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FREQUENCY OF MARIJUANA USE AND ANXIOUS AND FEARFUL RESPONDING

TO BODILY SENSATIONS: A LABORATORY TEST

A Dissertation Presented

by

Marcel Oliver Bonn-Miller

to

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements
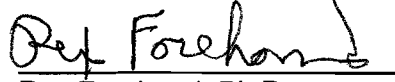for the Degree of Doctor of Philosophy
Specializing in Psychology

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Accepted by the Faculty of the Graduate College, The University of Vermont, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, specializing in Clinical Psychology.

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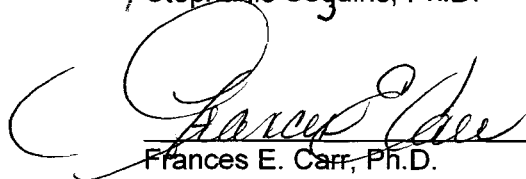
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Abstract

The current investigation examined the relation between frequency of marijuana use (no history of use, regular low-frequency use, and regular high-frequency use) and anxious and fearful responding to a biological challenge paradigm. Ninety-six participants (m_{age} = 22.60, SD = 9.01, 45 females) were recruited from the greater Burlington, Vermont community and matched on gender, alcohol, and tobacco use. Primary results indicated that frequency of marijuana use was not significantly related to post-challenge panic attack symptoms, interest in returning for another challenge (behavioral avoidance), or changes in anxiety focused on bodily sensations, heart rate, or respiration rate (breaths per minute). Post hoc analyses suggested that, among current users of marijuana, those who were dependent on marijuana had greater panic attack symptoms post-challenge than those who abused marijuana. Further analyses indicated that, among current marijuana users, those who used the drug for coping reasons were significantly more likely to exhibit greater avoidance post-challenge as well as greater panic attack symptoms post-challenge than those who primarily used for other motives. Additionally, greater frequency of marijuana use among current users was related to less avoidance post-challenge. Findings of the investigation are discussed in relation to clarifying which factors of marijuana use may play a role in anxious and fearful responding to bodily sensations.

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There are numerous individuals who I would like to thank for their help and guidance not only on this project, but throughout my graduate training. I'd like to begin by thanking my committee for their time and expertise in guiding me through this process. I would also like to thank Dr. Michael Zvolensky, for his support and guidance throughout my entire clinical training. He has not only been an outstanding mentor, but one of my closest friends. I would also like to thank my father for pushing me to work and think critically about the world and my grandmother, Dr. Sara Miller, for supporting me regardless of my decisions. The current and past members of the Anxiety and Health Research Laboratory (AHRL) cannot be thanked enough. They have been and will continue to be my closest family. In particular, from the AHRL, I would like to especially thank Dr. Amit Bernstein and Erin Marshall who assisted in the data collection for this project. I would also like to thank Will Reese, for always listening to me and constantly providing some levity to my years as a graduate student. Finally, I would like to thank Dr. Laura McKee for being my co-pilot throughout graduate school.

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Introduction

The primary goal of the present investigation was to examine the effects of varying degrees of marijuana use in relation to panic-relevant emotional responding to a biological challenge procedure.

Marijuana: An Overview of Nature and Use Parameters

Marijuana (also referred to as *cannabis*) is a drug that is derived from the flowers, stems, leaves and seeds of the hemp plant (*Cannabis sativa*). This drug can be consumed via smoking (e.g. hand rolled cigarettes, water pipes, non-water pipes), or ingestion (e.g. mixed into foods or used in the process of brewing tea). Marijuana shares some qualities with tobacco in that it is principally comprised of plant material, often is used via smoking routes (e.g., pipes, joints), and contains a myriad of chemical compounds. Unlike tobacco, however, the active agents in marijuana are *cannabinoids* (unique to the marijuana plant). There are at least 60 different cannabinoids in marijuana, and, it is striking that the pharmacokinetics of the vast majority of these compounds are largely unknown, meaning that there is literally no scientific data about the vast majority of them (Ashton, 2001). The most well-known, and perhaps (historically) important, cannabinoid is *tetrahydrocannabinol* (THC). THC is believed to be the most potent psychoactive agent in the cannabioid plant (Tanda & Goldberg, 2003).

The technology of growing and distributing marijuana has become a full-fledged and sophisticated industry (Eck & Gersh, 2000; O'Dea, Murphy, & Balzer, 1997). The THC content of plants from various sources and strains varies dramatically (O'Dea et al., 1997). With a focus on improved plant breeding and improved growing techniques, the THC content of marijuana has increased dramatically in a very short period of time. As one illustrative example, THC content from a typical marijuana cigarette (joint) in the

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1960's was 10 mg, whereas estimates suggest it currently is around 1 g (or 150 to 200 mg; Ashton, 2001). One potential large-scale consequence of this increased level of potency is that much of the scientific database on marijuana, beginning to take shape in the 1970's and 1980's, is not likely to be necessarily fully generalizable to current marijuana use and its correlates. Yet, given that marijuana effects are dose dependent (greater amount or potency yields greater effect; Tanda & Goldberg, 2003), it is of no small public health concern that greater "doses" of the drug are now more readily available in the current time period. As one illustrative, albeit hypothetical, example, one may theorize that due to greater THC potency, there is the possibility that more individuals, especially those that are "vulnerable" in some respect, may be more apt to develop severe problems with marijuana now than in the past.

Pharmacokinetics: a brief synopsis. Only since the discovery of a cannabinoid receptor within the brain in the late 1980's have researchers been able to explicate the exact process by which THC acts on the brain. Currently, there is evidence of three potential cannabinoid receptors, only one of which is located within the brain (CB1; Tanda & Goldberg, 2003). When THC is inhaled into the body via marijuana smoking, for example, it passes into the lungs and from the lungs into the blood stream (Herkenham et al., 1990). Once in the blood, THC attaches to cannabinoid receptors, such as CB1, adding to or reducing the naturally occurring endogenous ligands for these receptors (e.g. anandamide; Devane et al., 1992). This CB1 receptor in the brain has been found to mediate both neuro-chemical and behavioral properties of these cannabinoids including such things as physical dependence and tolerance (Tanda & Goldberg, 2003). It also is noteworthy that THC and other cannabinoids move rapidly into fat and other tissues, but are only slowly released from these tissues back into the blood system

(Hunt, Jones, Herning, & Bachman, 1981); eventually, they are cleared from the body via urine and fecal matter.

  Nature of use: intoxication features. In general, marijuana is used to produce a mild, relatively short period of intoxication (being "high"). More precisely, marijuana can produce a range of psychosensory experiences including anxiety, relaxation, acute paranoia, inhibition, perceptual distortions, and so on (Johns, 2001). Periods of intoxication depend on use patterns, but tend to last for at least a few hours (Chait & Zacny, 1992; Ohlsson, Lindgren, Wahlen, Agurell, Hollister, & Gillespie, 1980; Schuckit, 1989). Marijuana intoxication also impairs cognitive and psychomotor performance with complex, demanding tasks (Hall & Solowij, 1998; Solowij, 1998). Research suggests that there is a dose dependent relationship between marijuana use and psychomotor and cognitive impairment, with higher doses being associated with more impairment for more demanding tasks (Ashton, 2001; Hall & Solowij, 1998). Although cognitive impairment for hours after using marijuana is a well replicated phenomenon in laboratory studies (Solowij, 1998), there has been debate about the permanent cognitive effects of using marijuana (Ashton, 2001). Recent work, however, suggests that individuals who have used marijuana over long periods of time demonstrate impaired performance on a variety of neuropsychological tests even when not acutely intoxicated (Hall, Solowij, & Lemon, 1994), specifically, impairment in attention, memory, and processing complex information. These negative cognitive effects appear to be present months and even years after successful cessation (Solowij, 1998). It is interesting to note here that one key interpretative caveat to this work is that it has not yet been empirically demonstrated whether these individuals have pre-existing cognitive deficits or whether such deficits developed secondary to marijuana use.

Addictive characteristics. Empirical evidence suggests that marijuana effects on mood and behavior may develop rapidly (i.e., following relatively few exposures). This type of behavioral pattern is becoming readily apparent for many drugs, including tobacco (NIDA, 2001) and cocaine (NIDA, 2004). For many individuals who use marijuana, tolerance to the drug develops, and presumably, contributes to more frequent or heavier use patterns or dosing with higher-quality ("more pure THC") forms of the drug (Hall & Solowij, 1998). Though presumed by some segments of the general public to be relatively harmless (Ashton, 1999; Lancet, 1995), marijuana actually has cardinal features of addiction similar to more "hard drugs." For example, non-human research, and more recently, a smaller human empirical data base, suggests that marijuana discontinuation among regular users produces an internally consistent withdrawal pattern (see Budney, Hughes, Moore, & Vandrey, 2004, for a review). Examples of key withdrawal symptoms include disrupted sleep, nightmares, nausea, anxiety, tension, irritability, sweating, and chills (Budney Hughes, Moore, & Novy, 2001; Budney, Moore, Vandrey, & Hughes, 2003; Budney et al., 2004; Haney, Ward, Comer, Foltin, & Fischman, 1999). Many of these withdrawal symptoms appear early after drug discontinuation (Budney et al., 2003), and some may last for weeks beyond the quit day (e.g., disrupted sleep; Budney et al., 2003, 2004). This withdrawal profile can appear relatively quickly during the course of addictive use (Budney, Higgins, Radonovich, & Novy, 2000; Copeland, Swift, Roffman, & Stephens, 2001; Stephens, Roffman, & Simpson, 1993; Stephens, Babor, Kadden, Miller & the Marijuana Treatment Project Group, 2002) and may have clinical import in terms of predicting relapse (Budney, Novy, & Hughes, 1999), although current data are not yet sophisticated enough to yield conclusions about this matter. Not surprisingly, there also is research to suggest that, similar to tobacco use, exposure to marijuana earlier in the lifespan appears to be

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related to more severe and clinically significant forms of drug use, including but not limited to marijuana, in the future (Kandel, 1975).

   Classification of marijuana problems. The current diagnostic criteria for problematic patterns of marijuana use, according to the DSM-IV, include abuse and dependence (See Table 1 and 2 for diagnostic criteria for marijuana abuse and marijuana dependence, respectively; American Psychiatric Association (APA), 1994). *Marijuana abuse* is a pattern of marijuana use that includes significant and unpleasant consequences associated with frequent marijuana use. This pattern needs to have occurred within a 12-month period. Some of the consequences associated with marijuana abuse include multiple legal problems, repeated use in physically hazardous situations, and repeated social and interpersonal problems as a result of use. What differentiates substance abuse from *dependence* is that abuse only includes harmful consequences of frequent use, rather than compulsive use, tolerance or withdrawal (APA, 1994). Although there is evidence to suggest that marijuana withdrawal symptoms exist (Budney et al., 2004), withdrawal is not currently included in the DSM-IV criteria for marijuana dependence. It is also important to note that abuse cannot be diagnosed if marijuana dependence criteria can be met. This important distinction highlights the more severe nature of marijuana dependence.

   Although historically marijuana has been a commonly used drug, there is little empirical data pertaining to the validity of distinguishing among marijuana use, abuse, and dependence; that is, the validity and reliability of distinguishing three separate "types" or "forms" of marijuana use is not well established. Moreover, for a long period of time, scholars did not uniformly endorse or support a marijuana dependence syndrome (Budney et al., 2004). Current research has partially laid these earlier questions to rest in that heavy users of the drug tend to report problems controlling their use, despite noted

negative consequences, and experience withdrawal and other adverse symptoms when discontinuing use (see Hall et al., 1994, for a review). In fact, the best estimates suggest that approximately 1 out of every 10 individuals who use the drug become dependent on it at some point in the future (Anthony, Warner, & Kessler, 1994), a pattern of data consistent with alcohol use problems but markedly *lower* than that found with tobacco (Anthony et al., 1994).

To date, researchers have employed standardized interviews to index marijuana diagnoses in a manner identical to those for other types of substances (e.g., alcohol, tobacco). From this perspective, a DSM-driven classification system can thus be considered "state of the art." At the same time, due to the relatively recent emerging perspective that classification of marijuana along the lines of use, abuse, and dependence is the optimal and most accurate approach (Budney et al., 2004), it has been more common historically to denote marijuana use variability by asking respondents to indicate their level of use (e.g., frequency) over a specified period of time (Day, Wagener, & Taylor, 1985). From this perspective, having participants specify the frequency, and perhaps quantity, of marijuana use also can be a most common method (Chen, Kandel, & Davies, 1997). Collectively, then, deciding upon whether a DSM-driven classificatory scheme or a more use-oriented assessment protocol is ideal depends on the specific research question being posed and the theoretical basis for it.

Negative Consequences of Various Types of Marijuana Use: A Selective Overview

There are numerous empirically-established negative consequences of various forms of marijuana use, ranging from use to dependence or no use to greater amounts of use. These negative effects are evident in biological, social, interpersonal, and more recently, psychological realms. I will now highlight negative consequences for which

research exists in an effort to distill the larger context for understanding the clinical importance of studying marijuana in relation to psychopathology.

Medical problems. Perhaps the foremost negative effect linked to various types of marijuana use is its impact on biological processes, particularly the cardiovascular and pulmonary systems. On the one hand, as would be expected, many of these effects are similar to those typically found with tobacco. On the other hand, due to the potentially greater level of carcinogenic properties of marijuana relative to tobacco (Sridhar et al., 1994), among certain subpopulations of users (e.g., those using marijuana more frequently), the negative medical effects of this drug are perhaps even more clinically noteworthy. For example, more frequent marijuana use is associated with increased risk of severe respiratory illnesses, especially chronic bronchitis (Bloom, Kaltenborn, Paoletti, Camilli, & Lebowitz, 1987). Other work has shown that when compared to (1) nonsmokers of either tobacco or marijuana and (2) tobacco smokers with no marijuana use history, lung function of those who (3) use marijuana but not tobacco regularly is significantly poorer (Fligiel, Roth, Kleerup, Barsky, Simmons, & Tashkin, 1997). There has been a series of important large-scale prospective investigations in this field of inquiry that document the negative effects of marijuana over time on pulmonary functioning (e.g., Sherrill, Krzyzanowski, Bloom, & Lebowitz, 1991; Tashkin, 1993; Tashkin, Simmons, Sherrill, & Coulson, 1997). Though the results across investigations are not fully consistent, they converge on the observation that greater duration of marijuana use is related to increased bronchitis symptoms (e.g., coughing, wheezing; Tashkin, 1993). There are also studies of the relations between marijuana and cancer. Most studies show that there is an increased risk of lung cancer among more frequent users of the drug (Caplan & Brigham, 1989). Controlled studies of these cancer-related negative effects of marijuana use, however, are largely underrepresented

in the literature. In addition to the increased risk for lung cancer, it is noteworthy that some research suggests that marijuana use may be related to impaired immune system functioning, but these investigations, again, have not been consistently replicated (Coates et al., 1990; Hollister, 1992; Kaslow et al., 1989); upon close inspection of these studies, it becomes clear that some of the inconsistencies of these investigations may be related to inaccuracies of measurement of marijuana use patterns. A similar set of issues is evident for linkages between marijuana use and impaired reproductive effects. Non-human research suggests heavier marijuana use is related to impaired reproduction capacity (Hall et al., 1994), but controlled evidence among humans is currently lacking.

Social, interpersonal, and lifestyle problems. In addition to the potential risk of a number of negative physical consequences, adverse social and lifestyle consequences (e.g. driving while using) related to certain types of marijuana use have been reported. Here, research is emerging that indicates that certain types of marijuana use have negative effects on educational attainment and work productivity. Lynskey and Hall (2000), for example, reviewed evidence suggesting that marijuana use was a contributing factor to impaired educational attainment, and others have found that marijuana use leads to reduced workplace productivity (Lehman & Simpson, 1992), as well as impaired judgment even hours after marijuana use (e.g. among airline pilots; Leirer, Yesavage, & Morrow, 1991). In all of these studies, a consistent pattern emerges: the greater the amount of use (measured in frequency of use or severity of use), the greater the impairment. The mechanisms underlying these use-related effects are as yet theoretically and empirically unspecified.

Aside from educational and occupational impairment, marijuana use also has been shown to be related to lifestyle problems. For example, one cross-sectional study found that those who are dependent on marijuana compared to those who are not

demonstrate greater levels of clinically significant impairment in life activities (e.g. work

or school performance; Stephens et al., 1993). Additionally, quantity of marijuana use

and acute intoxication have been related to general risk taking behavior and impaired

judgment. For instance, marijuana use has been linked to fatal traffic accidents and

general driving impairment (Everest, Tunbridge, & Widdop, 1989) even after statistically

controlling for the variance accounted for by alcohol use (Gjerde & Kinn, 1991). Other

work suggests that frequent or more severe marijuana use may lead to using more

severe forms of other drugs (e.g., widely publicized, but often controversial, "gateway

theories" of the developmental nature of substance use patterns; Newcombe & Bentler,

1988). One overarching limitation to nearly all work linking certain types of marijuana use

to lifestyle and interpersonal functioning and even future use of other substances is that

there is a dearth of (controlled) prospective evaluations. Thus, conclusions drawn from

extant work should be viewed conservatively and with explicit recognition of the larger

explanatory context of this body of work.

Epidemiology of Various Types of Marijuana Use

With the general background on marijuana use and its disorders provided above,

it is now necessary to briefly describe evidence pertaining to its occurrence in the

population. Here, I have divided the review of the literature into two general sections –

representative and non-representative/community-based samples – for ease of

presentation.

Representative samples. Marijuana is one of the most commonly used

recreational drugs in the world and *the* most commonly used illicit drug in the United

States (Patton, Coffey, Carlin, Degenhardt, Lynskey, & Hall, 2002, Office of Applied

Studies [SAMHSA], 2004). According to large scale, representative surveys,

approximately 40% (94 million) of Americans above the age of 12 have tried marijuana

at least once in their lifetime (SAMHSA, 2003). Recent U.S. epidemiologic data also suggest approximately 25 million people (approximately 8.6%) have used marijuana in the past year (SAMHSA, 2004); similar findings have been reported outside of the U.S. (Fergusson & Horwood, 2000; Swift, Hall, & Teesson, 2001). Moreover, over 50,000 adolescents initiate marijuana use on a yearly basis (Office of Applied Studies [SAMHSA], 2002), and over 35% of current marijuana users (up from 30% ten years ago) meet criteria for marijuana abuse or dependence (Compton, Grant, Colliver, Glantz, & Stinson, 2004). In 2002, it was estimated that the prevalence of marijuana abuse in the past year was 1.1% in the general population, while the prevalence for dependence was 0.4% (Compton et al, 2004). Though I could not locate estimates of lifetime rates of marijuana abuse, 4.2% of people in the United States have been diagnosed as marijuana dependent in their lifetime (Anthony et al., 1994). Empirical reports suggest that marijuana use is highest among young adults (Ferguson, Horwood, & Swain-Campbell, 2002; NIDA, 1997) and may be on the rise among this particular segment of the population (Ogborne & Smart, 2000; Webb, Ashton, Kelly, & Kamali, 1996).

Non-representative/community samples. Of special relevance to the present study, many community studies (i.e., investigations that have not used representative sampling methods for the population as a whole) have examined prevalence rates of marijuana use among different samples suffering from a variety of medical and psychological problems. For example, studies have found that among those seeking treatment for psychosis, approximately 23% currently use marijuana with about half "misusing"[1] the drug (Green, Young, & Kavanagh, 2005). Another community-based study found that approximately 16% of those with spinal cord injury used marijuana (Young, Rintala, Rossi, Hart, & Fuhrer, 1995). Other work suggests that among those seeking residential drug treatment, marijuana use accounts for as much as 25% of the

primary drug problems (Didcott, Flaherty, & Muir, 1988). Yet another study has identified that, among adolescents seeking outpatient services for marijuana abuse or dependence, approximately 38% report suffering from depression and 29% report acute levels of anxiety (Diamond, Panichelli-Mindel, Shera, Dennis, Tims, & Ungemack, 2006). These sources of community data suggest marijuana use (1) may be overrepresented among certain "vulnerable" populations and (2) is a "serious" drug problem (a primary clinical concern). Unfortunately, to the best of my knowledge, there is no empirical work currently available that has addressed the prevalence of marijuana use and its disorders among treatment-seeking, anxiety-disordered samples.

Collectively, there are a variety of empirical reports that suggest that marijuana use, abuse, and dependence are among the most common substance use problems in the world. Moreover, there is emerging evidence that indicates psychiatric populations may be especially "at risk" for marijuana use and perhaps abuse and dependence (Isaac, Isaac, & Holloway, 2005). Though the above-reviewed literature does not speak to the link between marijuana and specific psychiatric disorders, it does raise questions as to whether marijuana would have higher rates of comorbidity with some disorders and not others. In an attempt to answer this question, given this background, I now introduce the constructs of anxiety and panic attacks, and then discuss their relevance to marijuana use and its disorders.

Anxiety-related Constructs: Conceptual Background and Operational Definitions

The main aim of the present study is to explore whether more frequent marijuana use is related to anxiety focused on bodily sensations and panic attacks using a laboratory paradigm. To understand why this research is being studied, an explication of contemporary conceptualizations of "anxiety" and "panic" are needed. This discussion of anxiety constructs is especially important to the present study as a central

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methodological shortcoming of the majority of work related to anxiety and marijuana associations has been poor conceptualization and measurement of anxiety variables.

Scholars have historically debated and intellectually struggled with conceptualization of emotional states. Not surprisingly, perhaps, there are numerous theories as to how to best describe emotional states (Izard, 1992; Ekman, 1992; Lang, 1994). These debates about the nature of emotion in general have been especially apparent in the study of panic attacks and distinguishing such events from other anxiety states like fear and worry. From the outset, it is important to note that there is no one "ultimate" definition of emotion; meaning, researchers from various theoretical backgrounds may operationalize these constructs somewhat differently based upon varying conceptual frameworks. However, there is nonetheless a growing consensus that emotional states have numerous "parts" that are systematically coordinated to respond (often automatically) to specific eliciting cues or stimuli.

For the purposes of the present study, I will build from integrative types of accounts of emotion, such as the work of Levenson (1994), Ekman (1992), and Fridja (1988). These theorists posit that emotions are biologically selected reactions that coordinate adaptive responding to environmental events and challenges (Fridja, 1988). Thus, specific emotional states like fear, sadness, or anger presumably "coordinate" a different (specific) set of responses to particular eliciting cues, and by extension, serve a unique function.[2] As emotions presumably serve unique functions, they naturally experientially possess an imperative quality; that is, they "prioritize" responding and can disrupt ongoing behavioral responses. Emotions, unlike mood states (prolonged affective states), tend to occur abruptly, persist for short periods of time, and involve more marked change across systems (biological, cognitive, and behavioral; Lang, Rice, & Sternbach, 1972). The abrupt nature of emotional states often means that they can

operate, especially *early* in the generative process, beyond conscious awareness (Lang, 1994). At the same time, emotion response tendencies can be modulated to varying degrees (e.g., enhanced, diminished) – an area of work often referred to as *emotion regulation* (Izard, 1990) – and one that may be central to self-regulation models of substance use and its disorders (Zvolensky, Bernstein, Marshall, & Feldner, 2006).

In contemporary work, "anxiety states" are typically viewed as multidimensional emotional processes that can be conceptually understood according to a "three channel response system" (sometimes referred to as a "triple-response mode" or "three-response mode") that includes physiological, cognitive, and overt behaviors (Lang, 1994). Physiological responses associated with anxiety involve a variety of bodily systems, and lead to such changes as increased heart rate, sweating, muscle tension, and respiration. Cognitive responses include processes such as thoughts, beliefs, and memories. Because it is impossible to directly observe thoughts, and often difficult to assess physiological processes, an individual's self-report of these events is frequently necessary for assessment. Overt anxious behavior most often involves avoidance of situations and/or objects, or may include prematurely leaving an event (i.e., "escaping").

It should be noted that channels of "anxiety states" (i.e., physiological, cognitive, and motor behavior) often are *independent* of one another (Rachman & Loptaka, 1986). As an example, a woman who abruptly experiences heart palpitations and feelings of impending doom associated with panic while in a movie theater may <u>not</u> verbally report a panic attack. Yet, she may leave the immediate situation (i.e., "escape"), if possible, and may be more likely to avoid such situations in the future. In this case, anxious physiological and overt behavioral responses are evident, even though verbal reports of anxiety are not present. Thus, there is often *discordance* among these response channels, and just because a person does not say, "I feel anxious," at any one time point

does not necessarily mean that he or she is not having problems with anxiety. In a similar way, there often is response *desynchrony* (Rachman & Loptaka, 1986), whereby the relation between two behavior channels responds to treatment at dissimilar rates over time. Often, one channel is expected to change first, and the others improve more slowly, although the exact sequence may vary by type of anxiety and setting events (Lang, 1994).

There are many qualitatively distinct states that are categorized under the general label of "anxiety." Although the scope of the present study does not permit a detailed description of all such states, it is clear that these negative emotional experiences overlap considerably. That is, all anxiety states are characterized by the aforementioned three channels of behavior, yet they differ in regard to core parameters of response such as duration and magnitude, as well as type of environmental cues associated with the specific form of anxiety being studied. From this perspective, many scholars suggest that sophisticated measurement of anxiety states requires (optimally) a multimethod approach whereby different response channels can be measured and understood in relation to one another (Lang, 1994). For the purposes of the present study, I drew on integrative perspectives of anxiety-related states to operationalize my key emotion constructs. I will now operationalize and discuss the constructs of anxiety, fear, and panic to provide an organizational basis to the present study.

Anxiety is conceptualized as a primarily cognitive-affective state characterized by cognitive shifts that focus attention on *approaching* threat and danger (Craske, 1999). It is thus best conceptualized as a state of "active mobilization and ongoing vigilance" and can be contrasted to that of worry, whereby the individual is in a state of "preparation and readiness." The future-oriented nature of anxiety for approaching sources of threat typically means that individuals show less dramatic signs of change in physiological

systems compared to fearful or panicked states, and greater levels of more elaborate

cognitive-based responses (e.g., "This is a dangerous situation and I need to be vigilant

in case I need to respond;" Lang, 1994). Anxiety also tends to be longer in duration (e.g.,

lasting for hours at times at the extreme) compared to fear or panic states, which last on

the order of 10 minutes or less (Lang, 1994). In this sense, anxiety can be considered

more of a mood state than a specific emotional episode (Lang, 1994).

      Though there has been debate about the distinctions between fear and panic

states, most scholars now theorize that these two states are more similar than different

(Craske, 1999). Fear and panic states both involve active fight-flight-freeze responses

and are characterized by a high degree of physiological activation (e.g., heart rate

change), threat-oriented behavioral responses (e.g., escape), and low-level cognition

(e.g., "I need to flee this situation now"). Thus, fear and panic states are oriented

towards *imminent* threat (cf. approaching or potential threat; Gray & McNaughton, 1996).

Notwithstanding these similarities between fear and panic, one domain in which they

sometimes differ is in regard to the identification of the source of threat (Craske, 1991).

Research suggests that when an individual experiences a fear state as "out of the blue,"

he or she typically refers to this experience as a "panic attack." In contrast, when a

source threat is identified, the individual is more apt to label the emotional state as "fear"

(see Norton, Cox, & Malan, 1992, for a review).

      Here, it is noteworthy to distinguish panic attacks from panic disorder. If one

suffers from a panic attack, one does not necessarily meet diagnostic criteria for panic

disorder. For one to be diagnosed with panic disorder, one must have recurrent

unexpected panic attacks followed by concern about having additional attacks, worry

about the implications of an attack, or change in behavior related to the attacks (APA,

1994). Broadly, a panic attack can be either "cued" (linked to an external stimulus) or

"uncued" (unable to be cognitively tied to an external stimulus), but must be described as "uncued" to be considered for panic disorder. *From this point forward, I will use the terms panic and fear interchangeably.*

With this background on the nature of emotion and anxiety-related constructs, I now turn to a discussion of the potential linkages between anxiety-related states and specific patterns of marijuana use.

Marijuana and Anxiety-related States: Extant Empirical Work

In general, little empirical work has examined the relation between various types of marijuana use and panic attacks. Indeed, the vast majority of investigations in this domain have centered on associations between specific types of marijuana use and depressive symptoms or problems (Chen, Wagner, & Antony, 2002; Degenhardt, Hall, & Lynskey, 2001, 2003; Green & Ritter, 2000; Kouri, Pope, Yurgelun-Todd, & Gruber, 1995; Patton et al., 2002;). Yet, anxiety and panic attacks have historically been linked – via clinical observation and case reports – to various types of marijuana use (e.g., Gale & Guenther, 1971). This work was initially stimulated by the observation that marijuana use may *acutely* promote heightened levels of anxiety symptoms and elicit panic attacks under certain conditions or among certain individuals (Hollister, 1986; Tunving, 1985). For example, when a person is intoxicated from using marijuana, they may experience acute paranoia, escalating anxiety symptoms, and perhaps a panic attack. This type of experience makes intuitive sense in that marijuana can elicit a wide range of sensory-oriented experiences, as described earlier.

At the same time, the acute effects of marijuana on anxiety and fear states may represent only one possible way in which marijuana and anxiety are linked. Indeed, drawing from models of anxiety-substance use comorbidity (Zvolensky & Bernstein, 2005; Zvolensky, Schmidt, & Stewart, 2003), there is increasing evidence that more

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regular or severe use of certain substances is related to the future risk of anxiety

problems (Zvolensky, Bernstein, Marshall et al., 2006).[3] These models and their

corresponding empirical support highlight the possibility that particular types of

marijuana use may function as a potential risk factor or marker for panic-related

problems. I will now present what is known about this body of knowledge by reviewing

studies that have been completed in this domain. For ease of presentation, I have

divided such work by methodological design and sampling approach. I will conclude this

section with a discussion of the methodological limitations of extant work.

     Cross-sectional studies: Community-recruited samples. The vast majority of

studies have explored marijuana use-anxiety associations using cross-sectional designs

and involved samples recruited through the community. In general, these investigations

have utilized assessment devices that are limited in coverage of anxiety processes or

not validated (e.g., Dannon, Lowengrub, Amiaz, Grunhaus, & Kotler, 2004; Tournier,

Sorbara, Gindre, Swendson, & Verdoux, 2003). Additionally, the findings from such work

tend to be mixed and interspersed within a larger *a priori* focus on depressive symptoms.

Due primarily to their limitations in assessment approaches for anxiety-related states,

and secondary theoretical focus, conclusions drawn from such work regarding panic are

highly suspect and therefore not reviewed in detail. That is, the data from these

investigations are highly questionable because the research designs did not employ

empirically-supported assessment devices that map theoretically onto contemporary

perspectives of anxiety constructs. Of the more recent investigations that utilize

psychometrically sound assessment devices and theoretically-driven approaches, a

number of interesting observations are becoming apparent.

     In the earliest study in this domain, Bonn-Miller, Zvolensky, Leen-Feldner,

Feldner, and Yartz (2005) evaluated the incremental validity of regular marijuana use

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and frequency of such use in relation to anxiety and depressive symptoms and perceived health among young adult tobacco smokers (n = 202). Approximately 72% of the sample were current marijuana smokers, using this drug an average of 7.6 (SD = 9.2) times per week. As expected, after controlling for theoretically-relevant smoking (cigarettes per day), alcohol use, affective and cognitive factors (i.e., negative affectivity and anxiety sensitivity), marijuana use predicted anxiety symptoms and perceived poor general health, whereas frequency of marijuana use predicted only anxiety symptoms. These findings suggest a potentially unique association (concurrent) between current marijuana use (yes/no; between group-effects) and frequency of such use (within-group effects) as being related to anxiety symptoms and worry about health status.

In a subsequent investigation, Zvolensky, Bonn-Miller, Bernstein, McLeish, Feldner, and Leen-Feldner (2006) evaluated whether anxiety sensitivity interacted with marijuana use in relation to the prediction of panic-relevant variables among young adult tobacco smokers (n = 265). Anxiety sensitivity reflects the fear of anxiety and its possible negative consequences (McNally, 2002). Approximately 73% of the sample was composed of current marijuana smokers, with 78.5% of this sub-sample using marijuana more than once per week. As expected, after covarying cigarettes per day, alcohol use, and negative affectivity, the interaction between marijuana use and anxiety sensitivity predicted anxiety symptoms and agoraphobic cognitions. Partially consistent with prediction, the interaction between frequency of marijuana use and anxiety sensitivity predicted only anxiety symptoms. There was no main effect for frequency of marijuana use. These results suggest individual differences in the fear of anxiety may moderate the association between marijuana use and frequency of such use in relation to panic-relevant variables among regular tobacco smokers.

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Buckner, Leen-Feldner, Zvolensky, and Schmidt (in press) recently replicated and extended the findings of Zvolensky, Bonn-Miller and colleagues (2006) to adolescents in the laboratory using a biological provocation paradigm. Here, they examined whether anxiety sensitivity increased anxious responding (using a three-minute voluntary hyperventilation procedure) among adolescent marijuana users. The sample consisted of 153 adolescents (46.4% female) between the ages of 11 and 17 (M_{age} = 14.92, SD = 1.49). Results indicated that anxiety sensitivity moderated the link between lifetime marijuana use frequency and both post-challenge physiological anxiety (as indexed by skin conductance) and post-challenge subjective anxiety in female adolescents (but not male adolescents) such that female adolescents with high anxiety sensitivity and more frequent marijuana use demonstrated the highest level of challenge-induced fear response. This effect remained even after controlling for relevant variables (e.g., age, trait anxiety, lifetime alcohol and cigarette use). There was no main effect for frequency of marijuana use. These data lend some further empirical support to work on marijuana-anxiety relations.

Collectively, these investigations suggest that, among community-recruited adult daily tobacco users and adolescents, marijuana use is related to panic-relevant variables.

Cross-sectional studies: Representative samples. One study examined marijuana use patterns and their relation to both anxiety and affective disorders (Degenhardt et al., 2001). Data for this study were obtained as part of a large nationwide survey, the Australian National Survey of Mental Health and Well-Being (NSMHWB). Participants were contacted using random sampling techniques (78% response rate). Participants consisted of a representative sample from the Australian general adult population. Approximately 5% of participants reported using marijuana more that 5 times

within that past year without meeting criteria for a DSM-IV marijuana use disorder. However, a remaining 0.8% and 1.5% of the participants met criteria for marijuana abuse and dependence, respectively. At a zero-order level, findings indicated that among those who met criteria for marijuana dependence, 17% also met criteria for an anxiety disorder. This finding is contrasted with only 5% of those who did not use marijuana who met criteria for an anxiety disorder. Once demographic characteristics (e.g., gender, age) as well as neuroticism and other drug use were entered into the model as covariates, this association became non-significant. Yet, because this investigation collapsed across anxiety disorders diagnoses, specific effects unique to one type of anxiety problem may have been missed (e.g., panic attacks compared to social phobia).

In the only other available epidemiological study evaluating marijuana use and panic, Zvolensky, Bernstein, Sachs-Ericsson, Schmidt, Buckner, and Bonn-Miller (2006) evaluated lifetime associations between marijuana use, abuse, and dependence and panic attacks after controlling for alcohol abuse, polysubstance use, and demographic variables. Data for this study were obtained as part of a large statewide survey, the Colorado Social Health Survey (CSHS). Participants were contacted using randomly sampled household addresses (72% response rate) and interviews took place in participants' homes. Participants consisted of a representative sample from the Colorado general adult population (n = 4,745; 52% female). The Diagnostic Interview Schedule (Robins, Helzer, Croughan, Williams, & Spitzer, 1981) was administered to obtain diagnoses. After controlling for polysubstance use, alcohol abuse, and demographic variables, lifetime history of marijuana dependence, but not use or abuse, was significantly related to an increased risk of panic attacks. Additionally, among participants reporting a lifetime history of both panic attacks and marijuana use, the age

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of onset of panic attacks ($M = 19.0$ years of age) was significantly earlier than for individuals with a lifetime panic attack history but no marijuana use ($M = 27.6$ years of age). These results suggest that lifetime marijuana dependence, but not use or abuse, is significantly associated with an increased risk of panic attacks.

The representative marijuana-panic studies add another degree of methodological rigor to the community-recruited cross-sectional studies. These investigations provide some (necessarily limited) evidence that only more severe forms of marijuana use may be related to panic attacks, although the data overall are not comprehensive. These studies both involve secondary analyses of larger data sets and were therefore not deigned, specifically, to address marijuana-panic associations. Given this context, from my perspective, there appears to be a reasonable degree of consistency across both sets of cross-sectional studies; and observed effects warrant further scholarly attention. Yet, while useful as an entry-level "benchmark" for gauging marijuana-panic relations, it should not be lost that the above cross-sectional studies cannot disentangle temporal order and therefore leave open issues related to (1) the directionality of the observed effects and (2) the time sequence of marijuana-panic associations.

Prospective studies. Whereas cross-sectional data document a concurrent association, prospective study is needed to explicate temporal time course. I am aware of only two prospective studies on marijuana use and panic variables.

In the earliest reported study, the nature of marijuana use and anxiety symptoms (as well as depressive symptoms) was examined (Brook, Rosen, & Brook, 2001). In the study, the investigators referred to anxiety and depressive symptoms collectively as "distress" variables and did not attempt to develop separate theoretical models for parsing their potential unique effects apart. This study involved a two time (1-2 year

interval) prospective study of Colombian adolescents (n = 2,226; 48.2% female) aged 12 to 17 years old. Data were examined in both directions; adolescent distress predicting later marijuana use and adolescent marijuana use predicting later distress. Findings indicated that marijuana use in early adolescence significantly predicted later anxiety symptoms (Time 2) after controlling for distress and interpersonal functioning in earlier adolescence (Time 1). These significant findings did not exist for depressive symptoms, though a trend seemed to emerge. These findings were specific to marijuana predicting later anxiety and were not apparent when anxiety symptoms were tested as a predictor of later marijuana use. These findings suggest marijuana use is systematically related to the future development of anxiety symptoms, but does not address associations with panic attacks or diagnosable anxiety conditions.

In another more recent investigation, Zvolensky, Lewinsohn, Bernstein, Schmidt, Buckner, Seeley, & Bonn-Miller (in press) prospectively evaluated marijuana use, abuse, and dependence in relation to panic attacks and panic disorder. Participants at the start of the study were adolescents (n = 1,709) with a mean age of 16.6 years (SD = 1.2) and were re-assessed 1 year later, and then again, as young adults (Mean age = 24.2 years, SD = 0.6). Results indicated that cannabis use was significantly prospectively associated with an increased odds for the development of panic attacks and panic disorder (OR = 2.5, p < .05, 95% CI = 1.2-5.3, and OR = 2.6, p < .05, 95% CI = 1.04-6.5, respectively). Similar findings also existed for cannabis dependence and panic attacks and panic disorder (OR = 3.7, p < .01, 95% CI = 1.4-9.3, OR = 4.9, p < .01, 95% CI = 1.7-14.0). Cannabis abuse, however, was not associated with a change in the odds of panic attacks or panic disorder incidence. The lack of an effect could possibly be due to measurement problems associated with marijuana abuse; namely, very few cases of abuse were noted in this study. An interpretative caveat to this investigation was that

cannabis was not found to be *incrementally* associated with the development of panic after daily cigarette smoking was controlled. These data suggest marijuana use and dependence are significantly and prospectively associated with an increased risk of panic attacks and panic disorder from adolescence through early adulthood. However, the marijuana-panic psychopathology effects do not appear stronger than the link between cigarettes and panic. No analysis was completed to evaluate the opposite scenario (marijuana contributing to panic psychopathology over and above daily cigarette use) or the effects of both forms of drug use on panic variables.

The two prospective studies on marijuana-anxiety associations are broadly, but not uniformly, consistent with the cross-sectional work reviewed earlier. There is some evidence that marijuana use (and possibly more severe or heavier forms of use) measured earlier in the time span is related to an increased risk for panic psychopathology in the future. There does not seem to be evidence that panic contributes to later development of marijuana use or its disorders, although this has received little empirical attention. These investigations are helpful to informing the extant knowledge base, but, again, are limited in scope and focus. Indeed, both studies involve secondary analysis of existing data and were thus not solely designed to address marijuana-panic associations.

Key limitations of existing work. Taken together, though there is an emerging literature on marijuana and its role in anxiety and panic processes, it is at a very early developmental stage. Thus, it is perhaps not surprising that there are notable limitations to the body of research in need of improvement from a variety of vantage points. I believe that there are at least two key methodological challenges that could be improved upon, and by extension, provide a higher-degree of scientific scrutiny to the issues at hand. Please note that this discussion focuses on two formative limitations of extant

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work and is not intended to represent a comprehensive discussion of all possible limitations of past studies.

First, each of the previous cross-sectional and prospective investigations has utilized self-report or structured interviews to index anxiety and panic states. Though this approach marks an improvement from earlier work that did not use validated instruments, it is problematic in the sense that it capitalizes on shared method variance and does not speak to the theoretically-based multidimensional nature of anxiety and fear processes. Thus, future work would benefit from including a theoretically-driven assessment of multiple aspects of anxious and fearful states. Such an approach is necessary to more accurately measure anxiety factors and to support the development of a cross-system perspective on the nature (specificity) of potential marijuana-panic associations.

Second, previous investigations addressing marijuana-panic associations have largely been field-based. There has been no laboratory study among adults. Though a natural starting point, solely relying on field-based research methodology does not permit a "real time" examination of anxiety and fearful states as they are elicited by bodily perturbation. Here, it is important to remember that even the most sophisticated real-world or prospective monitoring techniques employed in naturalistic conditions invite a range of interpretation-related errors (McNally, 1999). For example, participants may misinterpret anxiety states for panic attacks or vice versa. As a second example, participants may not be fully aware of certain anxiety states and therefore be unable to precisely identify the onset, duration, or offset of such states. To address these types of issues, the utilization of laboratory paradigms that elicit bodily sensations under controlled conditions may be a worthwhile next research step and help index the

potential merit of marijuana-panic associations with a higher degree of methodological rigor.

Overall, enhancing the methodological approach to explicating a potential marijuana-panic association is a "first step" in a larger sequence of research processes. That is, before more firm conclusions can be drawn and more advanced conceptual models of interplay between potential operative variables can be forwarded, it is necessary to ensure that there is, in fact, a relationship between certain forms of marijuana use and panic processes. Once this matter is resolved, then, researchers can evaluate other more advanced "main effect" oriented questions such as those dealing with malleability, and ultimately, integrate such work with multi-risk factor models (e.g., addressing moderating and mediating processes).

Theoretical Integration

Given the noted marijuana-panic associations, it is important to integrate past work and offer a conceptual basis as to how certain types of marijuana use would relate to panic attacks and anxious responding to bodily sensations more generally. From the outset, it is important to clarify that I am operating from a theoretical position that focuses on the potential role of certain types of marijuana use in relation to panic processes. This "risk factor approach" naturally represents only one possible pathway and there may be others worthy of further pursuit (e.g., the role of panic factors in relapse to marijuana during quit attempts).

Drawing from empirical observation, it appears – from cross-sectional and prospective designs – that heavier use or more severe forms of marijuana use are possibly more likely to show systematic relations to panic attacks and panic disorder. It is not fully clear whether frequency of marijuana use or severity of problematic types of use is the better explanatory variable for panic-relevant phenomena. Moreover, though it

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is presently empirically unclear why such types of marijuana use may relate to panic, there may be at least three possible, as of yet only theoretically postulated, pathways; these pathways should not be considered mutually exclusive.

Theoretical pathway one. Drawing from work on tobacco and panic, one pathway may be focused on repeated affect-relevant learning with aversive interoceptive cues (Zvolensky & Bernstein, 2005). Over long periods of time, heavier forms of marijuana use (e.g., dependence) can lead to increased risk of bodily sensations and aversive internal states via a number of routes, including withdrawal symptoms (Budney & Moore, 2002; Budney et al., 1999; Budney et al., 2003) and physical illness such as respiratory disturbances (Bloom et al., 1987; Fligiel et al., 1997; Tashkin, 1999). Exposure to these types of aversive stimuli may facilitate learning that internal cues can be personally harmful and anxiety-evoking (Barlow, 2002). A frequent marijuana user may experience interoceptive symptoms due to their drug use, and these symptoms may be associated with escalating anxiety.

From this type of perspective, there is a "pairing" of anxiety to bodily stimuli. For example, an individual who experiences aversive marijuana-related withdrawal symptoms may associate escalating anxiety states with internal cues. As such, they may become more sensitive and emotionally reactive to internal cues, perhaps promoting greater risk for experiencing a panic attack. Thus, more frequent or severe users of the drug would be more apt to experience panic problems. While intriguing, this model also would seemingly predict that more severe forms of marijuana use would lead to panic disorder. Extant data are not consistent with this perspective, and hence, may urge some degree of caution in using it as an exclusive conceptual guide. This model also assumes that panic onset would occur only after longer histories of use, predicting that bodily sensations related to heavier forms of use would be the mediating processes; an

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account consistent with Zvolensky and colleagues' (in press) most recent prospective investigation.

Theoretical pathway two. A second pathway may pertain to the nature of marijuana use motives among regular users of the drug. Here, it is noteworthy that among more frequent users of marijuana, drug use serves important affect regulatory functions (Bonn-Miller, Zvolensky, & Bernstein, 2007; Comeau, Stewart, & Loba, 2001). Specifically, individuals who use marijuana more frequently tend to be motivated to use the drug for affect regulation purposes (Simons, Correia, & Carey, 2000). For example, these marijuana users report using the drug to help cope with aversive emotional states like anxiety and fear (Simons et al., 2000). Although the objective mood-dampening qualities of marijuana use are not fully known, among experienced users of marijuana, available, albeit limited, laboratory work suggests that the use of the drug can, in fact, lessen acute states of anxiety (Mathew, Wilson, & Tant, 1989). Thus, for both perceived and potentially objective reasons, certain (perhaps especially emotionally vulnerable) regular users of marijuana may use the drug to cope with anxiety-related states. In the absence of other more adaptive coping strategies (e.g., not engaging in drug use, but rather, non-drug related behavior), experienced marijuana users may therefore potentially learn to rely on the drug to manage anxiety states in the short-term (i.e., proximal circumstances).

Recent marijuana-anxiety research would support such a prediction. For example, Mitchell, Zvolensky, Marshall, Bonn-Miller, and Vujanovic (2007) found marijuana used to reduce negative affect was uniquely related to a range of affective vulnerability factors (e.g., anxiety sensitivity, anxious arousal, and negative affectivity) among current marijuana users ($n = 131$ young adult marijuana users). Specifically, the motivation to smoke to reduce negative affect (coping motives) was significantly related

to anxiety sensitivity and negative affectivity; the observed significant effects were above

and beyond other theoretically-relevant factors (e.g., gender, past 30-day marijuana use,

alcohol consumption, and daily tobacco use). These findings provide support for the

possibility that motives underlying marijuana use may theoretically be involved in

shaping affective vulnerabilities and outcomes. That is, aside from drug-specific use

effects, learning to rely on drug use as a form of coping strategy may "mark" or perhaps

explain risk for affective vulnerability. This type of account would be fully consistent with

avoidance learning models of anxiety vulnerability, whereby response strategies aimed

at rigidly (consistently or in a context-insensitive fashion) eliminating or preventing

anxiety states is related to an increased risk of panic problems (see Feldner, Zvolensky,

& Leen-Feldner, 2004, for a review). More specifically, this type of perspective suggests

that there are important associations between certain marijuana use motives and negative

affective states and that such relations are not attributable to other marijuana use factors

(e.g., rate of use). Such a perspective also would be consistent with a gradient of use

effect, whereby greater potential for panic attacks would be evident among more frequent

or severe users. A possible challenge to this type of account is that it is not clear why the

effects would be specific to panic states and not other negative affective processes as well.

 Theoretical pathway three. A final pathway worthy of consideration pertains to

the social ecology of marijuana use. As described earlier, there is a wide range of

powerful effects related to marijuana use that includes changes to sensory-motor as well

as somatic processes. Thus, it is reasonable to speculate that being "high" can be

considered a potentially "challenging event" for certain types of (vulnerable) people.

From a larger developmental perspective, then, users who have negative experiences

with sensations induced from marijuana (and perhaps even panic attacks) early in the

history of their marijuana use would be likely to rapidly discontinue using the drug (Hall

et al., 1994). That is, outside of social peer-oriented pressure, it would be hard to imagine why an individual who experiences aversive sensations would continue to use marijuana after such an experience. I would indeed expect that the vast majority of these early-negative experience marijuana users would not continue using the drug.

Yet, those persons who do not experience significant anxiety or other negative consequences from marijuana use early on may be more apt to continue to use the drug. As their use continues, they are more apt to experience negative interoceptive effects (pathway one described above) and learn to use the drug for affect-regulatory reasons (pathway two). Outside of these other pathways, however, research suggests that even experienced and frequent marijuana users typically report "negative" experiences with the drug. For example, such negative experiences include states of paranoia, escalating anxiety, and aversive internal experiences more generally (Hall et al., 1994). It is not possible to know whether these "aversive internal experiences" are panic attacks per se in such studies because these studies do not assess for panic attacks. It is nonetheless interesting that many of these heavier users appear to attribute such symptoms to the situations in which they were using (e.g., social context) rather than the drug itself (Reilly, Didcott, Swift, & Hall, 1998). For example, Reilly et al. (1998) reported that among 269 long-term users of marijuana, approximately 20% reported acute negative emotion-specific effects related to the drug use. These data may indicate that even among frequent marijuana users, use of the drug under certain conditions (contexts) may be related to acute, adverse emotional experiences like panic attacks. These persons could attribute such reactions to the conditions rather than the drug use, as they have had numerous 'successful' trials in their drug use careers among other factors (e.g., presence of distracters in the specific situations). As applied to panic, this would suggest that these individuals "develop" (cued) panic attacks, but because they

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have a reason for them, they do not experience them as unexpected or unpredictable –

the sin qua non of panic psychopathology. In total, the third possible pathway may

represent problematic experiences across different contexts among frequent users of the

drug.

Summary. See Figure 1 for a graphical representation of the three pathways

identified here. While these pathways are not mutually exclusive, and may in fact be

related to a larger dynamic process of use, they do converge on a similar theme:

namely, that more frequent or severe forms of marijuana use should be related to an

increased risk of panic attacks. A prediction from such perspectives would be that,

regardless of the exact mechanism of action, more frequent or severe users of

marijuana should theoretically be at greater risk for responding with anxiety and fear to

aversive internal cues than individuals without such a history or individuals with lower-

frequency or less severe use.

Current Study

Global aim. The overarching aim of the present study was to evaluate anxious

and fearful responding to a biological challenge procedure as a function of different

levels of marijuana use among adults. This study was oriented *a priori* on a "main effect"

analysis with the primary goal of bringing a greater level of methodological rigor to the

larger marijuana-panic empirical literature. In the current study, a multimethod

assessment protocol was employed to track relevant types of emotional responding

across and between levels of analysis.

Participant categorization. I studied three separate groups of theoretical

relevance: (1) adults who have no history of marijuana use (defined as no history of

marijuana use at all; I refer to this group as "<u>no marijuana history</u>"), (2) those who

currently regularly use marijuana at relatively low rates (defined as no more than 3

occasions of use per month for the past 12 months; I refer to this group as "regular, low-frequency use"), and (3) those who are heavy users (defined as those using at least 5 times per week for the past 12 months; I refer to this group as "regular, high-frequency use") of marijuana. Please see Table 3 for a listing of the screening criteria for these groups.

This approach to participant categorization was theoretically-driven and viewed as potentially more powerful at this stage of research development than a strict DSM categorization (i.e., use, abuse, and dependence). Specifically, from the theoretical model proposed, greater frequency of use should increase the risk of bodily sensations via a number of routes (e.g., withdrawal symptoms, physical illness). It is not yet clear how these interoceptive processes are specifically related to use, abuse, and dependence criteria per se. *Thus, strictly categorizing participants on the basis of use, abuse, and dependence criteria may potentially miss a formative panicogenic mechanism(s) from the theoretically-driven perspective offered here.* As such, I conservatively opted to classify participants as a function of frequency of use, and at the same time, conduct diagnostic interviews to determine DSM criteria. Current alcohol and tobacco use, as well as gender were matched for each of the three groups prior to the challenge. Participants also were screened for major physical health problems (e.g., cardiovascular disease) prior to their inclusion in the study to ensure that groups did not differ in relation to pre-existing health problems and to prevent adverse complications that could arise from participating in the study. This is a standard approach in biological challenge research that still permits disease states that are not chronic in nature (e.g., bronchitis; Zvolensky & Eifert, 2000).

Hypotheses. Based upon the present conceptual and empirical analysis, there were a number of interrelated hypotheses for the investigation. First, in regard to self-

report of emotional distress, it was hypothesized that regular, heavy marijuana users would report greater levels of (a) post-challenge anxiety focused on bodily sensations (operationalized by post-challenge Subjective Units of Distress ratings (SUDs; Wolpe, 1958) and (b) post-challenge intensity of endorsed panic attack symptoms (operationalized by the Diagnostic Symptoms Questionnaire (DSQ); Rapee, Brown, Antony, & Barlow, 1992) compared to the other two groups, which were expected not to differ from one another. Second, in regard to avoidance responding in relation to bodily stress, it was expected that heavy marijuana users would show greater desire to avoid *future* exposure to somatic perturbation (operationalized as desire to participate in future CO_2 –based investigations, and hence, analogous to "behavioral avoidance") post-challenge than each of the other two groups. No differences were expected between the non-users and low regular users. Finally, in terms of physiological responding, it was expected that all three groups would show similar levels of respiration rate during the challenge, but that regular heavy marijuana users would show greater heart rate reactivity (operationalized as heart rate change from baseline to post-challenge) compared to the other two groups.

Collectively, these hypotheses were driven by research that has linked heavier levels of marijuana use to greater degrees of anxiety vulnerability, especially anxious arousal symptoms and panic attacks (Bonn-Miller, Zvolensky et al., 2005; Zvolensky, Bernstein, Marshall et al., 2006). These types of symptoms conceptually map on to panic vulnerability and therefore provided an initial basis for expecting the heavy marijuana using group to be more emotionally responsive to bodily sensations induced via a biological challenge.

Method

Participants

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The sample consisted of 96 participants (32 (15 female) participants per cell*;* m_{age} = 22.60, *SD* = 9.01, 45 females) who were recruited from the greater Burlington, Vermont community. Participants were recruited through the general community and university communities via newspaper ads and flyers advertising a laboratory study on 'emotion.' Overall, 95.8% of the sample was Caucasian, 1.1% identified themselves as "other," while 3.1% of participants chose not to specify their race. In terms of highest level of education completed, 2.1% did not graduate from high school, 76.0% graduated from high school, 12.5% reported partial college education, 2.1% graduated from a 2-year college, 4.2% graduated from a 4-year college, 2.1% reported partial graduate education, and 1% reported some graduate degree.

Within the sample, 46.9% of participants identified themselves as smokers; smoking an average 15.07 (*SD* = 6.85) cigarettes per day. When examined at a group level, each marijuana group contained 15 smokers. Within group 1 (no history of marijuana use), smokers reported averaging 15.60 (*SD* = 4.26) cigarettes per day, whereas smokers in group 2 (low rates of current marijuana use) reported smoking an average of 16.27 (*SD* = 9.48) cigarettes per day. In the third group (high marijuana use), smokers reported averaging 13.33 (*SD* = 5.88) cigarettes per day. See Results Section for further details.

Approximately 97% of participants reported current alcohol use, averaging between 5 and 6 drinks per occasion, 2 to 4 times per month. Regarding alcohol use problems, approximately 64% of the entire sample reported at least moderate alcohol use problems, as indexed by a score of 8 or greater on the Alcohol Use Disorders Identification Test (AUDIT; Babor, de la Fuente, Saunders, & Grant, 1992). At a group level, each group contained 31 individuals who described themselves as alcohol users. Among those with no history of marijuana use (group 1), participants reported drinking

an average of 2 to 4 times per month, with approximately 3 to 4 drinks per occasion, with

approximately 41% reporting at least moderate alcohol use problems. Those who

reported regular low rates of marijuana use (group 2) reported higher rates of alcohol

use, averaging between 5 and 6 drinks per occasion, 2 to 3 times per week, as well as

higher rates of alcohol use problems (69%). A similarly high rate of alcohol use was

observed among the regular high marijuana use group (group 3), though this group had

the highest percentage of participants reporting at least moderate alcohol use problems

(81%). See Results Section for further details.

Exclusionary criteria for the investigation included: (1) current axis I

psychopathology; (2) current use of psychotropic medication; (3) current suicidality or

homicidality; (4) current or past chronic cardiopulmonary illness (e.g., chronic obstructive

pulmonary disease; severe asthma), (5) current, acute respiratory illness (e.g.,

bronchitis), (6) seizure disorder, cardiac dysfunction, or other serious medical illness

(e.g., history of seizures, emphysema); (7) pregnancy (specific to females); and (8)

limited mental competency, inability to give informed, written consent. These

exclusionary criteria help ensure (1) the safety of participants during the challenge and

(2) the equivalence of the groups in terms of "background characteristics" that could

theoretically serve as alternative explanations to any observed effects. For example, if

individuals with current axis-I conditions were included, those in the more frequent

marijuana use group may have an overrepresentation of these conditions relative to the

other groups. Although it may have been useful to extend this exclusionary criteria

approach to other factors of interest (e.g., tobacco use and alcohol use), such an effort

would have (1) likely significantly diminished the generalizability of the present findings

and (2) been difficult to carry out from a practical perspective due to the high rates of

overlap between marijuana use and these factors. As such, I matched across groups for these others factors; please see Table 3 for a listing of each of the three groups.

The screening criteria that were employed in the present investigation have been successfully used in previous studies involving CO_2 administration (Zvolensky, Eifert, & Lejuez, 2001) and were assessed by validated medical and psychiatric history devices (please see Measures section). Upon request, all interested individuals meeting psychiatric exclusionary criteria were referred to our department clinic that is housed in the same building as our laboratory. Eligible participants were compensated monetarily for their participation. Please see the Procedure Section for further details.

Measures

Pre-experimental Interview Assessments

Structured Clinical Interview-Non-Patient Version for DSM-IV (SCID-NP). Lifetime and current prevalence of panic attacks, current marijuana abuse and dependence (with the inclusion of substance withdrawal criteria as defined by the DSM-IV for other drugs and as assessed by the SCID-NP for other drug classes), Axis I diagnoses, suicidal ideation, and medication use were determined using the SCID-NP (First, Spitzer, Gibbon, & Williams, 1995). The SCID-NP was used because subjects in the study were not identified as being a clinical population per se (i.e., recruited through the community). Adequate reliability of the Axis I SCID has been demonstrated generally (Spitzer & Williams, 1986) and in Dr. Zvolensky's laboratory, specifically, for both psychological disorders and substance use disorders (Zvolensky, Leen-Feldner et al., 2004). Demographic characteristics such as age, gender, ethnicity, marital status, and years of education also were collected using the SCID-NP.

Medical History Screening Interview (MHSI). The MHSI was used to examine (a) current or past cardiopulmonary (chronic) illness (e.g., chronic obstructive pulmonary

disease; asthma); (b) current acute respiratory illness (e.g., bronchitis); (c) possibility of being pregnant (by self-report); (d) seizure disorders; (e) current or past psychotropic medication use; (f) suicidal ideation; and/or (g) limited mental competency and the inability to give informed, written consent. These screening criteria have been successfully used in previous biological challenge research (e.g., Zvolensky, Eifert, & Lejuez, 2001) and are assessed by a validated medical history screening interview developed explicitly for this purpose (Forsyth & Eifert, 1998).

Pre-experimental Tobacco, Marijuana, and Alcohol Measures

Smoking History Questionnaire (SHQ). The SHQ is a well-established tool that includes items pertaining to smoking rate, age of onset at initiation, years of being a daily smoker, and quit history. The SHQ has been successfully used in previous studies as a descriptive measure of smoking history (Zvolensky, Schmidt et al., 2005). I used the smoking rate item from the SHQ as a primary index of "smoking exposure." The SHQ also was employed to provide a detailed descriptive analysis of the tobacco use histories more generally of participants in the present investigation.

Marijuana smoking history and pattern were assessed with the *Marijuana Smoking History Questionnaire – Version 2 (MSHQ).* The MSHQ is a self-report instrument that includes items pertaining to marijuana smoking rate (lifetime and past 30 days), quantity of marijuana smoked, age of onset at initiation, years of being a regular marijuana smoker, and other descriptive information (e.g., number of attempts to discontinue using marijuana). It was modeled after the SHQ. The MSHQ has been employed successfully in the past (Bonn-Miller et al., 2005; Zvolensky, Bonn-Miller et al., 2006). In the present investigation, the MSHQ was used to provide a detailed descriptive analysis of the marijuana smoking history characteristics of the sample.

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Motives for marijuana use were assessed with the Marijuana Motives Measure (MMM; Simons, Correia, Carey, & Borsari, 1998), a 25-item measure on which respondents indicate, on a 5-point Likert-type scale (1 = *"almost never / never"* to 5 = *"almost always / always"*), the degree to which they have smoked marijuana for a variety of possible reasons. Factor analysis of the scale indicates that it has five first-order factors entitled Coping ("To forget my worries," "To cheer me up when I am in a bad mood"), Expansion ("To know myself better," "To expand my awareness"), Conformity ("Because my friends pressure me to use marijuana," "To fit in the group I like"), Enhancement (e.g., "Because I like the feeling," "Because it's fun"), and Social motives ("Because it helps me enjoy a party," "Because it improves parties and celebrations") (Simons et al., 1998). The MMM has high levels of internal consistency for each of the five factors (range of alpha coefficients: .86 to .93) and has been successfully used in the past to tap motivation for using marijuana (Simons et al., 1998).

Alcohol Use Disorders Identification Test (AUDIT). The AUDIT is a 10-item screening measure developed by the World Health Organization to identify individuals with alcohol problems (Babor, de la Fuente, Saunders, & Grant, 1992). Most items are rated on a 5-point Likert scale from (0) never to (4) daily or almost daily. Scores range from 0-40 with a score of 8 indicating moderate alcohol use problems. Major areas of problematic drinking that are assessed include: alcohol consumption, drinking behavior (dependence), adverse psychological reactions, and alcohol-related problems. There is a large body of literature attesting to the psychometric properties of the AUDIT (e.g. Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). For example, the AUDIT has consistently demonstrated good levels of internal consistency (alpha coefficient: .81; Kokotailo, Egan, Gangnon, Brown, Mundt, & Fleming, 2004). In the present investigation, I used the frequency and quantity items of the AUDIT to index alcohol

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consumption as well as coded for history of problems with alcohol use (a secondary index of alcohol problems in addition to the SCID-NP interview data).

Laboratory Challenge Measures

Subjective Units of Distress Scale (SUDs; Wolpe, 1958*).* The SUDs was used to index pre and post experimental self-reported anxiety. Participants indicate how anxious they currently are on a scale ranging from 0 (*no anxiety*) to 100 (*extreme anxiety*). This is a well-established assessment of self-reported anxiety during laboratory provocations (e.g., Zvolensky, Lejuez, & Eifert, 1998).

Diagnostic Symptoms Questionnaire (DSQ; Rapee, Brown, Antony, & Barlow, 1992*).* The DSQ is a 16-item measure of the occurrence and intensity of DSM-IV panic symptoms. Specifically, the DSQ lists DSM-IV panic symptoms (both somatic and cognitive) and yields a composite score for mean intensity level of symptoms experienced. The mean intensity scores for the DSQ are made on a nine-point Likert type scale (0 = *not at all* to 8 = *very strongly felt*) and derived by averaging the symptoms endorsed (including zeros for those symptoms not endorsed). The DSQ has successfully been used in challenge studies to index panic symptoms in this manner (Sanderson, Rapee, & Barlow, 1989).

Behavioral Avoidance. In order to index behavioral avoidance post-challenge, participants' willingness to participate in another CO_2 administration was evaluated by a paper-and-pencil questionnaire at the end of the recovery period. This item asked participants to rate their *level* of willingness to participate in another CO_2 administration study. Specifically, at the end of the recovery phase, participants were told that other CO_2 studies would be recruiting individuals for participation within the next 2 weeks via a written statement on the questionnaire. Then, participants were asked to indicate their willingness on a 100-point Likert-style questionnaire intended to assess participants'

interest in returning for another CO_2 investigation (*0 = no desire to participate; 100 = definite desire to participate*). This type of index has been utilized successfully in the past with biological challenge paradigms, and such work has shown that this measure is related to avoidance due to fear and is not correlated with boredom or other related emotional states such as frustration (Eifert & Heffner, 2003).

Materials and Apparatus

Laboratory sessions were conducted in a 3-meter X 3-meter experimental room in the Department of Psychology at the University of Vermont. Participants sat at a desk supporting a Dell Pentium computer with color monitor, which was turned off during the entire duration of the procedure. After completing physiological hookup and providing experimental instructions (see *Procedure* for details), the experimenter ran and observed study participants from an adjacent control room containing an apparatus designed to provide participants with either room air or a mixture of 10% carbon dioxide-enriched air.

Carbon dioxide was stored in a 24-inch diameter hospital grade latex bag and delivered via 5-centimeter tubing to a positive-pressure C-pap mask worn by the participant. In addition to a one-way mirror, a video and audio monitoring system allowed the experimenter to observe all session events. It should be noted here that the risks for the CO_2 administration include temporary discomfort that may include racing heart sensations, increased breathing rate, shortness of breath, and dizziness. These effects are entirely harmless and painless; they disappear quickly when participants return to breathing normal room air. In one recent investigation, for example, a large sample of participants ($n = 125$) underwent recurrent CO_2 administration or room air (Prenoveau, Forsyth, Kelly, & Barrios, 2006). These participants were then prospectively monitored for up to 1 year. Results of this controlled investigation indicated that the percentage of people who developed subsequent panic attacks did not differ by condition. Thus, these

data indicate that CO_2 administration does not increase the risk of subsequent panic attacks in a nonclinical population, and hence, is a safe paradigm for use in research. The CO_2-inhalation was utilized as the panic-relevant challenge procedure because it can be safely employed, its parametric properties are well studied, and it can reliably produce bodily arousal and psychological symptoms relevant to panic states in nonclinical and clinical samples (Zvolensky & Eifert, 2000). Moreover, it has been safely and effectively used in previous work with adults across numerous research sites without incident for decades (e.g., Gorman et al., 2001).

A J&J Engineering I-330-C2 system was used to digitally record physiological data on-line at a sample rate of 1024 samples per second across all channels using J&J Engineering Physiolab Software. Two physiological variables were examined for the current study (Venables & Christie, 1980): respiration rate (a measure of breaths per minute), and heart rate (a measure of beats per minute). Respiration rate was obtained using a Pneumograph sensor cable with PS-2 sensors as a manipulation check. The sensors were placed across the chest and secured with a Velcro strap, allowing a measure of chest excursion during respiration. Raw electrocardiogram data were collected with disposable Ag/AgCl electrodes placed in a standard bilateral configuration on the palmar side of each wrist. Data were processed through a 1-100Hz bandpass filter designed to maximize R-wave frequency.

Procedure

Please see Figure 2 for a schematic diagram of the study procedure. Community and university-based populations were the focus of the recruitment process. Specifically, participants were recruited through newspaper advertisements and flyers that described a laboratory study on 'emotion.'

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Interested persons responding to advertisements who contacted the research team were given a detailed description of the study over the phone. After providing verbal consent, the SCID-NP (screener) was administered by a trained research assistant via telephone. Those meeting inclusionary criteria were scheduled to attend a single laboratory session. Upon arrival, participants completed a written informed consent, which indicated that the procedure involved a single 4-min 10% CO_2-enriched air presentation. Participants then completed the pre-experimental measures. Each participant was then introduced to the laboratory setting for the challenge procedure. During the session, participants sat alone in the 8-ft x 12-ft sound attenuated experimental room, which contained a computer, chair, desk, and intercom that allowed participants to communicate freely with the experimenter in the adjacent room. Participants were seated in front of a table, on which a binder with the experimental, paper-pencil self-report measures was placed. Once the electrodes were attached standardized instructions were provided, including:

> "*Following the (*10 minute*) adaptation period, we will start the experimental portion of the study which will last approximately 4 minutes. During this period you will receive several inhalations of CO_2-enriched air that may produce physical and mental sensations associated with bodily arousal. You may temporarily feel your heart racing, your palms might be sweaty, you might feel dizzy, and you might have some breathing problems.*"

The study consisted of two phases. The first phase involved a 10-min baseline adaptation period during which participants sat quietly in the testing room breathing regular room air. Participants completed SUDS ratings at the beginning and end of the adaptation period. Phase two consisted of the automated delivery of one 4-min 10% CO_2-enriched air presentation. Participants completed a SUDs rating and the DSQ

immediately after completing the 4-minute challenge exposure. Physiological data were gathered continuously across both phases. After the study, participants were debriefed and compensated $20.

General Analytic Approach

Means and standard deviations were first computed for each of the criterion variables and baseline characteristics (e.g., smoking rate, alcohol use) in relation to the three marijuana groups (no use, regular, low-frequency use, and regular, high-frequency use). A one-way ANOVA was then utilized to formally evaluate for group differences.

To test hypothesis 1, I examined the relation between the three marijuana use groups and SUDs and DSQ ratings via two separate analyses of variance (ANOVA's). In the first analysis, the difference score between the immediate pre and post-challenge SUDs ratings was the criterion variable, and the predictor variable was marijuana use levels (trichotomously coded; 1 = no use, 2 = low use, and 3 = heavy use). In the second analysis, total intensity of panic attack symptoms were calculated (via summation of each symptom's intensity rating) and employed as the criterion variable, and marijuana use levels remained as the predictor variable in an identical fashion to the SUDs analysis.

To test hypothesis 2, similar analyses were conducted. An ANOVA was employed, with the criterion variable as avoidance responding (operationalized as desire to participate in future CO_2 –based investigations; rated on a 100 point scale) and the independent variable as marijuana use level (coded trichotomously, as noted above).

Finally, to test hypothesis 3, both the respiration and heart rate reactivity criterion variables were first computed by creating a difference score between the average reactivity during the last minute of baseline (from 240 data points; one every ¼ second) and the reactivity during the first minute of post-challenge recovery (from 240 data

points; one every ¼ second). Once these two variables were computed, two ANOVA's were employed. One used respiration rate as the criterion variable and the other had heart rate reactivity as the criterion variable. The independent variable for each ANOVA was the trichotomously coded marijuana use variable.

Results

Data Reduction Approach and Manipulation Check of Provocation Paradigm

The first step in the data analysis procedure involved an evaluation of the utility of the challenge paradigm to elicit panic-relevant responsiveness. Thus, after screening for outliers due to sampling error (e.g., participant movement), the integrity of the 10% CO_2 – enriched air administered for 4-min to elicit anxiety and physiological responsiveness was examined. Standard data reduction strategies employed in past biological challenge work were employed for the physiological data screening and reduction process (Zvolensky et al., 1998); specifically, any non-readable data (i.e., missing data due to human error such as an electrode falling off a participant) were eliminated. The data also were inspected for falling beyond an 'expected range' per the recommendations of Venables and Christie (1980). If data were at an extreme (e.g., greater than 230 beats per minute and lower than 40 beats per minute), they were removed due to the likelihood of containing a sampling error.

A paired-samples *t*-test indicated that the mean SUDS score post-challenge ($M = 52.03$, $SD = 26.20$) was significantly greater than the mean SUDS score pre-challenge ($M = 20.85$, $SD = 18.70$), $t(95) = -11.23$, $p < 001$). In addition, paired-samples t-tests indicated that the mean heart rate and respiration rate scores post-challenge ($M = 92.39$, $SD = 13.46$; $M = 19.71$, $SD = 3.70$ respectively) were significantly greater than at the final minute of the pre-challenge time period ($M = 81.43$, $SD = 10.95$; $M = 16.91$, $SD =$

3.41 respectively), $t(94) = -8.49$, $p <.001$; $t(83) = -5.78$, $p < .001$ respectively. All of the manipulation check-oriented analyses were collapsed across the groups.

Success in Matching Procedure

The second step in data analysis activities involved evaluating the matching procedure employed across the groups to formally inspect my success in 'equating' groups on some key characteristics prior to the challenge exposure. As initially proposed, matching of gender, alcohol use and tobacco use was globally successful (please see Table 4 for a case by case breakdown). Specifically, each group contained 17 males and 15 females, while alcohol use was almost uniformly present, with each group only having 1 individual who did not report alcohol use.

Though the number of alcohol users did not vary between groups, the volume (frequency by quantity) of alcohol consumed did ($F(2,93) = 5.74$, $p < .01$). Here, there was a significant difference between those with no history of marijuana use and those who were classified as regular high-frequency marijuana users ($p < .05$). Specifically, those who were regular high-frequency users consumed a greater volume of alcohol than those with no history of marijuana use. No significant differences were observed between regular low-frequency marijuana users and those with no history of marijuana use ($p > .05$), or regular high-frequency marijuana users ($p > .05$).

In terms of tobacco use, each group had 15 current tobacco smokers and 17 individuals who reported no current tobacco use. No differences were found between groups in relation to frequency of tobacco use ($F(2,93) = .21$, $p > .10$).

Finally, in regard to the distribution of non-clinical panic attacks within the sample, though matching was not fully achieved,[5] no significant differences were found in regard to the report of non-clinical panic attacks (lifetime) between the 3 groups χ^2 (2, $N = 94$) = 1.68, $p > .10$. Among those with no history of marijuana use, 27 individuals

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reported never experiencing a panic attack, while 24 individuals who were regular low-frequency marijuana users and 26 individuals who were regular high-frequency marijuana users reported never having experienced a panic attack. Among those who did report a history of panic, 4 had no history of marijuana use, while 8 were regular low-frequency users and 5 were regular, high-frequency users.

Zero-Order Correlations among Theoretically-Relevant Variables

Next, the overall pattern of interrelations among the primary predictor and criterion variables were evaluated. Table 5 shows the inter-correlations, means, standard deviations, and the observed range (corrected for sampling error) for the predictor and criterion variables. In terms of the correlation between the grouping variable and the criterion variables, no significant relation was found between the trichotomously coded grouping variable and the SUDs difference score ($r = .04$, $p > .10$), DSQ ratings ($r = -.01$, $p > .10$), behavioral avoidance ratings ($r = .13$, $p > .10$), respiration rate change ($r = -.08$, $p > .10$), or heart rate change ($r = -.04$, $p > .10$).

Primary ANOVA Analyses

The primary analyses of challenge responsivity were then formally conducted. Although the absence of significant zero-order relations between the predictor and criterion variables places doubt in the utility of completing these analyses, they were run formally due to the fact that they represent the central test in the investigation as conceived on an *a priori* basis. In terms of the change in SUDs ratings from pre to post challenge, results indicated that none of the marijuana use groups differed in terms of change in SUDs scores ($F(2,93) = .09$, $p > .10$). Furthermore, no group differences were observed for panic attack symptoms ($F(2,93) = .00$, $p > .10$) or avoidance ($F(2,92) = 1.03$, $p > .10$) post-challenge. In terms of physiological variables, no group differences

were observed for either respiration rate ($F(2,81) = .25$, $p > .10$) or heart rate ($F(2,92) =$ 1.76, $p > .10$).[6, 7]

Post Hoc Analyses

Due to the lack of empirical support for any of the hypotheses, a series of theoretically-driven *post hoc* tests were completed. Tables 6 and 7 show the inter-correlations, means, standard deviations, and the observed range (corrected for sampling error) for the predictor and criterion variables for the second and third post hoc tests.

Re-evaluating panic responsivity. First, I re-evaluated the primary hypotheses by re-coding post-challenge panic responsivity. This approach was undertaken to help evaluate whether lower overall levels of variability decreased the chance of observing differences across the groups in the original tests. Here, individuals who reported 4 or more post-challenge panic attack symptoms on the DSQ, at a severity rating of 4 or greater, were coded as having had a panic attack (Barlow, Brown, & Craske, 1994; Sanderson et al., 1989). Specifically, based on these criteria, a categorical variable (panic attack) was created wherein participants were dummy coded as either 0 (no panic attack during challenge) or 1 (panic attack during challenge).

Descriptive analysis indicated that among those with no history of marijuana use, 21 participants reported experiencing a panic attack post-challenge whereas 11 did not. A similar although slightly higher, but non-statistically significant, number of participants reported experiencing a panic attack post-challenge in the other two groups; specifically, 23 in each group reported panic and 9 in each group reporting no panic attack.

A zero-order correlation was then computed between the marijuana use grouping variable and the new panic attack variable, and results indicated a non-significant relation ($r = .06$, $p > .10$). Although no significant zero-order effect was noted, a

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subsequent chi-square analysis was nonetheless conducted to formally determine if the 3 marijuana use groups differed in terms of the experience of a panic attack post-challenge. Results indicated no significant difference between the groups χ^2 (2, N = 96) = .40, p > .10.

DSM-IV marijuana use criteria. Next, I completed a re-analysis of challenge responsivity that focused on DSM criteria for use, abuse, and dependence of marijuana rather than frequency of use of the marijuana. It is possible this type of categorization of marijuana better tracks degrees of severity than the frequency approach originally employed. Specifically, among those who reported current marijuana use (both low and high regular marijuana users combined) diagnoses of marijuana abuse and dependence, based on criteria presented in Tables 1 and 2, were obtained via the SCID-NP. All those not meeting criteria for either abuse or dependence were classified as marijuana users. These three groups were then trichotomously coded (1 = marijuana use, 2 = marijuana abuse, and 3 = marijuana dependence).

Of the 64 participants who were regular marijuana users, slightly less than half (n = 30) were categorized as marijuana users (not meeting criteria for either abuse or dependence). Those meeting criteria for marijuana abuse represented 25% of the sample (n = 16) and the remaining 18 participants met criteria for marijuana dependence. Both ANOVA and chi-square analyses were conducted similar to the analyses described earlier for the main hypotheses (see above), with the dichotomous post-challenge panic attack variable as an additional criterion variable. In these analyses, the predictor variable was the newly trichotomously coded diagnostically-driven marijuana criteria variable.

In terms of the change in SUDs ratings from pre to post challenge, results indicated that none of the marijuana criteria groups differed in terms of change in SUDs

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scores (F(2,61) = .50, p > .10). Furthermore, no group differences were observed for avoidance post-challenge (F(2,61) = .29, p > .10). Total panic attack symptoms, on the other hand, were significantly different between groups (F(2,61) = 3.55, p < .05, η^2 = .10). Specifically, *post hoc* analyses indicated that the significant difference was evident between those abusing and those dependent on marijuana (p < .05), such that those who were marijuana dependent had greater panic attack symptoms than those who abused marijuana. No significant differences were found between marijuana users and those who abused (p > .05), or were dependent on marijuana (p > .05). Though significant differences were found in terms of total panic attack symptoms, chi-square analyses indicated no significant difference between groups in relation to the experience of a panic attack post-challenge χ^2 (2, N = 64) = 5.30, p = .07; it is noteworthy, however, that a trend toward significance was evident. In terms of physiological variables, no group differences were observed for either respiration rate (F(2,52) = .33, p > .10) or heart rate (F(2,60) = .56, p > .10).

Marijuana use motives. A final set of *post hoc* tests were completed that focused on motivational bases of marijuana use in terms of anxious and fearful responding to bodily sensations. As outlined in the Background and Significance Section of the present document, some work suggests coping-oriented marijuana use may play a formative role in negative affective responding (Mitchell et al., 2007). Given such empirical evidence, I opted to formally evaluate the utility of coping motives in relation to challenge responsivity. Here, among those who reported current marijuana use, motives for marijuana use were examined in relation to the above criterion variables. Separate multiple regression analyses (Cohen & Cohen, 1983) were conducted for each of the above criterion variables, with the exception of the dichotomous panic attack variable, where a logistic regression was used (Cohen & Cohen, 1983). At level 1 of every

regression analysis, each of the five factors of the MMM: (1) Coping, (2) Expansion, (3) Conformity, (4) Enhancement, and (5) Social were simultaneously entered into the equation in addition to frequency of past 30 day marijuana use. This analytic approach permits an evaluation of the predictive power of each variable in the context of one another.

In terms of the change in SUDs ratings from pre to post challenge, neither frequency of past 30 day marijuana use nor any of the marijuana use motives were significant predictors of change in SUDs scores (all p's > .10). Regarding avoidance post-challenge, both coping motives for marijuana use ($t = -2.51$; $\beta = -.35$; $sr^2 = .10$; $p < .05$) and frequency of past 30 day marijuana use ($t = 2.27$; $\beta = .34$; $sr^2 = .08$; $p < .05$) were significant predictors, such that those who used for greater coping reasons were <u>less</u> interested in returning for another challenge (greater avoidance), while those who used greater amounts of marijuana in the past 30 days showed <u>greater</u> interest in returning for another challenge (less avoidance). Regarding total panic attack symptoms, coping motives for marijuana use was a unique predictor ($t = 2.09$; $\beta = .30$; $sr^2 = .07$; $p < .05$), with all other variables at level 1 being non-significant (all p's > .10). In terms of the logistic regression predicting the experience of a panic attack post-challenge, none of the variables entered were significant predictors (all p's > .05). For respiration rate, none of the predictor variables in the regression significantly contributed to the prediction of change in respiration rate from pre to post-challenge (all p's > .10). Similar non-significance was evident in the prediction of heart rate change (all p's > .05).[8]

Discussion

The overarching aim of the present investigation was to examine the role of different levels of frequency of marijuana use in relation to panic-relevant responding in the context of a biological challenge paradigm. This investigation is important both

theoretically and clinically because it serves to help empirically elucidate whether

frequency of marijuana use is a possible vulnerability factor for anxious and fearful

responding to bodily sensations among adult marijuana users.

Main Findings

In contrast to expectation, there was uniformly no empirical evidence that

frequency of marijuana use among the present young adult sample was related to

greater panic responsivity to somatic perturbation from any measurement perspective.

These findings are inconsistent with a past field study that indicated greater frequency of

marijuana use is related to self-reported anxious arousal and lower levels of perceived

health vulnerability (Bonn-Miller et al., 2005). Although there are differences between the

samples studied in the current work and the previous investigation (e.g., percentage of

daily cigarette smokers; Bonn-Miller et al., 2005), the findings are nonetheless in

contrast to such previously reported results. The most parsimonious interpretation of

such results when considered across both investigations is that the previously observed

effect for anxious arousal symptoms and perceived health vulnerability in the Bonn-Miller

and colleagues (2005) study is not evident for panic-relevant symptoms elicited in 'real

time.' Thus, the tendency to report greater anxiety symptoms and poorer beliefs about

health status generally does not appear to extend to panic symptoms specifically. It

remains unclear whether such differences between the present study and the Bonn-

Miller et al. (2005) investigation are due to methodological reasons (e.g., reporting

biases obtained in real time, distinctions in the dependent variables across the two

studies).

Other past marijuana-anxiety research helps inform the understanding of the

distinctions observed across the Bonn-Miller et al. (2005) and the current investigation.

Here, it is noteworthy that some past work has indicated no main effect for frequency of

marijuana use in terms of enhanced vulnerability for panic (Buckner et al., in press; Zvolensky, Bonn-Miller et al., 2006). For example, in one field study, frequency of marijuana use (at the main effect level) was not related to greater reporting of panic-relevant catastrophic thinking or anxious arousal symptoms among young adult cigarette smokers (Zvolensky, Bonn-Miller et al., 2006). Similarly, among adolescent marijuana users, there was no main effect for frequency of marijuana use in regard to self-reported or physiological responsivity to hyperventilation-induced bodily sensations (Buckner et al., in press). However, both of these reports did indicate a significant interactive effect between frequency of marijuana use and anxiety sensitivity (fear of anxiety) for anxious arousal symptoms and panic-relevant catastrophic thinking. Thus, it may be that frequency of marijuana use is relevant to understanding panic-relevant symptoms (and perhaps affective vulnerability more generally) only when coupled with other risk candidates such as (high levels of) anxiety sensitivity.

At a broad-based level, the present findings, although not in support of the main hypotheses, help empirically enlighten understanding of marijuana and anxiety vulnerability associations noted in the literature (e.g., Hollister, 1986; Tunving, 1985). As noted in the Background and Significance Section, past work has typically employed a disparate array of assessment devices for anxiety symptoms and problems. Many of these devices have not been rigorously developed from an evidence-based standpoint (e.g., Hollister, 1986), often leaving unclear their construct validity as well as reliability and psychometric properties generally. The current investigation helps clarify those past studies by using an array of scientifically sound assessment devices from a multimethod perspective that map onto the experience of anxious and fearful responding. From the perspective of the current data, there is good reason to question past noted relations between frequency of marijuana use and anxiety and panic symptoms among young

adults (Hollister, 1986). To the extent that there is a lack of an association at the main effect level between frequency of marijuana use and panic symptoms, theoretical models that attempt to understand marijuana-panic (and perhaps other anxiety disorders) co-occurrence will need to be revised (please see *Post Hoc* test section below for a further discussion). To even more firmly establish a lack of marijuana frequency effect for panic-relevant symptoms and problems, it may be advisable for future work to replicate the current test among different types of marijuana users (e.g., older adults).

Sample characteristics. Although not a primary aim of the study per se, it is useful to briefly comment on the sample characteristics in regard to the nature of marijuana use and engagement in other forms of substance use (tobacco and alcohol). There is a growing recognition that marijuana use does not occur in isolation from other forms of substance use (Amos, Wiltshire, Bostock, Haw, & McNeill, 2004). For example, marijuana is the most frequently used illicit drug among cigarette smokers (Smart & Ogborne, 2000). Yet, the nature of marijuana use in regard to severity or use patterns is unclear from such prior work.

The current young adult marijuana using sample had slightly less than half not meeting criteria for either marijuana abuse or dependence, whereas the remaining half was split relatively equally between the two diagnoses. Of the marijuana using sample, almost every participant reported current alcohol use, with approximately 90% drinking alcohol at least 2 to 4 times per month. Regarding alcohol use problems, approximately 75% of the marijuana using sample reported at least moderate alcohol use problems, as indexed by a score of 8 or greater on the AUDIT (Babor et al., 1992). Daily tobacco use also was reported by slightly less than half of this sample. These individuals reported smoking an average of ¾ of a pack of cigarettes daily (a relatively high rate of cigarette use for young adults). Although the present study should certainly not be considered

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'representative' of all young adults in the sense that probability sampling methods were not employed, they are largely consistent with past observations (Amos et al., 2004). Moreover, the descriptive characteristics of the sample suggest that not only is cigarette and alcohol use common among young adult marijuana users, but that it occurs at relatively severe levels (indexed by daily cigarette use and alcohol use problems).

Together, these data suggest that young adult marijuana users do not simply use marijuana alone, but rather, engage in multiple forms of substance use simultaneously. It is likely that future research on substance use and anxiety co-occurrence will need to develop theoretical models that meaningfully address the relevance of such polysubstance use in terms of anxiety vulnerability. Regardless of the relevance of such polysubstance use in terms of anxiety vulnerability per se, it should not be lost that such high rates of substance use across numerous types of drugs (marijuana, tobacco, and alcohol) may be related to greater levels of 'early' medical problems (physical health disorders) among these individuals later in life (e.g., middle age; Bloom et al., 1987).

In the present investigation, I excluded for a variety of medical disorders that would be contraindicated from the challenge procedure. However, it would be interesting, and perhaps clinically useful, to formally evaluate the relative frequency and severity of medical disorders (physical health conditions) among marijuana users with and without varying degrees and types of polysubstance use in the future. It is possible that young adult marijuana users with concurrent polysubstance use may be more apt to demonstrate the early onset of certain medical conditions (e.g., asthma). It also would be helpful to empirically inspect the relative degree of use of other forms of substance use among this population (e.g., opiates) to better gauge the relative extent of 'clustering' of substance use to certain classes of drugs. This type of work would broaden the study of marijuana-anxiety work by tying it to a larger constellation of relevant medical and

psychological variables of possible theoretical relevance to this type of substance use behavior.

Post Hoc Tests

A series of *post hoc* tests were completed to further understand possible relations between marijuana variables and panic responsivity. As with any *post hoc* exploration, caution is needed to interpret these findings. It is perhaps most prudent to utilize these additional analyses as a 'theory-generating' tactic in future work focused on putative marijuana-panic relations as opposed to viewing such information as offering a definitive conclusion.

Measurement of panic. The first set of *post hoc* tests were focused on clarifying whether limited upper-end variability in panic symptom endorsement played a role in the null effects for the marijuana frequency factors and anxious and fearful responding to bodily sensations. By re-coding the DSQ panic symptom variables to conform to a panic attack, there was a pinpointing of those persons who demonstrated the most responsivity to the challenge. These persons were presumably the 'most vulnerable' to panic-related distress. Yet, even when panic responsivity was re-evaluated coding for the experience of an actual panic attack rather than simply mean DSQ panic symptoms, no difference was found between marijuana use groups. These findings are consistent with the continuous DSQ data and therefore do not support a differential effect for frequency of marijuana use. In total, these results are not consistent with the original hypothesized relation between frequency of marijuana use and panic responding to a biological challenge procedure.

DSM-IV marijuana use criteria. I then completed a re-analysis of challenge responsivity that focused on DSM criteria for use, abuse, and dependence of marijuana rather than frequency of marijuana use. The logic underlying this re-analysis was that it

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is possible this categorization approach better tracks degrees of severity than the frequency approach originally employed. Specifically, among those who reported current marijuana use (both low and high regular marijuana users combined), I examined diagnoses of marijuana abuse and dependence as well as those not meeting criteria for either diagnosis (marijuana users). This re-coding indicated that slightly less than half (n = 30) of the current marijuana users were categorized as marijuana users (not meeting criteria for either abuse or dependence), whereas 25% (n = 16) were classified as marijuana abusers, and the remaining (n = 18) 28% were categorized as marijuana dependent. Thus, there was an excellent range of differences in severity of marijuana use problems among the present sample.

Partially consistent with prior work among marijuana users, those meeting criteria for marijuana dependence were found to have greater panic attack symptoms (as indexed by mean DSQ scores) than those who abused marijuana with no differences found between those who used (users who did not meet criteria for abuse or dependence) and those who abused or were dependent on marijuana. This effect was of a medium size when evaluated using traditional effect size standards (Cohen, 1988). These differences were not evident when DSQ symptoms were evaluated in terms of the actual experience of a panic attack post challenge, although a trend was evident. There were no differences between the groups in regard to SUDS change, behavioral avoidance, or physiological changes. Despite concern about the attendant risk of Type I error due to the multiple number of analyses, these results may shed some (limited) insight into marijuana-panic relations.

One working interpretation of this set of *post hoc* findings is that, relative to frequency of marijuana use, a DSM-coding scheme may be a more fruitful strategy for understanding possible linkages between marijuana and panic psychopathology. In fact,

at least one other prospective investigation has found marijuana use and dependence, but not abuse, to be significantly related to an increased risk of panic attacks and panic disorder (Zvolensky, Lewinsohn et al., in press). Thus, there is some empirical consistency between the present investigation and that of Zvolensky, Lewinsohn and colleagues (in press). The lack of an effect for abuse for both investigations is interesting and may suggest that marijuana abuse is less fruitful for understanding panic vulnerability relative to use and dependence. The reason for this lack of abuse effect for panic variables is presently unclear. It may be that different populations of marijuana users are prone to differential panic risk due to their experience (learning experience with the drug). For instance, it is possible that there may be greater degrees of risk at current low (users) and high-levels of problematic (dependence), but less risk for individuals who are experienced in using the drug but have not progressed to a more severe level (abusers). This type of account sets the stage for a more fine-grained marijuana use disorder analysis using measurement that focuses on the types of experiences individuals have with drug and patterns of use more generally.

  Marijuana use motives. A final set of *post hoc* tests were completed that focused on motivational bases of marijuana use in terms of anxious and fearful responding to bodily sensations. This work was informed by a recent investigation that indicated that only certain motives for marijuana use --- namely, coping-oriented motives --- were uniquely, concurrently related to self-reported anxious arousal as well as a variety of other affective vulnerability factors (e.g. anxiety sensitivity; Mitchell et al., 2007). The theoretical basis for this type of model is that, to the extent that marijuana users believe that such drug use can be employed as a coping strategy for negative emotional experiences, those who use more often for negative affect reduction purposes may be most vulnerable for affect-based psychological vulnerability. Specifically, regardless of

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the actual objective mood dampening effects of using marijuana, regular users of the drug often believe that such drug use can improve their emotional states (Simons et al., 1998). In the absence of more adaptive coping skills or the utilization of alternative coping methods, marijuana users who tend to use for negative affect reduction purposes may, in fact, be more vulnerable to affective and cognitive distress. This type of perspective places a unique explanatory role on coping-oriented motivational processes for marijuana use in terms of affect-based psychological vulnerability factors.

Partially consistent with prediction, coping motives were a significant predictor of post-challenge avoidance ratings and panic attack symptoms. Greater coping motives were associated with greater levels of avoidance and more intense panic attack symptoms. The size of the observed effects for both dependent variables was medium in effect size using Cohen (1988) standards. It is noteworthy that no other marijuana use motive showed a similar type of relation. Interestingly, for avoidance ratings, frequency of past 30 day marijuana use was a significant predictor, such that those who used greater amounts of marijuana in the past 30 days showed greater interest in returning for another challenge (less avoidance). This effect is in the opposite direction of that originally proposed by the current study. There were no other significant effects for any of the other dependent variables. These data, in conjunction with past work (Mitchell et al., 2007), collectively suggest that coping motives for marijuana use may be a promising explanatory candidate for certain aspects of panic vulnerability. Also, there was no evidence that any other marijuana motives (beyond coping) were positively related to the studied dependent variables. Such data, considered with the coping motive results, suggest that very few of the studied motivational variables are systematically or independently related to anxiety factors. Thus, there is clear evidence of a differential pattern of associations between types of marijuana use motives and the studied factors

Although caution should be exercised in over-interpreting these coping-oriented effects due to, at a minimum, the multiple comparisons completed and underlying *post hoc* nature of them, there are a number of *possible* implications for the present findings. First, these findings may have important theoretical implications for better understanding previous research linking marijuana use to affect-based psychological vulnerability (Brook et al., 2001; Oyefeso, 1991; Zvolensky, Bernstein et al., 2006). One possibility is that coping motives underlying marijuana use may theoretically influence such drug use behavior and affective-cognitive processes. For example, coping-related marijuana use motives may increase the likelihood of experiencing negative emotional states like panic symptoms, and in turn, may promote more marijuana use. Future work is needed to follow-up on the present observations in order to clarify the nature of such potential relations. In this pursuit, it would likely be beneficial to utilize both structural equation modeling approaches that can model multiple variables concurrently and prospective assessment methodologies that permit observations across time. Overall, this type of work will help address whether motives for marijuana use are influenced by emotional vulnerability processes and/or whether emotional vulnerability shapes marijuana coping motives.

Study Limitations and Future Directions

Beyond the already noted interpretative caveats of the present study, there are a number of other points for clarification and targets for future study. First, the present sample was limited in that it is comprised of a relatively homogenous (e.g., primarily Caucasian) group of young adults who volunteered to participate in the study for monetary reward. To rule out potential self-selection bias among persons with these characteristics and increase the generalizability of these findings, it will be important for researchers to draw from other populations and utilize recruitment tactics other than

those used in the present study. For example, recruiting a minority based treatment seeking population would not only increase upper end variability but also the generalizability of the findings. Second, the behavioral avoidance findings should be viewed with caution. It is possible that the person's report of their desire to return for a future challenge may not be fully in line with their actual behavior, such that a participant may report that they would be willing to return, but may not actually follow through, and vice versa. It also is possible this measure of avoidance may tap boredom, frustration, or related factors rather than 'pure' fear-driven avoidance. Thus, future work should attempt to solidify this finding through a more rigorous methodology. For example, an experiment could be designed in which a second challenge is planned minutes following the first challenge, with which one could determine objectively which participants are willing to stay for the second administration. Additionally, participants could be called a week following the challenge to determine if they wish to schedule another appointment. These approaches allow for a behavioral confirmation of the participant's reported willingness to attend another CO_2 administration. Third, the present cross-sectional correlational design does not permit causal-oriented hypothesis testing. Although an attempt to strengthen confidence in the observed findings was achieved by matching for theoretically-relevant factors, causal directions of the observed relations cannot be fully determined.

Fourth, a persistent challenge to marijuana research is attaining reliable and valid assessments of the parameters of drug behavior (see Stephens, 1999). In the present investigation, I followed previous work and examined frequency of marijuana use. However, it was not possible to attain an assessment of quantity of use due to the wide degree of variability in marijuana types (i.e., potency) and reliance on recall of participants to identify an amount used (i.e., memory distortions; Stephens, 1999).

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Although there is no consensus regarding how to unambiguously address this issue, utilization of biochemical methods would perhaps be a useful tactic. Fifth, given that the present sample by virtue of selection criteria was psychologically and physically healthy, the findings are not generalizable to all marijuana users. These selection criteria were useful and necessary for the purposes of the present investigation to ensure that the observed marijuana effects were not attributable to correlated psychopathology or medical disorders. At the same time, to enhance the generalizability of the study results, future work may benefit by sampling from a more diverse marijuana population. More specifically, recruiting clinical samples as well as individuals from other racial, socio-economic, and ethnic backgrounds as well as age groups would possibly introduce a wider array of motivational patterns, stigma and worry surrounding illegality of use, as well as representations and severity of disordered use. This more broad-based sampling approach also may facilitate attaining higher degrees of top-end variability in anxiety as well as marijuana use variables. Finally, although the present investigation examined a variety of marijuana factors (e.g., frequency of use, severity of use, motives for use) in terms of panic responsivity to somatic perturbation, there are other possible factors that may warrant examination (e.g. marijuana withdrawal symptoms). By continuing to study possible mechanisms involved in the relation between marijuana and panic, progress should be made in terms of better understanding the nature of panic-marijuana co-occurrence.

Summary

Overall, the present investigation adds uniquely to the extant empirical literature on the relation between marijuana use and panic-relevant processes. Although frequency of marijuana use was not related to enhanced panic responsivity, *post hoc* tests suggested that a DSM-oriented categorization or motive-based approach may be

helpful in understanding marijuana-panic relations. Using this type of basic research to

guide understanding of clinically-relevant processes will continue to be an important task

for translational research efforts focused on marijuana, anxiety, and their disorders.

References

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Amos, A., Wiltshire, S., Bostock, Y., Haw, S., & McNeill, A. (2004). You can't go without a fag…you need it for your hash- a qualitative exploration of smoking, cannabis, and young people. *Addiction, 99,* 77-81.

Anthony, J. C., Warner, L. A., & Kessler, R. C. (1994). Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology, 2*, 244–268.

Ashton, C. H. (1999). Adverse effects of cannabis and cannabinoids. *British Journal of Anaesthesia, 83*, 637-649.

Ashton, C. H. (2001). Pharmacology and effects of cannabis: A brief review. *The British Journal of Psychiatry, 178,* 101-106.

Babor, T. F., de la Fuente, J. R., Saunders, J., & Grant, M. (1992). *The Alcohol Use Disorders Identification Test: Guidelines for use in primary care*. WHO Publication No. 92.4, World Health Organization, Geneva.

Barlow, D. H. (2002). *Anxiety and its disorders: The Nature and Treatment of Anxiety and Panic* (2nd ed.). New York: The Guilford Press.

Barlow, D. H., Brown, T. A., & Craske, M. G. (1994). Definitions of panic attacks and panic disorder in the DSM-IV: Implications for research. *Journal of Abnormal Psychology, 103,* 553-564.

Bloom, J. W., Kaltenborn, W. T., Paoletti, P., Camilli, A., & Lebowitz, M. D. (1987). Respiratory effects of non-tobacco cigarettes. *British Medical Journal, 295*, 1516-1518.

Bonn-Miller, M. O., Zvolensky, M. J., & Bernstein, A. (2007). Marijuana use motives: Concurrent relations to frequency of past 30-day use and anxiety sensitivity among young adult marijuana smokers. *Addictive Behaviors, 32,* 49-62.

Bonn-Miller, M. O., Zvolensky, M. J., Leen-Feldner, E. W., Feldner, M. T. & Yartz, A. R. (2005). Marijuana use among daily tobacco smokers: Relationship to anxiety-related factors. *Journal of Psychopathology and Behavioral Assessment, 27,* 279-289.

Brook, J. S., Rosen, Z., & Brook, D. W. (2001). The effect of early marijuana use on later anxiety and depressive symptoms. *NYS Psychologist, January,* 35-39.

Buckner, J. D., Leen-Feldner, E. W., Zvolensky, M. J., & Schmidt, N. B. (in press). The interactive effect of anxiety sensitivity and frequency of marijuana use in terms of anxious responding to bodily sensations among youth. *Psychiatry Research*.

Budney, A. J., Higgins, S. T., Radonovich, K. J., & Novy, P. L. (2000). Adding voucher-based incentives to coping skills and motivational enhancement improves outcomes during treatment for marijuana dependence. *Journal of Consulting and Clinical Psychology, 68,* 1051-1061.

Budney, A. J., Hughes, J. R., Moore, B. A., & Novy, P. L. (2001). Marijuana abstinence effects in marijuana smokers maintained in their home environment. *Archives of General Psychiatry, 58*, 917-924.

Budney, A. J., Hughes, J. R., Moore, B. A., & Vandrey, R. (2004). Review of the validity and significance of cannabis withdrawal syndrome. *American Journal of Psychiatry, 161,* 1967-1977.

Budney, A. J., & Moore, B. A. (2002). Development and consequences of cannabis dependence. *Journal of Clinical Pharmacology, 42,* 28S-33S.

Budney, A. J., Moore, B. A., Vandrey, R., & Hughes, J. R. (2003). The time course and

    significance of cannabis withdrawal. *Journal of Abnormal Psychology, 112(3),*

    393-402.

Budney A. J., Novy, P. L., & Hughes, J. R. (1999). Marijuana withdrawal among adults

    seeking treatment for marijuana dependence. *Addiction, 94,* 1311-1322.

Caplan, G.A., & Brigham, B.A. (1989). Marijuana smoking and carcinoma of the tongue.

    Is there an association? *Cancer, 66,* 1005-1006.

Chait, L. D., & Zacny, J. P. (1992). Reinforcing and subjective effects of oral Δ^9-THC and

    smoked marijuana in humans. *Psychopharmacology, 107,* 255–262.

Chen, C.-Y., Wagner, F. A. & Anthony, J. C. (2002). Marijuana use and the risk of major

    depressive episode: Epidemiological evidence from the United States National

    Comorbidity Survey. *Social Psychiatry and Psychiatric Epidemiology, 37,* 199-

    206.

Chen, K., Kandel, D. B., & Davies, M. (1997). Relationships between frequency and

    quantity of marijuana use and last year proxy dependence among adolescents

    and adults in the United States. *Drug and Alcohol Dependence, 46,* 53-67.

Coates, R. A., Farewell, V. T., Raboud, J., Read, S. E., MacFadden, D. K., Calzavara, L.

    M., Johnson, J. K., Shepherd, F. A., & Fanning, M. M. (1990). Cofactors of

    progression to acquired immunodeficiency syndrome in a cohort of male sexual

    contacts of men with human immunodeficiency virus disease. *American Journal*

    of Epidemiology, 132, 717-722.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences (2nd. Ed.).* New

    York: Academic Press.

Cohen, J. & Cohen, P. (1983). *Applied multiple regression/correlation analysis for the*

    behavioral sciences. Hillsdale, NJ: Erlbaum.

Comeau, N., Stewart, S. H., & Loba, P. (2001). The relations of trait anxiety, anxiety

    sensitivity, and sensation seeking to adolescents' motivations for alcohol,

    cigarette, and marijuana use. *Addictive Behaviors, 26,* 803-825.

Compton, W. M., Grant, B. F., Colliver, J. D., Glantz, M. D., & Stinson, F. S. (2004).

    Prevalence of marijuana use disorders in the United States: 1991–1992 and

    2001–2002. *Journal of the American Medical Association, 291*, 2114–2121.

Copeland, J., Swift, W., Roffman, R. & Stephens, R. (2001). A randomized controlled

    trial of brief cognitive-behavioural interventions for cannabis use disorder. *Journal*

    of Substance Abuse Treatment, 21, 55–64.

Craske, M. G. (1991). Phobic fear and panic attacks: The same emotional states

    triggered by different cues? *Clinical Psychology Review, 11,* 599-620.

Craske, M. G. (1999). *Anxiety disorders: Psychological approaches to theory and*

    treatment. Boulder, CO: Westview Press.

Dannon, P. N., Lowengrub, K., Amiaz, R., Grunhaus, L., & Kotler, M. (2004). Comorbid

    cannabis use and panic disorder: Short term and long term follow-up study.

    Human Psychopharmacology, 19, 97-101.

Day, N. L., Wagener, D. K., & Taylor, P. M. (1985). Measurement of substance use

    during pregnancy: Methodologic issues. *NIDA Research Monograph, 59*, 36–47.

Degenhardt, L., Hall, W., & Lynskey, M. (2001). Alcohol, cannabis, and tobacco use

    among Australians: A comparison of their associations with other drug use and

    disorders, affective and anxiety disorders, and psychosis. *Addiction, 96,* 1603-

    1614.

Degenhardt, L., Hall, W. & Lynskey, M. (2003) Testing hypotheses about the relationship

    between cannabis use and psychosis. *Drug and Alcohol Dependence, 71,* 37-48.

Devane, W. A., Hanus, L., Breuer, A., Pertwee, R. G., Stevenson, L. A., Griffin, G.,
Gibson, D., Mandelbaum, A., Etinger, A., & Mechoulam, R. (1992). Isolation and
structure of a brain constituent that binds to the cannabinoid receptor. *Science,
258,* 1946–1949.

Diamond, G., Panichelli-Mindel, S. M., Shera, D., Dennis, M., Tims, F., & Ungemack, J.
(2006). Psychiatric syndromes in adolescents with marijuana abuse and
dependency in outpatient treatment. *Journal of Child & Adolescent Substance
Abuse, 15*, 37-54.

Didcott, P., Flaherty, B., & Muir, C. (1988). *A profile of addicts in residential treatment in
New South Wales.* Directorate of the Drug Offensive, In House Report Series.
Sydney, New South Wales Department of Health.

Eck, J. E., & Gersh, J. S. (2000). Drug trafficking as a cottage industry. *Crime and
Prevention Studies, 11,* 241–271.

Ekman, P. (1992). An argument for basic emotions. *Cognition and Emotion, 6,* 169-200.

Everest, J. T., Tunbridge, R. J. & Widdop, B. (1989). *The Incidence of Drugs in Road
Accident Fatalities.* Department of Transport and Road Research Laboratory
Research Report 202. London: Department of Transport Publications.

Feldner, M. T., Zvolensky, M. J., & Leen-Feldner, E. (2004). A critical review of
the literature on coping and panic disorder. *Clinical Psychology Review, 24,* 123-
148.

Feldner, M. T., Zvolensky, M. J., Stickle, T. R., Bonn-Miller, M. O., & Leen-Feldner, E.
W. (2006). Anxiety sensitivity – physical concerns as a moderator of the
emotional consequences of emotion suppression during biological challenge: An
experimental test using individual growth curve analysis. *Behaviour Research
and Therapy, 44,* 249-272.
66

Fergusson, D. M. & Horwood, L. J. (2000). Does cannabis use encourage other forms of

illicit drug use? *Addiction, 95,* 505-520.

Fergusson, D. M., Horwood, L. J., & Swain-Campbell, N. (2002). Cannabis use and

psychosocial adjustment in adolescence and young adulthood. *Addiction, 97,*

1123-1135.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1995). *Structured Clinical*

Interview for DSM-IV Axis I Disorders- Non-Patient Edition. New York: New York

State Psychiatric Institute.

Fligiel, S. E., Roth, M. D., Kleerup, E. C., Barsky, S. H., Simmons, M. S., & Tashkin, D.

P. (1997). Tracheobronchial histopathology in habitual smokers of cocaine,

marijuana, and/or tobacco. *Chest, 112*, 319-326.

Forsyth, J. P., & Eifert, G. H. (1998). Intensity of systemic alarms in content-specific fear

conditioning: Comparing 20% versus 13% CO2-enriched air as a UCS. *Journal of*

Abnormal Psychology, 107, 291-304.

Fridja, N. (1988). The laws of emotion. *American Psychologist, 43(5),* 349-358.

Gale, E. N. & Guenther, G. (1971). Motivational factors associated with the use of

cannabis (marihuana). *British Journal of Addiction, 66,* 188-194.

Gjerde, H. & Kinn, G. (1991) Impairment in drivers due to cannabis. *Forensic Science*

International, 50, 57-60.

Gorman, J. M., Kent, J., Martinez, J., Browne, S., Coplan, J., & Papp, L. A. (2001).

Physiological changes during carbon dioxide inhalation in patients with panic

disorder, major depression, and premenstrual dysphoric disorder: Evidence for a

central fear mechanism. *Archives of General Psychiatry, 58*, 125-131.

Gray, J. A., & McNaughton, N. (1996). The neuropsychology of anxiety: Reprise. In D. A.

   Hope (Ed.), *Nebraska Symposium on Motivation: Vol. 43. Perspectives on*

   anxiety, panic, and fear (pp. 61-134). Lincoln: University of Nebraska Press.

Green, B. E. & Ritter, C. (2000). Marijuana use and depression. *Journal of Health &*

   Social Behavior, 41, 40-49.

Green, B., Young, R., & Kavanagh, D. (2005). Cannabis use and misuse prevalence

   among people with psychosis. *British Journal of Psychiatry, 187,* 306-313.

Hall, W., & Solowij, N. (1998). Adverse effects of cannabis. *Lancet, 352,* 1611-1615.

Hall, W., Solowij, N. & Lemon, J. (1994) The Health and Psychological Consequences of

   Cannabis Use. *Monographs of the Austrailian Government Department of Health*

   and Ageing, 25.

Haney, M., Ward, A. S., Comer, S. D., Foltin, R. W., & Fischman, M. W. (1999).

   Abstinence symptoms following smoked marijuana in humans.

   P*sychopharmacology, 141,* 395-404.

Harrington, P. J., Schmidt, N. B., & Telch, M. J. (1996). Prospective evaluation of panic

   potentiation following 35% CO2 challenge in nonclinical subjects. *American*

   Journal of Psychiatry, 153, 823-825.

Herkenham, M., Lynn, A., Little, M. D., Johnson, M. R., Melvin, L. S., de Costa, B. R., &

   Rice K. C. (1990). Cannabinoid receptor localization in the brain. *Proceedings of*

   the National Academy of Sciences, USA. 87, 1932-1936.

Hollister, L. E. (1986). Health aspects of cannabis. *Pharmacological Reviews, 38*, 1-20.

Hollister, L. E. (1992). Marijuana and immunity. *Journal of Psychoactive Drugs, 24,* 159-

   164.

Hunt, C. A., Jones, R. T., Herning, R. I., & Bachman J. (1981). Evidence that cannabidiol does not significantly alter the pharmacokinetics of tetrahydrocannabinol in man. *Journal of Pharmacokinetics and Biopharmaceutics, 9*, 245-60.

Isaac, M., Isaac, M., & Holloway, F. (2005). Is cannabis an anti-antipsychotic? The experience in psychiatric intensive care. *Human Psychopharmacology, 20,* 207-210.

Izard, C. E. (1990). Facial expressions and the regulation of emotions. J*ournal of Personality and Social Psychology, 58*, 487-498.

Izard, C. E. (1992). Basic emotions, relations among emotions, and emotion cognition relations. *Psychological Review, 99*(3), 561-565.

Johns, A. (2001). Psychiatric effects of cannabis. *British Journal of Psychiatry*, *178,* 116-122.

Kandel, D. (1975). Stages in adolescent involvement in drug use. *Science, 190,* 912-914.

Kaslow, R. A., Blackwelder, W. C., Ostrow, D. G., Yerg, D., Palenick, J., Coulson, A. H. & Valdiserri, R. O. (1989). No evidence for a role of alcohol or other psychoactive drugs in accelerating immunodeficiency in HIV-1-positive individuals: A report from the Multicenter AIDS Cohort Study. *Journal of the American Medical Association, 261,* 3424-3429.

Kokotailo, P. K., Egan, J., Gangnon, R., Brown, D., Mundt, M., & Fleming, M. (2004). Validity of the Alcohol Use Disorders Identification Test in college students. *Alcoholism: Clinical and Experimental Research, 28*, 914-920.

Kouri, E., Pope, H. G., Yurgelun-Todd, D. & Gruber, S. (1995). Attributes of heavy vs. occasional marijuana smokers in a college population. *Biological Psychiatry, 38*, 475-481.

Lancet. (1995). Deglamorising cannabis. *Lancet, 346,* 1241.

Lang, P. J. (1994). The motivational organization of emotion: Affect-reflex connections. In S. Van Goozen, N. E. Van de Poll, & J. A. Sergeant (Eds.). *The emotions: Essays on emotion theory* (pp. 61-93). Hillsdale, NJ: Erlbaum.

Lang. P. J., Rice. D. G.. & Sternbach, R. A. (1972). The psychophysiology of emotion. In N. S. Greenfield & R. A. Sternbach (Eds.).*Handbook of Psychophvsiology* (pp. 623-643). New York: Holt.Rinehart, &Winston.

Lehman, W. E. K., & Simpson, D. D. (1992). Employee substance use and on-the-job behaviors. *Journal of Applied Psychology, 77*, 309-321.

Leirer, V. O., Yesavage, J. A. & Morrow, D. G. (1991). Marijuana carry-over effects on aircraft pilot performance. *Aviation & Space Environmental Medicine*, *62,* 221-227.

Levenson, R. W. (1994). Human emotion: A functional view. In P. Ekman & R. Davidson (Eds.), *The nature of emotion: Fundamental questions* (pp. 123-126). New York: Oxford University Press.

Lynskey, M., & Hall, W. (2000). The effects of adolescent cannabis use on educational attainment: A review. *Addiction, 95,* 1621-1630.

Mathew, R. J., Wilson, W. H., & Tant, S. R. (1989). Acute changes in cerebral blood flow associated with marijuana smoking. *Acta Psychiatrica Scandinavica, 79*,118□ 128.

McNally, R. J. (1999). Anxiety sensitivity and information-processing biases for threat. In S. Taylor (Ed.), *Anxiety sensitivity: Theory, research, and treatment of the fear of anxiety* (pp. 183-197). Mahwah, NJ: Lawrence Erlbaum Associates.

McNally, R. J. (2002). Anxiety sensitivity and panic disorder. *Biological Psychiatry, 52,* 938-946.

Mitchell, H., Zvolensky, M. J., Marshall, E. C., Bonn-Miller, M. O., & Vujanovic, A. A. (2007). Incremental validity of coping-oriented marijuana use motives in the prediction of affect-based psychological vulnerability. *Journal of Psychopathology and Behavioral Assessment, 29,* 277-288.

National Institute on Drug Abuse (NIDA; 1997). *Monitoring the Future Study,* December 20th press release. Washington, DC: US Department of Health and Human Services.

National Institute of Drug Abuse. (NIDA; 2001). *Research Report – Nicotine Addiction.* Rockville, Md.: National Clearinghouse on Alcohol and Drug Information. NIH Publication No. 01-4342.

National Institute of Drug Abuse. (NIDA; 2004). *Research Report – Cocaine Abuse and Addiction.* Rockville, Md.: National Clearinghouse on Alcohol and Drug Information. NIH Publication No. 99-4342.

Newcombe, M. D., & Bentler, P. (1988). *Consequences of Adolescent Drug Use: Impact on the Lives of Young Adults.* Newbury Park, CA: Sage.

Norton, G. R., Cox, B. J., & Malan, J. (1992). Nonclinical panickers: A critical review. *Clinical Psychology Review, 12,* 121-139.

O'Dea, P. J., Murphy, B., & Balzer, C. (1997). Traffic and illegal production of drugs in rural America. In Robertson, E. B., Sloboda, Z., Boyd, G. M., Beatty, L. & Kozel, N. J. (Eds.) *Rural Substance Abuse: State of Knowledge and Issues.* NIH Publication No. 97-4177.

Office of Applied Studies. (2002). *Summary of findings from the 2001 National Household Survey on Drug Abuse* (DHHS Publication No. SMA 02–3758, NHSDA Series H-17; available at http://www.oas.samhsa.gov/nhsda.htm).

Rockville, MD: Substance Abuse and Mental Health Services Administration (SAMHSA).

Office of Applied Studies. (2004). *Summary of findings from the 2003 National Survey on Drug Use & Health* (DHHS Publication No. SMA 04–3964, NSDUH Series H-25; available at http://www.oas.samhsa.gov/nhsda.htm). Rockville, MD: Substance Abuse and Mental Health Services Administration.

Ogborne, A. C., & Smart, R. G. (2000). Cannabis users in the general Canadian population. *Substance Use and Misuse, 35,* 301-311.

Ohlsson, A., Lindgren, J. E., Wahlen, A., Agurell, S., Hollister, L. E., & Gillespie, H. K. (1980). Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clinical Pharmacology and Therapeutics, 28,* 409-416.

Patton, G. C., Coffey, C., Carlin, J. B., Degenhardt, L., Lynskey, M. & Hall, W. (2002) Cannabis use and mental health in younger people: Cohort study. *British Medical Journal, 325,* 1195-1198.

Pronoveau, J. M., Forsyth, J., Kelly, M. M., & Barrios, V. (2006). Repeated exposure to 20% CO(2) challenge and risk for developing panic attacks: A controlled 6- and 12-month follow-up in a nonclinical sample. *Journal of Anxiety Disorders, 20,* 1158-1167*.*

Rachman, S., & Loptaka, C. (1986). Do fears summate – III? *Behaviour Research and Therapy, 24,* 653-660.

Rapee, R. M., Brown, T. A., Antony, M. M., & Barlow, D. H. (1992). Response to hyperventilation and inhalation of 5.5% carbon dioxide-enriched air across the DSM-III-R anxiety disorders. *Journal of Abnormal Psychology, 101*, 538–552.

Reilly, D., Didcott, R., Swift, W., & Hall, W. (1998). Long-term cannabis use:

      Characteristics of users in an Australian rural area. *Addiction, 93*, 837–846.

Robins, L., Helzer, J., Croughan, J., Williams, J. & Spitzer, R. (1981). *NIMH Diagnostic*

      Interview Schedule: Version III, Rockville, National Institute of Mental Health.

Sanderson, W., Rapee, R., & Barlow, D. (1989). The influence of an illusion of control

      on panic attacks induced via inhalation of 5.5% CO_2 enriched air. *Archives of*

      General Psychiatry, 46, 157-162.

Saunders, J. B., Aasland, O. G., Babor, T. F., de la Fuente, J. R., & Grant, M. (1993).

      Development of the Alcohol Use Disorder Identification Test (AUDIT): WHO

      collaborative project on early detection of persons with harmful alcohol

      consumption- II. *Addiction, 88,* 791-803.

Schuckit, M. A. (1989). Cannabinols. In *Drug and alcohol abuse: A clinical guide to*

      diagnosis and treatment (3rd ed.) (pp. 143-157). New York: Plenum Medical.

Sherrill, D. L., Krzyzanowski, M., Bloom, J. W., & Lebowitz, M. D. (1991). Respiratory

      effects of non-tobacco cigarettes: A longitudinal study in general population.

      International Journal of Epidemiology, 20, 132-137.

Simons, J., Correia, C. J., & Carey, K. B. (2000). A comparison of motives for marijuana

      and alcohol use among experienced users. *Addictive Behaviors, 25,* 153-160*.*

Simons, J., Correia, C. J., Carey, K. B., & Borsari, B. E. (1998). Validating a five-factor

      marijuana motives measure: Relations with use, problems, and alcohol motives.

      Journal of Counseling Psychology, 45, 265–273.

Solowij, N. (1998). *Cannabis and Cognitive Functioning.* Cambridge: Cambridge

      University Press.

Smart, R. G., & Ogborne, A. C. (2000). Drug use and drinking among students in 36

      countries. *Addictive Behaviors, 25,* 455-460.

Spitzer, R. L., & Williams, J. B. (1986). *Structured Clinical Interview for DSM-III-R-Non-patient Version* (Modified for Vietnam veterans readjustment study 4/1/87). New York: New York State Psychiatric Institute, Biometrics Research.

Sridhar, K. S., Raub, W. A., Weatherby, N. L., Jr., Metsch, L. R., Surratt, H. L., Inciardi, J. A., Duncan, R. C., Anwyl, R. S., & McCoy, C. B. (1994). Possible role of marijuana smoking as a carcinogen in the development of lung cancer at a young age. *Journal of Psychoactive Drugs, 26,* 285-288.

Stephens, R. S., Babor, T. F., Kadden, R., Miller, M., & the Marijuana Treatment Project Group. (2002). The Marijuana Treatment Project: Rationale, design, and participant characteristics. *Addiction, 97* (Suppl. 1), 109-124.

Stephens, R. S., Roffman, R. A. & Simpson, E. E. (1993). Adult marijuana users seeking treatment. *Journal of Consulting and Clinical Psychology, 61*, 1100-1104.

Substance Abuse and Mental Health Services Administration. (SAMHSA; 2004). *Results from the 2003 National Survey on Drug Use and Health: National Findings.* NSDUH Series H-25. DHHS Pub. No. (SMA) 04-3964. Rockville, MD: SAMHSA.

Substance Abuse and Mental Health Services Administration. (SAMHSA; 2003). *Results from the 2002 National Survey on Drug Use and Health: National Findings.* NSDUH Series H-21. DHHS Pub. No. (SMA) 03-3774. Rockville, MD: SAMHSA.

Swift, W., Hall, W. & Teesson, M. (2001). Cannabis use and dependence among Australian adults: Results from the National Survey of Mental Health and Wellbeing. *Addiction, 96*, 737-748.

Tanda, G., & Goldberg, S. R. (2003). Cannabinoids: Reward, dependence, and underlying neurochemical mechanisms – a review of recent preclinical data. *Psychopharmacology, 169,* 115–134.

Tashkin, D. P. (1993). Is frequent marijuana smoking harmful to health? *Western Journal of Medicine, 158*, 635-37.

Tashkin, D. P. (1999). Effects of marijuana on the lung and its defenses against infection and cancer. *School Psychology International, 20*, 23-37.

Tashkin, D. P., Simmons, M. S., Sherrill, D. L., & Coulson, A. H. (1997). Heavy habitual marijuana smoking does not cause an accelerated decline in FEV1 with age. *American Journal of Respiratory Critical Care Medicine, 155,* 141-148.

Tournier, M., Sorbara, F., Gindre, C., Swendsen, J. D., & Verdoux, H. (2003). Cannabis use and anxiety in daily life: A naturalistic investigation in a non-clinical population. *Psychiatry Research, 118,* 1-8.

Tunving, K. (1985). Psychiatric effects of cannabis use. *Acta Psychiatrica Scandinavica, 72*, 209-217.

Venables, P. H. & Christie, M. J. (1980). Electrodermal activity. In I. Martin & P. H. Venables (Eds.). Techniques in psychophysiology (pp. 3-67). New York: John Wiley & Sons.

Webb, E., Ashton, C. H., Kelly, P., & Kamali, F. (1996). Alcohol and drug use in UK university students. *Lancet, 348,* 922-925.

Wolpe, J. (1958). Psychotherapy by reciprocal inhibition. Stanford, CA: Stanford University Press.

Young, M. E., Rintala, D. H., Rossi, C. D., Hart, K. A., & Fuhrer, M. J. (1995). Alcohol and marijuana use in a community-based sample of persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation, 76,* 525-532.

Zvolensky, M. J., & Bernstein, A. (2005). Cigarette smoking and panic psychopathology. *Current Directions in Psychological Science, 14*, 301-305.

Zvolensky, M. J., Bernstein, A., Marshall, E. C., & Feldner, M. T. (2006). Panic attacks, panic disorder, and agoraphobia: Associations with substance use, abuse, and dependence. *Current Psychiatry Reports, 8*, 279-285.

Zvolensky, M. J., Bernstein, A., Sachs-Ericcson, N., Schmidt, N. B., Buckner, J., & Bonn-Miller, M. O. (2006). Cannabis use, abuse, and dependence and panic attacks in a representative sample. *Journal of Psychiatric Research, 40*, 477-486.

Zvolensky, M. J., Bonn-Miller, M. O., Bernstein, A., McLeish., A. C., Feldner, M. T., & Leen-Feldner, E. W. (2006). Anxiety sensitivity interacts with marijuana use in the prediction of anxiety symptoms and panic-related catastrophic thinking among daily tobacco users. *Behaviour Research and Therapy, 44,* 907-924.

Zvolensky, M. J., & Eifert, G. H. (2000). A review of psychological processes affecting anxious responding during hyperventilation and inhalations of CO_2-enriched air. *Clinical Psychology Review, 21,* 375-400.

Zvolensky, M. J., Eifert, G. H., & Lejuez, C. W. (2001). Emotional control during recurrent 20% carbon dioxide-enriched air induction: Relation to individual difference variables. *Emotion, 2,* 148-165.

Zvolensky, M. J., Kotov, R., Antipova, A. V., & Schmidt, N. B. (2005). Diathesis-stress model for panic-related distress: A test in a Russian epidemiological sample. *Behaviour Research and Therapy, 43,* 521-532.

Zvolensky, M. J., Leen-Feldner, E. W., Feldner, M. T., Bonn-Miller, M. O., Lejuez, C. W., Kahler, C., & Stuart, G. (2004). Emotional responding to biological challenge as a function of panic disorder and smoking. *Journal of Anxiety Disorders, 18,* 19-32.

Zvolensky, M. J., Lejuez, C. W., & Eifert, G. H. (1998). The role of offset control in

    anxious responding: An experimental test using repeated administrations of 20%

    carbon dioxide-enriched air. *Behavior Therapy, 29,* 193-209.

Zvolensky, M. J., Lewinsohn, P, Bernstein, A., Schmidt, N. B., Buckner, J. D., Seeley, J.,

    & Bonn-Miller, M. O. (in press). Prospective associations between cannabis use,

    abuse, and dependence and panic attacks and disorder. *Journal of Psychiatric*

    Research.

Zvolensky, M. J., Schmidt, N. B., Antony, M. M., McCabe, R. E., Forsyth, J. P., Feldner,

    M. T., Leen-Feldner, E. W., Karekla, M., & Kahler, C. W. (2005). Evaluating the

    role of panic disorder in emotional sensitivity processes involved with smoking.

    Journal of Anxiety Disorders, 19, 673-686.

Zvolensky, M. J., Schmidt, N. B., & Stewart, S. H. (2003). Panic disorder and smoking.

    Clinical Psychology: Science and Practice, 10, 29-51.

Footnotes

[1] This study examined the "misuse" of marijuana rather than abuse or dependence. As a result, I am technically unaware of the precise percentage of those abusing or dependent on the drug in this specific study.

[2] Though researchers still debate about how many "basic" emotions exist, nearly all models suggest fear/panic represent one overarching (similar) emotional state.

[3] These same models posit that emotional factors – both specific and general – may play key roles in the maintenance and relapse of substance use. Thus, there are bi-directional pathways that are likely operative. However, the present study was concerned primarily with only one type of relation; specifically, the role of marijuana predicting future risk for anxious and fearful responding to bodily sensations.

[4] Though the inclusion of withdrawal is not currently consistent with DSM-IV criteria for marijuana dependence, it was included as it is consistent with the definition of marijuana dependence provided in this manuscript and by Budney and colleagues (2004). It is likely to be included as a core defining feature of dependence in future DSM iterations.

[5] Though matching was not quite achieved, a significant difference was not found between groups in relation to the experience of non-clinical panic (χ^2 (2, N = 94) = 1.68, $p > .10$). Given the insignificant difference and that matching was almost achieved, I chose not to include panic attacks as a covariate in the analyses.

[6] As significant differences were found between groups in relation to volume of alcohol consumed, all of the main analyses were re-calculated with the inclusion of alcohol use volume as a covariate. All of the original results were upheld in regard to statistical significance.

[7] Though matching was completed in the sample, the main analyses were recalculated by gender to assure that no differences were observed between male and female participants. Analyses indicated similar non-significant results for both female and male participants, though a trend was evident among males in regard to behavioral avoidance. Though non-significant, the direction was such that less avoidance was observed among those with greater marijuana use frequency. No other trends of statistical significance were noted. Thus, there was no empirical evidence of differential effects by gender for any of the studied dependent variables for any of the tests completed.

[8] All significant relations that were observed in the original regressions were upheld with the inclusion of both alcohol (volume – frequency by quantity) and tobacco use (cigarettes smoked per day) at level 1 in the model.

Table 1: *Criteria for Marijuana Abuse*

A. A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within 12-month period:

1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home.
2. Recurrent substance use in situations in which it is physically hazardous.
3. Recurrent substance-related legal problems.
4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.

B. The symptoms have never met the criteria for Marijuana Dependence.

Table 2: *Criteria for Marijuana Dependence*

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
    (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
    (b) markedly diminished effect with continued use of the same amount of the substance
2. Withdrawal, as manifested by either of the following [4].
    (a) the characteristic withdrawal syndrome for the substance
    (b) the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3. The substance is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
5. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
6. Important social, occupational, or recreational activities are given up or reduced because of substance use.
7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

Table 3: *Groups*

No Marijuana History	Regular, Low-Frequency Use
1. No lifetime history of marijuana use 2. Matched on current drug use (alcohol or tobacco use) 3. Excluded for chronic physical health problems 4. Excluded for current Axis I psychopathology (including substance use disorders with the exception of nicotine dependence) 5. Can have non-clinical panic attacks (strive for matching)* 6. Matched on gender	1. Marijuana use at low rates (no more than 3 occasions of use per month for the past 12 months) 2. Matched on current drug use (alcohol or tobacco use) 3. Excluded for chronic physical health problems 4. Excluded for current Axis I psychopathology (including substance use disorders with the exception of nicotine and marijuana abuse or dependence) 5. Can have non-clinical panic attacks (strive for matching)* 6. Matched on gender
Regular, High-Frequency Use 1. Must have used marijuana at least 5 times per week for the past 12 months. 2. Matched on current drug use (alcohol or tobacco use) 3. Excluded for chronic physical health problems 4. Excluded for current Axis I psychopathology (including substance use disorders with the exception of nicotine and marijuana abuse or dependence) 5. Can have non-clinical panic attacks (strive for matching)* 6. Matched on gender	

Table 4: *Matching by Subject Number*

Gender			No Marijuana History	Regular, Low-Frequency Use	Regular, High-Frequency Use
	Male		2,7,9,14,18,19,23,27,31,48,60,74,79,80,84,88,92 (n=17)	6,11,12,15,21,22,26,36,41,46,56,58,64,75,76,85,93 (n=17)	8,10,17,32,47,53,59,62,68,69,70,71,73,81,82,95,96 (n=17)
	Female		1,3,13,28,33,43,44,49,51,52,65,67,77,89,90 (n=15)	5,16,24,29,34,37,38,42,45,55,57,61,66,83,94 (n=15)	4,20,25,30,35,39,40,50,54,63,72,78,86,87,91 (n=15)
Current Alcohol Use					
	Yes		1,2,3,7,9,13,14,18,23,27,28,31,33,43,44,48,49,51,52,60,65,67,74,77,79,80,84,88,89,90,92 (n=31)	5,6,11,12,15,16,21,24,26,29,34,36,37,38,41,42,45,46,55,56,57,58,61,64,66,75,76,83,85,93,94 (n=31)	4,8,10,17,20,25,30,32,35,39,40,47,50,53,54,59,62,63,68,69,70,71,72,73,78,81,82,86,87,91,95 (n=31)
	No		19 (n=1)	22 (n=1)	96 (n=1)
Current Tobacco Use					
	Yes		1,2,3,7,9,13,	5,6,11,12,15,1	4,8,10,17,20,25

			14,18,19,23, 27,28,89,90, 92 (n=15)	6,21,22,24,26, 29,41,45,93,94 (n=15)	,30,32,47,53,63 ,68,91,95,96 (n=15)
	No		31,33,43,44, 48,49,51,52, 60,65,67,74, 77,79,80,84, 88 (n=17)	34,36,37,38,42 ,46,55,56,57,5 8,61,64,66,75, 76,83,85 (n=17)	35,39,40,50,54, 59,62,69,70,71, 72,73,78,81,82, 86,87 (n=17)
Non-Clinical Panic Attacks					
	Yes		23,28,67,89 (n=4)	5,11,24,26,29, 37,42,94 (n=8)	30,54,63,70,86 (n=5)
	No		1,2,3,7,9,13, 14,18,27,31, 33,43,44,48, 49,51,52,60, 65,74,77,79, 80,84,88,90, 92 (n=27)	6,12,15,16,21, 22,34,36,38,41 ,45,46,55,56,5 7,58,61,64,66, 75,76,83,85,93 (n=24)	4,8,10,20,25,32 ,35,39,40,47,50 ,53,59,62,68,69 ,71,72,73,78,81 ,82,87,91,95,96 (n=26)

Table 5: *Descriptive Data and Zero-Order (or Bi-variate for Dichotomous Factors) Relations between Primary Predictor and Criterion Variables*

_____

	Mean (*SD*)	Range	1	2	3	4	5	6
Predictor Variable								
1. Grouping	33 per group	1 - 3	-	.04	-.01	.13	-.08	-.04
Criterion Variables								
2. SUDS Change	31.18 (*27.21*)	-25 - 100	-	-	.33**	-.19	-.05	.18
3. DSQ	2.89 (*1.43*)	.19 – 6.19	-	-	-	-.32**	.02	.25*
4. Avoidance	65.65 (*31.22*)	0 – 100	-	-	-	-	-.23*	-.19
5. BPM Change	2.80 (*4.45*)	-9.10 – 16.65	-	-	-	-	-	.18
6. HR Change	10.95 (*12.57*)	-21.61 – 51.53	-	-	-	-	-	-

_____

Note. N = 84. * $p <$ .05, ** $p <$ .01. Grouping: Trichotomously coded marijuana grouping variable (1 = no history of use, 2 = regular, low-frequency use, 3 = regular, high-frequency use; SUDS Change: Change in Subjective Units of Distress Scale ratings from pre to post-challenge (Wolpe, 1958); DSQ: Diagnostic Sensations Questionnaire Total Score (Sanderson, Rapee, Barlow, 1989); Avoidance: Willingness to return for another challenge; BPM Change: Breaths per minute/Respiration rate change from pre to post-challenge ; HR Change: Heart rate change from pre to post-challenge.

Table 6: *Zero-Order (or Bi-variate for Dichotomous Factors) Relations between Post Hoc Predictor and Criterion Variables (Among Current Marijuana Users)*

	1	2	3	4	5	6	7	8	9	10	11	12	13
Predictor Variable													
1. Criteria	-	.65**	.58**	.38**	.07	.39**	.35**	-.05	.06	-.05	.03	-.10	-.08
2. MJ Use	-	-	.38**	.38**	-.04	.49**	.26*	-.04	-.03	.21	-.00	-.07	-.26*
3. Coping	-	-	-	.29*	.02	.39**	.43**	.01	.18	-.23	.03	-.05	-.02
4. Expansion	-	-	-	-	.06	.46**	.34**	.05	.14	-.07	.14	-.22	.05
5. Conformity	-	-	-	-	-	-.15	.30*	-.00	.20	-.13	.29*	-.05	-.09
6. Enhancement	-	-	-	-	-	-	.52**	-.04	-.14	-.01	-.04	-.05	-.24
7. Social	-	-	-	-	-	-	-	-.05	.01	-.10	.09	-.13	-.09
Criterion Variables													
8. SUDS Change	-	-	-	-	-	-	-	-	.38**	-.16	.30*	-.18	.09
9. DSQ	-	-	-	-	-	-	-	-	-	-.44**	.71**	-.02	.22
10. Avoidance	-	-	-	-	-	-	-	-	-	-	-.25*	-.29*	-.28*
11. Panic Attacks	-	-	-	-	-	-	-	-	-	-	-	-.18	.16
12. BPM Change	-	-	-	-	-	-	-	-	-	-	-	-	.08
13. HR Change	-	-	-	-	-	-	-	-	-	-	-	-	-

Note. $N = 55$. * $p < .05$, ** $p < .01$. Criteria: Marijuana use criteria (1 = marijuana use, 2 = marijuana abuse, 3 = marijuana dependence); MJ Use: Frequency of past 30 day marijuana use; Coping: Marijuana Motives Measure, Coping Subscale (Simons et al., 1998); Expansion: Marijuana Motives Measure, Expansion Subscale (Simons et al., 1998); Conformity: Marijuana Motives Measure, Conformity Subscale (Simons et al., 1998); Enhancement: Marijuana Motives Measure, Enhancement Subscale (Simons et al., 1998); Social: Marijuana Motives Measure, Social Subscale (Simons et al., 1998); SUDS Change: Change in Subjective Units of Distress Scale ratings from pre to post-challenge (Wolpe, 1958); DSQ: Diagnostic Sensations Questionnaire Total Score (Sanderson, Rapee, Barlow, 1989); Panic Attacks: Dichotomously coded panic attacks post-challenge (0 = no panic attack, 1 = panic attack); Avoidance: Willingness to return for another challenge; BPM Change: Breaths per minute/Respiration rate change from pre to post-challenge ; HR Change: Heart rate change from pre to post-challenge.

Table 7: *Descriptive Data of Post Hoc Predictor and Criterion Variables (Among Current Marijuana Users)*

	Mean (*SD*)	Range
Predictor Variable		
1. Criteria	1.81 (*.85*)	1 – 3.00
2. MJ Use	4.48 (*2.79*)	1 – 8.00
3. Coping	1.87 (*.95*)	1 – 4.25
4. Expansion	2.10 (*1.05*)	1 – 4.80
5. Conformity	1.40 (*.53*)	1 – 3.40
6. Enhancement	3.68 (*.99*)	1 – 5.00
7. Social	2.45 (*.96*)	1 – 4.20
Criterion Variables		
8. SUDS Change	31.97 (*28.68*)	-25 – 100
9. DSQ	2.88 (*1.38*)	.19 – 6.19
10. Avoidance	67.14 (*30.57*)	0 – 100
11. Panic Attacks	.72 (.45)	0 – 1.00
12. BPM Change	2.57 (*4.56*)	-9.10 – 16.65
13. HR Change	11.44 (*12.71*)	-21.61 – 46.34

Note. $N = 55$. Criteria: Marijuana use criteria (1 = marijuana use, 2 = marijuana abuse, 3 = marijuana dependence); MJ Use: Frequency of past 30 day marijuana use; Coping: Marijuana Motives Measure, Coping Subscale (Simons et al., 1998); Expansion: Marijuana Motives Measure, Expansion Subscale (Simons et al., 1998); Conformity: Marijuana Motives Measure, Conformity Subscale (Simons et al., 1998); Enhancement: Marijuana Motives Measure, Enhancement Subscale (Simons et al., 1998); Social: Marijuana Motives Measure, Social Subscale (Simons et al., 1998); SUDS Change: Change in Subjective Units of Distress Scale ratings from pre to post-challenge (Wolpe, 1958); DSQ: Diagnostic Sensations Questionnaire Total Score (Sanderson, Rapee, Barlow, 1989); Panic Attacks: Dichotomously coded panic attacks post-challenge (0 = no panic attack, 1 = panic attack); Avoidance: Willingness to return for another challenge; BPM Change: Breaths per minute/Respiration rate change from pre to post-challenge ; HR Change: Heart rate change from pre to post-challenge.

Figure 1: Graphical representation of the three theoretically postulated pathways of
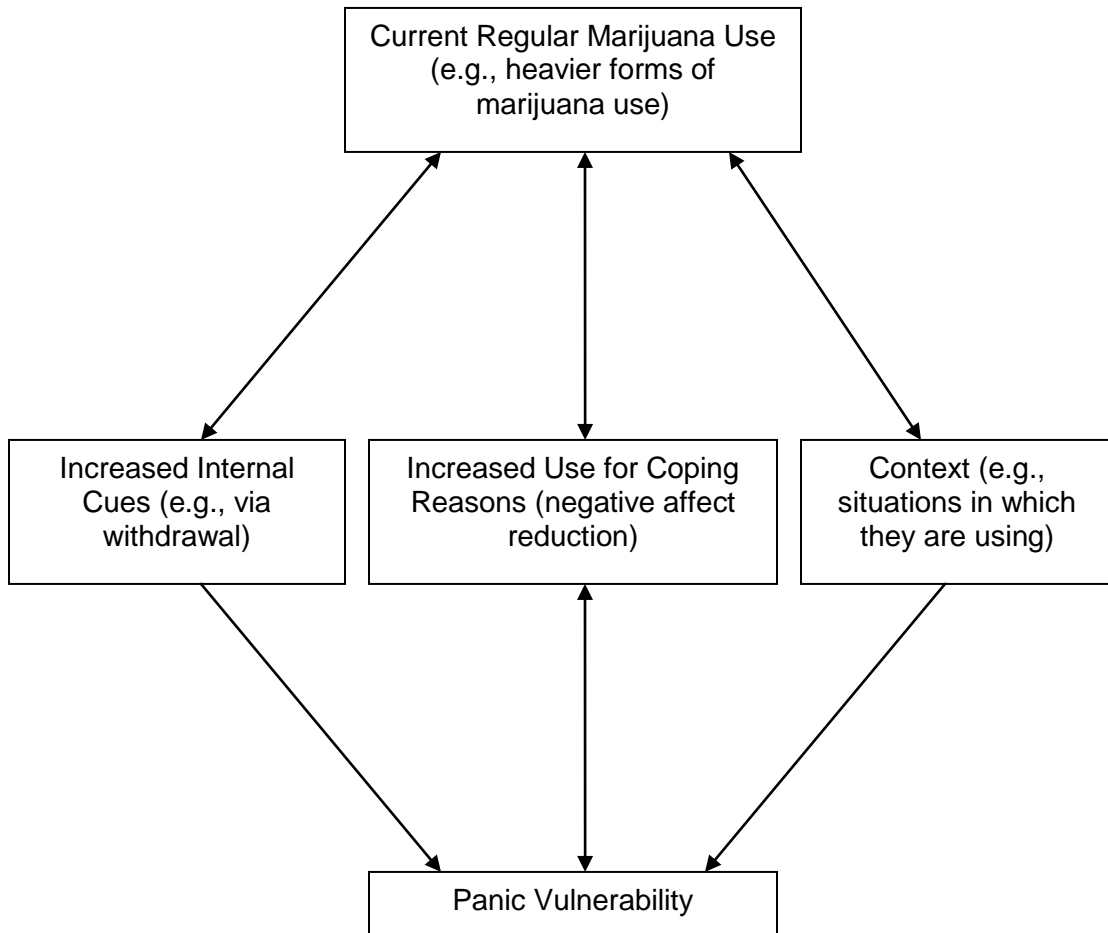
marijuana use leading to panic vulnerability

Figure 2: Schematic diagram of the study procedure