and non-therapeutic negative (e.g., risk for addiction) effects. They recorded their perceptions about the effects of each cannabinoid on a scale (0="definitely not true" to 10="definitely true"). Data was analyzed using linear mixed models.

Results. For most therapeutic effects, CBD-containing products (CBD, THC & CBD) were rated higher than THC. For most positive and negative non-therapeutic effects, THC-containing products (THC, THC & CBD) were rated higher than CBD. Those with prior cannabis use (vs. no prior use) rated all cannabinoids higher regarding their association with many therapeutic and positive effects, while endorsing weaker expectancies about their role in some negative effects.

Conclusions. Adults endorsed stronger expectancies that CBD-containing products are responsible for producing a rage of therapeutic effects. Those with prior cannabis use experience tended to emphasize the benefits and minimize potential harmful effects of cannabinoids.

Key words: cannabis, cannabinoids, CBD, THC, expectancies.

Introduction

The cannabis plant contains more than 100 cannabinoid compounds (Hanuš et al., 2016), of which delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are most well-recognized and studied. There has been increases in using specific cannabinoid compounds (i.e., THC, CBD), to treat various psychiatric and medical conditions (e.g., Khan et al., 2020). For example, the psychoactive cannabinoid, THC, and its synthetic analogues have been used to induce appetite and treat nausea/vomiting associated with chemotherapy (Boggs et al., 2018). THC also appears to have analgesic and anti-inflammatory properties (Pacher et al., 2006). However, THC has also been associated with a range of other effects including anxiety, paranoia, impairments in memory and motor coordination (D'Souza et al., 2004), the development of cannabis use disorder (Freeman & Winstock, 2015), and has been linked to the development of psychosis in those with genetic vulnerability (Caspi et al., 2005; Wainberg et al., 2021). Relative to THC, CBD is devoid of any reinforcing properties that could lead to its misuse (Babalonis et al., 2017). There is emerging evidence that CBD may have potential therapeutic benefits for anxiety and movement disorders, neuropathic pain, epilepsy, substance dependence (Crippa et al., 2010; Hurd et al., 2019), and psychotic symptoms (Khan et al., 2020). Interestingly, when administered in combination, CBD and THC may act synergistically to enhance some of their purported beneficial effects (Russo & Guy, 2006). For example, CBD and THC combined shows more promising results for pain management (Überall, 2020) over and above the effects of THC alone (Johnson et al., 2010), with insufficient evidence for CBD alone (Urits et al., 2020). Some studies suggest that CBD may also help minimize some of the side effects associated with THC (e.g.,

anxiety; Bhattacharyya et al., 2010; Russo and Guy, 2006; Zuardi et al., 1982); however, findings have been relatively inconsistent (Niesink & van Laar, 2013).

Despite some promising evidence for the medicinal effects of THC and CBD, there remains a dearth of research examining to what extent cannabis constituents possess various harmful and beneficial properties. Although some of the benefits and harms may be specific to individual constituent pharmacological actions, user perceptions may also play some role. Indeed, expectancies about the effects of a substance can predict the actual effects experienced when that substance is consumed (Kirsch, 2018). For example, our group recently reported that those who endorsed the strongest beliefs regarding CBD's anxiolytic effects reported the largest reduction in anxiety symptoms when they thought they had received CBD relative to a placebo (despite receiving a placebo both times; Spinella et al., 2021). Substance-related expectancies, or beliefs regarding anticipated effects from a substance, also influence patterns of substance use (e.g., frequency, amount; Jones et al., 2001). These expectancies can be formed and enhanced by factors such as information provided to the user (e.g., media, verbal transmission), observation of others, and one's own experience (Kirsch, 2018). Despite the importance of understanding cannabis-related expectancies, most prior research has evaluated cannabis as a single drug or entity (Hayaki et al., 2010; Skenderian et al., 2008). Only one study to our knowledge has evaluated expectancies associated with CBD (Walukevich-Dienst et al., 2022), with findings suggesting that CBD-specific expectancies may be associated with unique outcomes. Thus, there is a lack of information about expectancies related to the effects of cannabis constituents, like THC and CBD, when consumed on their own and together.

The present investigation evaluated the extent to which individuals who have at least some knowledge about cannabis have various perceptions about the effects of CBD, THC, and THC & CBD combined. Consistent with the surge of interest in using CBD for various therapeutic purposes (Hurd, 2020; Khan et al., 2020; Khoury et al., 2017), it was hypothesized that CBD-containing cannabis products would be endorsed as having the highest therapeutic efficacy, relative to THC only. Second, due to its reinforcing properties and ability to influence affective, behavioral, and cognitive processes, it was hypothesized that THC-containing cannabis products would be associated with positive and negative non-therapeutic effects. Third, in line with research linking more positive expectancies to greater use of a substance (Jones et al., 2001; Skenderian et al., 2008), it was hypothesized that individuals who reported prior cannabis use (CU) would have relatively higher expectancies about the therapeutic and non-therapeutic positive effects of cannabis, regardless of cannabinoid constituent, compared to those with no prior cannabis use (NCU). Fourth, consistent with evidence that users tend to minimize negative consequences associated with their use (Gaher & Simons, 2007), it was hypothesized that NCU individuals would have higher negative expectancies relative to CU individuals. Lastly, although we had no specific hypotheses related to interactions between constituent and cannabis use status, we explored the extent to which CU and NCU's differ in their perceptions of THC and CBD.

Methods

Study Design and Participants

A cross-sectional study was conducted using Qualtrics Survey Panels service. The Panels team was provided with a pre-determined recruitment target of 500 Canadian

adults (i.e., 150 NCU, 350 CU[3]; 250 men, 250 women) as part of a larger study. A simulation study of mixed effect models report sample sizes between 320-432 to detect medium interaction effects (i.e., standardized effect of .40) of two binary fixed effect factors at 80% power (Leon & Heo, 2009). These specifications closely mirror our proposed model specifications of two fixed effects (one binary, one within subject/nested). As such, a target of 500 participants would likely provide us with sufficient power (80%) to detect medium interactions between effects of interest.

Prospective participants received a notification informing them of the survey. Eligible participants were required to be at least 19 years old, currently residing in Canada, and fluent in English reading and writing. For the purposes of the present analyses, all participants were required to self-report having at least some knowledge about CBD and THC. After providing consent, participants completed the survey. Pre-determined compensation for participation was provided by Qualtrics upon survey completion. All study procedures were approved by the Dalhousie University Research Ethics Board (No. 2020-5264).

Measures

The survey collected information about demographics, cannabis use history and patterns, personality, and expectancies about different cannabis constituents (i.e., CBD, THC, THC & CBD) and strains. For the research questions relevant to this paper, we report data related to demographics, cannabis use history, and expectancies regarding cannabinoid constituents.

[3] A higher number of CU participants were recruited to facilitate within subgroup analyses evaluating the effect of cannabis use exposure on outcomes of interest.

Demographic and cannabis use information

Information about age was collected in an open-response format and level of education, sex, gender, ethnicity, and province of residence in closed response formats from several possible options. To evaluate cannabis use history, a slightly modified version of the Daily Sessions, Frequency of Use, Age of Onset, Quantity of Cannabis Use Inventory (DFAQ-CU; Cuttler and Spradlin, 2017) was administered. Items related to cannabinoid content of typical cannabis use were added (e.g., "what is the average CBD content of the cannabis you typically use?") to gain a more comprehensive picture of each participant's cannabis use.

Cannabinoid expectancies

Beliefs about the possible effects of THC and CBD (i.e., outcome expectancies) were collected through a researcher-compiled 15-item questionnaire (see Appendix B for supplemental files). Given that existing expectancy questionnaires (e.g., Marijuana Effect Expectancy Questionnaire; Schafer & Brown, 1991) have focused on the effects related to cannabis (vs. specific cannabinoids), and we were primarily interested in beliefs related to individual items (vs. subscale scores), the decision was made to derive a researcher-compiled questionnaire. The 15 items were statements about the potential therapeutic, and the positive, and negative non-therapeutic effects associated with cannabis use derived following a literature search of prior cannabis research that had identified motives or reasons for use, helpfulness for various conditions, and other expectancy questionnaires (Bohnert et al., 2018; Bonn-Miller et al., 2014; Hecimovic et al., 2014; Torrealday et al., 2008; Zeiger et al., 2010). Items were then decided upon by the authors of this report. The statements included: therapeutic expectancies about sleep, stress, anxiety, negative thoughts/feelings, pain, attention, and nausea; positive non-therapeutic expectancies about

positive thoughts/feelings, creativity, alertness, socializing, and sexual responsiveness; negative non-therapeutic expectancies about cognitive impairment, risk for addiction, and risk for psychosis. As part of the inclusion criteria for this study, participants were first asked about their level of familiarity and knowledge about CBD and THC, with five possible response options, from "I don't know what this is" to "I know a lot about it". Next, they were asked to answer each of the items according to their "personal thoughts, feelings, and beliefs" about how cannabinoids affect the average person, regardless of whether they had experience with CBD and/or THC. Instructions were modified from the Marijuana Effect Expectancy Questionnaire-Brief (Torrealday et al., 2008). Participants rated their perception about each statement for CBD, THC, and THC & CBD combined, on a sliding visual analogue scale anchored at 0="definitely not true" and 10="definitely true" with the marker initially set at "neutral". They were required to 'click' the marker for a response to be recorded.

Statistical Analyses

Statistical analyses were conducted in R (version 4.1). Linear Mixed Models (LMM) using 'lmerTest' package were selected as the primary analytic technique for the data to account for clustering of 'Cannabinoid' within each participant. With regards to model parameters, 'participant' was specified as having a random intercept and all other factors were specified to have random intercepts and fixed slopes.[4] Model residuals were screened for extreme multivariate outliers (>3 interquartile ranges) and excluded

[4] Due to the small number of categories within each predictor variable (i.e., <5), it was decided a priori that all slopes would be fixed.

accordingly. As part of a sensitivity analysis, any discrepancies in findings for models that include all extreme outliers will be reported in a footnote.

Outcome variables included the 15 expectancy items. Items were classified by the researchers of this report into three organizational categories based on the face validity of each item to facilitate interpretation: therapeutic, positive non-therapeutic, and negative non-therapeutic. Therapeutic items (*n*=7) included: helps with sleep, helps with stress, helps with anxiety, helps with pain, helps with nausea, improves attention and focus, and relieves negative thoughts, feelings, and/or mood. Positive non-therapeutic items (*n*=5) included: enhances positive thoughts, feelings, and/or mood, improves creativity, increases alertness/stimulation, helps with socializing, and helps with feeling more sexual. Negative non-therapeutic items (*n*=3) included: increases cognitive impairment, increases risk for addiction, and increases risk for psychosis and/or developing a psychotic disorder.

Predictor variables in each model included cannabinoid (CBD, THC, THC & CBD) and cannabis use status (CU, NCU). Gender and age were included in the model as a fixed factor and a covariate, respectively[5]. Due to the small number of individuals who do not identify with the gender binary (i.e., woman, man), participants who did not identify as a man or a woman or did not report their gender (*n*=4), were included for descriptive purposes, but their gender was re-coded as a "missing value" for all analyses. Participants who reported not knowing anything about CBD or THC (i.e., "I don't know

[5] R code of sample model: lmer (data = mydata, belief ~ cannabinoid + UseStatus + age + gender + cannabinoid * UseStatus (1 | ID), REML = TRUE)

what this is", "I recognize the term but know nothing about it") were excluded from analyses to minimize random responses.

Effects of interest included main effects and interactions of Cannabinoid and Cannabis Use status. All *p*-values less than .05 were considered significant. The Benjamini-Hochberg method (Benjamini & Hochberg, 1995) was used to control for the false discovery rate (FDR). The FDR threshold was set at .05 within each model, such that there was a 5% chance that any finding was a false positive. Each *p*-value is reported in its unadjusted format unless the FDR threshold is exceeded, in which case both adjusted and unadjusted *p*-values are reported. Planned post-hoc pairwise comparisons using tests of simple effects were used to probe main effects, for primary hypotheses, and interactions, for exploratory analyses.

As part of additional exploratory analyses, the impact of the degree of prior Cannabis Exposure on cannabinoid-related beliefs was explored among CUs. A median split was used to categorize participants in to Low (*n*=157; 1-100 cannabis-using occasions) and High exposure (*n*=130; 101-10,000+ cannabis-using occasions) groups from an ordinal variable with 9 unequal groupings/categories. Effects of interest included main effects of Cannabis Exposure.

Results

A total of 520 adults across Canada were recruited via Qualtrics Survey Panels and participated in the online survey in October 2020, with an additional 20 participants provided by the Qualtrics team. Of those participants, 33.7% of the initial sample recruited as part of a larger study (175 participants) reported having no knowledge about CBD and/or THC and were not included in the analyses. Demographic and cannabis use characteristics for the 345 participants included in the final sample are reported in Tables

1.1 & 2.2. Models contained between 0-18 cases of extreme multivariate outliers, which were excluded from the statistics reported in this paper.

Hypothesis Testing

All statistically significant findings will be described in text below. LMM coefficients and *p*-values are reported in Table 2.3 and estimated marginal means (EMM) and standard errors (SE) are reported in Supplemental Tables 2.1 and 2.2 (Appendix B). The *p*-values reported in text represent those from post-hoc pairwise comparisons, which were evaluated if the respective model coefficients were significant. Finally, coefficients for variables that were controlled for (i.e., age, gender), are reported in Supplemental Table 2.3 (Appendix B).

First, we hypothesized that CBD-containing cannabis (CBD alone, THC & CBD combined) would be endorsed as having higher therapeutic efficacy, relative to THC. To test this, we evaluated main effects of Cannabinoid among the seven therapeutic expectancies. For six of the seven therapeutic expectancies, CBD was rated higher than THC in terms of the extent to which participants thought that it helped with/improved sleep ($p<.001$), stress ($p=.029$), anxiety, pain (both $p<.001$), attention ($p=.013$), and nausea ($p=.002$). Descriptively, the largest mean difference (MD) in expectancy ratings between CBD and THC included items related to sleep (MD=1.31), pain (MD=0.97), and anxiety (MD=0.85), with CBD being rated highest overall for pain (EMM=7.47) relative to all other expectancy item ratings. Most expectancy items were rated at least one point above the 'neutral' marker (i.e., between 6 and 7) for CBD-containing products, whereas THC was often rated just above 'neutral' (i.e., between 5 and 6). Additionally, with regards to pain, CBD was also rated higher than THC & CBD combined ($p=.017$). For these same six expectancy items, THC & CBD combined was rated higher than THC

alone (attention: p=.019, others p<.001). With regards to negative affect, contrary to hypothesis, participants endorsed higher ratings for THC alone as well as THC & CBD combined relative to CBD alone (p=.002, p<.001, respectively).

Second, we hypothesized that THC-containing cannabis would be associated with greater positive and negative non-therapeutic effects. For four of the five positive non-therapeutic items, including positive affect, enhancing creativity, social facilitation, and sexual facilitation, THC was rated higher than CBD (all p<.001), and THC & CBD combined was rated higher than CBD (all p<.001). Descriptively, the largest mean difference in expectancy ratings between THC and CBD included items related to creativity (MD=1.13) and positive affect (MD=0.85), with THC being rated highest for facilitating positive affect (EMM=6.75) among positive non-therapeutic items. There were no differences in the ratings of cannabinoids on their ability to improve alertness (p>.05).

Main effects of Cannabinoid were identified for all three negative non-therapeutic items, including impaired cognition, risk for addiction, and risk for psychosis, wherein THC was rated higher than CBD (all p<.001), and THC & CBD combined was rated higher than CBD (all p<.001). Additionally, THC alone was rated significantly higher than THC & CBD combined for increasing the risk for psychosis (p=.003) and addiction (p=.024). Mean differences in expectancy ratings between THC and CBD were all close to or above 1 point for impaired cognition (MD=1.68), risk for addition (MD=0.89), and risk for psychosis (MD=1.32). THC-containing products were rated above the 'neutral' mid-point (EMM=5.44-6.52), whereas CBD was rated slightly below 'neutral' (EMM=4.54-5.0).

Third, we hypothesized that participants who had used cannabis before (vs. NCU) would rate cannabinoids higher for therapeutic and non-therapeutic positive effects. To test this, we first evaluated the main effects of Use Status among the seven therapeutic expectancies. Participants who used cannabis at least once in their lives rated cannabis (regardless of cannabinoid) significantly higher in terms of its' efficacy on four of the seven therapeutic items, including improved sleep, attention, anxiety (all p=.004), and stress (p=.013), relative to NCU individuals. The largest mean difference in expectancy ratings between CU and NCUs was for attention (MD=0.89) such that NCU individuals tended to believe cannabinoids were less helpful for attention (EMM=4.81) while CU individuals rated cannabinoids as being more helpful (EMM=5.70). Descriptively, CU individuals endorsed the highest mean rating of cannabinoids as being helpful for pain (EMM=7.29), relative to all other expectancy items. For all other therapeutic expectancy items, both CU and NCU participants tended to rate cannabinoids above the 'neutral' mid-point (EMM=5.96-7.14). There was no difference in how NCU vs. CU individuals rated the efficacy of cannabinoids for nausea (p>.05), and it the effects for pain and negative affect were considered potential false positives (FDR>5%).

With regards to non-therapeutic positive expectancy items, CU participants rated cannabinoids higher overall in terms of their ability to increase creativity (p=.027), alertness (p=.008), and social facilitation (p=.007), relative to NCU participants. The largest mean difference in expectancy ratings between CUs and NCUs was for alertness (MD=0.77) such that NCU individuals tended to believe cannabinoids were less helpful for attention (EMM=4.79) while CU individuals rated cannabinoids as being more helpful (EMM=5.56). For all other therapeutic expectancy items, both CU and NCU participants tended to rate cannabinoids above the 'neutral' mid-point (EMM=5.56-6.67). There was

no main effect of Use Status on positive affect or sexual facilitation expectancies (both $p>.05$).

Fourth, we hypothesized that NCU individuals (vs. CU) would rate cannabinoids higher for negative effects. The NCU group rated cannabinoids higher on one of the three non-therapeutic negative expectancy items: risk for addiction ($p<.001$), with a mean difference of 1.31, wherein CU participants rated cannabinoids below the mid-point (EMM=4.85) and NCU participants slightly above (EMM=6.16). There was no main effect of Use Status on impaired cognition expectancies ($p>.05$) and the effect on psychosis risk was identified as a potential false positive (FDR>5%).[6] It is also notable that SE values were approximately double the size among NCU relative to CU individuals.

Exploratory Analyses

No interactions between Cannabinoid and Use Status were evident (all $p>.05$). Figures 2.1-2.3 illustrate the ratings for each expectancy item plotted by Cannabinoid and Use Status among therapeutic, non-therapeutic positive, and negative items, respectively.

Main effects of Cannabis Exposure were identified for all expectancy items, with the exception of 'social facilitation'. Specifically, for therapeutic and non-therapeutic positive items, those with High exposure rated cannabinoids higher overall, however, they rated cannabinoids lower for non-therapeutic negative items, relative to those with Low

[6] When all extreme multivariate outliers were retained in analyses, 43 out of 45 p-values remained consistent in terms of conclusions. Among the two discrepancies: (i) the main effect of cannabinoid on beliefs related to improving attention and focus exceeded the FDR threshold, and (ii) the main effect of use status on beliefs related to increasing the risk for psychosis became significant. Broadly, results were similar with and without extreme outliers.

exposure. Coefficients for main effects of Cannabis Exposure as well as EMMs and SEs are reported in Supplemental Table 2.4 (Appendix B).

Discussion

This study is the first to explore expectancies related to the effects of THC and CBD. Two important patterns emerged from our data. First, participants endorsed stronger expectancies that CBD-containing cannabis (vs. THC alone) is responsible for producing a range of therapeutic effects. Second, participants with prior cannabis use experience tended to rate cannabinoids relatively higher in terms of their therapeutic efficacy and the facilitation of many positive effects, while also endorsing weaker expectancies about the role of cannabinoids in the production of negative effects. Additionally, relative to participants who had less lifetime cannabis use experience, those with more lifetime cannabis exposure tended to endorse stronger positive beliefs (i.e., therapeutic, positive non-therapeutic) about cannabinoids and weaker negative beliefs (i.e., negative non-therapeutic).

Consistent with the first hypothesis, CBD-containing cannabis (CBD alone, THC & CBD combined) was rated higher than THC for six of the seven therapeutic items measured, including sleep, stress, anxiety, attention, pain, and nausea. There was the largest difference between CBD and THC ratings for sleep, pain, and anxiety, suggesting that stronger CBD-specific expectancies may exist for these symptoms. Although the mean differences were still relatively small (~1 point difference), this may be meaningful as those who believe CBD is even slightly more helpful than THC for various therapeutic conditions could be using cannabis products differently (e.g., patterns, motives), leading to different downstream consequences (e.g., likelihood of experiencing harms). Overall, it is likely that therapeutic expectancies related to CBD are moderate in strength given that

most ratings for CBD-containing products were between 6 and 7.5. The highest overall mean (i.e., across all 15 items) was the belief that CBD was helpful for pain (EMM=7.47), suggesting that it would be important to control for response expectancies in future randomized controlled trials testing the effect of CBD for pain.

Recent observational and cross-sectional survey-based studies have shown that CBD is most frequently used to manage anxiety, stress, sleep, and pain (Corroon & Phillips, 2018; Moltke & Hindocha, 2021). Despite the perception of CBD's efficacy, it is currently unclear the extent to which CBD's reported benefits are pharmacologically driven versus driven by expectancy factors. For example, experimental studies of acute and long-term CBD administration demonstrated no impact on sleep indices (Linares et al., 2018; Shannon, 2019); however, cross-sectional survey-based studies demonstrated positive sleep-related outcomes from CBD use (Corroon & Phillips, 2018; Moltke & Hindocha, 2021). To date, there are only two cannabis-related uses approved by the US Food and Drug Administration, including synthetic THC for nausea associated with chemotherapy and AIDS, and CBD for severe childhood epilepsy. The National Academy of Science, Engineering and Medicine also concluded that there is strong evidence for the use of cannabinoids (primarily THC) in the treatment of chronic pain, with insufficient evidence for other conditions (National Academies of Sciences, Engineering, and Medicine, 2017). Despite such equivocal data, participants in our study endorsed expectancies that CBD-containing products are at least somewhat effective (and more effective than THC alone) at improving sleep, stress, anxiety, attention, pain, and nausea.

In contrast, and consistent with the second hypothesis, both positive (i.e., positive affect, creativity, social facilitation, sexual facilitation) and negative non-therapeutic effects (i.e., risk for addiction, risk for psychosis, impaired cognition), were largely

attributed more to THC than CBD alone. The largest difference in ratings between THC and CBD were for creativity, positive affect, impaired cognition, risk for psychosis, and risk for addiction, suggesting that stronger THC-specific expectancies may exist for these effects. Similar to the mean differences for therapeutic expectancies these were also relatively small (~1 point difference), though arguably still meaningful in possibly predicting different use patterns, motives, and harms. Participants also believed that THC & CBD combined poses significantly less risk towards the development of psychosis than THC alone. This would be suggestive of a believed protective effect of CBD on psychosis, for which some research has demonstrated preliminary support (Bhattacharyya et al., 2010; Englund et al., 2013). Overall, these findings suggest that, regardless of prior cannabis experience, individuals attribute a range of positive *and* negative effects to THC (vs. CBD alone), effects which are consistent with the psychoactive nature of this cannabinoid. Notably, however, estimated marginal mean ratings close to the neutral mark on the scale (~5) indicates that participants believed, on average, that the risk for addiction and psychosis associated with THC is minimal.

Findings are also largely consistent with the third hypothesis that those with cannabis use experience would rate cannabinoids higher in terms of perceived therapeutic efficacy with four of the seven items reaching significance (i.e., improved sleep, stress, anxiety, attention). This was similarly observed for three of the five non-therapeutic items that were *positive* in nature (i.e., creativity, alertness, social facilitation). Additionally, the degree of lifetime cannabis exposure appeared to reinforce this finding, such that those with more exposure rated cannabinoids higher on most therapeutic and positive items, except for social facilitation. It is possible that that more experienced cannabis users are may be more likely to use cannabis outside of a social context compared with less

frequent users (Spinella et al., 2019). The magnitude of these mean differences are smaller than those described previously related to cannabinoids (i.e., <1 point), suggesting that prior direct experience with cannabis use is likely not the only factor involved in the facilitation of various expectancies. As per expectancy theory, other forms of indirect learning (e.g., observation, verbal information) can also inform the development of expectancies.

The opposite trend was observed for one of the *negative* non-therapeutic items (i.e., risk for addiction), with NCU individuals rating cannabinoids higher in terms of risk than CU individuals. Interestingly, while NCU individuals rated cannabinoids above the midpoint in terms of increasing the risk for addiction, CU individuals actually rated cannabinoids *below* the midpoint. This suggests that those with prior cannabis use experience on average believe that cannabinoids are *less likely* to increase the risk for addiction. Overall, these findings are somewhat consistent with the fourth hypothesis and with evidence that negative drug-related expectancies tend to be more salient than positive expectancies among individuals who have never used the drug (Galen & Henderson, 1999), while CUs, on the other hand, tend to minimize the negative consequences associated with their use (Gaher & Simons, 2007). A similar pattern of findings were identified among CUs, such that those with more exposure tended to minimize all negative cannabis-related consequences. Moreover, it is worth noting that the standard error values were much higher among NCU individuals relative to CU individuals across all expectancy items (i.e., often more than double in size). This could in part suggest a higher level of variability in their expectancies, which may in part be due to not having direct experience with cannabis. Additionally, this subgroup was smaller

than the CU subgroup, thus it is also possible that having more NCU participants would decrease the size of standard errors.

The absence of interactions would suggest that expectancies about THC, CBD, and the two combined do not differ among those who have used cannabis at least once and those who have no experience with cannabis. However, main effects of both use status and cannabinoid would suggest that users may have stronger expectancies, overall, and that different cannabinoids are viewed as having distinct effects. Indeed, drug expectancies are developed and strengthened by many sources, including media, advertising, word-of-mouth, as well as direct experience. As such, many of these sources would be mostly consistent among CU and NCUs, though the added direct experience of CUs may strengthen their expectancies.

The present findings should be considered with the following limitations in mind. First, the cross-sectional nature of this design prevents causal inferences from being made. Second, although participants were recruited across Canada, our sample was comprised of predominantly White, well-educated adults from central Canada. Third, the 15 expectancy items were compiled by researchers in the present study. Although some items were adopted from cannabis expectancy questionnaires with pre-determined psychometric properties, many of the items we were interested in were taken from other literature regarding the possible therapeutic effects of cannabis due to absence of validated measures that capture expectancies of interest. Fourth, the *a* priori classification of the expectancy items into therapeutic, positive and negative non-therapeutic categories were based on researcher experience rather than empirical techniques (e.g., principal component analysis) and may have been imperfect. As such, caution is warranted when discussing findings in the context of these loosely-defined categories. Our evaluation of

expectancies did not include items related to desirability of effects. Future investigations would benefit from including valuation items, which may provide additional information to help understand cannabis use behaviours (Buckner et al., 2013). It is also worth noting that we assessed knowledge about cannabinoids via self-report instead of more objective questions that would 'test' participants knowledge. Though it was beyond the scope of the current investigation, in the future, it may be beneficial to explore other potential moderators of cannabinoid expectancies (e.g., cannabinoid knowledge) as well as how individuals' cannabinoid-related expectancies were formed (e.g., user experience, marketing). Additionally, unequal sample sizes between user groups may have exacerbated issues related to heterogeneity of variance. Although extreme multivariate outliers were removed to mitigate this issue, it is possible that coefficients are slightly biased. Replication is warranted.

Conclusion

This was the first study to explore expectancies with regards to the effects of common cannabinoids. Although cannabis expectancy questionnaires currently exist (e.g., MEEQ-B; Torrealday et al., 2008), they may not adequately capture the nuances of expectancy associated with different cannabis products. Our findings support the separate assessment of expectancies related to CBD, THC, and THC & CBD combined given that there were notable differences in expectancies across cannabinoids. Given the key role of substance-related expectancies in substance use behaviors/use patterns, findings highlight the importance of effectively communicating research about the effects of THC and CBD to the public, including the extent to which they can help with various symptoms and conditions and are linked to harms. These findings also highlight the need to develop quality research to further elucidate the therapeutic potential of CBD, as well as to

explore the effects of THC and CBD using designs that tease apart the expectancy- and pharmacologically- driven properties of these cannabinoids (i.e., balanced-placebo design).

Tables

Table 2.1. Participant demographic characteristics.

	NCU N (percent of NCU)	CU N (percent of CU)	Total N (percent total)
Cannabis use status			
NCU	58	--	58 (16.8)
CU	--	287	287 (83.2)
Age in years (mean (standard deviation))	45.4 (14.3)	44.85 (14.3)	47.9 (13.7)
Gender			
Woman	23 (39.7)	148 (42.9)	171 (49.6)
Man	35 (60.3)	135 (39.1)	170 (49.3)
Non-binary, two-spirit, prefer not to answer	--	4 (.01)	4 (1.2)
Ethnicity			
Indigenous	--	5 (1.7)	5 (1.4)
White	36 (62.1)	234 (81.5)	270 (78.3)
Black	4 (6.9)	4 (1.4)	8 (2.3)
Latin American	1 (1.7)	4 (1.4)	5 (1.4)
South Asian, West Asian, or Arab	6 (10.3)	9 (3.1)	15 (4.3)
Southeast Asian, Japanese, Chinese, Filipino, or Korean	8 (13.8)	17 (5.9)	25 (7.2)
Mixed ethnicity	2 (3.4)	12 (4.2)	14 (4.1)
Other	1 (1.7)	2 (.7)	3 (.9)
Highest level of education			
Some high school	1 (1.7)	5 (1.7)	6 (1.7)
High school diploma	5 (8.6)	53 (18.5)	58 (16.8)
Some college or university	4 (6.9)	53 (18.5)	57 (16.5)
College or university degree	32 (55.2)	131 (45.6)	163 (47.2)
Some graduate school	3 (5.2)	10 (3.5)	13 (3.8)
Graduate degree	13 (22.4)	35 (12.2)	48 (13.9)
Province or territory of residence			
Western Canada (Manitoba, Saskatchewan, Alberta, British Columbia)	15 (25.9)	70 (24.4)	85 (24.6)
Central Canada (Ontario, Quebec)	35 (60.3)	179 (62.4)	214 (62.0)
Eastern Canada (New Brunswick, Nova Scotia, Newfoundland & Labrador, Prince Edward Island)	8 (13.9)	37 (12.9)	45 (13.0)
Northern Canada (Northwest Territories, Yukon, Nunavut)	--	1 (0.3)	1 (<.0)

N=number of subjects. NCU: No prior cannabis use; CU: Any prior cannabis use. *N*(Total)=345; *n*(CU)=287; *n*(NCU)=58.

Table 2.2. Cannabis use characteristics.

	NCU N (percent of NCU)	CU N (percent of CU)	Total N (percent total)
THC knowledge			
'I know a little bit'	39 (67.2)	121 (42.2)	160 (46.4)
'I know a moderate amount'	16 (27.6)	97 (33.8)	113 (32.8)
'I know a lot'	3 (5.2)	69 (24)	72 (20.9)
CBD knowledge			
'I know a little bit'	38 (65.5)	125 (43.6)	163 (47.2)
'I know a moderate amount'	17 (29.3)	105 (36.6)	122 (35.4)
'I know a lot'	3 (5.2)	57 (19.9)	60 (17.4)
Frequency of current cannabis use			
Never	58 (100)	--	58 (16.8)
I do not currently use/less than yearly	--	74 (25.8)	74 (21.5)
1-12 times/year	--	74 (25.8)	74 (21.5)
2-3 times/month	--	28 (9.8)	28 (8.1)
1-2 times/week	--	27 (9.4)	27 (7.8)
3-6 times/week	--	26 (9.1)	26 (7.5)
Daily	--	17 (5.9)	17 (4.9)
More than once/day	--	41 (14.3)	41 (11.9)
Lifetime cannabis exposure (number of use occasions)			
0	58 (100)	--	58 (16.8)
1-5	--	35 (12.2)	35 (10.1)
6-10	--	28 (9.8)	28 (8.1)
11-50	--	53 (18.5)	53 (15.4)
51-100	--	41 (14.3)	41 (11.9)
101-500	--	38 (13.2)	38 (11.0)
501-1000	--	21 (7.3)	21 (6.1)
1001-2000	--	15 (5.2)	15 (4.3)
2001-5000	--	14 (4.9)	14 (4.1)
5001-10,000	--	13 (4.5)	13 (3.8)
>10,000	--	29 (10.1)	29 (8.4)
THC content of typically used cannabis			
0-4%	--	12 (4.2)	12 (3.5)
5-9%	--	19 (6.6)	19 (5.5)
10-14%	--	25 (8.7)	25 (7.2)
15-19%	--	21 (7.3)	21 (6.1)
20-24%	--	26 (9.1)	26 (7.5)
25-30%	--	10 (3.5)	10 (2.9)
30%+	--	5 (1.7)	5 (1.4)
Unsure	--	56 (19.5)	56 (16.2)
*Missing data	--	113 (39.4)	171 (49.6)

	NCU N (percent of NCU)	CU N (percent of CU)	Total N (percent total)
CBD content of typically used cannabis			
0-4%	--	37 (12.9)	37 (10.7)
5-9%	--	21 (7.3)	21 (6.1)
10-14%	--	27 (9.4)	27 (7.8)
15-19%	--	8 (2.8)	8 (2.3)
20-24%	--	9 (3.1)	9 (2.6)
25-30%	--	5 (1.7)	5 (1.4)
30%+	--	2 (.7)	2 (.6)
Unsure	--	65 (22.6)	65 (18.8)
*Missing data	--	113 (39.4)	171 (49.6)

N=number of subjects. NCU: No prior cannabis use; CU: Any prior cannabis use. *N*(Total)=345; *n*(CU)=287; *n*(NCU)=58.

Table 2.3. Linear mixed model (LMM) coefficients for main effects of Cannabinoid, Use Status, and interactions between Use Status and Cannabinoid.

	Main effect: Use Status				***Main effect: Cannabinoid***				***Interaction: Use Status by Cannabinoid***		
Outcome	**df**	***F***	***p***	**Direction of effect**	**df**	***F***	***p***	**Direction of effect**	**df**	***F***	***p***
Therapeutic											
Sleep	1, 337.00	8.427	**.004**	CU > NCU	2, 678.00	26.814	**<.001**	CBD > THC THC & CBD > THC	2, 678.00	1.611	.201
Stress	1, 334.95	6.287	**.013**	CU > NCU	2, 671.57	6.273	**.002**	CBD > THC THC & CBD > THC	2, 671.57	.108	.898
Anxiety	1, 336.30	8.536	**.004**	CU > NCU	2, 674.95	14.784	**<.001**	CBD > THC THC & CBD > THC	2, 674.95	.456	.634
Pain	1, 336.69	4.039	**.045†**	--	2, 671.83	23.726	**<.001**	CBD > THC CBD > THC & CBD THC & CBD > THC	2, 671.83	.792	.453
Nausea	1, 333.49	.288	.592	--	2, 658.76	7.190	**<.001**	CBD > THC THC & CBD > THC	2, 658.76	1.819	.163
Attention	1, 334.49	8.341	**.004**	CU > NCU	2, 665.03	3.919	**.020**	CBD > THC THC & CBD > THC	2, 665.03	.472	.624
Negative affect	1, 330.64	4.11	**.044†**	--	2, 660.69	7.164	**<.001**	THC > CBD THC & CBD > CBD	2, 660.69	.283	.754

	Main effect: Use Status				*Main effect: Cannabinoid*				*Interaction: Use Status by Cannabinoid*		
Outcome	**df**	***F***	***p***	**Direction of effect**	**df**	***F***	***p***	**Direction of effect**	**df**	***F***	***p***
Positive non-therapeutic											
Positive affect	1, 332.88	3.608	.058	--	2, 670.74	18.352	**<.001**	THC > CBD THC & CBD > CBD	2, 670.74	2.763	.064
Creativity	1, 331.71	4.943	**.027**	CU > NCU	2, 667.15	39.584	**<.001**	THC > CBD THC & CBD > CBD	2, 667.15	.372	.689
Alertness	1, 332.55	7.142	**.008**	CU > NCU	2, 660.11	.246	.782	--	2, 660.11	.100	.905
Social	1, 331.53	7.397	**.007**	CU > NCU	2, 663.13	24.277	**<.001**	THC > CBD THC & CBD > CBD	2, 663.13	.127	.881
Sexual	1, 334.77	.764	.383	--	2, 664.85	27.581	**<.001**	THC > CBD THC & CBD > CBD	2, 664.85	1.649	.193
Negative non-therapeutic											
Impairs cognition	1, 334.17	.505	.478	--	2, 673.60	49.487	**<.001**	THC > CBD THC & CBD > CBD	2, 673.60	.009	.991
Addiction risk	1, 335.57	12.194	**<.001**	NCU > CU	2, 660.09	26.490	**<.001**	THC > CBD THC > THC & CBD THC & CBD > CBD	2, 660.09	.218	.805

	Main effect: Use Status				*Main effect: Cannabinoid*				*Interaction: Use Status by Cannabinoid*		
Outcome	**df**	***F***	***p***	**Direction of effect**	**df**	***F***	***p***	**Direction of effect**	**df**	***F***	***p***
Psychosis risk	1, 334.54	4.411	**.036†**	--	2, 667.42	44.819	**<.001**	THC > CBD THC > THC & CBD THC & CBD > CBD	2, 667.42	.268	.765

Bolded coefficients indicate statistical significance ($p<.05$).

Note. Significant multivariate outliers (> 3 interquartile ranges) were excluded from each model.

†FDR threshold >5% exceeded (Pain: adjusted $p=.068$; Negative affect: adjusted $p=.066$; Psychosis risk: adjusted $p=.054$) indicates potential false positive findings.

NCU: No prior cannabis use; CU: Any prior cannabis use.

Figures

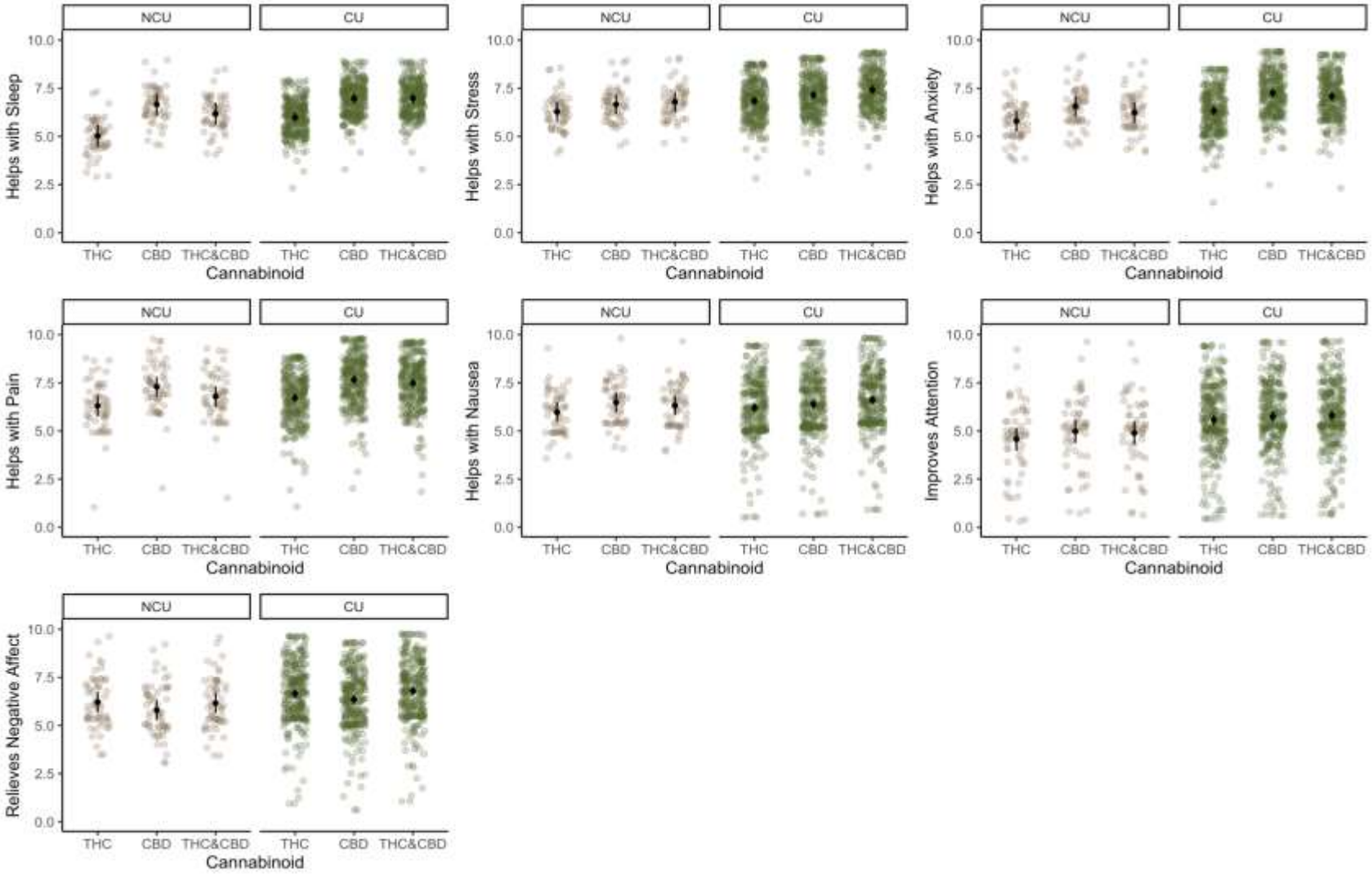
NCU
CU
Helps with Sleep
Helps with Stress
Helps with Anxiety
Helps with Pain
Helps with Nausea
Improves Attention
Relieves Negative Affect
10.0
7.5
5.0
2.5
0.0
THC
CBD
THC&CBD
Cannabinoid

Figure 2.1. Multi-plot of therapeutic expectancy items rated on a continuous visual analogue scale from 0-10 (0="definitely not true"; 5="neutral"; 10="definitely true") for each Cannabinoid (THC, CBD, THC & CBD), separated by Use Status (NCU: No prior cannabis use, CU: Any prior cannabis use). Colored dots represent model predicted values from linear mixed model analyses. Solid black dots with error bars represent estimated marginal means and corresponding 95% confidence intervals. Main effects of Use Status were identified for Sleep, Stress, Anxiety, Attention, and Negative Affect. Main effects of Cannabinoid were identified for Sleep, Stress, Anxiety, Pain, Nausea, and Negative Affect. No Cannabinoid by Use Status interactions were identified.

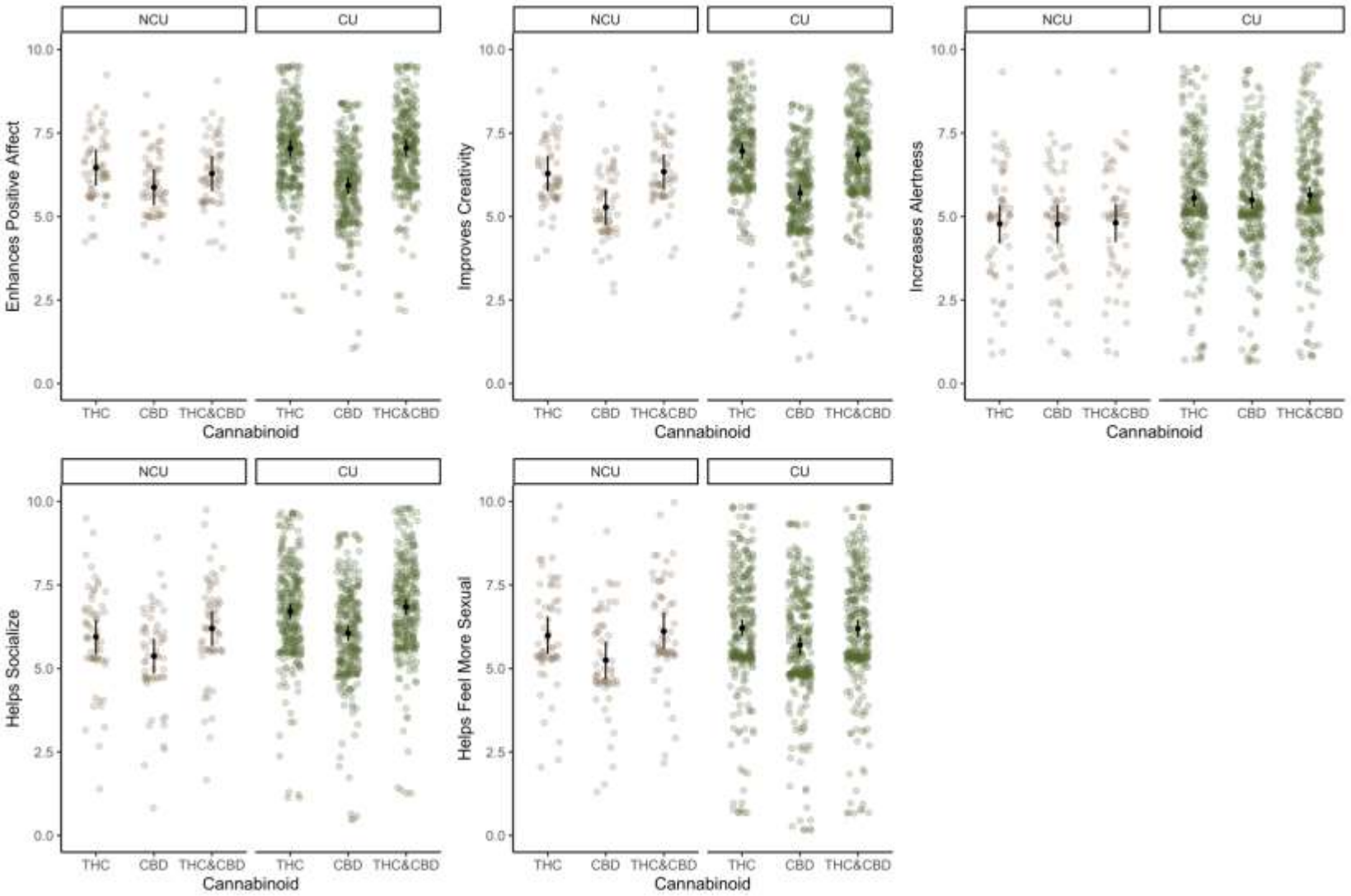
NCU
CU
Enhances Positive Affect
Improves Creativity
Increases Alertness
Helps Socialize
Helps Feel More Sexual
10.0
7.5
5.0
2.5
0.0
THC
CBD
THC&CBD
Cannabinoid

Figure 2.2. Multi-plot of positive non-therapeutic expectancy items rated on a continuous visual analogue scale from 0-10 (0="definitely not true"; 5="neutral"; 10="definitely true") for each Cannabinoid (THC, CBD, THC & CBD), separated by Use Status (NCU: No prior cannabis use, CU: Any prior cannabis use). Colored dots represent model predicted values from linear mixed model analyses. Solid black dots with error bars represent estimated marginal means and corresponding 95% confidence intervals. Main effects of Use Status were identified for Creativity, Alertness, and Social facilitation. Main effects of Cannabinoid were identified for Positive affect, Creativity, Social facilitation, and Sexual facilitation. No Cannabinoid by Use Status interactions were identified.

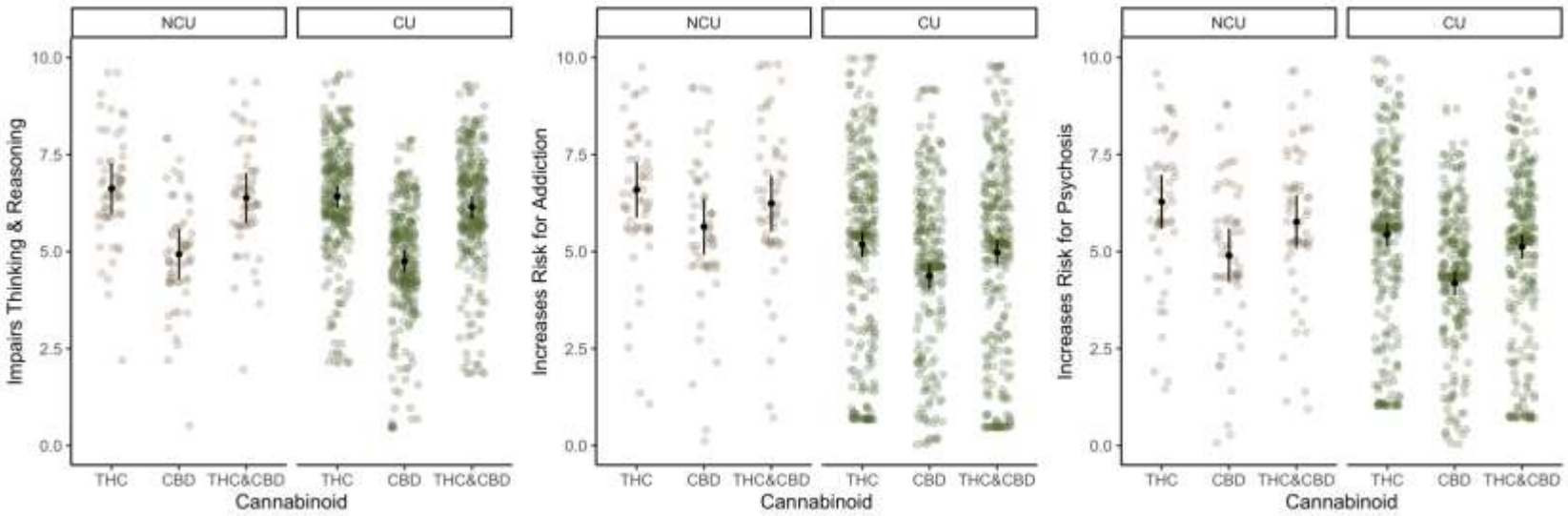

Figure 2.3. Multi-plot of negative non-therapeutic expectancy items rated on a continuous visual analogue scale from 0-10 (0="definitely not true"; 5="neutral"; 10="definitely true") for each Cannabinoid (THC, CBD, THC & CBD), separated by Use Status (NCU: No prior cannabis use, CU: Any prior cannabis use). Colored dots represent model predicted values from linear mixed model analyses. Solid black dots with error bars represent estimated marginal means and corresponding 95% confidence intervals. Main effects of Use Status were identified for Risk for addiction and Risk for psychosis. Main effects of Cannabinoid were identified for Impaired cognition, Risk for addiction, and Risk for psychosis. No Cannabinoid by Use Status interactions were identified.

CHAPTER 3. TRANSITION FROM STUDY 1 TO STUDY 2A

Study 1 demonstrated that people have different expectancies regarding the effects of THC- and CBD- containing products. Specifically, CBD-containing products are believed to possess more therapeutic effects (including stress- and anxiety-relieving effects), relative to THC-containing products, which is largely consistent with research evaluating self-reported reasons or motives for using CBD (Moltke & Hindocha, 2021). Study 1 also revealed that those who have prior cannabis use experience (relative to those who had never used cannabis) as well as the extent of prior use (i.e., high exposure, >100 use occasions) generally had higher positive expectancies regarding the effects of both THC and CBD. These findings highlight the role of prior substance use experience in informing substance-related response expectancies (Colloca & Benedetti, 2006). Additionally, it may also speak to the self-confirming nature of response expectancies, such that they are reinforced with continued use (Kirsch, 1985; Montgomery & Kirsch, 1997).

Stress relief and anxiety reduction appear to be frequently endorsed reasons for CBD use among those who use cannabis non-medicinally and/or recreationally (Corroon & Phillips, 2018; Moltke & Hindocha, 2021; Tran & Kavuluru, 2020) and medically (Kalaba & Ware, 2022). While many people describe positive therapeutic expectations and benefits related to CBD for stress and anxiety, the mechanisms through which CBD facilitates these therapeutic effects is unclear. As reviewed in Chapter 1, drug responses are thought to be comprised of pharmacological and non-pharmacological factors, where the role of expectations are crucial. However, relatively little is known about expectancy-related influences in the effects of CBD. In fact, no studies have experimentally evaluated the role of CBD-related stimulus and/or response expectancies on stress and anxiety

outcomes. In this chapter, I will briefly discuss the relationship between stress and anxiety processes, including how they are simulated and measured in research studies with humans.

Stress and Anxiety Processes

Stress and anxiety are related constructs and appear to influence each other in a bi-directional fashion. For example, a stress response, as described in Chapter 1, is a physiological and behavioral response prompted by the perception of an internal or external threat. Various laboratory research protocols have been designed to induce a stress response in humans. A meta-analysis found that stress-induction protocols associated with significant cortisol responses are those with an aspect of uncontrollability and the presence of social evaluation during an active performance task (i.e., goal-relevant situation) (Dickerson & Kemeny, 2004). Stress is often measured through physiological indices representative of ANS and/or HPA reactivity (Glier et al., 2022; Grillon et al., 2007), such as HR, HRV, blood pressure, cortisol, electrodermal skin conductance response, alpha amylase, and adrenocorticotropic hormone. Subjective indices of stress have also been used (e.g., single-item stress measure, multi-item measures; Cohen et al., 1983). Notably, the extent to which these subjective and physiological indices of stress are interrelated is not fully clear. The degree of correspondence is likely at least in part moderated by various assessment/measurement features, underlying psychological traits, and physiological disposition factors (Campbell & Ehlert, 2012).

In anticipation of a threat, the stress response also includes an associated emotional component, which is often fear or anxiety (Campbell & Ehlert, 2012). Anxiety is a future-oriented emotional state that tends to arise in the context of uncertainty and can

be prompted by stressors (for a review, see Grillon et al., 2019). Specifically, anxiety tends to manifest as hyperarousal (i.e., apprehension, hypervigilance, rumination about past failures/negative experiences) during the anticipation of perceived threats (Sylvers et al., 2011). Research has found conflicting results regarding the association between anxiety and stress responsivity.

First, there is evidence to suggest that those with social anxiety have an elevated cortisol responses to stressors (Condren, 2002; Roelofs et al., 2009). In this population, hyperresponsivity of the HPA axis was associated with increased avoidance tendencies (Roelofs et al., 2009), suggesting that cortisol can help mobilize individuals to respond to perceived threats via avoidance. Alternatively, there is evidence for blunted stress-induced cortisol responses (i.e., smaller increase in cortisol; hyporesponsivity) and/or slowed cortisol recovery among healthy adults with elevated anxiety symptoms (Crişan et al., 2016; Fiksdal et al., 2019). Blunted cortisol reactivity in response to stress has also been observed in a subset of individuals with other stress- and anxiety- related conditions, such as social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), as well as conditions like chronic fatigue syndrome and fibromyalgia (Beaton et al., 2006; Heim et al., 2000). It has been hypothesized that reduced cortisol reactivity in these populations is an indicator of allostatic load and may be a transdiagnostic marker of chronic stress experiences (Heim et al., 2000; McEwen, 2015). As a result, lower cortisol reactivity prevents appropriate energy mobilization and adaptation to stressors, leading to poor coping and performance (e.g., avoidance, disengagement). One explanation for these discrepant findings is that life-long or more chronic social phobia or developmental trauma may lead to allostatic load and changes in the HPA axis such that blunted cortisol is observed in these populations. This may serve to prevent glucocorticoid-driven

decreases in immunological defenses, which would theoretically be adaptive in the context of chronic threat (perceived or actual) (for a review, see Fries et al., 2005). As such, it is possible that chronicity of the stressor (actual or perceived threats) contributes to the change in hyper- to hypo- responsivity of the HPA axis.

Given that anxiety can be implicated in stress responding, research interested in inducing acute anxiety tend to use stress-induction paradigms that include a social evaluation component or classical conditioning of anticipatory anxiety (Graeff et al., 2003). To evaluate state anxiety, subjective measures are often used (e.g., single-item anxiety measures, multi-item measures; Rossi & Pourtois, 2012). There is also evidence that cortisol is implicated in anxiety (Grillon, 2008), though to a lesser extent than it is implicated in stress (Grillon et al., 2019). While physiological indices that parallel symptoms of anxiety also exist (e.g., heart rate, breathing rate, electrodermal skin response), these indices may not be coherent with subjective measures given the larger cognitive component characterizing anxiety (Mauss et al., 2004). In fact, Mauss et al. (2004) found that, although subjective anxiety and perceived physiological responses were correlated, there was no correlation between either of these variables and actual physiological responses. This highlights the key role of cognitive processes in anxiety, such as interpretation of bodily signals and stimuli.

The relationship between stress and anxiety is important to consider as changes in one process likely influence the other process. As relevant to this dissertation, measuring indices of both stress and anxiety can provide mechanistic insight regarding the extent to which CBD-related expectation influences various subjective-emotional and psychophysiological processes. Rationale for evaluating these processes is also informed by research on CBD use patterns and expectancies. Indeed, Study 1 highlighted beliefs

that CBD is at least somewhat effective for managing symptoms of both stress and anxiety (Spinella, Bartholomeusz, et al., 2023), and that individuals tend to use CBD and self-report that it is helpful for these symptoms (Moltke & Hindocha, 2021). Evaluating the extent to which these purported effects are related to stimulus and response expectancies is a crucial step in further understanding outcomes related to CBD use.

Study 2a seeks to evaluate the extent to which CBD-related expectation alone contributes to the reported and stress- and anxiety-dampening effects of CBD. A sample of healthy adults were recruited to participate in a laboratory-based randomized, crossover half-balanced-placebo design. Response expectancies regarding the believed helpfulness of CBD for stress, anxiety, and mood were assessed at the outset of the experiment and stimulus expectancies were facilitated by administering the CBD expectancy condition in a CBD labeled bottle with verbal instructions that the administered oil contained CBD. Study 2a evaluated the extent to which these stimulus and response expectancies influenced various stress- and anxiety-related processes in healthy adults.

CHAPTER 4. STUDY 2A: EVALUATING CANNABIDIOL (CBD) EXPECTANCY EFFECTS ON ACUTE STRESS AND ANXIETY IN HEALTHY ADULTS: A RANDOMIZED CROSSOVER STUDY

This study is included in the manuscript presented below. Under the supervision of Dr. Sean Barrett, I was involved in collaborating on a successful CIHR grant to fund this study. I was also directly involved in developing the research questions and hypotheses, data collection, electrophysiological (i.e., HR, HRV) data processing, preparing the dataset for analysis, conducting the analyses, and interpreting the study findings. I wrote the initial draft of the manuscript, incorporated feedback from co-authors, submitted the original investigation to a peer-reviewed journal and subsequently led each round of revisions. This manuscript was published as an Open Access article in *Psychopharmacology* (2021) under a Creative Commons Attribution v4.0 International license (CC BY). See Appendix C for copyright details under this license. Please note that the manuscript included in this dissertation has been slightly modified from the final published version. The full reference is as follows:

Spinella, T. C., Stewart, S. H., Naugler, J., Yakovenko, I., & Barrett, S. P. (2021). Evaluating cannabidiol (CBD) expectancy effects on acute stress and anxiety in healthy adults: A randomized crossover study. *Psychopharmacology*, *238*(7), 1965–1977. https://doi.org/10.1007/s00213-021-05823-w

Abstract

Rationale. Cannabidiol (CBD) has been reported to attenuate stress and anxiety, but little is known about the extent to which such effects result from pharmacological versus expectancy factors.

Objectives. We evaluated whether CBD expectancy alone could influence stress, anxiety, and mood, and the extent to which beliefs regarding CBD effects predicted these responses.

Methods. In this randomised crossover study, 43 health adults (23 women) attended two experimental laboratory sessions, where they self-administered CBD-free hempseed oil sublingually. During one session, they were (incorrectly) informed that the oil contained CBD and in the other session, that the oil was CBD-free. Following administration, participants engaged in the Maastricht Acute Stress Test (MAST). Heart rate variability (HRV) was assessed continuously, and subjective state was assessed at baseline, 90-minutes following oil administration, immediately following the MAST, and after a 10-minute recovery period.

Results. The CBD expectancy condition was associated with increased sedation as well as with changes in HRV that were consistent with heightened anticipatory stress regulation. Overall, there were no systematic changes in subjective stress, or anxiety, according to expectancy condition. However, participants who endorsed strong *a* priori beliefs that CBD has anxiolytic properties reported significantly diminished anxiety in the CBD expectancy condition.

Conclusions. CBD expectancy alone impacted several subjective and physiological responses. Additionally, expectancy-related factors were implicated in anxiolytic effects of CBD for those who believed it was helpful for such purposes, emphasizing the need to measure and control for CBD-related expectancies in clinical research that involves the administration of CBD.

Key words: Cannabidiol, CBD, Cannabis, Expectancy, Placebo, Stress, Anxiety, Affect, Anxiolytic, Subjective response.

Introduction

In the past decade, there have been notable increases in cannabidiol (CBD) use globally for therapeutic purposes (World Health Organization (WHO), 2018). One potential application that has generated considerable interest is for the treatment of stress- and anxiety-related disorders. In animal models, CBD has been shown to diminish several anxiety- and stress-related responses (Blessing et al., 2015), while in humans, CBD's effect on stress and anxiety has been somewhat mixed. For example, while one study found that CBD had less of an impact on anxiety symptoms relative to placebo in a sample of adults with obsessive-compulsive disorder (Kayser et al., 2020), other investigations have found that CBD reduces the anxiogenic effects induced by THC (Zuardi et al., 1982), and attenuates anxiety associated with social stress in both healthy individuals (Zuardi et al., 1993, 2017) and individuals with social anxiety disorder (Bergamaschi, Queiroz, Chagas, et al., 2011; Masataka, 2019). However, the extent to which any such anxiolytic effects result from the pharmacological properties of CBD, and/or CBD-related expectancy, has never been systematically examined.

Drug effects in humans are believed to be comprised of both direct pharmacological effects related to the drug itself and a placebo response (Kirsch, 1985). The placebo effect is thought to be mediated by the patient's beliefs or expectations regarding the content and effects of a substance. Indeed, such expectations can be formed by verbal information about the content and supposed effects of a substance, prior experience, and observational learning (Kirsch, 2018). Evidence suggests that placebo responses may account for a significant portion of the therapeutic response to drugs such as nicotine replacement therapies (Dar & Barrett, 2014), antidepressants (Laferton et al., 2018), and analgesics (Klinger et al., 2018). Though active treatment versus placebo

study designs can control for some of the influence of non-pharmacological variables, it is not possible to completely disentangle placebo effects from pharmacologically driven treatment effects using such designs (Lund et al., 2014; Wampold et al., 2005). Thus, given the current state of research to our knowledge, CBD-related placebo responses have never been systematically examined. If a placebo effect is observed for CBD, it would bolster the case for future evaluation of whether CBD pharmacology interacts with expectancy to dampen stress- and anxiety-related responses using a full balanced placebo design (Rohsenow & Marlatt, 1981).

We designed the present randomised crossover study to evaluate whether CBD expectancy, independent from pharmacology, could impact acute stress, anxiety, and mood responses to a standardized stressor in a sample of healthy adults. Following one orientation session, subjective and physiological data were gathered at numerous time points throughout two experimental laboratory sessions in the context of a validated stress induction protocol. In terms of physiological measures, heart rate (HR) and heart rate variability (HRV) were chosen as indices of stress and anxiety. The root mean square successive difference (RMSSD) is a widely-used index of HRV that is thought to reflect parasympathetic output and successful emotional regulation (Laborde et al., 2017). Thus, lower mean RMSSD is thought to indicate a larger stress response. Additionally, we sought to examine the extent to which individual differences in beliefs regarding CBD effects (i.e., response expectancies) are activated to influence responses to perceived CBD vs. perceived placebo administration. Consistent with prior expectancy research (e.g., Klinger et al. 2018; Laferton et al. 2018), we hypothesized that the CBD expectancy condition would be associated with distinct patterns of subjective and physiological responses relative to the CBD-free expectancy condition. Specifically, we expected the

CBD expectancy condition would be associated with lower levels of subjective and physiological indices of stress, anxiety, and negative affect. Additionally, response expectancies tend to be self-confirming such that simply expecting a specific response to occur (e.g., anxiety reduction) will enhance the likelihood of said response to actually occur (Kirsch, 1985). As such, it was also hypothesized that endorsing stronger beliefs regarding the potential stress-, anxiety-, and mood-related benefits of CBD would be linked to the largest differences in the corresponding subjective responses between the two conditions.

Methods

Study design and participants

We conducted a three-session (one orientation session, two experimental sessions), within-subjects experimental laboratory study with healthy adults who were community-recruited from the Halifax Regional Municipality (Nova Scotia, Canada). We were unable to conduct an *a* priori power analysis for our specific analytic approach (Generalized Estimating Equations) due to our within-subject study design parameters. To address this barrier, we conducted a power calculation after data collection using a similar, but less powerful analytic approach (repeated-measure ANOVA) in G*Power. Based on aggregated effect sizes of placebo effects for conditions that are very amenable to the placebo effect (e.g., anxiety; d=.29; Wampold et al., 2005), we are expected to have at least 85% power to detect within-factor effects with the sample size used in this study. As such, we expected to have sufficient statistical power to test our study hypotheses (i.e., main effects, two-way interactions).

Participants were required to be at least 19 years of age, as this is the age of majority in Nova Scotia. Selection criteria included ≥1 lifetime uses of cannabis, which

was required to ensure that subjects had some experience with and knowledge about cannabis in attempt to standardize expectations to some extent. To help ensure that participants could meet the abstinence requirements, only individuals reporting cannabis use two or fewer days per week in the past month were enrolled in the study. In order to ensure cold pressor test (CPT) would be well-tolerated, participants were required to be medically healthy, and free of any serious medical conditions, or any history of fainting, seizures, circulatory disorders, heart problems, high blood pressure, diabetes, frostbite, or any current cut, sore, or fracture to their right hand/arm (Birnie et al., 2011; Mitchell et al., 2004). Subjects were also excluded if they reported current prescription medication use (except birth control in females) or any current psychiatric disorder, as diagnosed by a health care professional, including substance use disorders (American Psychiatric Association, 2013). These exclusions helped prevent pre-existing neurophysiological or psychological conditions from influencing subjective and physiological stress, mood, and anxiety responses to the laboratory stressor. Participants were also required to be cannabis oil naïve (to enhance believability of the oil manipulation), and to have never previously participated in a study conducted by our group that involved deception.

Stress and anxiety induction

The Maastricht Acute Stress Test (MAST; Smeets et al., 2012) was used to induce stress and state-anxiety in our sample. The MAST was chosen since it possesses both physical and psychological features that have been demonstrated to reliably provoke subjective and physiological responses associated with stress and anxiety in laboratory settings (Bali & Jaggi, 2015; Smeets et al., 2012) over multiple sessions, with little habituation (Quaedflieg et al., 2017). The physical feature is a CPT and the psychological

feature mental arithmetic challenges that include a psychosocial evaluative threat (Bali & Jaggi, 2015; Smeets et al., 2012).

As per the validated protocol (Smeets et al., 2012), the MAST involved a five-minute anticipation phase, in which instructions and procedures are explained to participants, followed by a ten-minute acute stress phase. During the stress phase, participants engaged in trials alternating between (i) immersing their hand into ice-cold water (2◦C) (i.e., CPT), and (ii) counting backwards in steps of 17 or 13 starting at a random four-digit number. Both tasks are combined with negative social-evaluative pressure (i.e., negative feedback and videotaping).

Measures

Physiological measures

Electrocardiogram (ECG) data was collected continuously throughout the experimental sessions using an Equivital EQ02 sensor electronic module (SEM) equipped to a fitted Life Monitor belt (ADInstruments; [ADI], Colorado Springs, United States). The EQ02 device measured ECG signal on two channels via three electrodes at a sampling rate of 1,000 Hz. The raw ECG signals were later transferred to a computer and used to compute indices of heart rate and HRV, a robust, non-invasive physiological measure that has been used to assess stress and anxiety responses (H.-G. Kim et al., 2018).

Demographics and CBD belief ratings

Demographic information, including age, sex, ethnicity, and level of education, were collected with a researcher-compiled self-report questionnaire. Additionally, information about participants' baseline/*a* priori beliefs regarding the effects of CBD were collected using three researcher-compiled single-item questions. Participants

reported on the extent to which they believed statements about the mood-, stress-, and anxiety-related properties of CBD (i.e., "improves mood", "reduces stress", "reduces anxiety") on a 10-point scale (1- "Not at all", 10- "Completely"). Lifetime and past month cannabis use frequency information was collected using single items via telephone screening as part of the study selection criteria.

Subjective stress, anxiety, mood, and drug effect ratings

Participants reported their current subjective state using a combination of validated measures and researcher-compiled single-item scales. Subjective stress was assessed with a single-item Numerical Rating Scale (NRS) where subjects rated the extent to which they felt "stressed" on a 10-point scale (1- "Not at all", 10- "Extremely"). Similar single-item scales have been shown to demonstrate adequate construct validity (correlations between .45 and .66 with other validated stress measures) and discriminant validity (i.e., stressed vs. non-stressed states) (Lesage et al., 2012).

Subjective anxiety was assessed with a six-item shortened state version of the State-Trait Anxiety Inventory (STAI-S-SF; Marteau & Bekker, 1992). Participants rated six statements about their current state (e.g., "I am tense") and rate them on a 4-point scale (1- "Not at all", 4- "Very much"). The STAI-S-SF has been shown to possess good reliability (α=.82; Marteau & Bekker, 1992). It also produces acceptable validity, generating similar scores to those obtained using the full 20-item STAI-S (Spielberger, 1983) (.91 total score correlation; Marteau & Bekker, 1992), which is sensitive to rapid state-dependent fluctuations in anxiety (Rossi & Pourtois, 2012). To calculate total anxiety scores, the three positive STAI-S-SF items were first reverse scored. Next, all scores were summed then multiplied by 20/6 to yield total scores between 20 and 80.

Subjective mood was assessed with the ten-item International Positive and Negative Affect Schedule, Short Form (I-PANAS-SF; Thompson, 2007). Participants were asked to rate the extent to which they presently feel a list of positive affect (e.g., "Alert", "Inspired") and negative affect (e.g., "Upset", "Hostile") related items on a 5-point scale (1- "Very slightly or not at all", 5- "Extremely"). Both positive and negative affect subscales of the I-PANAS-SF have been shown to possess adequate reliability (α=.78 and .76, respectively), as well as acceptable convergent validity with measures of subjective well-being (Thompson, 2007). To calculate total scores, the five items from each subscale within the I-PANAS-SF were summed to create a positive affect and negative affect score (subscale scores range between 5 and 25).

Subjective drug effects were assessed using the six-item Brief Biphasic Alcohol Effects Scale (B-BAES; Rueger et al., 2009). Participants rated how well three sedation items (e.g., "Sedated") and three stimulation items (e.g., "Energized") described their current feelings on a 10-point scale (1- "Not at all", 10- "Extremely"). The subscales within the B-BAES correlated highly (.92-.97) with the full form of the BAES (Martin et al., 1993), demonstrating adequate criterion validity, and showed excellent internal consistency reliability (α=.89-.91; Rueger & King, 2013). Though the B-BAES was initially developed to evaluate the biphasic stimulation and sedation effects associated with alcohol use, the questions are not specific to alcohol and thus were used to assess subjective sedation- and stimulation-related drug effects in this study. To calculate total scores, the three items from each of the two subscales within the B-BAES were summed to create a sedation and stimulation score (subscale score range between 10 and 30). Additionally, two researcher-compiled NRS items ("intoxicated", "relaxed") rated on a

10-point scale (1- “Not at all”, 10- “Extremely”) were included in the assessment of potential drug-related effects.

Procedures

Once eligibility was confirmed via telephone screening, participants were scheduled for an initial orientation session (~30-minutes). After providing consent, participants had their weight measured, which they were informed would determine the dose of oil that they would be given during their experimental sessions. Demographic and CBD belief rating information was collected. Two experimental sessions were then scheduled between 10:30 and 18:00 h. The laboratory setting, testing procedure, and time of day was kept constant for each participant across all sessions to minimize circadian fluctuations in the stress response (Nicolson & van Diest, 2000). Female participants not using birth control were tested during the luteal phase of their menstrual cycle to minimize menstrual cycle-related fluctuations in the stress response (Barel et al., 2018). Experimental sessions were separated by a minimum of one week and a maximum of one month.

All participants received CBD-free hemp seed oil across both experimental sessions but received different instructions during each session about the CBD content of the oil (told CBD-containing vs. told CBD-free), in randomized order. This produced two conditions: (a) told CBD, administered CBD-free; (b) told CBD-free, administered CBD-free, allowing for an assessment of the effects of CBD-related expectancy, independent from pharmacology (Sutton, 1991b). Experimenters were blind to the expectancy condition, as oil was administered by an independent blinder who otherwise did not interact with the participant, and participants were blind to the actual pharmacology of the oil.

Experimental sessions (~three hours) took place following a minimum of 72-hours of abstinence from cannabis, given the ~31 hour half-life of CBD and THC in infrequent users (Millar et al., 2018; Smith-Kielland et al., 1999). Additionally, twelve-hours of abstinence from alcohol, tobacco smoking, and other drug consumption was required (Benowitz & Jacob, 1994; Holford, 1987). Participants were also required to abstain from caffeine for a minimum of two-hours (Benowitz et al., 1995) as well as to fast for one hour prior to their session. Abstinence from substances was verified via self-report since all participants were pre-screened to be healthy, infrequent cannabis users with no current substance dependencies. To increase compliance to the study procedures, participants were sent multiple email reminders about their upcoming experimental sessions and the respective abstinence requirements.

Following the collection of baseline subjective and HRV data, participants were administered hemp seed oil sublingually by an independent blinder. To enhance the believability of the drug content instructions, participants were presented with their assigned oil in packaging consistent with the instructions provided. Participants were informed during the consent process and by the independent blinder there would be a 90-minute "absorption period" following oil administration (to mimic the absorption period of CBD; Zuardi et al., 2017). During this period, participants were provided with neutral word puzzles and reading material to pass the time. For the second time (post-absorption), participants completed the same battery of assessments as used at baseline. To induce stress and state-anxiety, the MAST protocol was administered by the experimenter. Immediately following completion of the MAST, subjective measures were re-administered for the third time (post-stress), and for a final time ten minutes later (recovery).

At the end of each experimental session, participants were asked about the CBD content of the oil that they had self-administered, with the following response options 'CBD oil', 'CBD-free/Hemp seed oil' or 'Unsure'. This served as a manipulation check to determine whether participant beliefs regarding drug assignment were consistent with the CBD content stated in their instructions. It was decided *a* priori that sessions where participant did not believe the CBD content information provided would be excluded from the analyses to avoid confounding the interpretation of results. Lastly, to ensure that the deceptive nature of the study was not revealed to potential future participants, full debriefing of the nature and aims of the study was delayed until study data collection concluded.

Data acquisition and ECG pre-processing

Raw ECG data were extracted from Lead II with LabChart Pro software (HRV 2.0 module; ADI). HRV was calculated by extracting beat-to-beat RR intervals. Ectopic beats were excluded from analyses, using the Lomb-Scargle Periodogram, to enable exclusion of ectopic beats without interpolation. To reduce baseline wandering, all ECG signals were passed through a high pass filter (.5Hz). All segments used in analyses were visually inspected for ectopic beats and noise. If noise or ectopic beats exceeded 5% of total beats in an ECG segment, they were excluded. An artifact-free five-minute segment during the first 70 minutes of the session was selected as a baseline. A five-minute segment was selected during the anticipation phase of the MAST (anticipation), and the two five-minute segments during the arithmetic and cold pressor components of the MAST were averaged to compute HRV during acute stress (stress). The final five-minute segment was selected ten-minutes after the MAST (recovery). Additionally, an ECG-derived

respiration rate (EDR) was manually calculated from raw Lead II ECG as per recommendations (Brugnera et al., 2018).

Heart rate (HR) and the root mean square successive difference (RMSSD), a time-domain index of HRV, were extracted from the RR data. RMSSD is a widely-used index of HRV that is thought to reflect parasympathetic output and successful emotional regulation (Laborde et al., 2017).

Statistical analyses

Statistical analyses were conducted in SPSS, version 25.0. Generalized Estimating Equations (GEE) were used for all primary analyses because they have robust estimators and can accommodate non-normal distributions (Hubbard et al., 2010). Multiple models per outcome were conducted to determine the optimal fit for the data based on the lowest number of parameters and the lowest Quasi Likelihood under Independence Model Criterion (QIC). First, the dependent variable was visually screened to identify plausible distributions, which were then compared with the covariate structure specified as Unstructured. Once an optimal distribution was chosen, plausible covariance structures were tested. The Exchangeable correlation matrix tended to be most parsimonious among all models.

Subjective outcomes included stress, state anxiety (STAI-S-SF), mood (I-PANAS-SF positive affect and negative affect), and drug effects (B-BAES sedation and stimulation; intoxication; relaxation). For subjective outcomes, Time (baseline, post-absorption, post-stress, recovery), and Expectancy condition (CBD, CBD-free) were entered as repeated factors. Physiological outcomes included HR and HRV (i.e., RMSSD). The physiological outcomes were analyzed in a similar fashion to the subjective outcomes. Specifically, Time (baseline, anticipation, stress, recovery) and

Expectancy condition (CBD, CBD-free) were entered as repeated factors, and EDR was entered as a covariate to control for respiratory influences on HR and HRV (Brugnera et al., 2018). Effects of interest for subjective and physiological outcomes included main effects of Time and interactions between Time and Expectancy condition. Planned post-hoc pairwise comparisons using tests of simple effects were used to probe main effects of Time and Time by Expectancy condition interactions. We also examined whether *a* priori beliefs about CBD influenced corresponding stress, anxiety, and mood responses according to expectancy condition. The corresponding CBD belief rating and baseline outcome values were entered as covariates. Time (all time points following oil administration: post-absorption, post-stress, recovery) and Expectancy condition (CBD, CBD-free) were entered as repeated factors. Effects of interest included Expectancy condition by Belief interactions on overall stress, anxiety, and mood ratings. Given that GEE in SPSS does not have the capability of probing interactions involving continuous predictors using tests of simple effects, we used 'geepack' in R (version 4.0) to probe significant interactions involving CBD Belief rating. Post-hoc tests of simple effects involved contrasts between Expectancy condition across three levels of CBD Belief ratings (i.e., terciles). All *p*-values less than .05 were considered significant. Additionally, the Benjamini-Hochberg method (Benjamini & Hochberg, 1995) was used to control for the false discovery rate (FDR) within each model (i.e., family) tested. The FDR threshold was set at .05 such that there was a 5% chance that any finding within each model was a false discovery. All *p*-values were reported in their original format unless the FDR threshold was exceeded, in which case both adjusted and unadjusted *p*-values were reported.

Results

Forty-three participants, community-recruited between February 2019 and March 2020, were included in the study (Age 19-62 years). Five participants withdrew after one session, but their data was retained from the session they completed. One participant withdrew six minutes into the MAST on their second session, thus their data was excluded after post-absorption. Among the 302 physiological data points collected, 43 were excluded due to excess ECG noise or artifacts exceeding 5%. Additionally, four sessions contained excess noise during one half (i.e., five-minutes) of the stress time-point; thus, the mean from the remaining five-minute segment was used to represent acute stress. For subjective data, one case was excluded due to missing data (only for STAI-S-SF). During the manipulation check, all subjects reported oil contents consistent with instructions in 100% of sessions. A summary of participant characteristics is provided in Table 4.1. All GEE coefficients for interactions, as well as the corresponding estimated marginal means and standard errors are listed in Tables 4.2-4.3. Main effects of Time are reported and described in Supplemental files and Supplemental Table 4.1 (Appendix D). All GEE model coefficients that are not part of the initial hypotheses are reported in the Supplemental Table 4.2 for descriptive purposes (Appendix D).

We first evaluated whether there were differences in subjective intoxication, relaxation, sedation, and stimulation according to expectancy condition (Table 4.2). No significant Time by Expect interactions were observed for intoxication, relaxation, and stimulation; however, there were differences in subjective sedation. In the CBD expectancy condition, sedation *increased* significantly from baseline to post-absorption (p=.007). In fact, post-absorption sedation was higher in the CBD expectancy condition relative to the CBD-free expectancy condition (p=.002). Alternatively, in the CBD-free

expectancy condition, subjects reported *lower* levels of sedation during recovery relative to post-stress (p=.019) and baseline (p=.037).

Next, we examined whether CBD expectancy alone would dampen subjective stress, anxiety, and mood responses to an acute laboratory stressor (Table 4.2). First, main effects of Time indicated that the MAST was effective at inducing subjective stress, anxiety, and negative affect among all subjects, regardless of expectancy condition (baseline vs. post-stress, all p<.001). See Supplemental files for a breakdown of findings related to main effects of Time. None of the Time by Expectancy condition interactions reached statistical significance (Figure 4.1).

To test whether expectancy influenced physiological markers of acute stress, we evaluated Time by Expectancy condition interactions predicting HR and RMSSD, a time-domain index of HRV (Table 4.2). First, main effects of Time were observed for both HR and RMSSD, which tended to change significantly from anticipation to stress (HR increase, p=.020; RMSSD decrease, p=.002), indicating that the MAST was successful at inducing physiological stress. See supplemental files for a breakdown of findings related to main effects of Time. No Time by Expectancy condition interaction was observed for HR; however, a significant interaction was observed for RMSSD (Figure 4.2). Parasympathetic nervous system activity dominates RMSSD (Laborde et al., 2017); thus, lower mean RMSSD is thought to represent a larger stress response. In the CBD expectancy condition, RMSSD increased significantly from baseline to anticipation (p=.007), then decreased during stress (p<.001), and subsequently increased at recovery (p<.001). RMSSD was significantly higher at recovery, relative to baseline (p<.001). On the other hand, in the CBD-free expectancy condition, RMSSD was comparable during baseline, anticipation, and stress. However, similar to the CBD expectancy condition,

RMSSD was lower during stress relative to recovery in the CBD-free expectancy condition (p<.001). RMSSD during recovery was also higher than baseline (p<.001). Next, to explore the possibility that expectancy-related influences on subjective stress, anxiety, and mood responses were suppressed by the stress task, we evaluated whether expectancy condition influenced *overall* stress, anxiety, and mood ratings following oil administration (i.e., post-absorption, post-stress, and recovery) (Table 4.3). A main effect of Expectancy condition was observed for positive affect such that higher overall ratings of positive affect were reported when participants expected CBD-free versus CBD-containing oil. However, the FDR for this finding exceeded the 5% threshold, suggesting that it may have been a false positive. No significant main effects of Expectancy condition were identified for any other subjective rating, indicating that they did not differ by expectancy condition.

To assess whether *a priori* beliefs about CBD effects on stress, anxiety, and mood differentially impacted subsequent stress, anxiety, and mood responses, we explored interactions between belief ratings and expectancy condition. Beliefs about the potential effects of CBD are illustrated in the Supplemental Figure 4.1 (Appendix D). Briefly, stress, anxiety, and mood belief ratings were negatively skewed such that the majority of participants endorsed beliefs closer to the upper end of the scale (i.e., 10). A significant Belief by Expectancy condition interaction was observed for subjective ratings of anxiety (Figure 4.3). Post-hoc tests of simple effects in R indicated that endorsing stronger beliefs that CBD reduces anxiety (third tercile [range: 9-10]) impacted overall anxiety levels according to expectancy condition (p=.009). Specifically, those who endorsed higher *a* priori beliefs that CBD reduces anxiety reported significantly less anxiety when they were led to expect CBD oil than when they were led to expect CBD-free oil. Those who

endorsed lower belief ratings (first tercile [range: 1-6] and second tercile [range: 7-8]) reported similar anxiety levels across expectancy conditions. No significant Belief by Expectancy condition interactions were observed for overall ratings of stress or mood.

Discussion

This was the first study to our knowledge to experimentally manipulate and evaluate the effects of CBD-related expectancy. Prior research has shown that CBD administration dampens anxiety and stress responses in humans (Bergamaschi, Queiroz, Chagas, et al., 2011; Masataka, 2019; Zuardi et al., 1993, 2017); however, it is unclear whether such effects result from pharmacological properties and/or CBD-related expectancy (i.e., the placebo effect). We were therefore specifically interested in examining whether CBD expectancy, independent from pharmacology, could impact acute stress, anxiety, and mood in a sample of healthy adults. Overall, findings suggested that expectation likely plays some role in the purported stress- and anxiety-reducing effects of CBD.

Various subjective and physiological indices of stress, anxiety, and mood were measured across four time points during each of the two laboratory sessions (expect CBD vs. expect CBD-free). With respect to HRV, we found that the pattern of RMSSD values differed significantly according to expectancy condition. In the CBD-free expectancy condition, RMSSD only changed significantly (i.e., increased) from stress to recovery. Conversely, in the CBD expectancy condition, RMSSD increased significantly during the anticipation to stress, then decreased significantly during stress and increased again at recovery. The mean differences between these timepoints in the CBD expectancy condition (i.e., >15ms from anticipation to stress and from stress to recovery) is slightly larger than what has been reported in previous investigations of acute stress (Castaldo et

al., 2015; Pulopulos et al., 2018). Taken together, the magnitude of this observed effect is likely small-to-medium, suggesting notable shifts in parasympathetic activity in the CBD expectancy condition taking place between anticipation, stress, and recovery.

There are a number of interpretations that could explain this pattern of findings. First, anticipation-induced, but not stress-induced changes in HRV have been associated with hypothalamic-pituitary adrenal axis reactivity (Pulopulos et al., 2018), wherein better anticipatory stress regulation (reflected in less HRV decrease during stress anticipation) is thought to represent enhanced overall physiological stress response regulation. Our finding could therefore suggest that CBD expectancy, independent from pharmacology, may dampen physiological indices of stress. Second, the observed fluctuations in HRV in the CBD expectancy condition could indicate a pattern of adaptive emotional responding or normal physiological processes (Porges, 1995; Thayer et al., 2012). For instance, challenges that disrupt homeostasis require the individual to respond appropriately (i.e., via the autonomic nervous system) to maintain homeostasis (for a review, see Kim et al., 2018). This could be reflected through fluctuations in vagal output from anticipation to stress, and then from stress to recovery. Third, cannabis use has been shown to increase HRV (Schmid et al., 2010). It is therefore possible that expecting CBD was sufficient to induce similar effects to the drug itself such that HRV increased during anticipation (i.e., post-product absorption). Alternatively, the observed pattern of physiological findings could indicate that CBD expectancy alone dampens physiological indices of stress during anticipation, as illustrated by the significant increase in HRV from baseline to stress anticipation. However, during the stressor itself, there appears to be the opposite effect such that HRV decreases significantly from anticipation to stress. Interestingly, neither of these patterns were observed in the CBD-free expectancy

condition. It is therefore possible that participants showed a typical placebo response initially (i.e., lower physiological stress) in the CBD expectancy condition; however, when confronted with the actual stressor, a significant stress response was still elicited.

Interestingly, the lack of change in HRV from baseline to anticipation to stress in the CBD-free expectancy condition suggests that a significant physiological stress response may not have been elicited. It is possible that our baseline assessment of HRV in both conditions may have been confounded by the nature of our study design. Specifically, participants were told at the beginning of each session that they would be randomly assigned to an oil and a task that would either be physically and cognitively demanding, or non-demanding, but they would not know which condition they were assigned to until immediately before. This may have elicited some degree of anticipatory stress and/or anxiety that impacted their baseline/resting HRV assessment.

Among all subjects, the stress task induced self-reported stress, anxiety, and negative affect. Both expectancy conditions appeared to be similar in their subjective stress responses, which seems to partially contradict the physiological data and would lend support to the notion that CBD expectancy does not impact stress and anxiety. However, our findings that the stressor reliably increased subjective indices of stress and anxiety could also suggest a potential ceiling effect wherein the strength of the stressor (comprised of physical, mental, and social challenges) suppressed any expectancy-driven influences. It is also possible that rapid expectancy-induced changes in affective state are more difficult to capture, especially when such changes are small (Campbell & Ehlert, 2012). Alternatively, there may be other individual difference factors that interact with expectancy condition to predict subjective stress and anxiety responses.

To explore the possibility that expectancy-related influences on subjective stress, anxiety, and mood responses were being suppressed by the stress task, we evaluated differences in subjective affect ratings following oil administration (i.e., post-absorption, post-stress, and recovery). Only positive affect differed according to expectancy condition such that those in the CBD expectancy condition reported *less* positive affect compared to the CBD-free expectancy condition. However, this finding may have been a false positive as indicated by the >5% FDR. Nevertheless, it would not be particularly surprising that the CBD expectancy condition is associated with lower positive affect given that one of the reported side effects of CBD is sedation (Iffland & Grotenhermen, 2017), and some of the positive affect items appeared to be related to physiological arousal (e.g., "Alert", "Active"). A significant interaction involving subjective sedation supports this explanation, as subjects in the expect CBD condition reported higher levels of sedation post-absorption relative to those in the expect CBD-free condition. The mean difference between expectancy conditions at the post-absorption time-point (MD=2.54) was relatively small. However, this is comparable to other investigations showing differences between placebo and an active drug known to increase sedation (e.g., alprazolam; Aitken et al., 2023). Combined with data from the manipulation check indicating that all subjects reported perceived oil contents consistent with instructions during 100% of sessions, the difference in subjective sedation between expectancy groups suggests that the instruction manipulation was indeed successful.

Our findings generally supported the idea that affective responses can be elicited or amplified by the mere expectation of their occurrence (Kirsch, 2018). While the majority of participants endorsed moderate-to-high beliefs that CBD was effective at reducing stress, anxiety, and improving mood, their level of endorsement varied widely

(i.e., from 1 to 10). Interestingly, the extent to which participants believed that CBD reduced anxiety interacted with expectancy condition to predict their subjective anxiety levels following oil administration (post-absorption, post-stress, recovery). That is, subjects who endorsed the strongest beliefs that CBD reduces anxiety tended to experience the lowest levels of anxiety when they expected CBD oil and the highest levels of anxiety when they expected CBD-free oil. On the other hand, when subjects endorsed low or moderate beliefs, there was very little difference in anxiety outcomes according to expectancy condition. Among participants with the strongest beliefs that CBD reduces anxiety, the mean difference in overall anxiety post-administration between expectancy conditions is notable. Their anxiety is in the moderate range when they expected a CBD oil, whereas it is in the severe range when they expected a CBD-free oil, suggesting a clinically meaningful effect. Such findings emphasize the importance of individual expectancies and their role in moderating the placebo effect. They are also consistent with prior research demonstrating that expectations regarding the success of treatment (or effects of a substance) are paramount in predicting treatment (or substance administration) outcomes (Schedlowski et al., 2015). Lastly, there was no observed association between *a* priori stress- and mood- related CBD beliefs and respective subjective outcomes. It is possible that these expectancy effects may be specific to anxiety. Alternatively, the assessment used to measure anxiety may have been more sensitive to short-term affective changes, relative to the subjective stress and mood assessments.

Findings should be considered in light of the following methodological considerations. First, our sample was a relatively homogenous population of healthy, mostly white adults with college or university education, thus limiting our study's

generalizability. Moreover, because we used a sample of healthy adult participants, it is not clear the extent to which our findings would extend to individuals suffering from stress- and anxiety-related conditions for which CBD is often considered. We were also likely underpowered to examine sex-related effects. Additionally, though we were interested in making population level inferences, the use of GEE as an analytic strategy with less than 40 clusters can yield biased results (Kauermann & Carroll, 2001). This could be a possibility in our study but is unlikely given our cluster size (i.e., 43) exceeded this threshold. Lastly, since CBD-free hempseed oil was administered to all participants, we could only make inferences about the role of CBD expectancy alone, on various stress, anxiety, and mood responses. Future studies would benefit from using a full balanced-placebo research design (Rohsenow & Marlatt, 1981), such that more inferences could be made about whether CBD pharmacology interacts with expectancy or whether CBD pharmacology alone has stress and/or anxiety-dampening effects.

Overall, the present findings provided mixed support towards the first hypothesis that the CBD expectancy condition would be associated with distinct patterns of subjective and physiological responses relative to the CBD-free expectancy condition. While there were no differences in subjective stress, anxiety, and mood between expectancy conditions, higher levels of sedation were reported in the CBD expectancy condition following absorption relative to the CBD-free expectancy condition. Additionally, compared to the similar HRV response over time in the CBD-free expectancy condition, CBD expectancy was associated with a fluctuating pattern of HRV, possibly indicative of a more adaptive physiological stress response or successful emotional adaptation during stress anticipation (but not during the stress challenge). Consistent with our second hypothesis, only those who had the strongest *a* priori beliefs

regarding the anxiety-dampening effects of CBD exhibited decreased subjective anxiety following administration of oil in the CBD relative to CBD-free expectancy conditions. Those with lower *a* priori beliefs about the anxiolytic properties of CBD did not show any effects of expectancy condition on their ratings of anxiety. Contrary to our hypothesis however, no significant effects were identified for mood- or stress-related belief models. Our findings demonstrate, for the first time, that expectancy-related factors likely play a key role in the purported anxiolytic effects of CBD, at least among those who *believe* that it is helpful for such purposes. Our results also provide novel insight into the mechanisms through which CBD may be facilitating medicinal effects for stress- and anxiety-related psychiatric conditions (e.g., Blessing et al., 2015). Future research would also benefit from evaluating the influence of CBD-related expectancy effects in clinical populations and replicating these findings. Though previous reports suggest that CBD may be a promising medicine for psychiatric disorders like anxiety, our findings emphasize the need for more research evaluating the relative contributions of pharmacological and non-pharmacological factors for such conditions, which could be done through a full balanced placebo research design (Rohsenow & Marlatt, 1981). These findings also highlight the need to evaluate and control for *a* priori CBD expectancies in gold standard randomized controlled clinical trials. Lastly, given the dramatic increase in the use of CBD for psychiatric conditions (WHO, 2018) (despite the dearth of strong empirical support), and the beliefs about its efficacy as demonstrated through our findings, it may be beneficial to allocate resources towards education-focused initiatives to correct these misperceptions that are accessible to the lay public.

Tables

Table 4.1. Participant characteristics

	N (percent)
Age in years (mean (standard deviation))	27.7 (9.3)
Sex	
Female	23 (53.5%)
Male	20 (46.5%)
Females using contraceptives (% of females)	8 (38.4%)
Ethnicity	
Aboriginal and White	3 (7.0%)
White	33 (76.8%)
Black	1 (2.3%)
Latin American	1 (2.3%)
Arab	1 (2.3%)
Southeast Asian, Chinese, or Korean	3 (7.0%)
Other	1 (2.3%)
Highest level of education	
High school diploma	4 (9.3%)
Some college or university	13 (30.2%)
College or university degree	26 (60.5%)
Current (non-dependent) cigarette smoker	2 (4.6%)
Average number of cannabis-using days per week	
0 days	24 (55.8%)
0.5 days	4 (9.3%)
1 days	7 (16.3%)
1.5 days	2 (4.6%)
2 days	6 (14.0%)

N=number of subjects.

Table 4.2. Estimated marginal mean (standard error) values and generalized estimating equation (GEE) coefficients for Time by Expectancy condition interactions involving subjective drug effects, stress, anxiety, mood, and heart rate variability

Interaction: Time by Expectancy condition

	Baseline	**Post-absorption**	**Post-stress**	**Recovery**	**Outcome**	**df**	**Wald Chi-square**	***p***
Intoxication					Intoxication	3	7.13	.068
Expect CBD	1.00 (.01)	1.27 (.09)	1.35 (.15)	1.25 (.10)				
Expect CBD-free	1.01 (.03)	1.11 (.07)	1.18 (.09)	1.13 (.08)				
Relaxation					Relaxation	3	3.05	.385
Expect CBD	6.21 (.31)	6.80 (.33)	2.19 (.29)	4.95 (.35)				
Expect CBD-free	6.31 (.35)	6.26 (.34)	2.40 (.29)	4.39 (.33)				
Stimulation					Stimulation	3	2.15	.542
Expect CBD	14.93 (.74)	11.65 (1.00)	11.09 (.94)	12.14 (.86)				
Expect CBD-free	13.69 (.76)	11.62 (.76)	11.63 (.93)	11.94 (.85)				
Sedation					**Sedation**	**3**	**16.57**	**.001**
Expect CBD	7.29 (.57)	9.93 (.96)	8.12 (.71)	7.61 (.76)				
Expect CBD-free	7.81 (.68)	7.39 (.56)	8.24 (.94)	6.36 (.54)				
Stress					Stress	3	4.50	.212
Expect CBD	2.33 (.25)	1.65 (.14)	4.69 (.40)	1.82 (.19)				
Expect CBD-free	2.07 (.27)	1.79 (.18)	5.01 (.43)	1.98 (.20)				
Anxiety					Anxiety	3	5.04	.169
Expect CBD	31.04 (1.23)	29.64 (1.21)	54.62 (1.79)	36.35 (1.52)				
Expect CBD-free	31.45 (1.48)	33.38 (1.53)	56.04 (1.66)	38.45 (1.54)				
Negative affect					Negative affect	3	.23	.973
Expect CBD	5.75 (.16)	5.63 (.19)	9.32 (.54)	6.17 (.25)				
Expect CBD-free	6.06 (.22)	6.01 (.23)	9.63 (.56)	6.37 (.25)				
Positive affect					Positive affect	3	1.88	.599
Expect CBD	13.32 (.62)	10.99 (0.72)	12.24 (.67)	11.82 (.63)				

Interaction: Time by Expectancy condition

	Baseline	**Post-absorption**	**Post-stress**	**Recovery**	**Outcome**	**df**	**Wald Chi-square**	***p***
Expect CBD-free	12.91 (.57)	11.60 (0.54)	12.64 (.70)	12.11 (.59)				
	Baseline	**Anticipation**	**Stress**	**Recovery**				
HR					HR	3	2.55	.466
Expect CBD	68.86 (1.20)	71.69 (1.13)	75.94 (1.68)	63.86 (1.18)				
Expect CBD-free	68.45 (1.26)	72.47 (1.80)	74.07 (1.60)	63.21 (1.31)				
RMSSD					**RMSSD**	**3**	**8.09**	**.044**
Expect CBD	59.59 (6.03)	70.41 (4.85)	54.59 (3.80)	81.05 (5.64)				
Expect CBD-free	62.68 (5.97)	62.60 (5.00)	61.88 (4.90)	81.61 (5.93)				

Bolded coefficients indicate statistical significance ($p<.05$).

Subjective measures: Baseline (T1): +00; Post-absorption (T2): +95; Post-stress (T3): +110; Recovery (T4): +120

Physiological measures: Baseline (T1): +00-+70; Anticipation (T2): +95; Stress (T3): +100; Recovery (T4): +120

Table 4.3. Estimated marginal mean (standard error) values and generalized estimating equation (GEE) coefficients for main effects of Expectancy condition and Expectancy condition by Belief interactions involving subjective stress, anxiety, and mood

Main effect: Expectancy condition

		Outcome	**df**	**Wald Chi-square**	***p***
Stress		Overall stress post-administration	1	.15	.698
Expect CBD	2.29 (.14)				
Expect CBD-free	2.57 (.14)				
Anxiety		Overall anxiety post-administration	1	3.27	.070
Expect CBD	38.70 (.96)				
Expect CBD-free	41.23 (1.01)				
Negative affect		Overall negative affect post-administration	1	.50	.481
Expect CBD	6.89 (.20)				
Expect CBD-free	7.04 (.20)				
Positive affect		**Overall positive affect post-administration**	**1**	**3.92**	**.048†**
Expect CBD	11.29 (.45)				
Expect CBD-free	12.00 (.48)				

Interaction: Expectancy condition by Belief

		Overall stress post-administration	1	.69	.406
		Overall anxiety post-administration	**1**	**5.81**	**.016**
		Overall negative affect post-administration	1	.98	.321
		Overall positive affect post-administration	1	2.45	.118

Bolded coefficients indicate statistical significance ($p<.05$).

†False discovery rate threshold >5% exceeded (adjusted $p=.096$) indicates a potential false positive finding.

Note. Overall scores post-administration includes all three timepoints following oil self-administration (i.e., post-absorption, post-stress, recovery).

Figures

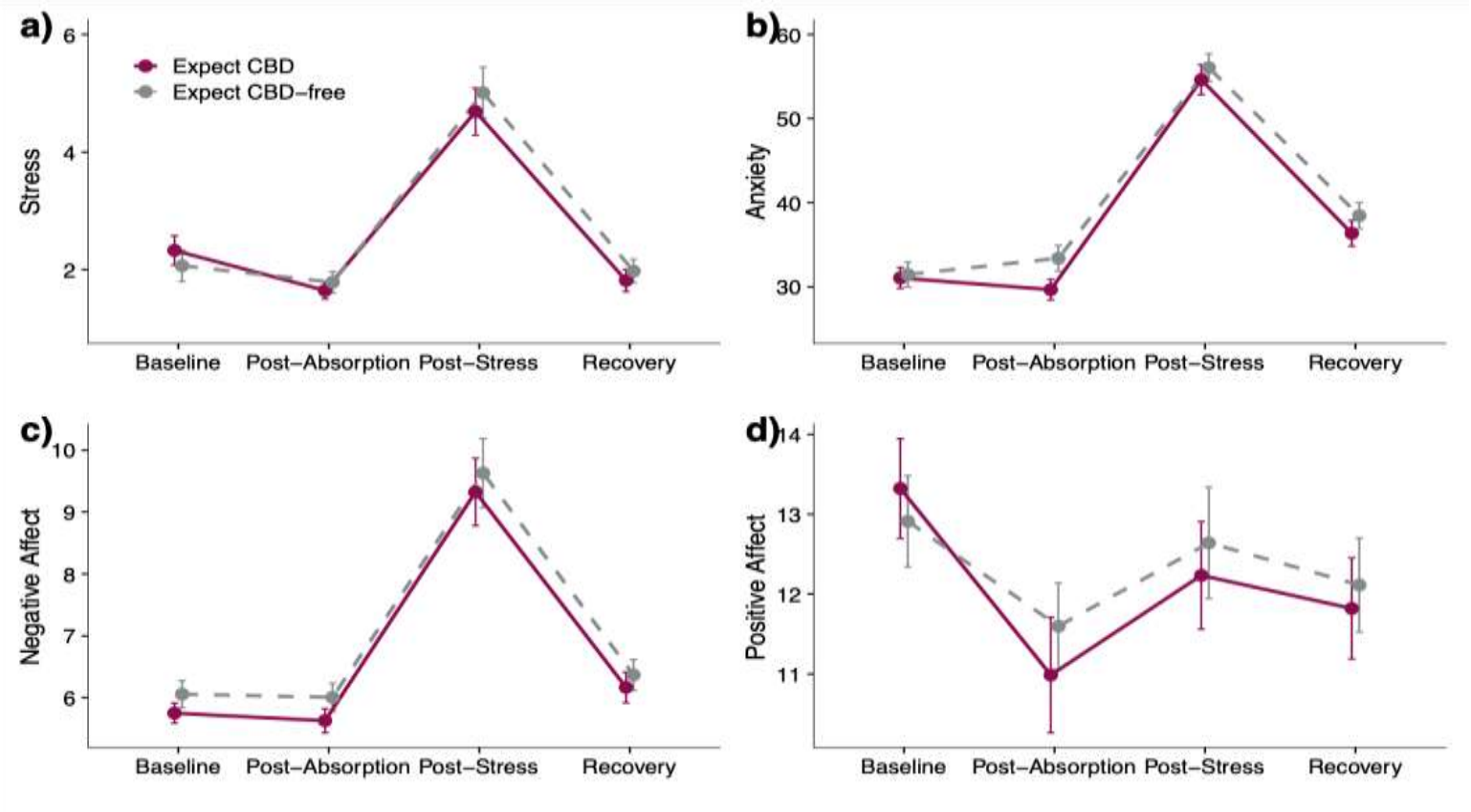

Figure 4.1. Estimated marginal mean (+/- standard error) a) Stress [Numeric Rating Scale 'Stress'; score range 1-10], b) Anxiety [State-Trait Anxiety Inventory- State Version, Short Form; total score range: 20-80], c) Negative Affect [International Positive Negative Affect Schedule- Short Form; total score range: 5-25], and d) Positive Affect [International Positive Negative Affect Schedule- Short Form; total score range: 5-25] ratings over Time by Expectancy condition. No significant Time by Expectancy condition interactions were observed for any of the subjective ratings.
Baseline (T1): +00; Post-absorption (T2): +95; Post-stress (T3) : +110; Recovery (T4): +120

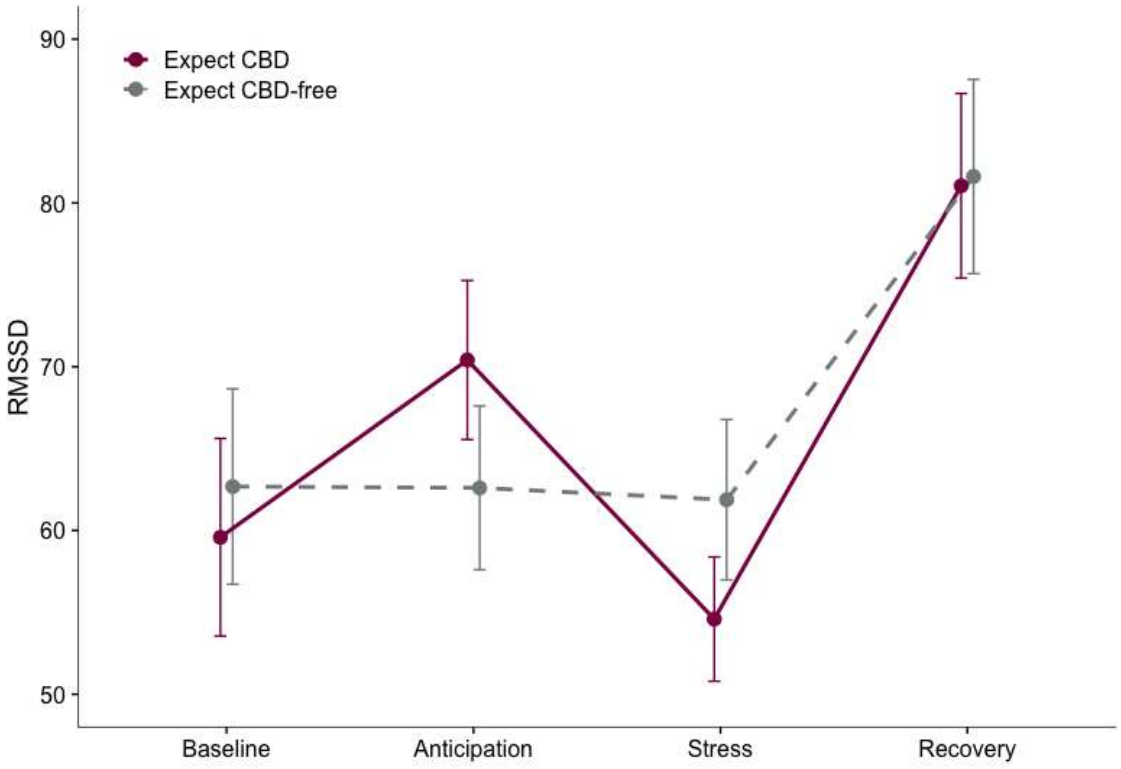

Figure 4.2. Estimated marginal mean (+/- standard error) RMSSD, an index of heart rate variability, over Time by Expectancy condition. RMSSD is a measure of vagal tone, thus higher RMSSD is thought to represent more parasympathetic output. A decrease in RMSSD is thought to represent a greater physiological stress response. In the CBD expectancy condition, RMSSD changed sequentially over time, and was higher at Recovery relative to Baseline. In the CBD-free expectancy condition, RMSSD was lower during Stress relative to Recovery, and higher at Recovery relative to Baseline.
RMSSD: root mean square of successive differences.
Baseline (T1): +00-+70; Anticipation (T2): +95; Stress (T3): +100; Recovery (T4): +120

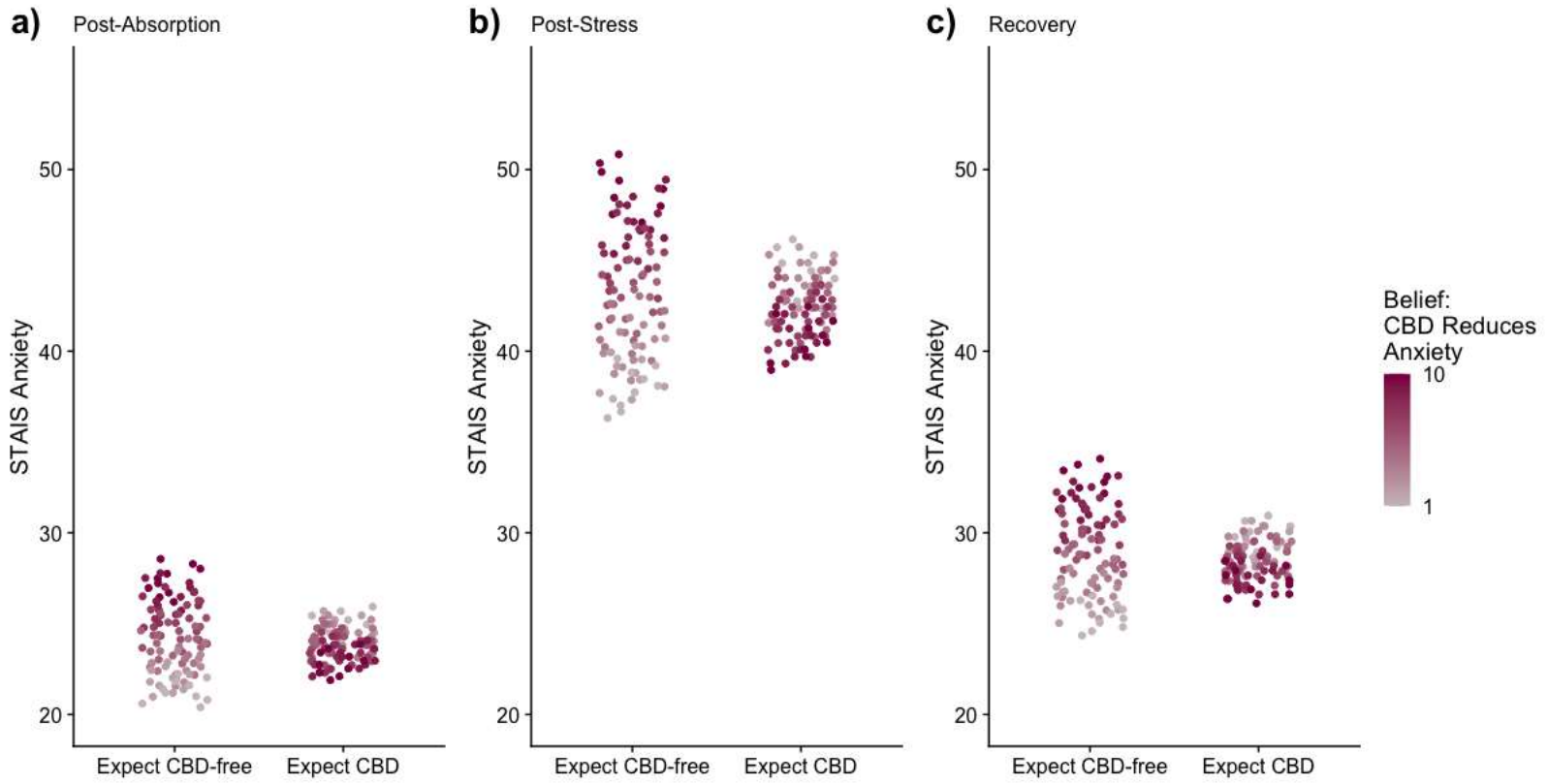

Figure 4.3. Plot of Generalized Estimating Equation (GEE) model predicted values for ratings of anxiety [State-Trait Anxiety Inventory- State Version, Short Form; total score range: 20-80] (adjusted for Baseline scores) by Expectancy condition at a) Post-Absorption, b) Post-Stress, and c) Recovery. Darker points indicate higher endorsement of belief that CBD reduces anxiety, whereas lighter points indicate lower endorsement of belief [Numeric Rating Scale 'CBD reduces anxiety'; score range 1-10]. A Belief by Expectancy condition interaction was observed such that participants who endorsed the highest beliefs that CBD reduces anxiety (third tercile; 9-10) had significantly lower anxiety ratings in the CBD Expectancy condition relative to CBD-free condition (across all three time points post-administration).
Baseline (T1): +00; Post-absorption (T2): +95; Post-stress (T3) : +110; Recovery (T4): +120

CHAPTER 5. TRANSITION FROM STUDY 2A TO STUDY 2B

The results of Study 2a provide preliminary insight into the expectancy-driven mechanisms that may be underlying at least some of the purported stress- and anxiety-dampening effects associated with CBD. First, the only instance when self-reported anxiety was influenced by the expectancy manipulation (i.e., lower anxiety when expecting CBD vs. CBD-free) was when participants endorsed strong beliefs that CBD was helpful for these purposes. This finding emphasizes the importance of both stimulus expectancies (i.e., an individual's belief about the content of the stimulus they receive) and response expectancies (i.e., an individual's prediction of their automatic reaction to administering a given stimulus) in certain CBD-related outcomes. Second, the finding that HRV differed according to the expectancy condition, particularly during the anticipation of stress, may suggest that CBD expectancy influences stress-related processes. The interpretation of this finding would be best understood through the lens of the stress response system, which includes both the ANS and HPA axis (Glier et al., 2022; see Chapter 1 for a review).

It is also important to note that in terms of limitations, potential sex-related influences on physiological responses had not initially been considered in Study 2a. In this chapter, I will briefly review the literature on sex differences in stress responding and the placebo effect. I will also replicate the analytic approach used in Study 2b on the physiological outcomes (i.e., HR, HRV) from Study 2a to assess for potential sex-related influences. All supplemental analysis related to Study 2a will be described in detail in Appendix E. The findings from these supplemental analyses will be also discussed in more detail as they relate to other findings presented within this dissertation in Chapter 7.

Sex Considerations for Study 2a & 2b

It is noteworthy that while biological sex and gender do not necessarily align, these terms have often been used interchangeably in research. Sex is biological and assigned at birth, whereas gender refers to the attitudes, feelings, and behaviours prescribed by a given culture based on one's biological sex (American Psychological Association, 2012). It is difficult to fully disentangle the sociocultural aspects related to gender versus the biological sex-specific influences on a given outcome. Fully separating these constructs and viewing them as distinct (e.g., sex and gender operating in a vacuum) would also be overly reductionistic in terms of considering their dynamic interplay (e.g., Curley et al., 2011).

To further exacerbate this issue, trans, non-binary, and gender-queer populations (e.g., assigned male sex at birth, identifying as a woman) have been poorly represented in health research. It is therefore unclear to what extent sex and gender discordance influences psychobiological stress and placebo responsivity. Many research reports also do not specify how sex and/or gender was evaluated, making it difficult to ascertain which construct was assessed. As a result, the research reviewed in this dissertation assumes the alignment of sex and gender (e.g., assigned female sex at birth and identifying as a woman), which limits the applicability of findings to cis-gendered populations. Despite these acknowledged limitations, efforts will be made to distinguish these constructs, when possible, in the subsequent section and chapters. For example, given that sex hormones are known to play a major role in the stress response system, biological sex was selected as the dependent variable in analyses for Study 2b and the terms 'male' and 'female' were used accordingly. Although all participants included in

Study 2a/2b were cis-gendered, it is hoped that the use of appropriate terminology adds nuance to the existing literature.

Sex and Gender Differences in Anxiety and Stress

Epidemiological reports have consistently identified sex and gender differences in the prevalence of most anxiety and depressive disorders, in that they tend to be higher among women relative to men (Altemus et al., 2014). Women are also more likely to experience subclinical depressive and anxiety symptoms relative to men (Hankin, 2009). Indeed, women have been shown to be more attuned to emotions in others, which is thought to support adaptive childrearing abilities (Thompson & Voyer, 2014). Concurrently, however, these behavioral and neurobiological differences may also be implicated in features associated with anxiety, such as increased sensitivity to experiences of rejection or criticism (Stroud et al., 2002). On the other hand, men tend to be more sensitive to threats related to social status or achievement (Stroud et al., 2002; Taylor et al., 2000), suggesting that there may be sex differences in the perception of various stressors. Although depression has also been shown to be related to stress response system dysfunction (i.e., altered HPA axis functioning; Fiksdal et al., 2019), it is largely beyond the scope of this dissertation. The mechanisms underlying observed sex and gender differences in anxiety- and stress-related processes will be discussed further.

Given the intimate relationship between stress and anxiety processes (see Chapter 3), one might expect that women are more physiologically reactive to stressors (i.e., stronger stress response). Indeed, women appear to report a higher level of perceived stress (Graves et al., 2021), as well as more minor daily stressors, chronic stress, and tend to experience stressors as more uncontrollable, relative to men (Matud, 2004). However, this does not necessarily translate to reliable sex differences in subjective and

psychological stress-related responses in the laboratory. For example, various experimental studies have failed to find any sex differences in subjective anxiety, stress, and affect in response to a stressor (Ennis et al., 2001; Stroud et al., 2002). Despite not finding any differences in subjective indices of stress responding, these same studies identified sex differences in cortisol excretion (i.e., men have a stronger cortisol response relative to women). Taken together, these equivocal findings would support the dissociation between subjective and physiological measures of stress responding, which may be at least in part due to measurement sensitivity, timing, and analytic approach.

Hamidovic et al. (2020) found that women have lower HRV during acute stress anticipation, relative to men, but the evidence is weak and best considered inconclusive (p=.06) (. Since lower HRV indicates more parasympathetic withdrawal, the authors of this meta-analysis propose that these findings may reflect poor autonomic coping during stress among women; however, the effect size was small (Hamidovic et al., 2020). Despite women having lower HRV during stress as well as a higher prevalence of anxiety disorders and symptoms, meta-analyses illustrate patterns of increased cortisol reactivity in response to laboratory stressors (i.e., higher peak cortisol) among non-clinical samples of men relative to women (Gu et al., 2022; Liu et al., 2017; moderate-to-large effect). Interestingly, this effect was also observed in infants (i.e., 1-year-olds), wherein a mild stressor elicited cortisol increases among males but not females (Davis & Emory, 1995). This would suggest that the observed differences in stress responsivity may be more related to innate biological sex processes (vs. gender role socialization). Notably, a previous study by Pulopulos et al. (2018) found an association between HRV during the *anticipation* of stress and stress-related cortisol release, noting that HRV *during* stress was unrelated to cortisol. As such, it is possible that that sex differences in HPA and ANS

responsivity during stress represent distinct physiological strategies for coping with stressors. Specifically, as proposed by Hamidovic et al. (2020), men may rely more on HPA activation to mobilize them to cope with the stressor, whereas women tend to rely on parasympathetic withdrawal. This may, in turn, explain the observed sex and gender differences in overt and covert behavioral coping strategies (e.g., differential recruitment of the ANS and HPA axis facilitated by specific cognitive, emotional, and/or behavioral coping strategies).

Indeed, with regards to coping style, sex differences have been observed throughout the lifespan and appear to be influenced by cultural/gendered expectations (Carter et al., 2011). For example, in response to a perceived threat, men tend to react by escaping the situation or taking immediate action, while women are more likely to seek support from others (Taylor et al., 2000), or use passive or emotion-focused coping strategies (Matud, 2004).

Taken together, in addition to a relatively higher prevalence of many stress- and anxiety-related disorders among women, there is evidence that women experience more daily and chronic stressors, as well as a higher degree of perceived stress, relative to men. Variations in what women and men perceive to be more stressful and strategies they use to cope with stressors also exist. In laboratory environments, however, there is more equivocal evidence regarding the extent to which women experience stressors as more subjectively stressful. In terms of physiological indices of stress responding, women tend to have a more significant initial response mediated by the ANS (e.g., increased HR, decreased HRV during a stressor). Interestingly, men tend to have a stronger HPA axis response to stressors (e.g., increased cortisol following a stressor). In sum, men and

women appear to recruit distinct physiological processes to respond to stressors, which may be facilitated, in part, by observed differences in coping strategies.

Sex and Gender Differences in the Placebo Response

Research has consistently found that men, relative to women, are more responsive to placebo effects for a variety of conditions, such as pain (Butcher & Carmody, 2012), distress (Abrams & Kushner, 2004), cognitive performance (Oken et al., 2008), and dopamine function (Haltia et al., 2008). In fact, a systematic review found that while placebo responses were more frequently observed among males, nocebo responses were more often seen among females (Vambheim & Flaten, 2017). Interestingly, while males appear to respond more strongly to verbal suggestion, females tend to be more responsive to conditioning procedures (Klosterhalfen et al., 2009). However, the exact mechanisms underlying these observed sex/gender differences remain relatively unclear.

As reviewed in Chapter 1, placebo effects are thought to be mediated by expectancies, which are informed by several factors, including verbal information, conditioning, and learning processes (Kirsch, 2018). Broadly, men appear to have more trust towards medical professionals and systems relative to women (Kim et al., 2018). This may in part be due to the longstanding history of bias towards women by medical professionals (e.g., viewing women's pain as emotional; Samulowitz et al., 2018). Presumably, having more trust in medicine would therefore facilitate stronger positive response expectancies and, as a result, a stronger placebo effect. In the context of placebo analgesia, there is also evidence to suggest that verbally induced placebo responses are facilitated by the opioid system while other mechanisms mediate conditioned placebo responses (Amanzio & Benedetti, 1999). Thus, one possibility for the observed sex

differences is that males may have a more efficient endogenous opioid system, relative to females (for a review, see Vambheim & Flaten, 2017).

Another possibility is that observed sex differences in placebo responding are mediated by sex differences in the mechanisms underlying stress and anxiety processes. First, the positive association between negative affect (e.g., stress, low mood, anxiety) and pain has been well-established (Lyby et al., 2010). One experimental study found that relaxation training reduced the physiological stress response; however, this effect was blocked when naloxone was administered (McCubbin et al., 1996). Second, there is also evidence for a positive correlation between the magnitude of positive affect and increased endogenous opioid activity (Koepp et al., 2009). Given that women tend to experience a higher level of perceived stress and anxiety symptoms, relative to men, it is possible that this may be contributing to the smaller observed placebo effects in women (vs. men). Aslaksen et al. (2011) found that pain unpleasantness, but not pain intensity, was impacted by the placebo response, and only among males. They also found that males responded to the placebo with a significant reduction in anticipatory stress, which then significantly impacted the placebo response (i.e., pain unpleasantness). The authors concluded that the observed sex-specific placebo analgesia responses appeared to be related to the cognitive and emotional reactions to pain versus the sensory component of the pain itself (Aslaksen et al., 2011). This lends further support to the key underlying role of stress and anxiety processes in mediating placebo responding to which men appear more reactive.

Orienting to Study 2b

Study 2b sought to expand on the results of Study 2a by evaluating the extent to which CBD expectancy alone impacts cortisol in response to a laboratory stressor. This

report utilized the same dataset as Study 2a; however, as described previously, in addition to evaluating cortisol responses, we also assessed potential sex-related influences on both stress responsivity and placebo responding. Evaluating multiple processes of the stress response system (e.g., ANS, HPA axis) is imperative for gleaning insight into the mechanisms through which CBD expectancy acts on these processes.

CHAPTER 6. STUDY 2B: THE IMPACT OF CANNABIDIOL EXPECTANCY ON CORTISOL RESPONSIVITY IN THE CONTEXT OF ACUTE STRESS: ASSOCIATIONS WITH BIOLOGICAL SEX

This study is included in the manuscript presented below. It is an extension of Study 2a and involves data collected as part of this study. Thus, my roles for the present study were similar as for Study 2a. Briefly, I was involved in obtaining funding, as well as study conceptualization and design, under the supervision of Dr. Sean Barrett. I was also involved in developing the research questions and hypotheses, data collection, preparing the dataset for analysis, conducting the analyses, and interpreting the study findings. I wrote the initial draft of the manuscript, incorporated feedback from co-authors, submitted the original investigation to a peer-reviewed journal, and subsequently led each round of revisions. This manuscript was published in *Cannabis and Cannabinoid Research* (2023). See Appendix F for copyright details under the Mary Ann Liebert Inc. Copyright Transfer Agreement. Please note that the manuscript included in this dissertation has been slightly modified from the final published version. The full reference is as follows:

Spinella, T. C., Burdeyny, V., Oprea, A., Perrot, T. S., & Barrett, S. P. (2023). The impact of cannabidiol expectancy on cortisol responsivity in the context of acute stress: Associations with biological sex. *Cannabis and Cannabinoid Research*, X:X, 1-9. https://doi.org/10.1089/can.2022.0326

Abstract

Background: Cannabidiol (CBD), a non-psychoactive cannabinoid found in the cannabis plant, has gained interest for its purported stress- and anxiety-reducing effects. However, the mechanisms underlying these effects remain unclear. Our group previously found that CBD expectancy alone resulted in lower state anxiety (vs. CBD-free expectancy) among those who strongly believed it was helpful for such purposes, in addition to influencing physiological measures (i.e., heart rate variability [HRV]).

Aims: Using data collected as part of this previously-published larger study, we aimed to explore the extent to which CBD expectancy alone impacts cortisol in the context of a laboratory stressor. We were also interested in evaluating the extent to which sex moderates these outcomes.

Methods: A sample of 43 healthy adults (23 female) participated in one orientation and two experimental laboratory sessions. They received the same oil (CBD-free) during both experimental sessions but were told they received CBD oil in counterbalanced order in one of their sessions. Participants then engaged in a laboratory stressor (the Maastricht Acute Stress Test; MAST) and salivary cortisol samples were collected throughout (T1: baseline; T2: 90-minutes post-absorption (PA); T3: post-stress (0-PS); T4: 10-minutes post-stress (10-PS); T5: 30-minutes post-stress (30-PS)). Linear marginal models were used for analyses.

Results: Findings indicated that a physiological stress response was elicited in the context of the MAST, which is consistent with what has been reported previously. Interestingly, while cortisol levels were significantly lower in the CBD expectancy condition (vs. CBD-free) immediately following the MAST (0-PS) and 10-minutes later (10-PS), this effect seems to be largely driven by males, evidenced by a 3-way interaction. Cortisol levels did not reliably vary across expectancy conditions at any other timepoint.

Conclusion: Overall, these results suggest that CBD expectancy appears to blunt cortisol in *anticipation* of a stressor, particularly in males. Findings suggest that it is important to consider the impact of drug related expectations when assessing CBD-related effects on stress related processes.

Key words: expectancies, cannabidiol (CBD), cortisol, stress, stress anticipation, biological sex.

Introduction

Recent reports suggest that stress and anxiety reduction are the two most common reasons for CBD use among adults who use cannabidiol (CBD; Moltke & Hindocha, 2021), and that CBD-containing products are more helpful than THC alone at decreasing stress and anxiety (Spinella, Bartholomeusz, et al., 2023). Although there is empirical support for CBD's anxiolytic and stress-dampening effects in some (Bergamaschi, Queiroz, Chagas, et al., 2011; Blessing et al., 2015; Masataka, 2019; Zuardi et al., 1982, 2017), though not all, previous research (Kayser et al., 2020), the mechanisms underlying these purported effects of CBD remain to be elucidated.

Our group recently reported that these effects may be in part related to expectancy factors (Spinella et al., 2021; see Chapter 4). Specifically, in a sample of healthy adults with at least one lifetime cannabis exposure, those who held the strongest *a* priori beliefs that CBD was helpful for anxiety, had the lowest subjective anxiety when they thought they had consumed CBD relative to when they thought they received a placebo (despite receiving placebo both times). Additionally, we observed differences in heart rate variability (HRV) according to expectancy condition. While in the CBD-free expectancy condition, HRV remained relatively consistent across time, in the CBD expectancy condition participants displayed relatively increased HRV during stress anticipation, which may be consistent with superior *anticipatory* stress regulation. However, the extent to which this finding is supported by other physiological measures of stress, such as cortisol, is not clear. Although we collected salivatory cortisol samples as part of this study, these were not available for analysis at the time of dissemination due to the COVID-19 pandemic. The present report presents these data to evaluate the impact of CBD expectancy on cortisol and provides additional insight into the pattern of HRV

described previously. It was hypothesized that (1) CBD expectancy alone would be sufficient to decrease cortisol in anticipation of a stressor, (2) consistent with known sex differences in cortisol reactivity, males would have higher cortisol than females in response to acute stress, and (3) consistent with expectancy research (Butcher & Carmody, 2012; Compton et al., 2003; Vambheim & Flaten, 2017), males would have a larger placebo response than females.

Materials and Methods

These data were collected as part of a larger study. Details regarding other subjective and physiological measures collected, as well as the full study protocol, and participant demographics are described in detail in Spinella et al. (2021), Chapter 4. The power analysis conducted as part of our previous report had determined that we likely had at least 85% power to detect placebo effects for anxiety (i.e., main effects and two-way interactions) based on aggregated effect sizes for the placebo effect (*d*=.29; Wampold et al., 2005). Although no power analysis was conducted for all hypotheses in the present manuscript as data was already collected, a prior meta-analysis reported that at least 40 participants (using a single session study design) are required to obtain adequate power to detect cortisol responses (Gu et al., 2022). Further, sex differences have been shown to explain a substantial part of the variance in cortisol reactivity to a stressor (η_p^2=.56; Reschke-Hernández et al., 2017). Given the more powerful within-subject nature of this design, it is likely that we have sufficient power to detect main effects and two-way interactions as they relate to study hypotheses. A three-way interaction will also be tested with the caveat that we are likely underpowered for this test.

Participants

Briefly, participants were medically and psychologically healthy adults, not taking prescription medication (except for hormonal contraceptives; HCs), 1+ lifetime uses of cannabis, with current use not exceeding two days per week, and no prior experience using cannabis oil.

Salivary cortisol

Salivettes (Sarstedt; Nümbrecht, Germany) were used to collect saliva samples for cortisol analyses. Participants placed the swab in their mouths and moved it around for 60 seconds after which the experimenter replaced the swab in the sterile tube. Samples were labeled, capped, and stored at -20◦C until assay. The concentrations of cortisol in saliva samples collected were determined by competitive binding enzyme-linked immunosorbent assay (ELISA) using a kit specifically designed to measure cortisol in saliva (High Sensitivity Salivary Cortisol ELISA, no. 1-3002; Salimetrics™, USA). All samples were analyzed in duplicate using procedures performed in accordance with the kit instructions supplied by the manufacturer. Cortisol standard curves were constructed in the range of .012-3.0 μg/dL, using standards supplied by the manufacturer and the inter-assay coefficient of variation (CV) was 1.9%.

Stress induction

The Maastrict Acute Stress Test (MAST; Smeets et al., 2012) was used to induce acute stress as it has been shown to reliably induce robust indices associated with stress (Shilton et al., 2017), including cortisol (Smeets et al., 2012), across multiple sessions (Quaedflieg et al., 2017) and has been shown to induce cortisol responses comparable to

other gold-standard methods (i.e., Trier Social Stress Test; Smeets et al., 2012). See Figure 6.1 caption for MAST procedure.

Procedure

Full study procedures are described in detail in Chapter 4. In summary, participants completed two experimental sessions at the same time 1-4 weeks apart between 10:30h and 18:00h, to minimize intra- and inter-individual diurnal fluctuations in cortisol. Women not using HCs (HC-) completed sessions during the luteal phase of their menstrual cycle (days 15-26) using a self-report menstrual cycle calendar from the first day of their last menstruation as a reference point. The luteal phase of the menstrual cycle was selected (vs. follicular phase) as it tends to be associated with a more similar salivatory cortisol response to men in response to acute stress (Kirschbaum et al., 1999). Participants were asked to abstain from cannabis for 72 hours, alcohol and other substances for 12 hours, caffeine for 2 hours, and one hour from food and teeth brushing. They were sent email reminders about abstinence requirements leading up to the experimental sessions. Abstinence was verified via self-report at the outset of sessions. All participants rinsed their mouths with water to remove any food particles that could impact the salivary cortisol assessment and waited quietly in the laboratory room for 20-minutes prior to providing their first cortisol sample. Participants self-administered a CBD-free hemp-seed oil sublingually given to them by another experimenter ("blinder") not otherwise involved in the session. The blinder informed them of the kind of oil they were receiving and, in one session, deceptively informed them that they received CBD oil. Following a 90-minute "absorption" waiting period, participants then engaged in a laboratory stressor (MAST; Smeets et al., 2012) in a separate testing room. Experimental sessions were identical aside from the Expectancy condition (i.e., Expect CBD, Expect

CBD-free), which was counterbalanced across participants. Cortisol was collected at five timepoints throughout each session: Baseline (T1), Post-absorption (T2; PA), Post-stress (T3; 0-PS), 10-minutes Post-stress (T4; 10-PS), and 30-minutes Post-stress (T5; 30-PS). See Figure 1 for a detailed timeline of experimental sessions. All participants were debriefed about the true nature of the study following data collection via telephone and re-consented to having their data included.

Statistical analyses

Linear marginal models were conducted using SPSS (version 27). Expectancy condition (Expect CBD, Expect CBD-free) and Time (T2-T5) were entered as repeated factors, Sex (male, female) as a fixed factor, and Baseline Cortisol (T1) as a covariate. Effects of interest included main effects of Expectancy, Time, and Sex, as well as Time by Expectancy, Sex by Time, and Sex by Time by Expectancy interactions. Additionally, the Benjamini-Hochberg method (Benjamini & Hochberg, 1995) was used to control for the false discovery rate for main model coefficients, using a threshold of 5%. Likelihood tests and model simplicity were used to determine optimal covariance structures. Cortisol values were excluded if a high CV (>20%) was obtained between plates to facilitate adequate precision in cortisol estimates.

Supplemental marginal model analyses were conducted to explore the influence of potential confounds on the data. First, to evaluate whether hormonal contraceptive (HC) status influenced cortisol responses, an analysis comparing females using and not using HCs was conducted. Second, given previous findings that females taking HCs (HC+) tend to have a blunted cortisol response to stressors (Gervasio et al., 2022; Roche et al., 2013), another analysis was conducted excluding these participants. Lastly, given evidence that

cortisol tends to increase with age, we conducted a follow-up analysis including Age as a covariate.

Results

See Table 6.1 for sample characteristics. Briefly, 43 participants (age range=19-62 years) enrolled in the study. Just over half reported their biological sex as female (n=23) and of those, 8 (34.8%) were HC+. Five participants withdrew after one session, but their data were retained from the session they completed. One participant withdrew 6 minutes into the MAST on their second session; thus, their data were excluded after T2. Among the 402 cortisol datapoints analyzed, 10 were excluded due to CV >20%, 10 excluded due to experimenter labeling error, and 9 due to insufficient saliva (372/402 [92.5%] retained). Findings presented in text relate to the primary research question and hypotheses. The *p*-values described below are derived from the post-hoc pairwise comparisons associated with significant effects. Table 6.2 includes marginal model coefficients for the main analyses and models used to determine potential impacts of HC on the outcomes. Table 6.3 includes all estimated marginal means, standard errors, and 95% confidence intervals associated with the primary model (Model 1; see Appendix G [Supplemental Tables 6.1 & 6.2] for these statistics in models excluding males (Model 2) and excluding HC+ (Model 3), respectively).

Primary analysis

First, main effects of Time were identified, such that cortisol increased from PA to 0-PS and 0-PS to 10-PS ($p<.001$), indicating that the stressor produced a physiological stress response. No overall main effect of Expectancy was identified. Main effects of Sex indicated that overall, males had higher cortisol levels than females.

Consistent with our hypothesis, a Time by Expectancy condition interaction was observed, wherein cortisol was lower at 0-PS and 10-PS when participants expected CBD relative to CBD-free oil (p=.001, p=.038). Descriptively, the mean difference between the CBD and CBD-free expectancy conditions was slightly larger at 10-PS (MD=0.041) than 0-PS (MD=0.031), however, standard errors were also larger at 10-PS in both conditions. Additionally, in both expectancy conditions, there was a temporal increase in cortisol (i.e., PA to 0-PS, 0-PS to 10-PS; p<.001). Descriptively, mean differences indicated that the slopes from PA to 0-PS and 0-PS to 10-PS were slightly larger in the CBD-free expectancy condition relative to CBD expectancy (mean difference [MD]=0.018, 0.010, respectively).

No Time by Sex or Expectancy by Sex interactions were observed. However, by a three-way interaction between Sex, Expectancy, and Time was evident (Figure 6.2). Specifically, while both males and females had temporal increases in cortisol from PA to 0-PS and 0-PS to 10-PS across both expectancy conditions, males had higher cortisol at 0-PS in the CBD-free expectancy condition, relative to CBD expectancy (all p<.001). Moreover, in the CBD expectancy condition, at 10-PS and 30-PS (p=.016, p=.038), and the CBD-free expectancy condition, at 0-PS and 10-PS (p=.007, p=.023), males had higher cortisol than females. Visual observation of means (Figure 6.2) indicated that the three-way interaction largely appears to be driven by males between 10-PS and 30-PS. Specifically, in the CBD-free expectancy condition, their cortisol levels decrease from 10-PS to 30-PS (MD=0.045). In the CBD expectancy condition, however, their cortisol levels increase from 10-PS to 30-PS (MD=0.074).

Supplemental analyses

First, among the sample of females, a main effect of HCs was identified indicating that HC- had higher cortisol levels, overall, relative to HC+ (p=.006). The interaction between Time and HC was inconclusive (p=.051). For descriptive purposes, this result was explored further. Post-hoc pairwise comparisons revealed that HC+ had lower cortisol at 0-PS (p=.007), 10-PS (p=.006), and 30-PS (p=.034), relative to HC-. The largest mean difference between HC- and HC+ was at 30-PS (MD=0.146), however, this timepoint also had the largest standard errors relative to all other timepoints. Additionally, HC- had significant changes in cortisol from PA to 0-PS, and 0-PS to 10-PS (both p<.001), with a larger change from 0-PS to 10-PS (MD=0.146), corresponding to increased stress reactivity. There was minimal observed difference over time among HC+. A significant main effect of Time was identified (PA to 0-PS, 0-PS to 10-PS; all p<.001); however no main effect of Expectancy, or interactions of Time by Expectancy, or HC were observed.

Second, in a sample that included females not taking hormonal contraceptives (HC-) (i.e., excluding females taking hormonal contraceptives [HC+]) and males, findings were largely consistent with the original model that included all participants. Specifically, a main effect of Time and a Time by Expectancy interaction were identified and remained identical in terms of post-hoc pairwise comparisons[7]. A three-way interaction between Time, Expectancy, and Sex was also identified. Post-hoc comparisons revealed that

[7] Time: PA to 0-PS, 0-PS to 10-PS; all p<.001; Time*Expectancy: CBD & CBD-free: PA to 0-PS, 0-PS to 10-PS, all p<.001; 0-PS: CBD<CBD-free, p=.003; 10-PS: CBD<CBD-free, p=.023.

nearly all differences remained the same[8]; however, males no longer had significantly higher cortisol levels than females at 10-PS (p=.113) or 30-PS (p=.096) in the CBD expectancy condition, or at 0-PS (p=.058) or 10-PS (p=.213) in the CBD-free expectancy condition. A main effect of Sex was no longer statistically significant (p=.063).

Third, among the full sample, Age was not a significant predictor in the model (F(1, 33.88)=1.121, p=.297), nor did it influence any of the significant effects identified and described above. Given that Age decreased model fit, it was not included in the primary analyses.

Discussion

This study sought to evaluate the impact of CBD expectancy on the stress-related cortisol response in healthy adults. Overall, findings suggest that CBD expectancy alone may influence cortisol in the context of a laboratory stressor, particularly during anticipation of stress among males. The specific pattern of findings is largely consistent with hypotheses.

First, while CBD expectancy did not appear to influence cortisol levels *overall*, a Time by Expectancy interaction suggests that CBD expectation may have dampened HPA-axis reactivity during stress anticipation. Specifically, immediately following the stressor (0-PS) and 10-minutes after the stressor (10-PS), cortisol was significantly lower in the CBD expectancy condition (vs. CBD-free). The magnitude of the differences in cortisol slopes between expectancy conditions was relatively small. Absolute cortisol value differences (i.e., EMMs) were slightly larger, particularly at 10-PS, however, the

[8] CBD & CBD-free, males & females: PA to 0-PS, 0-PS to 10-PS, p<.001; 0-PS, males: CBD<CBD-free, p=.001.

precision of this effect was lower given the larger standard error values (relative to PA and 0-PS). Anticipatory stress tends to be best captured 14-20 minutes following the onset of anticipation (Engert et al., 2013) which aligns most closely with T3/0-PS (i.e., 15-minutes after the start of the 5-minute preparation/anticipation phase) in our study. While it is possible that anticipation-related stress carried over to 10-PS, it is difficult to disentangle that from reactive cortisol levels related to the stress-induction itself (Qi et al., 2016). Additionally, in terms of the holistic pattern of findings between expectancy conditions, cortisol appeared to continue increasing throughout all timepoints in the CBD expectancy condition (i.e., up until 30-PS/the last timepoint assessed), whereas in the CBD-free expectancy condition, cortisol levels decreased at 30-PS. The effects at 10-PS and 30-PS are notably less precise and given the larger standard errors and variability at these timepoints.

With regards to sex differences, males had higher cortisol levels overall while also being more reactive to the stressor, relative to females. A Sex by Expectancy by Time interaction was also observed. First, hypothesis testing illustrates that the males (vs. females) had higher salivary cortisol at 0-PS and 10-PS in the CBD-free expectancy condition, and 10-PS and 30-PS in the CBD expectancy condition. Sex differences in HPA axis reactivity have been observed in previous literature, wherein males tend to have a higher cortisol peak in response to stressors (including the MAST), relative to females (Gu et al., 2022; Liu et al., 2017; Quaedflieg et al., 2017). Interestingly, this difference no longer existed when HC+ were removed from the model. This is largely consistent with studies showing that cortisol in response to stressors tends to be blunted among HC+ (Gervasio et al., 2022; Liu et al., 2017; Roche et al., 2013), and that females in their luteal phase have similar cortisol responses to males (Kirschbaum et al., 1999). Given that the

main effect of sex was close to the threshold of significance, it is also possible that removing this subsample of HC+ females reduced the power required to detect a significant effect.

Next, post-hoc hypothesis testing revealed that males in our study appeared to be more influenced by expectancy in anticipation of a stressor, wherein their cortisol was lower at 0-PS when they expected CBD (vs. CBD-free), an effect that was not observed among females. Indeed, other reports evaluating pain and analgesia have shown that males tend to be more responsive to the placebo effect compared to females (Butcher & Carmody, 2012; Compton et al., 2003; Vambheim & Flaten, 2017). This finding was maintained when HC+ were removed from the analyses. On one hand, hypothesis testing probing this three-way interaction suggests that males may be more influenced by drug expectancy in anticipation of stress relative to females during their luteal phase. Prior research has suggested that an increase in cortisol over .05ug/dL likely represents a cortisol secretory episode (i.e., stress response; Miller et al., 2013). Males in the CBD-free condition experienced an increase in cortisol (i.e., mean difference) from PA to 0-PS that exceeded this threshold while they did not exceed this threshold when they expected CBD. Although the magnitude of this effect appears to be small, it is arguably meaningful in this context and may reflect a CBD placebo effect among males in anticipation of a stressor (i.e., blunted cortisol response). Further research is required to determine the extent to which findings would extend to females during their follicular phase, or HC+.

On the other hand, holistic observation of the overall pattern of findings further explains the Time by Expectancy interaction effect observed and described above (also see Figure 4.2). Among females, there is a pattern of increasing cortisol levels from PA to 10-PS in both expectancy conditions (i.e., similar slopes and absolute values). The change

in cortisol levels from 10-PS to 30-PS is minimal and appears to plateau. Among males, however, a different pattern emerges between expectancy conditions. First, the slope in the CBD expectancy condition between PA and 0-PS is smaller (i.e., less of a cortisol increase). Next, although cortisol levels among males in the CBD-free expectancy condition decreases between 10-PS and 30-PS, the opposite pattern is observed in the CBD expectancy condition wherein cortisol levels *increase* from 10-PS to 30-PS. The magnitude of the observed differences between 10-PS and 30-PS appears to be small-to-medium, given that we were able to detect the overall three-way interaction effect with our sample size. However, the precision is low due to the high variability in cortisol at 10-PS and 30-PS. As a result, we likely required more participants to observe this effect in post-hoc hypothesis testing. It is also notable that the observed increase in cortisol levels from 0-PS to 10-PS is much larger among males compared to what was observed among females (i.e., steeper slope, higher absolute cortisol level at 10-PS, relative to females). Taken together, holistic interpretation of this three-way interaction expands on the hypothesis that males may have been more sensitive to the effects of CBD expectation. This effect was primarily observed during the anticipation of a stressor (i.e., lower cortisol vs. CBD-free expectancy). However, an expectancy-driven effect was also observed at 30-PS, though it occurred in the opposite direction (i.e., increased cortisol). Possible explanations for this observation are discussed in more detail below.

Overall, there are several possible explanations for why cortisol differences exist according to CBD expectancy, but only in the context of stress anticipation and the outset of the stressor. First, it is possible that the stressor was too powerful to observe smaller differences in expectancy in response to stress given the constraints of our sample size. Second, allostatic processes may be implicated, which would also offer insight into the

observed three-way interaction effect. It is possible that during stress anticipation, those who expected to receive CBD-free oil experienced physiological changes to appropriately prepare them for the stressor (i.e., larger cortisol increase), whereas those who expected CBD oil did not. Increased cortisol prior to stress is thought to be adaptive (Garcia-Banda et al., 2011; Het & Wolf, 2007; McEwen, 1998). Thus, when the adaptation to a stressor (i.e., allostasis) did not occur, cortisol levels peaked later than when allostasis did occur (i.e., cortisol peak at 30-PS among males when expecting CBD vs. peak at 10-PS when expecting CBD-free). This interpretation is consistent with the pattern of HRV observed previously, such that in the CBD expectancy condition, HRV increased during stress anticipation (i.e., more parasympathetic output, lower physiological stress), then decreased significantly during the stressor (i.e., less parasympathetic output, higher physiological stress) (Chapter 4). Thus participants, particularly males, showed a 'placebo response' initially when they expected to receive CBD oil; however, when confronted with the stressor, a significant stress response was still elicited.

Results should be considered in light of the following methodological considerations, in addition to those described previously (Spinella et al., 2021). First, our sample size may have been insufficient to fully explore three-way interactions. Although our power calculation from Study 2a (Chapter 4) had been based on aggregated effect sizes for the placebo effect, it is possible that effect sizes for CBD placebo effects in the context of a stressor are smaller. As such, a larger sample size is likely also required to evaluate expectancy effects for CBD in response to stress given the larger observed standard errors at 10-PS and 30-PS (relative to PA and 0-PS). These larger standard errors could also represent the individual differences/variability in cortisol reactivity in response to a stressor and in the context of expectancies. Replication is therefore warranted with a

larger sample. Second, although it is known that cortisol tends to lag a stressor by ~10-30 minutes, and the anticipatory stress process may have been captured at 0-PS, this is not certain. This should be confirmed in future investigations using appropriate procedures designed to capture anticipatory stress processes (Engert et al., 2013). Relatedly, although we assessed cortisol up to 30-minutes post-stress, it is not clear whether peak cortisol reactivity was captured by our final assessment. As such, future investigations may benefit from adopting methods previously used to evaluate anticipatory stress processes (Pulopulos et al., 2018), and include additional post-stress cortisol measures to capture recovery. Third, while efforts were made to minimize potential confounds via selection criteria and account for moderators via analytic approach, it is known that other factors such as age, BMI, sleep, and time of day also influence cortisol secretion and recovery (Nicolson, 2008). While age did not appear to influence our results, sleep was not evaluated and, since participants' height was not recorded, we were unable to calculate BMI. Additionally, although the time of day was kept constant within individuals and testing was limited to a discrete time period, there is evidence to suggest that cortisol collected in the mid-to-late afternoon may display more robust stress responses (Dickerson & Kemeny, 2004). Taken together, this may have added more variability to our cortisol data. Finally, females, regardless of HC use, were eligible to participate in the study to be more inclusive, and HC- females were scheduled to be tested during the luteal phase of their menstrual cycle. There are several considerations related to this decision. First, the self-report method of determining the luteal phase may not have precisely captured it among all women given inter-individual variability in menstrual cycles. However, because standard errors between males and females are very similar, this did not appear to have a major impact on our findings. Additionally, among HC+, the type of

HC they were using was not assessed or controlled for in our analyses. HC+ tend to have a blunted cortisol response relative to HC- (Gervasio et al., 2022; Roche et al., 2013). Supplemental analyses showed that HC+ had lower cortisol levels relative to HC-. Nevertheless, removing these participants from the model did not impact the nature or direction of most of our findings.

Findings from this study provide preliminary insight, for the first time, into the impact of CBD expectancy on cortisol in response to a stressor. Despite their preliminary nature, and the need for replication, our findings suggest that CBD expectancy alone appears to blunt cortisol in *anticipation* of a stressor, and this effect appears to be most pronounced in males.

Taken together with findings reported as part of a larger study (Chapter 4), our results emphasize the need to distinguish temporal dynamics of stress responses to include both anticipatory and stress/reactive components when designing research studies. This may provide more insight into the mechanisms through which different interventions influence the stress response. For example, anticipatory stress regulation appears to be mediated by cognitive appraisals about the situation and one's ability to cope (Lazarus, 1999). Interventions that target anticipatory stress processes may therefore be more promising with regards to interfering in mechanisms contributing to and maintaining various stress- and anxiety-related disorders. In the context of our findings, placebo/expectancy mechanisms associated with CBD appear to be implicated in improved anticipatory stress regulation. Alternatively, the anticipation period prior to a stressor may represent a mild stressor in and of itself. If this is the case, CBD expectancy may only be helpful for mild stressors. Future studies could explore the extent to which CBD pharmacology influences stress- and anxiety-related processes in response to less

and more demanding stressors. Overall, our results highlight the importance of considering the impact of drug-related expectations when assessing CBD effects on stress-related processes.

Tables

Table 6.1. Participant characteristics

	N (percent)
Sex	
Female	23 (53.5%)
Male	20 (46.5%)
Age in years (mean (standard deviation))	27.7 (9.3)
Ethnicity	
Arab	1 (2.3%)
Black	1 (2.3%)
Indigenous & White	3 (7.0%)
Latin American	1 (2.3%)
Other	1 (2.3%)
Southeast Asian, Chinese, or Korean	3 (7.0%)
White	33 (76.8%)
Highest level of education	
High school diploma	4 (9.3%)
Some college or university	13 (30.2%)
College or university degree	26 (60.5%)
Average number of cannabis-using days per week	
0 days	24 (55.8%)
0.5 days	4 (9.3%)
1 days	7 (16.3%)
1.5 days	2 (4.6%)
2 days	6 (14.0%)

N=number of subjects.

Table 6.2. Coefficients from the three linear marginal model analyses examining the impact of Time, Expectancy (and Sex, for Models 1 & 3) on mean Cortisol (ug/dL) values, with Baseline Cortisol serving as a covariate.

1- Overall model including all participants			
Effect	**df**	**F-value**	***p*-value**
Time	**3, 37.50**	**32.427**	**<.001**
Expectancy	1, 34.15	.774	.385
Sex	**1, 38.93**	**9.020**	**.005**
Time*Expectancy	**3, 30.82**	**4.361**	**.011**
Time*Sex	3, 37.49	1.636	.197
Sex*Expectancy	1, 34.08	.328	.571
Time*Expectancy*Sex	**3, 30.83**	**4.176**	**.014**
Covariate			
Baseline Cortisol	**1, 56.43**	**20.545**	**<.001**
2- Female-only model (excluding males)			
Effect	**df**	**F-value**	***p*-value**
Time	**3, 18.23**	**10.879**	**<.001**
Expectancy	1, 18.09	1.109	.306
Hormonal contraceptive	**1, 24.86**	**9.228**	**.006**
Time*Expectancy	3, 17.51	.121	.947
Time*Hormonal Contraceptive	3, 18.74	3.118	.051
Hormonal Contraceptive*Expectancy	1, 20.90	.084	.774
Time*Expectancy* Hormonal Contraceptive	3, 17.69	1.159	.353
Covariate			
Baseline Cortisol	**1, 32.48**	**69.780**	**<.001**
3- Overall model excluding females using hormonal contraceptives			
Effect	**df**	**F-value**	***p*-value**
Time	**3, 31.19**	**29.299**	**<.001**
Expectancy	1, 27.87	1.619	.214
Sex	1, 32.67	3.701	.063
Time*Expectancy	**3, 25.24**	**3.757**	**.023**
Time*Sex	3, 31.19	.555	.648
Sex*Expectancy	1, 27.99	.983	.330
Time*Expectancy*Sex	**3, 25.25**	**3.739**	**.024**
Covariate			
Baseline Cortisol	**1, 41.59**	**10.937**	**.002**

Time (T2, T3, T4, T5); Expectancy (Expect CBD, Expect CBD-free); Sex (Female, Male); Hormonal Contraceptive (Using hormonal contraceptives, Not using hormonal contraceptives); Baseline Cortisol (T1).
Bolded coefficients indicate statistical significance ($p<.05$).

Table 6.3. Estimated marginal mean (standard error) values, and 95% confidence intervals from linear marginal model analysis (Model 1- with all participants) examining the impact of Time, Expectancy, and Sex on mean Cortisol (ug/dL) values, with Baseline Cortisol serving as a covariate.

Effect of interest				**Cortisol (ug/dL)**	
				EMM (SE)	**95% CI**
Sex	Female			.195 (.016)	.163-.227
	Male			.264 (.017)	.230-.298
Expectancy	Expect CBD			.223 (.014)	.195-.250
	Expect CBD-free			.236 (.014)	.208-.265
Time	T2			.108 (.007)	.094-.123
	T3			.164 (.008)	.147-.180
	T4			.317 (.022)	.273-.361
	T5			.328 (.024)	.279-.378
Expectancy*Time	Expect CBD	T2		.102 (.010)	.081-.123
		T3		.148 (.009)	.131-.165
		T4		.297 (.021)	.253-.340
		T5		.344 (.038)	.268-.420
	Expect CBD-free	T2		.115 (.007)	.101-.129
		T3		.179 (.010)	.159-.200
		T4		.338 (.026)	.286-.391
		T5		.312 (.030)	.251-.373
Sex*Time	Female	T2		.099 (.010)	.079-.119
		T3		.144 (.011)	.121-.166
		T4		.260 (.030)	.199-.320
		T5		.276 (.034)	.207-.346
	Male	T2		.117 (.011)	.096-.139
		T3		.184 (.012)	.159-.208
		T4		.375 (.032)	.311-.439
		T5		.380 (.035)	.309-.451
Sex*Expectancy* Time	Expect CBD	T2	Female	.092 (.014)	.063-.120
			Male	.112 (.015)	.082-.142
		T3	Female	.136 (.012)	.113-.160
			Male	.159 (.012)	.134-.184
		T4	Female	.243 (.030)	.182-.303
			Male	.350 (.031)	.288-.413
		T5	Female	.263 (.054)	.155-.372
			Male	.424 (.052)	.319-.530
	Expect CBD-free	T2	Female	.106 (.009)	.087-.125
			Male	.123 (.010)	.102-.144
		T3	Female	.151 (.013)	.123-.178
			Male	.208 (.015)	.178-.238
		T4	Female	.277 (.035)	.206-.348
			Male	.400 (.038)	.322-.477
		T5	Female	.290 (.040)	.208-.371

Effect of interest		Cortisol (ug/dL)	
		EMM (SE)	**95% CI**
	Male	.335 (.045)	.244-.426

EMM: Estimated marginal mean; SE: Standard error; CI: Confidence interval.
T2: post-absorption (PA); T3: post-stress (0-PS); T4 : 10-minutes post-stress (10-PS); T5: 30-minutes post-stress (30-PS).

Figures

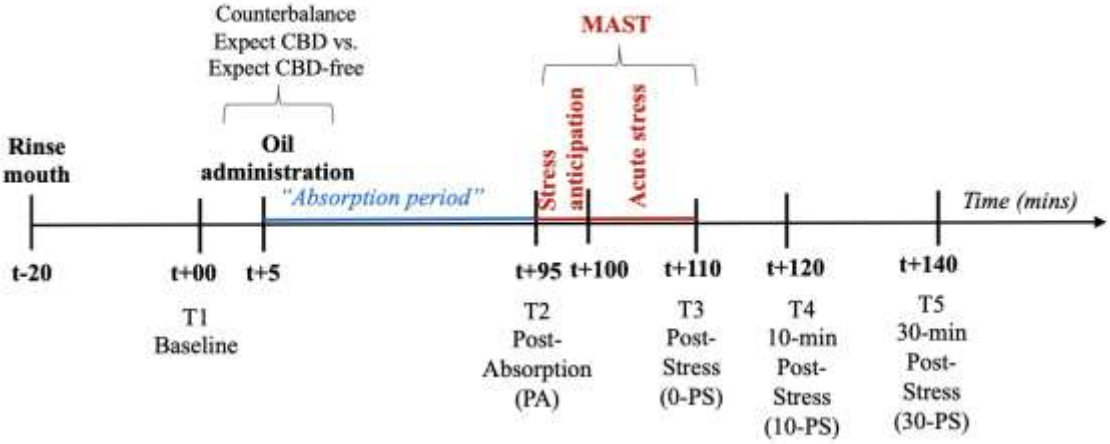

Figure 6.1. Protocol timeline of experimental sessions. Participants were introduced to the MAST via a 5-minute anticipatory/preparation phase wherein they are guided through a PowerPoint presentation of instructions for the upcoming task. This is followed by a 10-minute acute stress phase, wherein participants engage in alternating trials of a physical stressor (i.e., cold pressor task) and a psychological stressor (i.e., mental arithmetic), combined with social evaluation (i.e., video recording, experimenter observation) and negative experimenter feedback.
MAST: Maastricht Acute Stress Test.

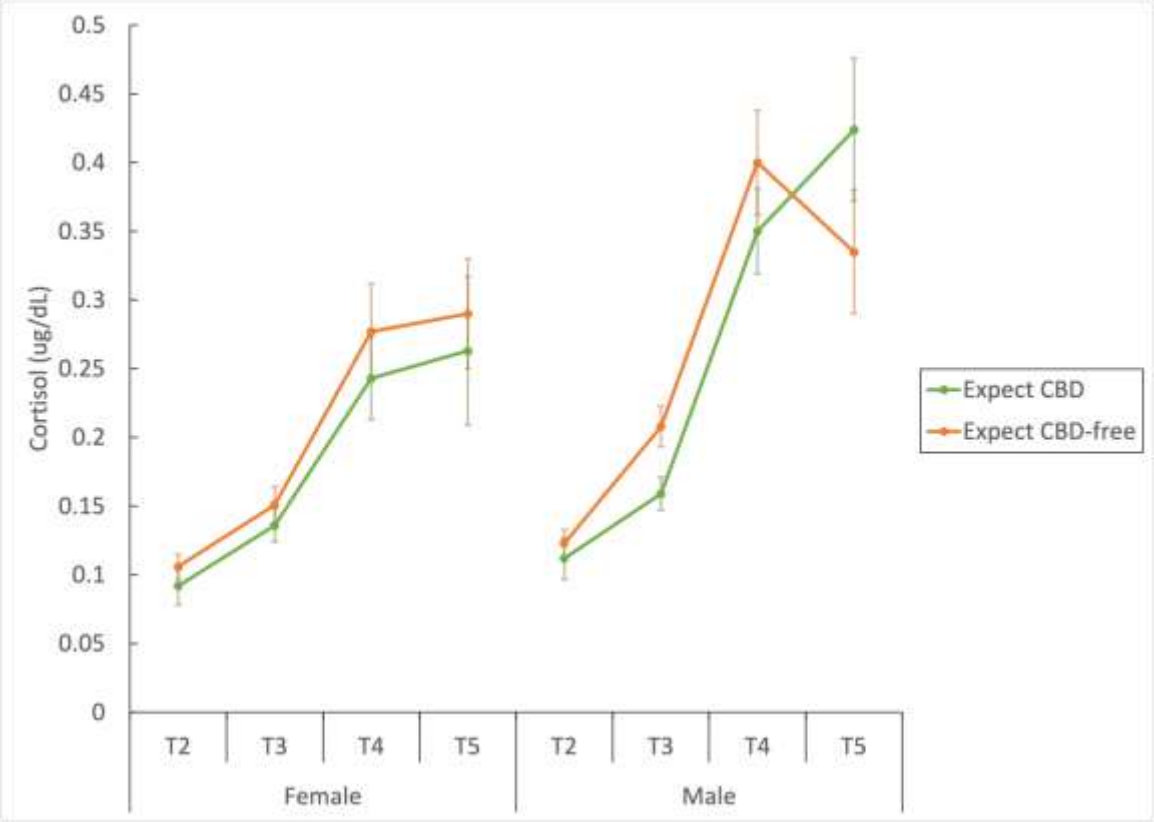

Figure 6.2. Line graph depicting a three-way interaction between Sex (male, female), Time (T2, T3, T4, T5), and Expectancy condition (Expect CBD, Expect CBD-free) on salivary Cortisol (ug/dL). Points represent estimated marginal mean (EMM) values, and error bars are associated standard error (SE) values from the Linear Marginal Model analysis with all participants. Values are adjusted for T1 Cortisol as a covariate.
T1: baseline; T2: post-absorption (PA); T3: post-stress (0-PS); T4: 10-minutes post-stress (10-PS); T5: 30-minutes post-stress (30-PS).

CHAPTER 7. GENERAL DISCUSSION

My dissertation sought to offer preliminary insight into the non-pharmacological, expectancy-related components of commonly known cannabinoids (i.e., THC, CBD), with particular emphasis on the effects of CBD. As part of this goal, I aimed to improve our understanding of cannabinoid-related response expectancies and evaluate the extent to which CBD-related expectation (i.e., the placebo effect) contributes to CBD's purported stress- and anxiety-dampening effects. This involved first evaluating beliefs or expectancies about cannabinoids, then testing the extent to which CBD placebo (i.e., stimulus and response expectancy factors) contribute to stress- and anxiety-reducing effects that have been reported previously in relation to CBD use. Quantitative methods were used throughout this dissertation with selected statistical approaches chosen based on their abilities to work with clustered data. The following subsections summarize and integrate findings from the three studies included in this dissertation as they pertain to the existing literature. This is proceeded by an in-depth discussion related to potential theoretical, clinical, and practical implications, as well as general strengths and limitations, and suggested directions for future research.

Summary and Integration of Findings

Summary

Study 1 (Chapter 2) broadly examined response expectancies associated with the most widely known and studied cannabinoids (i.e., THC, CBD, THC & CBD combined). Specifically, Study 1 evaluated the extent to which a community sample of adults across Canada have specific beliefs about cannabis effects that vary according to cannabinoid (i.e., CBD, THC, and THC & CBD combined) and prior cannabis use experience (i.e., prior use, no prior use/cannabis naïve), using a cross-sectional, survey-based design. At

the time of publication, other studies evaluating cannabis-related expectancies had conceptualized cannabis as a single entity and not considered individual cannabinoids, despite their drastically different mechanisms of action, effects, motives for use, and use patterns. To evaluate these questions, a LMM approach was selected as it can account for within-subject clustering.

Results from Study 1 demonstrated that people appear to have different expectancies about the effects of cannabis depending on the cannabinoid and whether they have prior direct experience with cannabis (i.e., prior use). Specifically, CBD-containing products were believed to be associated with more therapeutic effects relative to THC-containing products. Additionally, those with prior cannabis experience and more exposure to cannabis (i.e., >100 lifetime usage occasions) tended to have higher positive expectancies overall regarding the effects of cannabinoids, relative to those who never used cannabis.

These findings reinforced observations from prior cross-sectional research of participants associating CBD with a plethora of beneficial or therapeutic outcomes (e.g., Corroon & Phillips, 2018; Moltke & Hindocha, 2021). Recently, however, researchers have cautioned the widespread popularity and use of CBD given its obscure mechanisms of action, limited conclusions regarding dosing and long-term safety, as well as equivocal empirical support for various therapeutic purposes (National Academies of Sciences, Engineering, and Medicine, 2017; Revol et al., 2024). Stress and anxiety reduction appear to be among the most frequently reported reasons or motives for CBD use (e.g., Moltke & Hindocha, 2021). Given the discrepancy in findings from self-report studies supporting CBD's stress dampening and anxiolytic effects (Kalaba & Ware, 2022; Moltke & Hindocha, 2021; Tran & Kavuluru, 2020) and the equivocal results from experimental

and clinical research (e.g., Blessing et al., 2015; Leen-Feldner et al., 2022; Rossi et al., 2023; Zuardi et al., 2017), it is possible that expectancies were contributing to outcomes. As such, it was important to evaluate the placebo-driven mechanisms underlying these described effects.

Study 2a (Chapter 4) broadly evaluated the extent to which CBD-related expectation alone (i.e., the placebo effect) influences subjective-emotional and psychophysiological indices of stress, anxiety, and mood. Specifically, Study 2a tested the effects of placebo CBD administration (i.e., stimulus expectancy) on subjective anxiety, stress, and mood, as well as HR and HRV, in the context of a laboratory stressor. We were also interested in evaluating the extent to which response expectancies moderated subjective-emotional and psychophysiological outcomes. This study utilized a community-recruited sample of healthy adults and employed a randomized, crossover, half-balanced-placebo design (i.e., administered CBD-free both sessions, alternating content instructions provided [told CBD-free, told CBD]). To evaluate research questions of interest, a GEE approach was selected to account for within-subject clustering as well as potential impacts related to non-normality in a relatively smaller sample where these assumption violations may be more influential.

Results from Study 2a demonstrated that expectancy processes play at least some role in facilitating previously observed and self-reported stress and anxiety dampening effects associated with CBD. Briefly, subjective anxiety was significantly reduced when participants thought they had received CBD vs. CBD-free oil; however, this was only observed in those who had the highest response expectancies (i.e., beliefs that CBD helps with anxiety). Additionally, HRV appeared to differ between expectancy conditions. One

possibility is that the observed pattern of HRV in the CBD expectancy condition may be indicative of improved stress regulation, particularly in anticipation of the stressor.

Study 2a provided key insight into how placebo CBD influences subjective and ANS reactivity to a stressor. Specifically, we identified a pattern of HRV that appeared to be influenced by CBD expectancy; however, the implications of this finding within the context of the stress response system were not fully clear. To make meaningful inferences about how placebo CBD influences stress and anxiety processes, it is important to consider all aspects of the stress response system, including the ANS and HPA axis, in addition to self-report/subjective methods.

Study 2b represented the first examination of how placebo CBD influences HPA reactivity to acute stress. Using the same dataset from Study 2a, Study 2b (Chapter 6) extends the findings of Study 2a by evaluating the extent to which CBD expectancy alone impacts cortisol in response to a laboratory stressor. We also recognized the importance of considering biological sex in Study 2b given the previously observed sex differences in stress responsivity (e.g., cortisol secretion in response to stressors) as well as sensitivity to the placebo effect. As such, we included sex as a fixed factor and interaction term in these analyses. To evaluate research questions of interest, we used a linear marginal model approach. While this analytic approach has similarities to GEE, it does not tend to be as biased by smaller sample sizes. Given that supplemental analyses were conducted with a smaller subsample of participants in Study 2b (i.e., excluding females using hormonal contraceptives), marginal models were selected as the approach for all analyses.

Results from Study 2b demonstrated that males appear to be more reactive than females in terms of HPA responsivity (i.e., higher overall cortisol, higher cortisol response to stress and/or stress anticipation); however, when females using hormonal

contraceptives were removed from the analysis, this effect disappeared. Additionally, CBD expectancy alone appears to blunt cortisol, but only in anticipation of a stressor. Interestingly, this effect tends to be predominantly driven by males, and was uninfluenced by variability introduced by females using hormonal contraceptives (i.e., findings were sustained when removing females using hormonal contraceptives from analyses). Moreover, a holistic interpretation of these results can be facilitated through the observation of mean cortisol levels over time, expectancy condition, and sex. Specifically, when males expected to receive CBD oil, their cortisol levels continued to increase 30-minutes after the stressor had concluded, whereas their cortisol levels decreased at this same timepoint when they expected to receive (and actually received) CBD-free oil. Study 2b added notable contributions to the results of Study 2a, together providing the first comprehensive evaluation of the extent to which placebo CBD administration influences various subjective-emotional and psychophysiological stress and anxiety processes.

Integration of Findings

Figure 7.1 in Appendix H synthesizes the timepoints discussed throughout Study 2a and 2b as they relate to the study protocol and collection of cortisol, HR, HRV, and subjective measures. Briefly, my dissertation sought to offer preliminary insight into the expectancy-driven components of commonly known and abundant cannabinoids (i.e., THC, CBD), with a specific focus on CBD. My findings have provided an important glimpse into these largely unexplored areas of research, with results from all three studies emphasizing the significance of evaluating and considering expectancy factors in cannabis research.

As a first step towards this overall goal, my dissertation aimed to improve our understanding of cannabinoid-related response expectancies. Study 1 contributed to the literature suggesting that Canadian adults generally have distinct beliefs about the effects of cannabis, depending on the predominant cannabinoid (i.e., THC- vs. CBD-containing products) and their own prior use/experience with cannabis (i.e., prior use vs. no prior use; number of uses in lifetime). Prior cannabis use was associated with stronger positive beliefs about the effects of cannabinoids. This is largely consistent with what has been reported previously such that prior substance use is thought to facilitate the development and/or strength of response expectancies (Colloca & Benedetti, 2006), which tend to be further reinforced and strengthened with continued use (Kirsch, 1985; Montgomery & Kirsch, 1997). Results from Study 1 are also in line with substance use literature demonstrating positive associations between strong positive expectancies and more extensive use (Jones et al., 2001; Skenderian et al., 2008).

The second step towards my overall dissertation goal was to evaluate the extent to which CBD expectancy alone contributes to its alleged stress and anxiety dampening effects. Our findings generally support the importance of expectancy factors in at least some of the observed effects of CBD. Both Study 2a and 2b found that simply believing that CBD had been administered (i.e., stimulus expectancy) influenced physiological indices of the stress response system, including the ANS and HPA axis, related to a laboratory stressor. In fact, a distinct pattern of HRV was identified in Study 2a when participants were told they had received CBD oil (vs. a CBD-free oil). Specifically, there were minimal changes observed across baseline, anticipation, and stress in the CBD-free expectancy condition. In the CBD expectancy condition, however, HRV increased significantly from baseline to anticipation, then decreased significantly from anticipation

to stress. Based on prior research, the leading hypotheses for this finding as they related to the CBD expectancy condition were as follows: (i) higher HRV during the anticipation to stress could represent improved overall stress regulation, regardless of the HRV response during stress; (ii) fluctuations in HRV could be indicative of an adaptive response to environmental demands; (iii) higher HRV in the anticipation of stress could indicate more successful stress regulation during this preparatory period, but since these allostatic processes did not occur, the individual was more vulnerable to the effects of the stressor (i.e., stronger stress response during stress); (iv) the anticipation of stress may represent a mild stressor, with expectancy-driven effects limited to mild stressors. Although the study protocol was not optimally designed to answer these questions directly, evaluating indices of HPA reactivity (i.e., salivary cortisol; Study 2b) provides at least some insight into the observed HRV findings.

Study 2b corroborated the physiological findings of Study 2a suggesting that the stress response system had indeed been influenced by the mere expectation of CBD administration (i.e., stimulus expectancy). Specifically, cortisol was lower post-stressor and 10-minutes post-stressor in the CBD expectancy condition, relative to the CBD-free expectancy condition. Given the known time lag in cortisol responsivity, it is certainly possible that the post-stressor period represents the anticipatory stress response. When we evaluated potential influences of biological sex, it appeared likely that males were driving this observed effect as this pattern of lower cortisol in the CBD expectancy condition was not seen among females in our sample. These expectancy-driven effects were maintained even after removing females using hormonal contraceptives (HC+).

Although the following observation did not reach statistical significance in post-hoc tests, likely related to insufficient power, visual inspection of mean values plotted by

sex, expectancy, and time illustrate a classic interaction pattern among men. Specifically, in the CBD expectancy condition, males had lower cortisol relative to the CBD-free condition, until the final measure (30-minutes post-stressor) wherein their cortisol levels increased significantly to their peak value, exceeding the CBD-free expectancy condition. Alternatively, in the CBD-free expectancy condition, cortisol levels peaked at the second last timepoint (10-minutes post-stress) and began declining at this final timepoint. In terms of possible explanations for this pattern of findings, allostatic processes may be implicated. Specifically, males appeared more sensitive to the effects of the expectancy manipulation (i.e., stimulus expectancy), thus when they expected to receive CBD oil, they did not experience the preparatory psychophysiological changes to appropriately prepare them for the stressor (i.e., smaller cortisol increase during anticipation to stress). As such, when confronted with the stressor, they required more psychophysiological resources than initially anticipated in absence of any active drug, thereby resulting in a delay in their peak cortisol response.

A phenomenon observed in classical conditioning known as a "conditioned compensatory response", may further explain our findings (Siegel, 1975, 1984). Briefly, instead of responding to a conditioned stimuli with a typical conditioned response that mirrors the unconditioned response (as per classical conditioning theory), the conditioned response occurs in the opposite direction (i.e., conditioned compensatory response). Conditioned compensatory responses tend to occur because the body is attempting to prepare for the pharmacological changes accompanied by a given substance. Thus, in absence of the pharmacological agent, there is an expectancy violation effect (Colloca et al., 2019) which often results in a response in the opposite direction. It is thought that this type of response most often occurs in the context of nonconscious classical conditioning

mediated learning and in the absence of strong, conscious response expectancies (Stewart-Williams & Podd, 2004).

In Study 2b, we also observed that removing the subgroup of HC+ negated findings that males had higher cortisol levels than females both overall, as well as in response to the stressor. While this appears to contradict reports of men displaying increased cortisol reactivity to stress relative to women (Gu et al., 2022; Liu et al., 2017)[9], it is largely consistent with prior research observations of blunted cortisol responses among HC+ (Gervasio et al., 2022; Roche et al., 2013). Notably, the subgroup of HC+ in our research only accounted for approximately one third of females included in the study. As such, comparing findings with and without HC+ does not necessarily allow us to make inferences about the HC+ subgroup and removal of HC+ may have decreased our power to detect smaller effects.

Given that males were found to be the main contributors to the CBD expectancy effect on cortisol responsivity in Study 2b, it was important for us to assess this potential influence across the other physiological outcomes examined in Study 2a. As such, supplemental analyses evaluating the impact of sex on HR and HRV were conducted (Appendix E) linking Studies 2a and 2b. We opted to use an identical analytic approach for these supplemental analyses to that used in Study 2b to allow for more direct comparisons between findings of Study 2a and 2b. These analyses revealed that sex appears to also have at least some impacts on ANS stress responsivity within the context of an expectancy manipulation. The effect was specific to HR and may suggest that males

[9] These studies acknowledged that they were unable to control for the influence of hormonal contraceptives due to missing information.

experienced a typical placebo response following the perceived administration of CBD oil (i.e., lower HR overall relative to perceived CBD-free administration). Alternatively, the increase in overall HR following perceived CBD administration among females (vs. lower overall HR in the CBD-free condition) may be more consistent with a nocebo response (i.e., negative outcomes prompted by beliefs that an intervention will cause these adverse outcomes). These findings are consistent with prior research illustrating that men are more responsive to the placebo effect relative to women (Abrams & Kushner, 2004; Butcher & Carmody, 2012; Haltia et al., 2008; Oken et al., 2008; Vambheim & Flaten, 2017), and that women more often experience nocebo responses relative to men (Vambheim & Flaten, 2017). Further, our results illustrating a sex difference on HR, but not HRV, may suggest that the sympathetic branch of the ANS is more sensitive to placebo influences among males. Additionally, the relationship between sex and HRV was found to be insignificant. Based on these analyses, it remains inconclusive whether the observed placebo effects on HRV is impacted by biological sex remains inconclusive. Finally, the interaction between Time and Expectancy condition on HRV reported in Study 2a (Chapter 4) was not observed in the marginal model analyses with sex. It is possible that adding a new predictor decreased our power to detect this smaller effect, or that the previously observed expectancy effect was less robust.

Theoretical Implications

Theoretical and practical research implications will be outlined within this subsection as they relate to specific fields of study. Pertinent research domains in the context of this dissertation include the stress response system, expectancy and placebo effects, cannabis, and finally, an integration of theories to provide insight into the relationship between CBD, stress, and anxiety.

The Stress Response System

Although Studies 2a & 2b included in this dissertation were not designed to evaluate questions related to the stress response system, particularly given the confounding effects of our expectancy manipulation, important contributions can nevertheless be gleaned from these dissertation findings. First, our results generally support the idea that sex differences in the stress response system exist and that sex hormones may play a role in modulating the physiological stress response. While males tended to have a more robust cortisol response in the context of a stressor, this effect became inconclusive when females taking hormonal contraceptives were removed from analyses. Further, when evaluating the subsample of females, we found that those using hormonal contraceptives had significantly lower cortisol levels overall relative to females not using contraceptives. While no sex significant differences emerged in HR or HRV reactivity to a laboratory stressor, it is possible that we were underpowered. Prior meta-analyses have suggested that females tend to have a relatively stronger HRV response during a stressor; however, this effect is small (Hamidovic et al., 2020). Our expectancy manipulation, combined with known sex differences in placebo responding, may have made it difficult to detect this small sex by time interaction effect for HRV. Taken together, our study findings therefore reinforce the importance of considering hormone fluctuations in females as well as sex differences in stress-related research.

Second, this dissertation offers several practical considerations for laboratory-based stress research. Specifically, since most of Study 2a and 2b findings occurred around the anticipation of stress, this period may be particularly relevant to include and evaluate in stress and anxiety research. Our findings support the idea that expectancy-related processes likely have a key role in mobilizing emotional and psychophysiological

resources for a perceived stressor as well as one's ability to respond to the actual demands of a stressor (McEwen, 1998; Pulopulos et al., 2018). In fact, one leading hypothesis for our findings is that failing to engage appropriate allostatic processes during this preparation phase may render an organism more vulnerable to the effects of a stressor. This also speaks to the importance of measuring various indices of stress to obtain a more comprehensive picture of the stress response. A dynamic interplay between the ANS and HPA axis exists (e.g., Pulopulos et al., 2018; Thayer & Sternberg, 2006), with mixed findings regarding the exact relationship between the two systems in the context of a stress response (e.g., La Marca et al., 2011; Looser et al., 2010). Although we did not directly test the association between ANS and HPA axis, our findings suggest that evaluating both systems can offer unique insight into what mechanisms may underlie altered stress responding (also see Glier et al., 2022). In other words, since we measured indices of PNS activity (HRV/RMSSD), SNS and PNS activity (HR), HPA axis activity (cortisol), as well as subjective state (self-report stress, anxiety), we were better able to holistically contextualize our findings within the stress response system. The hypotheses for our pattern of findings will be discussed in detail in the proceeding subsections as they integrate frameworks related to the stress response system and expectation/placebo effects.

Expectancies and Placebo Effects

As reviewed in Chapter 1, non-pharmacological factors, or those that are not directly associated with the chemical properties of a given substance, significantly impact outcomes and effects associated with substance use (Amanzio et al., 2001; Kirsch, 1985; Ulrich, 1984; Uthaug et al., 2021; Volkow et al., 2003). The "placebo effect" describes the cascade of biophysiological, behavioral, and psychological changes that occur

following administration of an inert compound. The effects or outcomes associated with placebos vary depending on the illness or state being targeted (e.g., Benedetti, Amanzio, et al., 2011; Wager et al., 2007). As such, placebo research focuses on identifying mechanisms through which various placebos exert their effects and tends to have direct clinical implications. "Set and setting" theory is another field of research that emphasizes on the importance of non-pharmacological influences on substance use outcomes (Zinberg, 1984). Set includes individual factors related to the affective state, intention, and expectations of the person using the substance, while setting speaks to the environmental component (e.g., location, the presence of other people). Similarly, the placebo effect is thought to be mediated by separate and combined effects of expectation and learning mechanisms. Set and setting theory initially developed to understand the variability in experiences related to psychedelic use; however, its implications can be relevant to those who use substances recreationally. While these two fields are often separate, researchers have proposed that set and setting factors could be conceptualized as the ingredients underlying placebo effects (Hartogsohn, 2016; Pronovost-Morgan et al., 2023). In fact, core similarities exist between these theories as both appear to emphasize the key role of expectation in substance-related outcomes. The results from this dissertation can therefore have implications for both set and setting and placebo research.

First, it is thought that response expectancies are at least in part developed via prior experience, which can subsequently strengthen or reinforce expectations (Kirsch, 1985). Study 1 supports this idea in that participants who had prior cannabis use experience had stronger expectations about the effects of THC and CBD, relative to those who had no direct experience with cannabis. Additionally, we found that more extensive cannabis use experience was associated with stronger beliefs, thereby bolstering the

possibility that prior use strengthens expectancies and that expectancies are indeed self-confirming.

Second, building on the idea that response expectancies are directly related to the placebo effect, Study 2a found that *a* priori beliefs about the helpfulness of CBD for anxiety (i.e., response expectancies) moderated the effect of stimulus expectancy (i.e., expecting to receive CBD oil) on subjective anxiety. This would also lend support to the hypothesized framework through which placebo effects occur. Specifically, there may be interactions between unconscious learning mechanisms as they relate to aspects of the setting (e.g., verbal information provided and characteristics of the 'substance', administration method, administrator) and response expectancies related to set (e.g., beliefs about the effects of the substance). Future research would therefore benefit from measuring and controlling individual differences in response expectancies. Although we did not directly manipulate or measure these unconscious learning mechanisms, it is plausible that some degree of conditioned processes were activated when participants were deceptively told they would be self-administering CBD (i.e., stimulus expectancy). First, the presence of a labeled CBD bottle with a syringe paired with verbal information about the content of the oil and the presence of a research assistant likely enhanced believability of the manipulation. This stimulus expectancy manipulation may have subsequently activated pre-conceived/conditioned ideas about the meaning behind these stimuli which may have been historically paired with positive outcomes (e.g., symptom reduction, improved performance). This possibility should be evaluated more explicitly in future investigations. Moreover, Studies 2a and 2b showed that stimulus expectancies alone are sufficient to facilitate changes in the biophysiological stress response system, including the ANS and HPA axis. While the exact interpretation of these findings is not

fully clear (see below for hypothesized explanations), it is evident that the mere expectation that CBD had been administered is powerful enough to cause a shift in physiological reactivity (i.e., placebo effect). Taken together, the results of this dissertation suggest, for the first time, that a placebo effect explains at least some of the purported stress and anxiety dampening effects associated with CBD.

Finally, placebo research has tended to focus on pain and placebo analgesia (e.g., Adamczyk et al., 2019; Meeuwis et al., 2023) while set and setting research often involved applications related to psychedelic substances (e.g., Hartogsohn, 2016; Uthaug et al., 2021). As such, our work evaluating the impact of CBD-related expectancies on outcomes related to acute stress and anxiety adds novel breadth to these research fields which have historically been more limited in scope. Study 2a and 2b findings suggest that previously described sex differences in placebo analgesia are also observed in the context of physiological indices of stress and/or anxiety, wherein males appear to be more responsive to placebo CBD. Additionally, despite the emphasis on pain and analgesia in extant placebo research, it appears that one of the proposed mechanisms through which placebos exert their effects is through anxiety modulation (Benedetti, Carlino, et al., 2011; Vase et al., 2005). My dissertation findings lend support to this theory by showing the physiological responses to placebo CBD could be mediated by anxiety reduction. The proposed mechanisms underlying this CBD-specific placebo effect are discussed in more detail in the proceeding subsections.

Theoretical Integration: Implications for the relationship between CBD, stress, and anxiety

This subsection outlines potential theoretical implications and contributions based on the synthesis of findings from my dissertation. It integrates the theories and research

described previously, including the stress response system as well as expectancy/placebo effects. At the time of writing this dissertation, there had not been any research evaluating placebo effects related to CBD; thus, the hypotheses described below require further experimental evaluation and replication.

Taken together, the physiological findings from Study 2a and 2b generally lend support towards two theoretical possibilities. First, it is possible that higher HRV during the anticipation of stress in the CBD expectancy condition is associated with more successful stress regulation during this period. Prior research has shown that higher HRV represents increased PNS activation, which may be an indicator of improved emotional regulation (Perna et al., 2020). For example, participants who engaged in positive reappraisal prior to a stressful task had a smaller decrease in HRV during the anticipation of a stressor (Nasso et al., 2019).[10] Our findings similarly suggest that, in the CBD expectancy condition, higher HRV occurred in anticipation of the stressor, which appears to coincide with lower anticipation-related cortisol. Sex differences in cortisol responsivity suggests that this latter effect appeared to be specific to males. However, during stress, a statistically significant stress response was still elicited among all participants, as evidenced by significantly decreased HRV and an increase in cortisol. Although it was not statistically significant, cortisol in the CBD expectancy condition appeared to increase above the CBD-free expectancy condition among males in response to the stressor (i.e., 30-minutes post-stressor). It is possible that, unlike prior studies where participants were instructed to engage in a psychological process or intervention

[10] It is noteworthy that this study did not actually have participants engage in a stressor and only had them participate in the preparing for a stressful event (i.e., job interview).

(e.g., cognitive reappraisal, acceptance) (Aldao & Mennin, 2012; Nasso et al., 2019), the CBD expectancy manipulation did not actually provide participants with psychological skills required to better cope with the effects of the stressor. As a result, a significant stress response was still elicited among those in the CBD expectancy condition when participants were required to participate in the stressful task. As discussed previously, expectancy violation and conditioned compensatory responding may have also contributed to these observed outcomes.

The anticipatory stress appraisal process, wherein individuals evaluate the stressor and their own abilities to cope, tends to be key in facilitating an adaptive stress response as it allows individuals to engage various allostatic processes (e.g., resource mobilization) required for effective coping (Pulopulos et al., 2020; Schulkin, 2011). For example, further activation of the PNS (via an *increase* in HRV during anticipation) would not adequately prepare the individual to engage in immediate action, if required. Since participants had believed they ingested a substance (i.e., CBD), they may have relied on this substance to elicit certain effects that would improve their ability to cope with the stressor (versus beliefs about their own abilities). This external locus of control may have impeded their ability to adequately prepare for the stressor (i.e., HRV *increased* initially in anticipation then significantly decreased when confronted with the stressful task), likely leading to the observed delay in HPA axis activation in the CBD expectancy condition among males (i.e., peak cortisol occurring at 30-minutes post-stress in CBD expectancy condition vs. 10-minutes post-stress in CBD-free expectancy condition). Indeed, this can also be explained by conditioned compensatory responses and the expectancy violation effect, which occurs when there is a discrepancy between what one expects and what is actually presented, thereby disrupting homeostatic processes and

decreasing or inverting placebo effects (Colloca, 2019; Siegel, 1975; Stewart-Williams & Podd, 2004).

In summary, it is possible that CBD expectancy alone improved stress regulation during the anticipation of stress. However, in the absence of any pharmacologically active substance, expectancy violation occurred in the context of the actual demands of the stressor, since the necessarily allostatic processes did not occur during anticipation. As such, the effects of placebo CBD alone appear limited to the anticipatory period of a stressor, which could be one mechanism through which CBD influences future-oriented cognitive processes as they relate to anxiety. This would also fit with placebo research emphasizing anxiety reduction as one of the mechanisms through which expectancies promote placebo effects (Benedetti, Carlino, et al., 2011; Vase et al., 2005). In fact, a recent fMRI study from our group (Perry et al., *submitted*) reported that CBD expectancy promoted decreased resting state functional connectivity in brain regions associated with anxiety modulation (i.e., left amygdala, right anterior cingulate cortex).

The second explanation for Study 2a and 2b findings is that CBD expectancy alone can dampen indices of stress, but only as they relate to mild stressors. Indeed, anticipating a stressful event is thought to be a stressor in and of itself and has been effectively used as such in various investigations to elicit a psychophysiological stress response (Kirschbaum et al., 1992; Nasso et al., 2019; Waugh et al., 2010). It is therefore possible that placebo CBD facilitated improved stress regulation (and possibly anxiety) processes during a mild stressor (i.e., anticipation); however, when the stressor increased in intensity and required responses to a physically, socially, and cognitively demanding situation (i.e., MAST participation), expectation alone was no longer sufficient.

Although Study 2a and 2b supported the idea that CBD expectancy (i.e., stimulus expectancy) alone was sufficient to induce changes in the physiological stress response system, it is unclear to what extent this translates to subjective measures of stress and anxiety. Study 2a failed to find an effect of CBD expectancy on any subjective outcomes except sedation. Sedation levels were higher post-absorption when participants were told they received CBD (relative to CBD-free oil), which lends support to the reliability of the expectancy manipulation given that sedation is a documented side-effect of CBD (Iffland & Grotenhermen, 2017). It was only when analyses included participant's *a* priori beliefs about the perceived helpfulness of CBD for anxiety that a significant interaction was observed. Indeed, subjective anxiety was significantly lower overall (i.e., across all post-administration timepoints) when participants thought they had administered CBD oil relative to CBD-free oil; however, this effect was only observed among participants who endorsed the strongest beliefs that CBD was helpful for anxiety. In terms of subjective stress, it is possible that our single-item measure was not adequately sensitive to capture rapid changes in affective state, particularly if they are small. Given that the significant physiological findings from Studies 2a and 2b were specific to the anticipatory period, it is also possible that it was not captured by or reflected in the timing of subjective measures (i.e., pre- and post-stressor). Overall, these findings suggest that strong response expectancies moderated the effect of stimulus expectancy on subjective anxiety in the context of a laboratory stressor.

Practical and Clinical Implications

In light of the anecdotal and survey-based reports of CBD being frequently utilized and perceived as beneficial for stress- and anxiety-related states and conditions (Corroon & Phillips, 2018; Kalaba & Ware, 2022; Moltke & Hindocha, 2021; Tran &

Kavuluru, 2020), various experimental trials were prompted to investigate the impact of CBD on these subjective-emotional and psychophysiological processes. Human CBD administration studies have evaluated samples of healthy participants as well as those with clinical disorders (e.g., SAD, PTSD) or non-clinical analogue samples with elevations on anxiety-related traits. Clinical and non-clinical samples may represent distinct subgroups and processes. For instance, clinical populations are thought to experience less adaptive, chronic stress and/or anxiety experiences, with observed differences in their appraisals of and neurophysiological responses to stressors (Nitschke et al., 2009). They may therefore be using CBD for ongoing symptom management in regular dosing regimens, which also tends to be reflected in experimental trials evaluating clinical populations. Alternatively, given that non-clinical populations tend to experience non-pathological patterns of stress and anxiety in response to stressors, they may be using CBD to manage acute stress and/or anxiety. Experimental investigations with healthy populations often evaluate outcomes following acute doses of CBD in the context of a laboratory stressor. This dissertation was interested in evaluating the impact of CBD expectancy in a sample of healthy adult participants; thus, the following implications are discussed with the caveat that inferences may not be directly generalizable to clinical populations.

Briefly, mixed findings have been observed in prior research evaluating the effect of CBD among clinical populations including SAD (Bergamaschi et al., 2011; Berger et al., 2022; Crippa et al., 2011; Kwee et al., 2022; Masataka, 2019), PTSD (Bolsoni et al., 2022b, 2022a; Elms et al., 2019), and those with high trait anxiety (Bidwell et al., 2024; Dahlgren et al., 2022; Gournay et al., 2023). Taken together, results provide preliminary support that CBD has at least some positive or therapeutic effects for anxiety and stress;

however, many studies were limited by smaller sample sizes and/or open label, unblinded designs. Among 12 experimental studies with healthy participants, results were similarly mixed with eight studies finding at least one positive effect on anxiety or fear-related processes (Crippa et al., 2004; Das et al., 2013; Fusar-Poli et al., 2009, 2010; Linares et al., 2018; Zuardi et al., 1982, 1993, 2017), whereas four studies only had null or negative findings (Bloomfield et al., 2022; Leen-Feldner et al., 2022; Rossi et al., 2023; Stanley et al., 2022). It appears that the positive effects were specific to self-reported anxiety reductions in response to a social stressor with some evidence that connectivity between specific brain regions had been altered in response to CBD administration (Crippa et al., 2004; Fusar-Poli et al., 2009, 2010). Alternatively, there was minimal evidence that CBD impacts many other physiological indices of stress and anxiety (e.g., HR, blood pressure, skin conductance). Overall, it is difficult to form conjectures about the efficacy of CBD for various stress- and anxiety-related processes due to the variability in CBD dosages and administration parameters that impact pharmacokinetics, as well as small sample sizes, open-label designs, and non-replicated findings. As is particularly relevant to this dissertation, expectancy and placebo-related influences have not been adequately considered or evaluated.

Although RCTs are the gold standard design for evaluating pharmacologically driven drug effects (i.e., true drug effect) in humans, they rely on the validity of the "additive model" wherein the magnitude of the placebo effect is equal in both active drug and placebo conditions. Critics of the additive model argue that participants tend to guess their group assignment because the active drug condition tends to be associated with changes in internal state or side effects (Wampold et al., 2005). As a result, activated response expectancies amplify the placebo effect in the active drug condition and

minimize the placebo effect in the placebo condition (Fisher & Greenberg, 1997; Kirsch & Sapirstein, 1998). In fact, studies using balanced-placebo designs to tease apart relative contributions of pharmacology and expectancy found that only four studies supported the additivity assumption whereas 16 identified interaction effects (Boussageon et al., 2022). The implication of these interactions suggests that RCTs likely over- or under-estimate true drug effects. Although CBD is associated with few changes in physiological markers as well as subjective and behavioral effects, it tends to be associated with feelings of sedation (Bergamaschi, Queiroz, Zuardi, et al., 2011). Additionally, since expectancies are often triggered in the context of ambiguity, any small change in internal state or physiological signal could be attributed to placebo.

The results from this dissertation suggest that acute placebo CBD administration influences subjective state (i.e., sedation) as well as physiological parameters associated with stress and anxiety, including HRV and cortisol among healthy participants. There was also evidence that placebo CBD influences subjective anxiety, though this effect was specific to participants with strong positive expectancies (i.e., stimulus expectancy moderated by response expectancies). As such, the placebo effect appears to contribute to at least some of the previously reported anxiety-dampening effects associated with CBD. Our findings also suggest that this effect is most robust among males and those who have strong response expectancies for CBD anxiolysis. It is noteworthy that many of the previously reported positive findings related to CBD administration only included samples of males (Crippa et al., 2004; Crippa et al., 2011; Fusar-Poli et al., 2009, 2010; Linares et al., 2018). As such, while the "true drug effect" remains to be elucidated, the placebo effect likely plays an important role in these outcomes, particularly when strong response expectancies exist.

Although we cannot rule out statistical artifacts like regression to the mean in the observed outcomes from Studies 2a and 2b, these potential influences have theoretically been minimized by our study design choices. Regression to the mean is more likely to occur when samples are selected for elevated scores on a given outcome measure (e.g., anxiety) (Barnett et al., 2005). Given that we selected an otherwise healthy sample of participants with no current mental health diagnoses, their anxiety scores would theoretically fall within the population average range. We also had participants come into the lab for an orientation session prior to any experimental manipulation or testing, which may have helped with acclimation to a novel environment. Additionally, we randomized the order of the expectancy manipulation across both experimental sessions, thereby minimizing the potential influence of higher baseline state anxiety in the first experimental session.

Overall, the studies included in my dissertation were unable to fully clarify specific contributions related to true drug and placebo effects due to not having an active drug administration condition. As a result, they cannot confidently inform clinicians, patients, and policy decision-makers about whether to invest more resources into exploring CBD as treatment for stress and anxiety-related conditions. Important implications can nevertheless be deduced from my dissertation findings, particularly for individuals who use cannabis.

While placebo research seeks to determine specific contributions of drug pharmacology and expectancy to gain insight into the mechanisms of action and therapeutic utility of a given substance, set and setting research considers these factors inseparable and of equal importance (Hartogsohn, 2016). Combined with prior equivocal research findings regarding the efficacy of CBD for acute stress- and anxiety-related

difficulties, this dissertation suggests that people's expectations contribute significantly to these outcomes. This knowledge can be useful in multiple ways. Clinically, our findings emphasize the importance of measuring and controlling for response expectancies in clinical and non-clinical RCTs evaluating the therapeutic efficacy of CBD. Kirsch (2018) proposes single item questions such as "what do you expect your level of [outcome of interest] to be?" Practically, our findings can inform decisions regarding CBD use among those who use cannabis recreationally, empowering them to take an active role in their health. It may be that they decide to invest less resources into CBD and more resources into other stress and anxiety modulation strategies (e.g., emotion regulation and coping skills). Alternatively, it may offer insight into the importance of expectancies in outcomes. Since placebo effects are a key part of total treatment effects in that people know they are administering a specific substance, they are still important in the context of positive treatment outcomes. If a true drug effect does indeed exist for CBD in the context of modulating acute stress and/or anxiety, enhancing this effect through positive response expectancies would likely strengthen the therapeutic outcome. Furthermore, if people become actively aware of their CBD expectancies and the role of these expectancies in facilitating CBD outcomes, they may be able to generalize this knowledge (e.g., expecting that the skills-based strategies they use will help them manage stressors and/or anxiety). Finally, we found that those with more extensive cannabis use experience had higher positive/therapeutic expectancies as well as lower negative/harmful expectancies across both cannabinoids. Knowing the self-reinforcing nature of expectancies could be informative among those who decide to use cannabis recreationally. Specifically, it may help them make more informed decisions about their use, or prompt them to seek out reliable information, knowing that they may be underestimating potential harms, and

over-estimating potential benefits. It may also provide insight into expectancies that could be positively contributing to their use patterns (i.e., high positive expectancies, low negative expectancies), which may facilitate increased self-monitoring.

Strengths and Limitations

Strengths

My dissertation has numerous strengths. First, I would like to highlight the novel nature of the research questions I evaluated. At the time of publication, there had not been any prior research manipulating and evaluating CBD expectancies within the context of stress and anxiety. Utilizing a half-balanced-placebo design, we were able to directly evaluate the placebo effect related to CBD and gain preliminary insight into expectancy-driven mechanisms that may underlie potential stress- and anxiety-dampening effects. By evaluating beliefs about the helpfulness of CBD, we were able to better understand the role of both stimulus and response expectancies in CBD-related placebo effects. Moreover, Study 1 provided insight, for the first time, into expectancies associated with commonly known and studied cannabinoids (THC, CBD), instead of expectancies associated with cannabis overall.

Another general strength of this dissertation was in the attempts to synthesize placebo theories with set and setting research. Doing so bridges the gap between historically distinct fields and highlights key similarities (i.e., the importance of non-pharmacological drug factors and expectancies). Synthesizing these theories also allows for more broad-based implications, including clinical, mechanistic, and practical/applied considerations for those who use cannabis and specific cannabinoids recreationally.

Third, this dissertation uses multiple quantitative methodologies, including a large cross-sectional survey and an experimental laboratory-based cross-over design. Response

expectancies related to the effectiveness of CBD for stress and anxiety were assessed in both samples and, although they were not assessed in the same way, yielded similar replicable results. As such, we have been able to make conjectures that this finding is likely reliable and robust. The cross-sectional survey included a large nationwide sample of adults, which provides a more comprehensive understanding of cannabinoid-related expectancies across provinces that have different cannabis regulations (e.g., public vs. private sector). Moreover, research has largely treated cannabis as a single homogenous substance, despite the variability in cannabinoid composition and cannabinoid-specific mechanisms of action, effects, and use patterns. Study 1 provided nuanced insight regarding cannabinoid-specific expectancies that reflects the differences that exist between cannabinoids. Additionally, the experimental study included multiple controls to minimize potential confounds and increase internal validity (e.g., sample characteristics: healthy adults, no prescription medication use, history of cannabis use with limits on current use to minimize dependence/withdrawal, no prior CBD oil use; study controls: minimizing hormonal and circadian influences on physiological measures, standardized abstinence protocols). We also statistically considered other potential confounds such as response expectancies, and the influence of sex and hormonal contraceptives on physiological outcomes without excluding female participants from our sample. Relatedly, our sample was largely sex-balanced and included community-recruited adults (vs. a more limited undergraduate sample). We conducted a within-subject, repeated measure design, which helped to limit the influence of inter-participant variability on expectancy-related outcomes (i.e., each participant served as their own statistical control) thereby increasing statistical power. Moreover, we were able to keep the expectancy condition blind to the experimenter, and the true oil administration condition (i.e., inert

placebo hempseed oil across all participants and sessions) double-blind to the participant as well as the experimenter administering the oil (i.e., 'blinder'). This helped to prevent experimenter-related factors from influencing participant reactions or expectations. With regards to measurement, we collected multiple physiological indices of our outcome variables of interest (i.e., stress, anxiety), including subjective stress and anxiety, cortisol, HR, and HRV, which helped us better understand the mechanisms through which CBD expectancy influenced these processes.

Limitations

My dissertation results need to be considered in relation to the following general limitations and methodological considerations. First, some of the findings from these studies (e.g., HRV, cortisol) have not yet been replicated. Since the time of publication, I have been involved in other experimental studies within our lab that addressed some of the limitations or follow up questions we had. For instance, the stress induction task used in Study 2a and 2b (i.e., the MAST) produced near ceiling effects for subjective anxiety and the 90-minute mock absorption period may have decreased the salience of the expectancy manipulation. In a follow-up study with a less powerful stressor and shorter 10-minute sham absorption period, our group found trend-level evidence of dampened self-reported stress and anxiety in anticipation of stress following placebo CBD administration (Zhekova et al., 2024). Second, and related to the robustness of our results, different control variables and analytic approaches were selected to analyze each dataset. Each approach was selected based on knowledge at the time of data analyses and prioritization of different factors for each study. Although linear mixed models, marginal models, and generalized estimating equations tend to yield similar results, their *p*-values may differ. In the synthesis of my dissertation research, I have made attempts to not only

focus on statistically significant findings, but also discuss the observed differences between groups based on observed patterns of EMMs and associated SEs. Future investigations would benefit from replicating our research.

There are several measurement and design-related methodological considerations worth noting as they relate to this dissertation. Although many of our findings appeared to be specific to the anticipatory phase prior to a stressor, the studies in this dissertation were not adequately designed to tease apart the anticipation and acute stress phases with a high degree of specificity. For example, we did not assess subjective state following anticipation only nor did we assess cortisol responsivity to anticipation without the potential confounding effects of the actual stress task. It would be beneficial to further tease apart and evaluate the impact of placebo CBD during the preparation/anticipation to a stressor, active stress task participation, and recovery from a stressor. Fourth, we did not evaluate any behavioral indices of stress and anxiety. Evaluating an index of behavioral distress tolerance, such as persistence in goal-directed behavior or reduction of escape behaviour, may provide ancillary information regarding outcomes associated with dampened stress- and/or anxiety-related processes. Importantly, high behavioral distress tolerance exists in the context of negative affective states (Howell et al., 2010); thus, it could be another mechanism through which these purported therapeutic effects occur. Fifth, our findings could only provide insight into expectancy-driven components related to cannabinoids, and in particular CBD for stress and anxiety. Due to COVID-19 interrupting data collection for Study 2a/2b and policy preventing research access to CBD, we were required to modify our study design to a half-balanced-placebo design. As a result, we were unable to evaluate the role of CBD pharmacology and interactions between pharmacology and expectancy on stress and anxiety outcomes.

Sixth, we did not obtain a reliable baseline measurement for HRV in Study 2a nor did we obtain a sufficient number of cortisol assessments taken sufficiently far out from the stressor in Study 2b. As a result, we likely had an over-inflated baseline for HRV, which made it difficult to compare timepoints to a reliable baseline and make inferences about these differences in our analyses. Additionally, we did not capture a true recovery timepoint for cortisol, which also prevented us from calculating potentially useful indices of HPA responsivity, such as the area under the curve with respect to increase and ground (Pruessner et al., 2003). This latter limitation prevented us from making inferences about the extent to which CBD expectancy influences stress recovery, an important component of adaptive stress responding.

Seventh, it is notable that we assessed strength of beliefs regarding the effects of cannabinoids across all studies in this dissertation and not specifically related to how participants believe they will react or respond in a specific situation. While these expectations are likely correlated, the former may lack specificity to the individual within a certain context. Moreover, this dissertation is overly reductionistic in its assumptions regarding sex and gender. Gender was a control variable of interest in Study 1 and given the small number of non-binary participants (i.e., too small to make any meaningful comparisons or inferences), we made the decision to only include men and women as categories for analytic purposes. Additionally, the sample of participants in Study 2a/2b only included cis-gendered adults. At times, sex and gender terms were used interchangeably in this dissertation (see Chapter 5 for a detailed explanation), particularly when summarizing other literature, largely due to a lack of specificity in many previous studies (e.g., uncertainties about whether biological sex or gender was assessed). Overall, participants in these studies were predominantly white, cis-gendered, well-educated

adults, thereby potentially limiting the generalizability of findings to these groups. The results of Study 2a/2b are further limited to healthy adults using CBD for acute stress and anxiety management. It is notable that these studies had particularly low ecological validity, which is often a trade-off in experimental research for high experimental control (i.e., internal validity). Additionally, it is unlikely that individuals using CBD for acute stress and anxiety management are administering via daily dosing regimens. They are more likely administering *reactively* in response to a stressor or increased anxiety (i.e., an 'as needed' or prn dosing regimen) and may also be using a faster delivery method (e.g., inhalation) (Russell et al., 2018).

Eighth, we utilized a survey panel service to recruit participants as part of Study 1. Individuals who are a part of commercial panels are self-selected, thus may not be fully representative of our target population (i.e., community adults). The generalizability of the results from Study 1 may therefore be limited to those with characteristics of this self-selected sample. Relatedly, we assessed lifetime cannabis use exposure using an item from a validated questionnaire (i.e., DFAQ-CU; Cuttler & Spradlin, 2017), which resulted in ordinal data (i.e., 10 categories representing degrees of cannabis use exposure). We decided to categorize these unequal response options into 'high' and 'low' cannabis exposure based on a median split to facilitate improved interpretation in follow-up analyses. Together, the decision to measure cannabis use exposure in this way and analyze the data using a median split limited our statistical power and also decreased our sensitivity to detecting nuanced relationships between levels of cannabis use exposure and cannabinoid expectancies (e.g., non-linear relationships). However, running analyses on the original variable (i.e., unequal groups of participants split across 10 relatively ambiguous categories of cannabis use exposure) would have made it challenging to draw

any meaningful inferences from this data. As a result, a median split in this situation allowed us to make meaningful comparisons between two levels/degrees of cannabis use exposure.

Future Directions

In addition to the future directions outlined in each manuscript as well as in the previous subsections, there are various other ways in which future research could expand on findings from my dissertation. As previously discussed, replication of these novel results is warranted to gain insight into the robustness of our findings. Studies designed to tease apart the numerous stages of the stress response (i.e., anticipation, acute stress, recovery), as well as behavioral metrics of stress and anxiety-related behaviors, will help provide specificity to the mechanisms through which placebo CBD influences these outcomes. Moreover, to increase the ecological validity of experimental research, future designs could consider an *ad libitum* administration paradigm utilizing a preparation of placebo CBD that aligns with their typical method of administration. Measuring the latency to and quantity of administration may provide a behavioral index of stress and/or anxiety responding. For instance, laboratory analogues of cigarette smoking lapse behaviour as well as smoking self-administration have been shown to be sensitive to expectancy and pharmacological manipulation (Barrett, 2010; McKee, 2009; McKee et al., 2012). These paradigms could be adapted to assess *ad libitum* CBD use in controlled laboratory environments. Although Studies 2a and 2b were largely focused on the role of CBD expectancy on acute stress and anxiety in healthy populations, there is also a need to explore these questions in clinical populations in both experimental/laboratory-based, and clinical/naturalistic settings with extended, daily dosing. It would be helpful to see whether outcomes differ based on population (healthy vs. clinical), use parameters (acute

vs. chronic), and stress exposure (acute vs. daily; stress induction paradigm vs. daily stressors). Additionally, research designed to explore the neural correlates of stress and anxiety-related processes would also be vital in pursuit of better understanding placebo CBD's mechanisms of action. Given that prior fMRI research has found that CBD influences emotional processing (Fusar-Poli et al., 2010), it would be important to determine the extent to which expectancy factors are involved in these responses. Recently, I have been involved with a study evaluating this question (Perry et al., *under review*). Preliminary results suggest that expectancy factors explain at least some of the previously reported outcomes associated with CBD administration.

Numerous considerations for psychopharmacological research with CBD can be gleaned from the results of this dissertation. First, given that the impact of placebo CBD on subjective anxiety tended to be pronounced among those who had strong response expectancies, it would therefore be important to assess and control for these in future clinical and experimental research evaluating CBD (e.g., RCTs). Further, the physiological changes appeared to be specific to the anticipation phase of a stressor. Since prior research has not evaluated the effect of CBD during the anticipation of stress, it would be valuable to explore this further as it may help gain insight into CBD's mechanisms of action. Additionally, it will be important to evaluate the unique contributions of CBD pharmacology on outcomes related to stress and anxiety using a full balanced-placebo design. Results from these studies would provide key information about whether to continue investing resources into RCTs for CBD as a therapeutic agent for stress and anxiety related conditions. Finally, it would be important for RCTs (or balanced-placebo designs) to include a no placebo control condition. Doing so would help

distinguish true placebo effects from extra-placebo factors, namely regression to the mean.

The results of Study 1 supported the separate assessment of THC and CBD. Given that expectancy research helps understand substance use patterns and harms, it would be important to evaluate cannabinoid-specific use patterns and harms as they relate to expectancies for distinct cannabinoids. For example, it may be that those who frequently use CBD versus THC for medicinal or coping motives have distinct levels of risk for various harms. This may not be captured in other cannabis research due to the lack of specificity. Given the emergence of other cannabinoids, like cannabigerol (CBG) and cannabinol (CBN), in recreational cannabis products, it may be beneficial to explore associated expectancies. Relatedly, given the range of purported effects associated with CBD and THC, as well as beliefs that emerged from Study 1, it would be beneficial to explore relative contributions of expectancy and pharmacology for various outcomes (e.g., CBD for pain reduction, THC for creativity enhancement).

Conclusions

In conclusion, my dissertation sought to gain insight into the expectancy-related factors of commonly known cannabinoids (i.e., THC, CBD), both broadly, and specifically as they relate to the placebo effect for CBD on acute stress and anxiety. My dissertation demonstrates that individuals tend to hold more positive beliefs about the therapeutic effects of CBD compared to THC (including expectancies for stress and anxiety management), with prior cannabis use experience influencing overall positive beliefs. Additionally, the placebo effect appears to explain at least some of the previously reported stress and anxiety dampening effects associated with CBD administration. Our research findings reveal, for the first time, that CBD expectancy alone significantly

impacts self-reported anxiety levels among individuals who endorse strong beliefs that it is helpful for these purposes as well as physiological responses to acute stress, particularly in terms of HRV and cortisol reactivity during anticipation. Overall, these results highlight the importance of expectancy in shaping cannabinoid effects.

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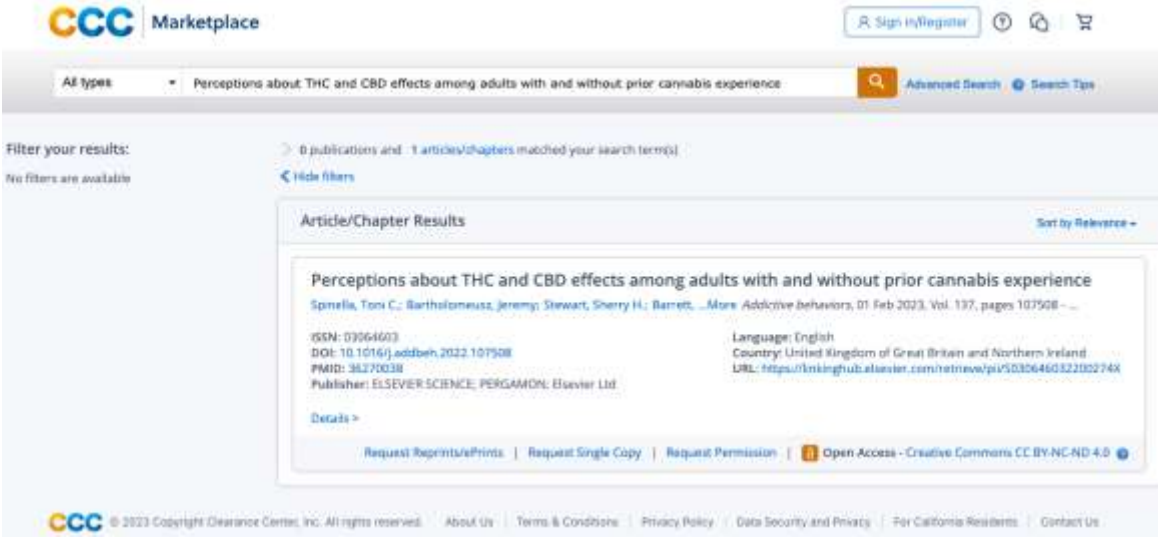
APPENDIX A. COPYRIGHT PERMISSION TO INCLUDE STUDY 1



APPENDIX B. CHAPTER 2 STUDY 1 SUPPLEMENTAL FILES

Cannabinoid Expectancy Rating Inventory

(Adapted from Torrealday et al., 2008)

Please read the following questions and mark the response that best describes your familiarity and knowledge regarding specific cannabis strains and ingredients. There are no wrong answers.

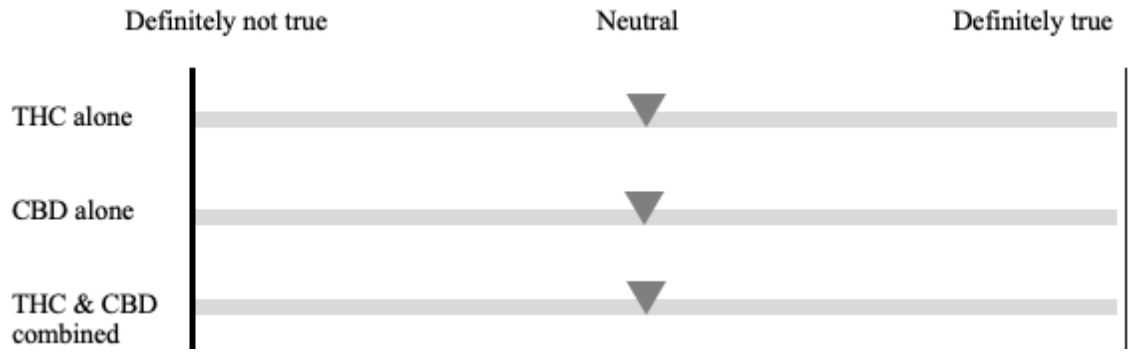
1. THC (tetrahydrocannabinol) and CBD (cannabidiol) are some of the main active ingredients in cannabis. Please rate your level of familiarity and knowledge about these ingredients.

	I don't know what this is	I recognize the term, but know nothing about it	I know a little bit about it	I know a moderate amount about it	I know a lot about it
THC	○	○	○	○	○
CBD	○	○	○	○	○

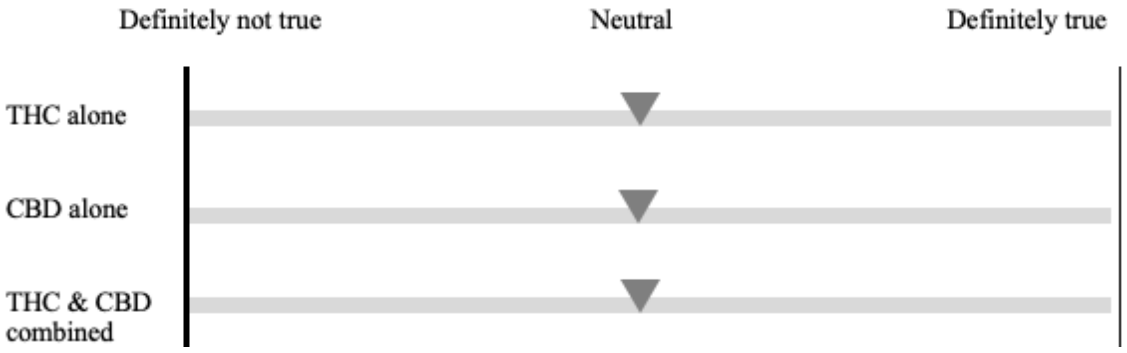
The following items contain descriptors about the possible effects of specific cannabis ingredients (THC, CBD, THC & CBD). Answer each item according to your own personal thoughts, feelings, and beliefs about these cannabis ingredients. We are interested in what you think, not what others might think. Whether or not you have had actual experience with cannabis, you should answer in terms of how you think these cannabis ingredients affect the average person.

Slide the marker to indicate how much you think the following statements are true or not true.

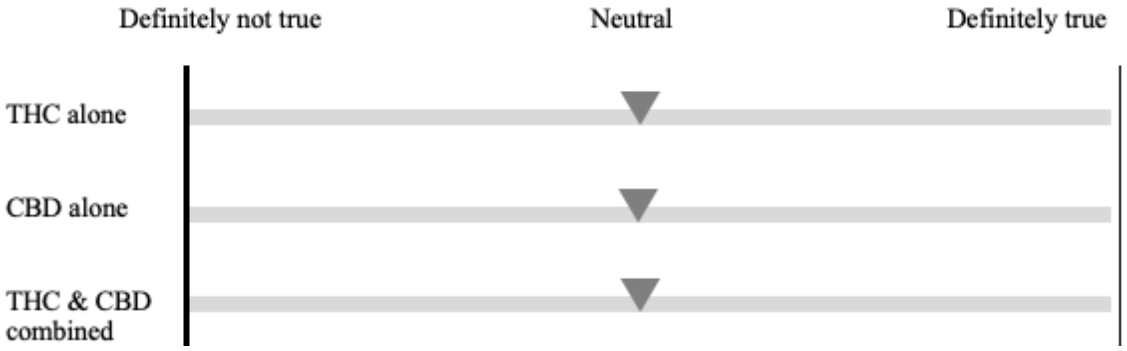
1. **Helps with anxiety** (for example, to reduce worrying or slow down racing thoughts).



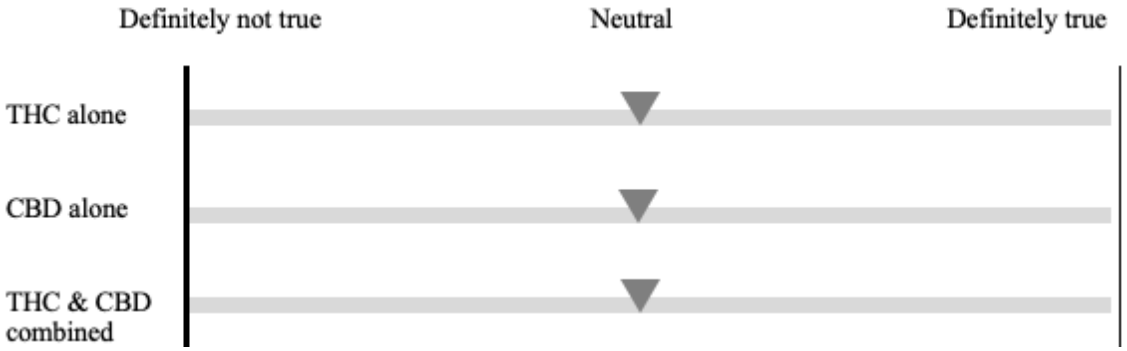
2. **Helps with pain** (for example, to reduce or distract from pain).



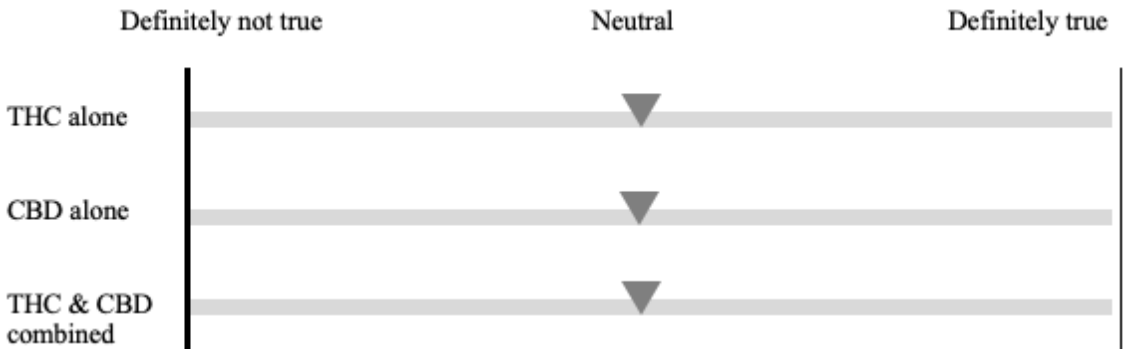
3. **Helps with sleep** (for example, to fall asleep more quickly or improve the quality of sleep).



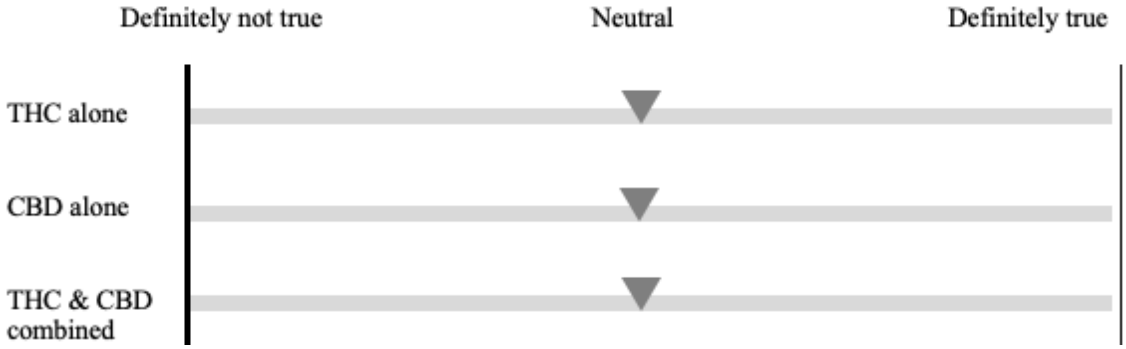
4. **Helps with stress** (for example, to unwind, relax, or feel less tense).



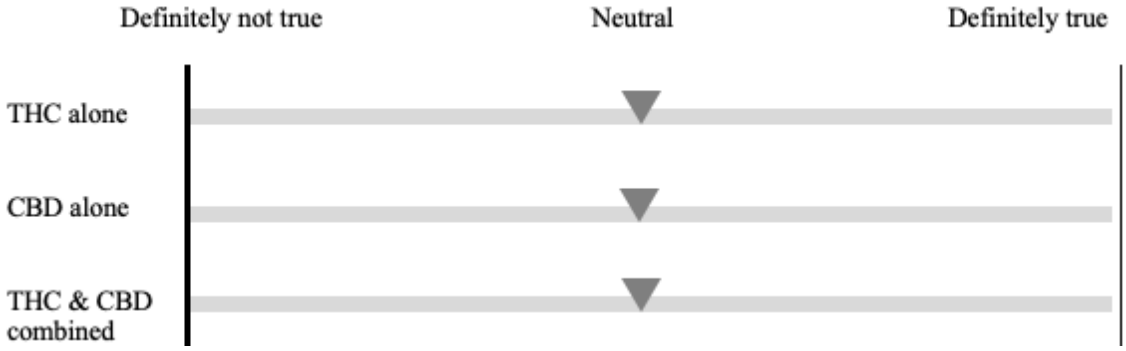
5. **Enhances positive thoughts, feelings, and/or mood** (for example, increases feelings of joy and/or euphoria).



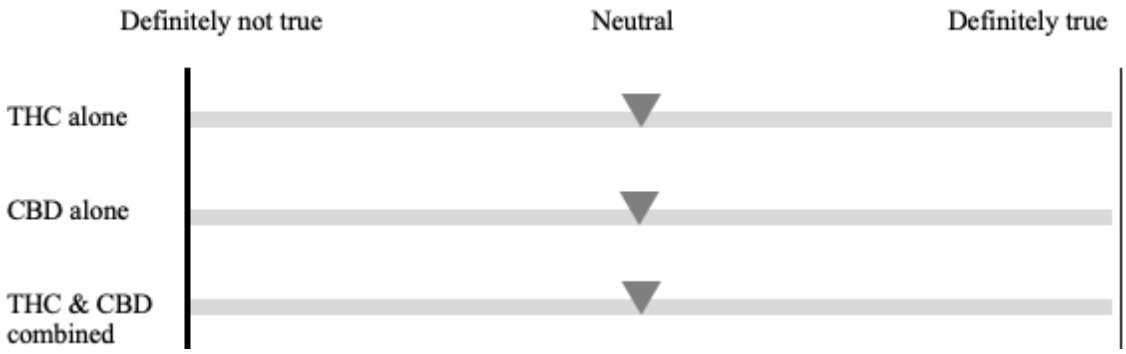
6. **Relieves negative thoughts, feelings, and/or mood** (for example, decreases feelings of sadness and/or feeling less depressed).



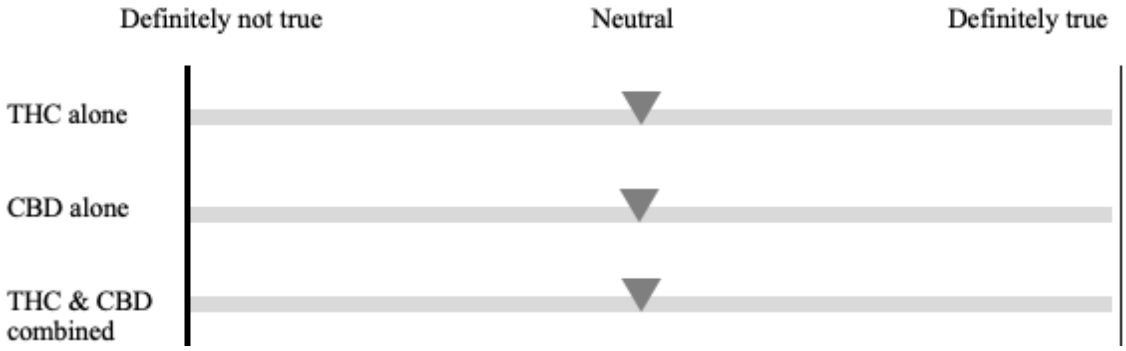
7. **Helps with nausea** (for example, to reduce or distract from nausea).



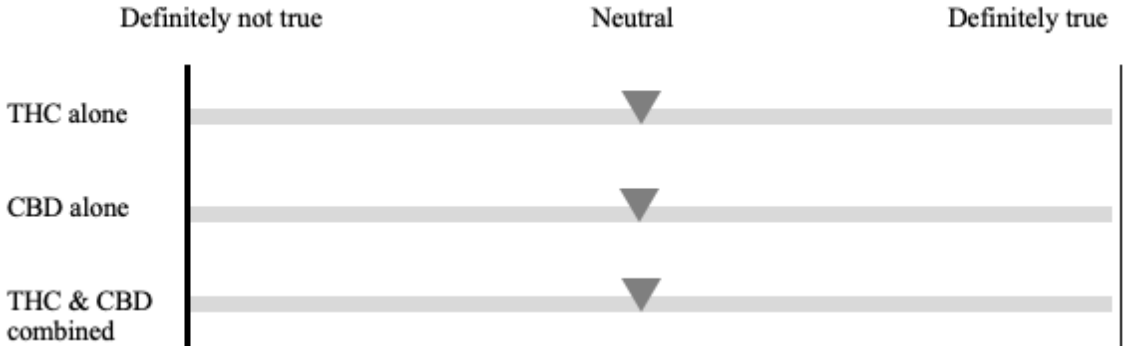
8. **Improves creativity** (for example, opens your mind to experience/perceive things differently).



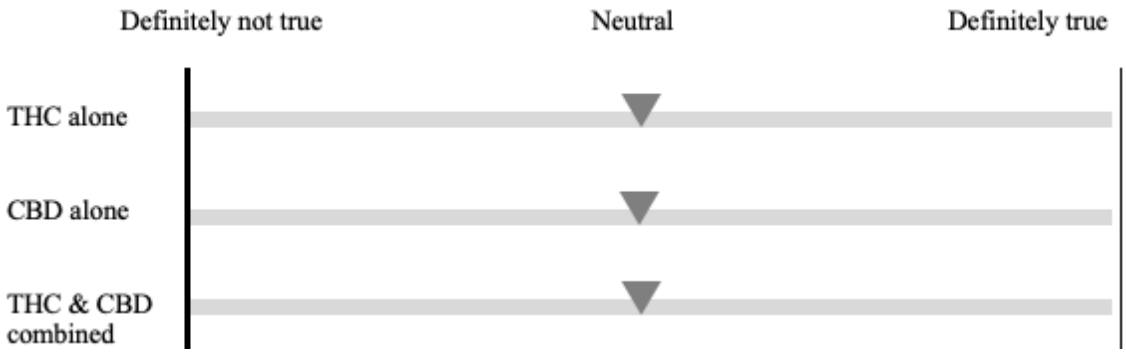
9. **Increases alertness/stimulation** (for example, to feel more awake).



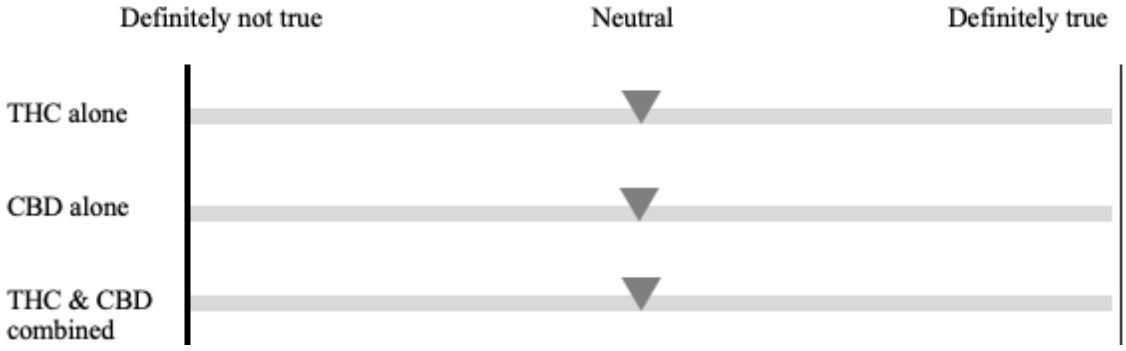
10. **Improves attention and focus** (for example, makes it easier to pay attention and focus on tasks).



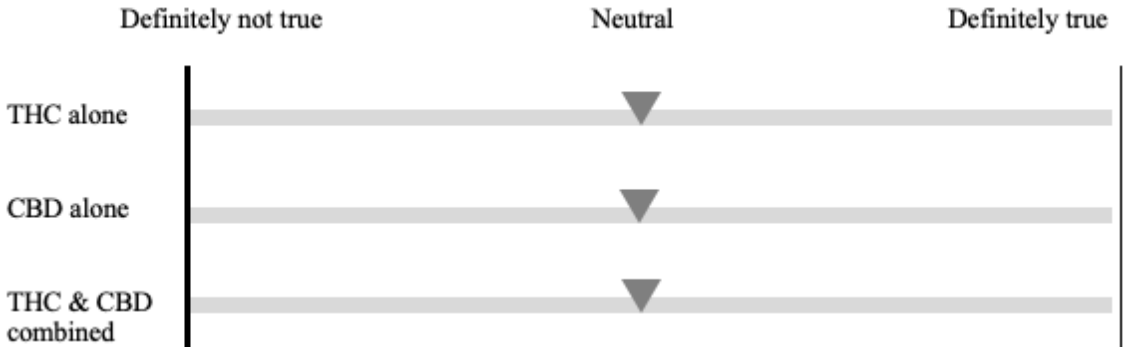
11. **Helps with socializing** (for example, makes it easier to talk or connect with others).



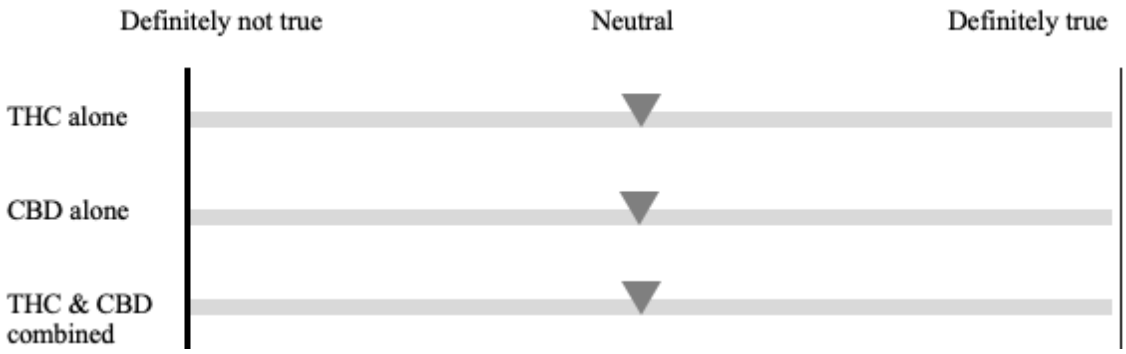
12. **Helps with feeling more sexual** (for example, to feel more sexually responsive, to enhance sexual pleasure, or to feel more romantic).



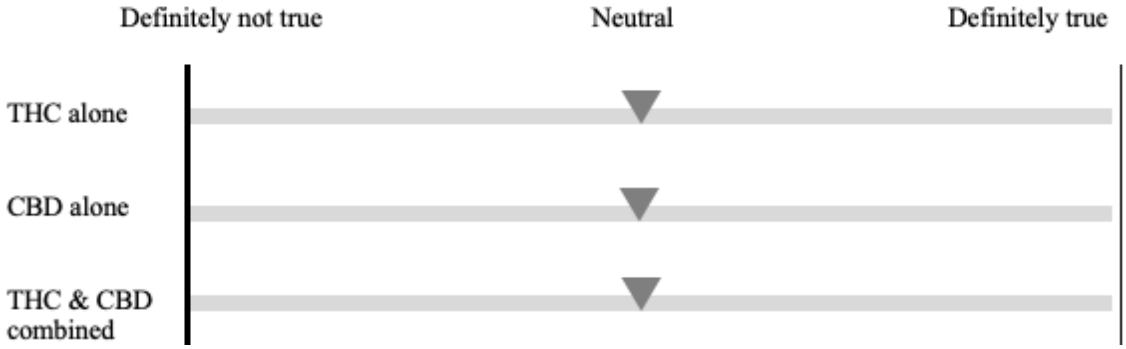
13. **Impairs thinking and reasoning abilities** (for example, impairs memory, makes it difficult to concentrate or perform mental tasks).



14. **Increases risk for addiction** (for example, experiencing strong urges to use the substance and feeling withdrawal/negative effects when use stops).



15. **Increases risk for psychosis and/or developing a psychotic disorder** (for example, schizophrenia).



Supplemental Table 2.1. Estimated marginal mean (standard error) values from linear mixed models (LMM) for main effects of Use Status and Cannabinoid.

Main effect: Use Status			***Main effect: Cannabinoid***		
	NCU	**CU**	**THC**	**CBD**	**THC & CBD**
Therapeutic					
Sleep	5.96 (.21)[a]	6.64 (.10)[a]	5.50 (.16)[c,d]	6.81 (.16)[c]	6.58 (.16)[d]
Stress	6.58 (.20)[a]	7.14 (.09)[a]	6.56 (.14)[c,d]	6.90 (.14)[c]	7.11 (.14)[d]
Anxiety	6.20 (.22)[a]	6.89 (.10)[a]	6.06 (.15)[c,d]	6.91 (.15)[c]	6.66 (.15)[d]
Pain	6.79 (.22)	7.29 (.10)	6.50 (.15)[c,d]	7.47 (.15)[c,h]	7.14 (.15)[d,h]
Nausea	6.26 (.24)	6.40 (.11)	6.09 (.15)[c,d]	6.43 (.14)[c]	6.46 (.14)[d]
Attention	4.81 (.28)[a]	5.70 (.13)[a]	5.06 (.17)[c,d]	5.36 (.17)[c]	5.34 (.17)[d]
Negative affect	6.06 (.24)[a]	6.60 (.11)[a]	6.44 (.15)[e]	6.07 (.15)[e,f]	6.47 (.15)[f]
Positive non-therapeutic					
Positive affect	6.21 (.22)	6.67 (.10)	6.75 (.15)[e]	5.90 (.15)[e,f]	6.67 (.15)[f]
Creativity	5.97 (.22)[a]	6.51 (.10)[a]	6.62 (.15)[e]	5.49 (.15)[e,f]	6.60 (.15)[f]
Alertness	4.79 (.26)[a]	5.56 (.12)[a]	5.17 (.16)	5.14 (.16)	5.22 (.16)
Social	5.84 (.23)[a]	6.53 (.11)[a]	6.32 (.15)[e]	5.71 (.15)[e,f]	6.52 (.15)[f]
Sexual	5.78 (.26)	6.03 (.12)	6.10 (.15)[e]	5.47 (.16)[e,f]	6.15 (.15)[f]
Negative non-therapeutic					
Impairs cognition	5.98 (.27)	5.77 (.12)	6.52 (.18)[e]	4.84 (.18)[e,f]	6.27 (.18)[f]
Addiction risk	6.16 (.34)[b]	4.85 (.15)[b]	5.89 (.20)[d,e]	5.00 (.20)[e,f]	5.61 (.20)[d,f]
Psychosis risk	5.65 (.32)[b]	4.91 (.14)[b]	5.86 (.19)[e,g]	4.54 (.19)[e,f]	5.44 (.19)[f,g]

NCU: No prior cannabis use; CU: Any prior cannabis use.

Note. Significant differences as identified in post-hoc pairwise comparisons are denoted by superscripts.

[a] CU > NCU.

[b] NCU > CU.

[c] CBD > THC.

[d] THC & CBD > THC.

[e] THC > CBD.

[f] THC & CBD > CBD.

[g] THC > THC & CBD

[h] CBD > THC & CBD.

Supplemental Table 2.2. Estimated marginal mean (standard error) values from linear mixed models (LMM) for interactions between Use Status and Cannabinoid.

Interaction: Use Status by Cannabinoid			
	THC	**CBD**	**THC & CBD**
Therapeutic			
Sleep			
NCU	5.02 (.29)	6.66 (.29)	6.18 (.29)
CU	5.98 (.13)	6.96 (.13)	6.97 (.13)
Stress			
NCU	6.29 (.26)	6.66 (.26)	6.79 (.26)
CU	6.84 (.12)	7.15 (.12)	7.42 (.12)
Anxiety			
NCU	5.79 (.27)	6.56 (.27)	6.24 (.27)
CU	6.33 (.12)	7.25 (.12)	7.09 (.12)
Pain			
NCU	6.30 (.27)	7.29 (.27)	6.79 (.27)
CU	6.71 (.12)	7.66 (.12)	7.49 (.12)
Nausea			
NCU	5.97 (.27)	6.47 (.26)	6.32 (.26)
CU	6.21 (.12)	6.38 (.12)	6.60 (.12)
Attention			
NCU	4.57 (.31)	4.98 (.31)	4.89 (.31)
CU	5.56 (.14)	5.74 (.14)	5.80 (.14)
Negative affect			
NCU	6.21 (.27)	5.80 (.27)	6.16 (.27)
CU	6.66 (.12)	6.34 (.12)	6.79 (.12)
Positive non-therapeutic			
Positive affect			
NCU	6.46 (.28)	5.87 (.28)	6.29 (.28)
CU	7.04 (.12)	5.93 (.13)	7.04 (.12)
Creativity			
NCU	6.28 (.27)	5.28 (.27)	6.34 (.27)
CU	6.96 (.12)	5.70 (.12)	6.86 (.12)
Alertness			
NCU	4.78 (.29)	4.78 (.29)	4.81 (.29)
CU	5.55 (.13)	5.49 (.13)	5.64 (.13)
Social			
NCU	5.94 (.27)	5.37 (.27)	6.20 (.27)
CU	6.70 (.12)	6.06 (.12)	6.84 (.12)
Sexual			
NCU	5.99 (.28)	5.25 (.28)	6.11 (.28)
CU	6.21 (.13)	5.70 (.13)	6.20 (.13)
Negative non-therapeutic			
Impairs cognition			
NCU	6.62 (.33)	4.93 (.33)	6.38 (.33)

Interaction: Use Status by Cannabinoid			
	THC	**CBD**	**THC & CBD**
CU	6.42 (.15)	4.74 (.15)	6.15 (.15)
Addiction risk			
NCU	6.59 (.37)	5.64 (.37)	6.24 (.37)
CU	5.19 (.17)	4.37 (.17)	4.98 (.17)
Psychosis risk			
NCU	6.28 (.35)	4.90 (.35)	5.77 (.35)
CU	5.44 (.16)	4.18 (.16)	5.12 (.16)

NCU: No prior cannabis use; CU: Any prior cannabis use.

Supplemental Table 2.3. Linear mixed model (LMM) coefficients for main effects of Age and Gender.

	Main effect: Age			***Main effect: Gender***		
Outcome	**df**	***F***	***p***	**df**	***F***	***p***
Therapeutic						
Sleep	1, 337.00	1.639	.201	1, 337.00	.015	.901
Stress	1, 335.39	1.281	.259	1, 336.33	.653	.419
Anxiety	1, 336.29	.003	.955	1, 336.69	.005	.944
Pain	1, 336.37	1.104	.294	1, 336.58	.379	.539
Nausea	1, 333.48	.179	.673	1, 334.18	.001	.979
Attention	1, 334.49	3.463	.064	1, 335.84	.538	.464
Negative affect	1, 330.49	.260	.611	1, 331.79	.003	.957
Positive non-therapeutic						
Positive affect	1, 332.89	1.540	.216	1, 333.60	1.657	.199
Creativity	1, 331.38	2.404	.122	1, 331.87	4.948	**.027**[b]
Alertness	1, 333.78	7.237	**.008**[a]	1, 334.57	4.064	**.045**†
Social	1, 331.11	.305	.581	1, 332.17	.001	.981
Sexual	1, 334.74	.229	.633	1, 335.21	0.561	.454
Negative non-therapeutic						
Impairs cognition	1, 334.43	.068	.795	1, 334.65	.314	.575
Addiction risk	1, 336.34	1.168	.281	1, 336.18	.117	.733
Psychosis risk	1, 334.59	.573	.449	1, 334.74	4.175	**.042**†

Bolded coefficients indicate statistical significance ($p<.05$).

†FDR threshold >5% exceeded (Attention: adjusted $p=.075$; Psychosis risk: adjusted $p=.054$) indicates potential false positive findings.

[a] Beta = -.021.

[b] Men > Women.

Supplemental Table 2.4. Linear mixed model (LMM) coefficients and estimated marginal mean (standard error) values for main effects of Cannabis Exposure among participants with prior cannabis use (CU) experience (n=287).

	Main effect: Cannabis Exposure				**EMM (SE)**	
Outcome	**df**	***F***	***p***	**Direction of effect**	**Low (n=157)**	**High (n=130)**
Therapeutic						
Sleep	1, 279.00	10.109	**.002**	High > Low	6.36 (.13)	6.97 (.14)
Stress	1, 277.97	11.329	**<.001**	High > Low	6.85 (.12)	7.47 (.14)
Anxiety	1, 278.48	13.550	**<.001**	High > Low	6.56 (.13)	7.28 (.14)
Pain	1, 278.79	6.957	**.009**	High > Low	7.05 (.14)	7.59 (.15)
Nausea	1, 276.31	12.371	**<.001**	High > Low	6.04 (.15)	6.83 (.17)
Attention	1, 277.09	7.253	**.008**	High > Low	5.39 (.17)	6.08 (.19)
Negative affect	1, 271.70	11.607	**<.001**	High > Low	6.25 (.15)	7.01 (.16)
Positive non-therapeutic						
Positive affect	1, 275.47	14.663	**<.001**	High > Low	6.32 (.14)	7.11 (.15)
Creativity	1, 273.29	6.224	**.013**	High > Low	6.27 (.14)	6.79 (.15)
Alertness	1, 276.05	6.919	**.009**	High > Low	5.28 (.16)	5.91 (.17)
Social	1, 276.02	1.845	.175		6.39 (.14)	6.68 (.16)
Sexual	1, 276.53	6.781	**.010**	High > Low	5.74 (.16)	6.36 (.18)
Negative non-therapeutic						
Impairs cognition	1, 276.90	8.374	**.004**	Low > High	6.09 (.16)	5.38 (.18)
Addiction risk	1, 278.21	27.767	**<.001**	Low > High	5.57 (.21)	3.95 (.23)
Psychosis risk	1, 276.68	17.542	**<.001**	Low > High	5.48 (.94)	4.27 (.21)

Bolded coefficients indicate statistical significance ($p<.05$).
Note. Significant multivariate outliers (> 3 interquartile ranges) were excluded from each model.
Low: 1-100 lifetime uses of cannabis; High: 101-10,000+ lifetime uses of cannabis;
EMM: Estimated marginal mean; SE: Standard error.

APPENDIX C. COPYRIGHT PERMISSIONS TO INCLUDE STUDY 2A

APPENDIX D. CHAPTER 4 STUDY 2A SUPPLEMENTAL FILES

Main effects of Time

See Supplemental Table 4.1 for generalized estimating equation (GEE) coefficients as well as estimated marginal means and standard error values for all main effects of Time. First, main effects of Time were observed for ratings of sedation, stimulation, intoxication, and relaxation. Subjective intoxication and sedation ratings increased from baseline to post-absorption (p=.008, p=.043, respectively), while stimulation ratings decreased from baseline to post-absorption (p<.001). Sedation then decreased from post-stress to recovery (p=.041). At baseline (relative to post-stress and recovery), intoxication was rated lowest (both p=.01) while stimulation was rated highest (both p<.001). Additionally, subjective relaxation was lowest post-stress relative to all other time points (baseline, post-absorption, and recovery; all p<.001). Subjects also reported higher ratings of relaxation at baseline relative to recovery (p<.001).

Next, main effects of Time indicated that the MAST was effective at inducing subjective stress, anxiety, and negative affect (baseline vs. post-stress, all p<.001) among all subjects, regardless of expectancy condition. Only ratings of stress decreased from baseline to post-absorption (p<.001). All subjective ratings decreased significantly from post-stress to recovery (all p<.001). Ratings of anxiety and negative affect were higher at recovery relative to baseline (p<.001, p=.029, respectively). A main effect of Time was also observed for positive affect. Ratings of positive affect decreased from baseline to post-absorption (p<.001), then increased from post-absorption to post-stress (p=.028). Positive affect was higher at baseline than recovery (p=.007).

Lastly, main effects of Time were observed for both time-domain indices of HRV, HR and RMSSD, indicating that the MAST was effective at inducing physiological

markers of acute stress. HR increased from baseline to anticipation and stress (both $p \leq .001$). RMSSD and HR changed significantly from anticipation to stress (RMSSD decrease, $p = .002$; HR increase, $p = .020$), then from stress to recovery (RMSSD increase, $p < .001$; HR decrease, $p < .001$), indicative of a physiological stress response. Physiological stress during recovery was significantly lower than baseline (RMSSD higher, $p < .001$; HR lower, $p < .001$).

Supplemental Table 4.1. Estimated marginal mean (standard error) values and generalized estimating equation (GEE) coefficients for main effects of Time involving subjective drug effects, stress, anxiety, and mood, and heart rate variability.

Main effect: Time								
	Baseline	**Post-absorption**	**Post-stress**	**Recovery**	**Outcome**	**df**	**Wald Chi-square**	***p***
Intoxication	1.01 (.01)	1.19 (.07)	1.26 (.10)	1.19 (.08)	**Intoxication**	**3**	**10.04**	**.018**
Relaxation	6.26 (.25)	6.52 (.26)	2.29 (.23)	4.66 (.28)	**Relaxation**	**3**	**124.36**	**<.001**
Stimulation	14.30 (.63)	11.64 (.78)	11.36 (.80)	12.04 (.77)	**Stimulation**	**3**	**44.90**	**<.001**
Sedation	7.55 (.52)	8.56 (.65)	8.18 (.64)	6.96 (.54)	**Sedation**	**3**	**17.10**	**.001**
Stress	2.20 (.22)	1.72 (.14)	4.85 (.36)	1.90 (.16)	**Stress**	**3**	**222.76**	**<.001**
Anxiety	31.25 (1.09)	31.46 (1.08)	55.33 (1.49)	37.38 (1.21)	**Anxiety**	**3**	**299.71**	**<.001**
Negative affect	5.90 (.15)	5.81 (.15)	9.48 (.47)	6.27 (.21)	**Negative Affect**	**3**	**148.49**	**<.001**
Positive affect	13.12 (.54)	11.29 (.58)	12.44 (.61)	11.97 (.58)	**Positive Affect**	**3**	**27.41**	**<.001**
	Baseline	**Anticipation**	**Stress**	**Recovery**				
HR	68.66 (1.10)	72.08 (1.23)	75.00 (1.53)	63.53 (1.10)	**HR**	**3**	**148.23**	**<.001**
RMSSD	61.12 (5.69)	66.39 (4.51)	58.12 (3.89)	81.33 (5.35)	**RMSSD**	**3**	**66.94**	**<.001**

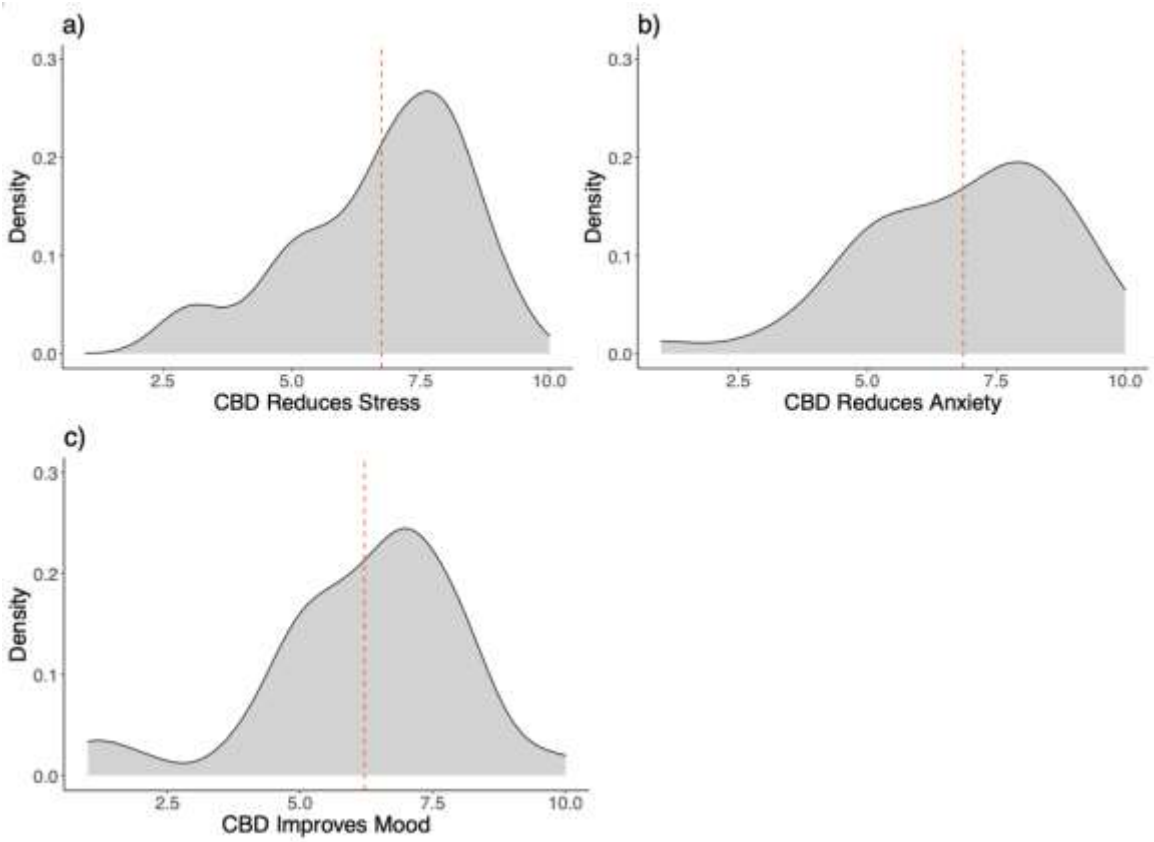
Bolded coefficients indicate statistical significance ($p<.05$).
Subjective measures: Baseline (T1): +00; Post-absorption (T2): +95; Post-stress (T3): +110; Recovery (T4): +120
Physiological measures: Baseline (T1): +00-+70; Anticipation (T2): +95; Stress (T3): +100; Recovery (T4): +120

Supplemental Table 4.2. Generalized estimating equation (GEE) coefficients from factors and covariates included in each model.

Covariate: Baseline scores			
Outcome	**df**	**Wald Chi-square**	***p***
Overall stress post-administration	**1**	**28.89**	**<.001**
Overall anxiety post-administration	**1**	**24.83**	**<.001**
Overall negative affect post-administration	**1**	**23.70**	**<.001**
Overall positive affect post-administration	1	1.64	.200
Covariate: Belief rating			
Outcome	**df**	**Wald Chi-square**	***p***
Overall stress post-administration	1	2.37	.124
Overall anxiety post-administration	1	.78	.378
Overall negative affect post-administration	**1**	**3.86**	**.049**
Overall positive affect post-administration	**1**	**19.40**	**<.001**
Factor: Time			
Outcome	**df**	**Wald Chi-square**	***p***
Overall stress post-administration	**2**	**187.86**	**<.001**
Overall anxiety post-administration	**2**	**332.72**	**<.001**
Overall negative affect post-administration	**2**	**146.45**	**<.001**
Overall positive affect post-administration	**2**	**6.75**	**.034**
Covariate: ECG-derived breathing rate			
Outcome	**df**	**Wald Chi-square**	***p***
HR	**1**	**6.86**	**.009**
RMSSD	**1**	**9.34**	**.002**
Factor: Expectancy condition			
Outcome	**df**	**Wald Chi-square**	***p***
HR	1	.35	.557
RMSSD	1	.15	.697
Stress	1	.14	.706
Anxiety	**1**	**3.94**	**.047**
Negative affect	1	2.26	.133
Positive affect	1	.52	.472
Intoxication	1	2.42	.120
Relaxation	1	.16	.692
Stimulation	1	.12	.729
Sedation	1	2.41	.121

Bolded coefficients indicate statistical significance ($p<.05$).

Note. The coefficients listed in this table were not included in the Benjamini-Hochberg adjustment as they were not effects of interest.



Supplemental Figure 4.1. Density plots illustrating *a* priori CBD belief ratings on a scale from 1 (not at all) to 10 (completely) for the following items: a) Reduces Stress (*M*=6.74, *SD*=1.63), b) Reduces Anxiety (*M*=6.86, *SD*=1.95), and c) Improves Mood (*M*=6.21, *SD*=1.88). Vertical dashed lines represent mean ratings.

APPENDIX E. CHAPTER 5 SUPPLEMENTAL ANALYSES FROM STUDY 2A: ASSOCIATIONS WITH BIOLOGICAL SEX

Supplemental Analyses for Study 2a

Given the observed sex differences in physiological stress and placebo responsivity described in Chapter 5, a follow-up supplemental analysis was conducted on the HR and HRV (RMSSD) parameters from Study 2a. To facilitate direct comparison between the cortisol findings in Study 2b, the same model specifications and analytic approach were used. Specifically, linear marginal models were conducted with an optimal covariance structure chosen based on likelihood tests and model simplicity parameters. Expectancy condition (Expect CBD, Expect CBD-free) and Time (Anticipation, Stress, Recovery) were entered as repeated factors, Sex (male, female) as a fixed factor, with Respiration Rate and Baseline HRV or HR as covariates. Effects of interest included main effects of Expectancy, Time, and Sex, as well as Time by Expectancy, Sex by Time, and Sex by Time by Expectancy interactions. Post-hoc pairwise comparisons were used to probe any identified significant main effects and interactions. The results from these analyses, including all model coefficients and corresponding EMMs and SEs are reported within Supplemental Tables 5.1-5.3 and Figures 5.1 and 5.2. The *p*-values reported in text represent those related to the post-hoc pairwise comparisons.

Briefly, for HR, a main effect of Time was identified, such that HR increased from anticipation to stress (p=.002), then decreased from stress to recovery (p<.001), indicative of a significant stress response. No overall main effect of Expectancy or Sex were identified. A significant interaction between Sex and Expectancy was identified, such that opposite patterns of HR were observed within each expectancy condition (collapsed across all post-administration timepoints) according to sex. Among males, HR

was significantly lower in the CBD expectancy condition relative to the CBD-free expectancy condition (p=.024). However, among females, HR was significantly higher in the CBD expectancy condition relative to the CBD-free expectancy condition (p=.006). There were no other significant interactions involving Time, Sex, and Expectancy for HR.

For HRV, a main effect of Time was identified, such that HRV decreased significantly from Anticipation to Stress (p=.002) and increased significantly from Stress to Recovery (p<.001), consistent with a stress response. No other main effects of Expectancy or Sex, or any interactions involving Time, Sex, and Expectancy were observed for HRV.

Supplemental Table 5.1. Coefficients from linear marginal model analyses examining the impact of Time, Expectancy, and Sex on heart rate and heart rate variability.

Dependent variable: Heart Rate			
Effect	**df**	**F-value**	***p*-value**
Time	**2, 60.1**	**76.993**	**<.001**
Expectancy	1, 47.5	.353	.555
Sex	1, 33.1	.088	.768
Time*Expectancy	2, 38.7	.641	.532
Time*Sex	2, 57.1	1.548	.222
Sex*Expectancy	**1, 48.7**	**13.576**	**<.001**
Time*Expectancy*Sex	2, 38.4	.396	.676
Covariate			
Baseline Heart Rate	**1, 81.9**	**30.061**	**<.001**
EDR	**1, 181.9**	**13.913**	**<.001**
Dependent variable: Heart Rate Variability (RMSSD)			
Effect	**df**	**F-value**	***p*-value**
Time	**2, 152.8**	**34.822**	**<.001**
Expectancy	1, 159.6	.429	.513
Sex	1, 36.1	1.176	.285
Time*Expectancy	2, 150.6	1.890	.155
Time*Sex	2, 150.4	.037	.964
Sex*Expectancy	1, 161.8	.488	.486
Time*Expectancy*Sex	2, 150.6	.231	.794
Covariate			
Baseline RMSSD	**1, 74.6**	**56.620**	**<.001**
EDR	**1, 185.9**	**14.974**	**<.001**

Note. Covariates included in each model include ECG-derived respiration rate (EDR) and baseline values.
Time (Anticipation, Stress, Recovery); Expectancy (Expect CBD, Expect CBD-free); Sex (Female, Male).
RMSSD: Root mean square of successive differences.
Bolded coefficients indicate statistical significance ($p<.05$).

Supplemental Table 5.2. Estimated marginal mean (standard error) values, and 95% confidence intervals from linear marginal model analysis examining the impact of Time, Expectancy, and Sex on heart rate.

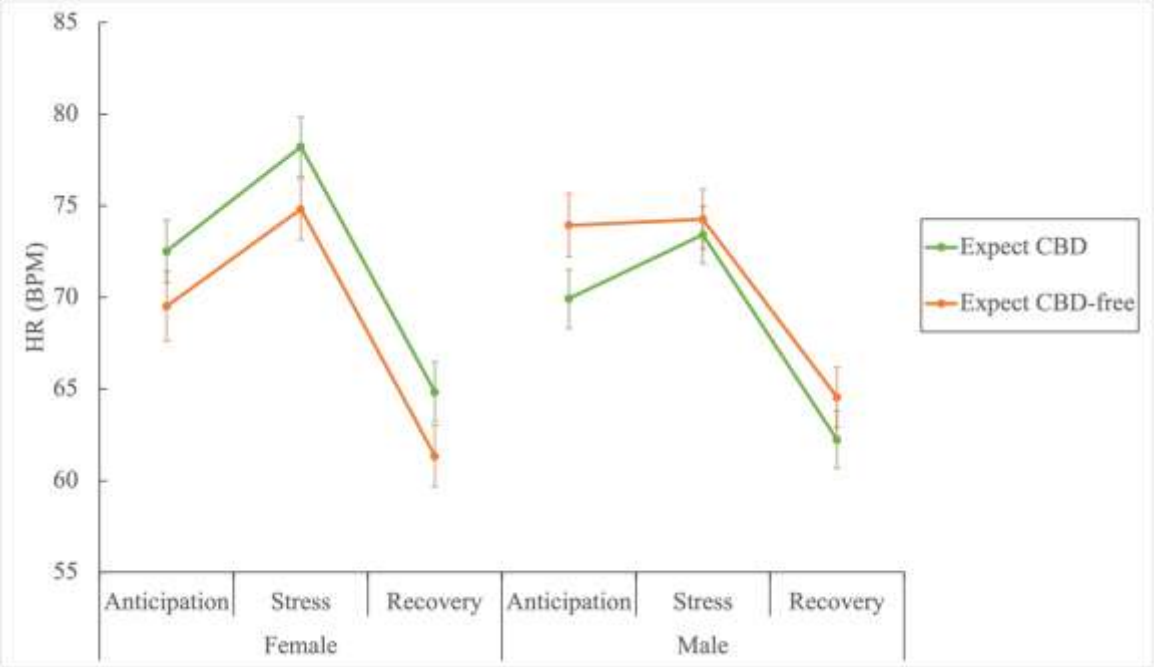
Effect of interest				**Heart Rate**	
				EMM (SE)	**95% CI**
Sex	Female			70.21 (1.17)	67.83-72.59
	Male			69.72 (1.15)	67.38-72.05
Expectancy	Expect CBD			70.19 (.87)	68.43-71.95
	Expect CBD-free			69.74 (.92)	67.90-71.58
Time	Anticipation			71.47 (1.05)	69.38-73.56
	Stress			75.18 (.99)	73.20-77.17
	Recovery			63.24 (.99)	61.27-65.21
Expectancy*Time	Expect CBD	Anticipation		71.21 (1.16)	68.91-73.51
		Stress		75.83 (1.12)	73.61-78.04
		Recovery		63.53 (1.11)	61.33-65.74
	Expect CBD-free	Anticipation		71.73 (1.30)	69.16-74.92
		Stress		74.54 (1.17)	72.22-76.87
		Recovery		62.95 (1.16)	60.64-65.25
Sex*Time	Female	Anticipation		71.02 (1.52)	67.99-74.04
		Stress		76.53 (1.42)	73.70-79.36
		Recovery		63.09 (1.43)	60.24-65.94
	Male	Anticipation		71.92 (1.44)	69.05-74.80
		Stress		73.84 (1.40)	71.05-76.63
		Recovery		63.39 (1.39)	60.61-66.17
Sex*Expectancy* Time	Expect CBD	Anticipation	Female	72.52 (1.71)	69.12-75.90
			Male	69.92 (1.60)	66.75-73.09
		Stress	Female	78.23 (1.62)	75.02-81.44
			Male	73.42 (1.56)	70.32-76.51
		Recovery	Female	64.84 (1.62)	61.62-68.05
			Male	62.23 (1.56)	59.14-65.32
	Expect CBD-free	Anticipation	Female	69.52 (1.91)	65.74-73.31
			Male	73.93 (1.73)	70.50-77.36
		Stress	Female	74.82 (1.67)	71.52-78.12
			Male	74.27 (1.64)	71.01-77.52
		Recovery	Female	61.34 (1.67)	58.03-64.66
			Male	64.55 (1.63)	61.32-67.78

Note. Covariates included ECG-derived respiration rate (EDR) and baseline heart rate. EMM: Estimated marginal mean; SE: Standard error; CI: Confidence interval.

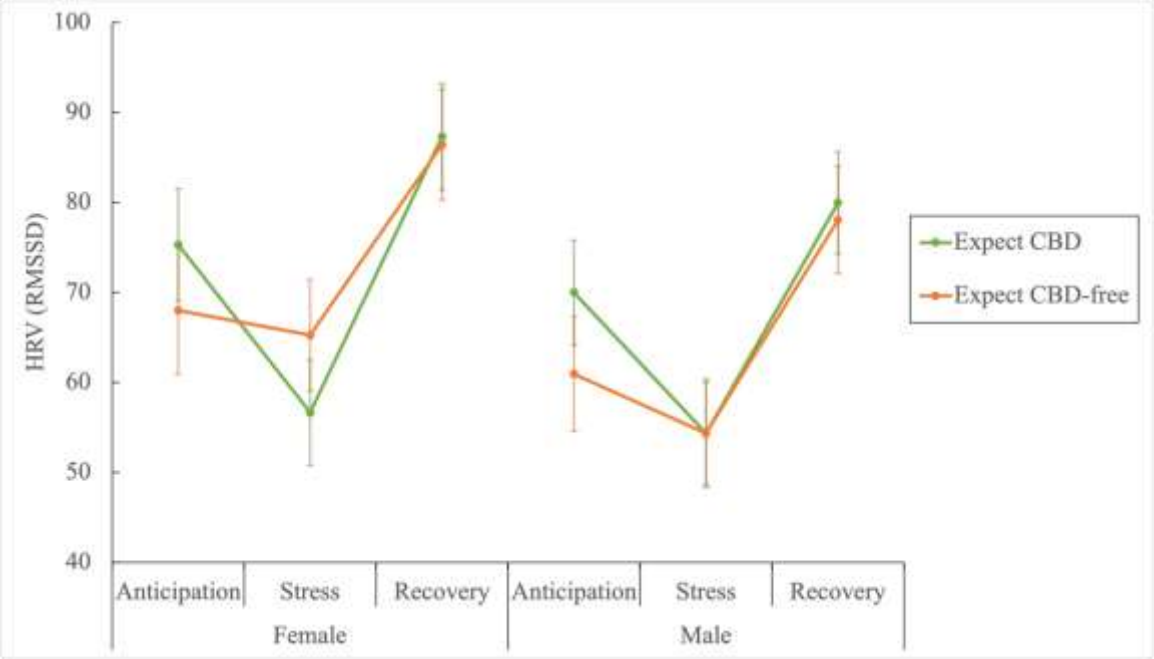
Supplemental Table 5.3. Estimated marginal mean (standard error) values, and 95% confidence intervals from linear marginal model analysis examining the impact of Time, Expectancy, and Sex on heart rate variability.

Effect of interest				**Heart Rate Variability (RMSSD)**	
				EMM (SE)	**95% CI**
Sex	Female			73.16 (4.55)	63.98-82.35
	Male			66.27 (4.42)	57.29-75.26
Expectancy	Expect CBD			70.59 (3.45)	63.84-77.34
	Expect CBD-free			68.85 (3.51)	61.81-75.88
Time	Anticipation			68.56 (3.82)	60.95-76.16
	Stress			57.64 (3.62)	50.39-64.88
	Recovery			82.96 (3.59)	75.78-90.14
Expectancy*Time	Expect CBD	Anticipation		72.64 (4.27)	64.18-81.11
		Stress		55.48 (4.11)	47.32-63.63
		Recovery		83.65 (4.08)	75.54-91.77
	Expect CBD-free	Anticipation		64.47 (4.77)	55.04-73.90
		Stress		59.80 (4.33)	51.21-68.39
		Recovery		82.27 (4.28)	73.78-90.75
Sex*Time	Female	Anticipation		71.66 (5.54)	60.61-82.70
		Stress		60.95 (5.14)	50.67-71.23
		Recovery		86.88 (5.15)	76.58-97.17
	Male	Anticipation		65.46 (5.19)	55.09-75.83
		Stress		54.32 (5.06)	44.20-64.45
		Recovery		79.04 (5.02)	68.99-89.09
Sex*Expectancy* Time	Expect CBD	Anticipation	Female	75.30 (6.24)	62.94-87.67
			Male	69.98 (5.80)	58.48-81.50
		Stress	Female	56.65 (5.88)	44.98-68.33
			Male	54.30 (5.70)	42.99-65.60
		Recovery	Female	87.32 (5.88)	75.65-98.99
			Male	79.99 (5.67)	68.72-91.27
	Expect CBD-free	Anticipation	Female	68.01 (7.08)	54.00-82.01
			Male	60.93 (6.37)	48.32-73.54
		Stress	Female	65.25 (6.18)	52.99-77.51
			Male	54.35 (6.03)	42.38-66.32
		Recovery	Female	86.44 (6.16)	74.24-98.65
			Male	78.09 (5.97)	66.24-89.93

Note. Covariates included ECG-derived respiration rate (EDR) and baseline heart rate variability.
RMSSD: Root mean square of successive differences; EMM: Estimated marginal mean; SE: Standard error; CI: Confidence interval.



Supplemental Figure 5.1. Line graph depicting a three-way interaction between Sex (male, female), Time (Anticipation, Stress, Recovery), and Expectancy condition (Expect CBD, Expect CBD-free) on HR (BPM). Points represent estimated marginal mean (EMM) values, and error bars are associated standard error (SE) values from the Linear Marginal Model analysis. A significant main effect of Time, as well as an interaction between Sex by Expectancy was observed. Values are adjusted for T1 HR and ECG-derived respiration rate as covariates.
HR: Heart Rate; BMP: Beats Per Minute.



Supplemental Figure 5.2. Line graph depicting a three-way interaction between Sex (male, female), Time (Anticipation, Stress, Recovery), and Expectancy condition (Expect CBD, Expect CBD-free) on HRV (RMSSD). Points represent estimated marginal mean (EMM) values, and error bars are associated standard error (SE) values from the Linear Marginal Model analysis. A significant main effect of Time was observed. Values are adjusted for T1 HRV and ECG-derived respiration rate as covariates.
HRV: Heart Rate Variability; RMSSD: Root mean square of successive differences.

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Name of Author: Ms. Toni Spinella
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APPENDIX G. CHAPTER 6 STUDY 2B SUPPLEMENTAL FILES

Supplemental Table 6.1. Estimated marginal mean (standard error) values, and 95% confidence intervals from linear marginal model analysis (Model 2- excluding males) examining the impact of Time, Expectancy, and Hormonal Contraceptive status on mean Cortisol (ug/dL) values, with Baseline Cortisol serving as a covariate.

Effect of interest				**Cortisol (ug/dL)**	
				EMM (SE)	**95% CI**
Hormonal Contraceptive (HC)	Not using hormonal contraceptives (HC-)			.219 (.016)	.186-.252
	Using hormonal contraceptives (HC+)			.146 (.021)	102.-.190
Expectancy	Expect CBD			.172 (.019)	.132-.211
	Expect CBD-free			.193 (.017)	.158-.227
Time	T2			.099 (.008)	.082-.117
	T3			.137 (.008)	.121-.154
	T4			.238 (.024)	.188-.289
	T5			.254 (.034)	.182-.325
Expectancy* Time	Expect CBD	T2		.091 (.013)	.063-.118
		T3		.129 (.010)	.108-.150
		T4		.225 (.025)	.173-.276
		T5		.242 (.041)	.154-.330
	Expect CBD-free	T2		.108 (.006)	.094-.121
		T3		.146 (.009)	.127-.165
		T4		.252 (.031)	.188-.316
		T5		.266 (.041)	.181-.351
HC*Time	HC-	T2		.092 (.009)	.072-.111
		T3		.155 (.008)	.138-.173
		T4		.301 (.027)	.246-.357
		T5		.327 (.038)	.247-.407
	HC+	T2		.107 (.013)	.080-.134
		T3		.119 (.011)	.096-.143
		T4		.176 (.036)	.100-.251
		T5		.181 (.054)	.069-.294
HC*Expectancy *Time	Expect CBD	T2	HC-	.085 (.015)	.054-.117
			HC+	.096 (.020)	.154-.138
		T3	HC-	.149 (.011)	.127-.171
			HC+	.108 (.014)	.080-.137
		T4	HC-	.276 (.027)	.220-.333
			HC+	.173 (.034)	.102-.244
		T5	HC-	.311 (.047)	.212-.410
			HC+	.174 (.063)	.041-.307
	Expect CBD-free	T2	HC-	.098 (.008)	.082-.114
			HC+	.117 (.010)	.095-.139
		T3	HC-	.162 (.010)	.140-.183
			HC+	.130 (.014)	.101-.160

Effect of interest			Cortisol (ug/dL)	
			EMM (SE)	**95% CI**
	T4	HC-	.326 (.035)	.254-.398
		HC+	.178 (.049)	.077-.280
	T5	HC-	.343 (.046)	.247-.439
		HC+	.189 (.067)	.050-.328

EMM: Estimated marginal mean; SE: Standard error; CI: Confidence interval.
T2: post-absorption (PA); T3: post-stress (0-PS); T4: 10-minutes post-stress (10-PS); T5: 30-minutes post-stress (30-PS).

Supplemental Table 6.2. Estimated marginal mean (standard error) values, and 95% confidence intervals from linear marginal model analysis (Model 3- excluding females using hormonal contraceptives) examining the impact of Time, Expectancy, and Sex on mean Cortisol (ug/dL) values, with Baseline Cortisol serving as a covariate.

Effect of interest				**Cortisol (ug/dL)**	
				EMM (SE)	**95% CI**
Sex	Female			.209 (.021)	.167-.251
	Male			.262 (.018)	.225-.298
Expectancy	Expect CBD			.224 (.016)	.190-.257
	Expect CBD-free			.247 (.016)	.213-.280
Time	T2			.102 (.008)	.085-.120
	T3			.166 (.010)	.146-.185
	T4			.334 (.026)	.282-.386
	T5			.339 (.029)	.281-.398
Expectancy*Time	Expect CBD	T2		.096 (.012)	.071-.120
		T3		.148 (.010)	.128-.169
		T4		.306 (.026)	.254-.358
		T5		.345 (.045)	.253-.437
	Expect CBD-free	T2		.109 (.008)	.093-.125
		T3		.183 (.012)	.158-.207
		T4		.361 (.030)	.300-.423
		T5		.334 (.035)	.261-.407
Sex*Time	Female	T2		.090 (.013)	.065-.116
		T3		.150 (.014)	.120-.179
		T4		.294 (.038)	.216-.372
		T5		.302 (.044)	.213-.391
	Male	T2		.115 (.011)	.092-.138
		T3		.181 (.013)	.154-.208
		T4		.374 (.034)	.305-.443
		T5		.376 (.037)	.301-.451
Sex*Expectancy* Time	Expect CBD	T2	Female	.082 (.018)	.044-.119
			Male	.110 (.016)	.077-.142
		T3	Female	.141 (.015)	.110-.172
			Male	.156 (.013)	.129-.183
		T4	Female	.265 (.039)	.186-.344
			Male	.348 (.033)	.281-.416
		T5	Female	.267 (.071)	.123-.411
			Male	.422 (.056)	.308-.537
	Expect CBD-free	T2	Female	.099 (.011)	.075-.122
			Male	.120 (.010)	.099-.141
		T3	Female	.159 (.018)	.123-.195
			Male	.206 (.016)	.173-.239
		T4	Female	.323 (.045)	.231-.414
			Male	.400 (.041)	.317-.482
		T5	Female	.338 (.052)	.230-.445

Effect of interest		Cortisol (ug/dL)	
		EMM (SE)	**95% CI**
	Male	.330 (.048)	.232-.429

EMM: Estimated marginal mean; SE: Standard error; CI: Confidence interval.
T2: post-absorption (PA); T3: post-stress (0-PS); T4 : 10-minutes post-stress (10-PS); T5: 30-minutes post-stress (30-PS).

APPENDIX H. INTEGRATING DISSERTATION FINDINGS

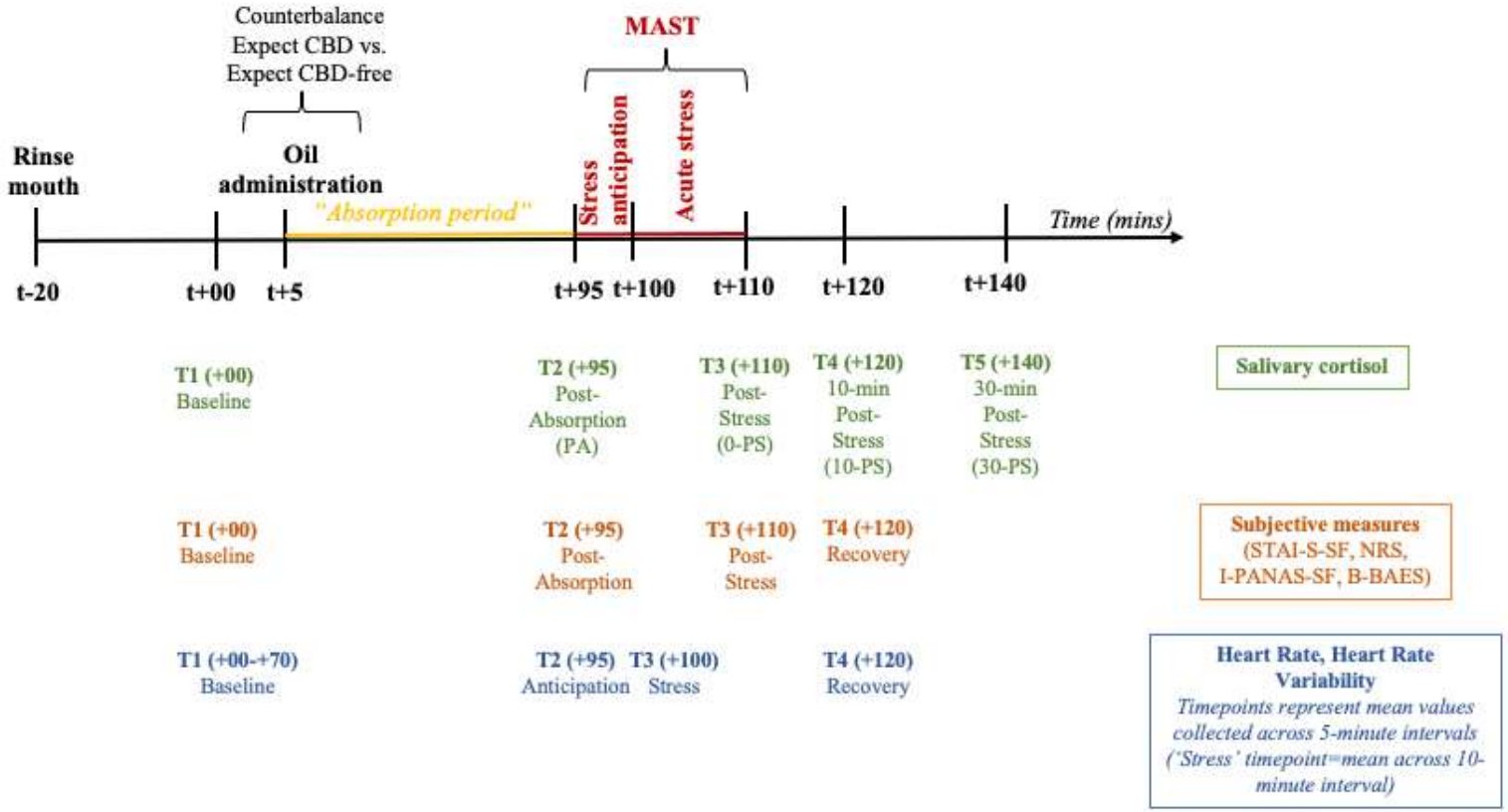

Figure 7.1. Protocol timeline integrating subjective and physiological timepoints from Study 2a and 2b.
MAST: Maastricht Acute Stress Test; STAI-S-SF: State-Trait Anxiety Inventory-State version-Short Form; NRS: Numeric Rating Scale; I-PANAS-SF: International Positive and Negative Affect Schedule-Short Form; B-BAES: Brief-Biphasic Alcohol Effects Scale.