6-24-2008

Anxiety Sensitivity As Moderator of the Association Between Nicotine withdrawal and Panic-Relevant Responding to a Carbon Dioxide-Enriched Air Laboratory Challenge

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ANXIETY SENSITIVITY AS MODERATOR OF THE ASSOCIATION BETWEEN NICOTINE WITHDRAWAL AND PANIC-RELEVANT RESPONDING TO A CARBON DIOXIDE-ENRICHED AIR LABORATORY CHALLENGE

A Dissertation Presented

by

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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 Clinical Psychology

October, 2009

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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Date: March 25, 2008

Abstract

Individuals high in anxiety sensitivity (AS), a cognitive risk factor denoting a fear of anxiety-related sensations (Reiss & McNally, 1985), may be at increased risk of misinterpreting nicotine withdrawal-relevant interoceptive cues as harmful, thus amplifying their risk for panic problems. This study tested the moderating role of AS on the association between nicotine withdrawal and panic-relevant responding to a carbon dioxide-enriched air laboratory challenge. Specifically, it was hypothesized that AS moderates the relation between nicotine withdrawal (group status) and responding to a carbon dioxide-enriched air procedure (controlling for anticipatory anxiety, gender, negative affectivity, number of axis I diagnoses, and average daily smoking rate), as indexed by: (1) level of anxiety focused on bodily sensations and intensity of panic attack symptoms; (2) skin conductance reactivity; and (3) level of behavioral avoidance of a future challenge. To test this hypothesis, 90 daily smokers (35 women; M_{age} = 28.87, *SD* = 12.12, *Range* = 18-60 years) were enrolled and enlisted to attend two study sessions. At the conclusion of the first session, participants were randomly assigned to one of two groups (12-hour nicotine deprivation or smoking 'as usual'). At the second scheduled session, participants in both groups underwent a 10% carbon dioxide-enriched air laboratory challenge to assess panic-relevant responding. Contrary to hypothesis, the AS by nicotine withdrawal (group status) interactive effect was not significantly predictive of post-challenge anxiety, panic attack symptoms, skin conductance reactivity, or behavioral avoidance. However, *post hoc* tests indicated that the AS by nicotine withdrawal (group status) interaction was significantly predictive of *peri*-challenge anxiety ratings. Furthermore, *post hoc* tests demonstrated that between-group (significant) differences in withdrawal symptoms diminished after the first assessment of the challenge session. Results are discussed in the context of the theoretical and clinical implications of the current work, limitations of the current study, and future directions for work relevant to this line of inquiry.

Acknowledgements

First, I would like to thank my mentor, Dr. Michael Zvolensky, for his unconditional encouragement, kindness, and guidance through all the phases of this project and throughout my years of graduate school. His dedication to my professional growth and genuine enthusiasm for my research endeavors has been truly instrumental in shaping my graduate training and my development as a clinical scientist.

Thank you also to the members of the Anxiety and Health Research Laboratory (AHRL) for all the support and good humor they have shared with me throughout the past five years. The friendships I have formed during my years in the AHRL will stay with me for many years to come. Special thanks to the research assistants who worked on the various phases of this project and assisted with recruitment, telephone screening interviews, scheduling, data management, and general administrative responsibilities: Marley Cloyes, Benjamin Coleman, Matthew Hoffman, Emily Garai, Kristen Kutler, Amanda Kutz, Megan Malgeri, and Sarah Nelson.

Furthermore, I would like to thank my husband, Jim Morrison, for his unwavering patience, understanding, and confidence in my ability to accomplish my goals. Not only has he been an amazing source of emotional support, but he was a tremendous help with the participant recruitment efforts for this project, as well. Thanks also to our dog, Moonyi, whose boundless love and excitement is always a (very) welcome distraction.

Finally, I would like to thank my dissertation committee members for their time and expertise in reviewing my dissertation. I also wish to acknowledge the National Institute on Drug Abuse for funding this work (1 F31 DA 021006-02).

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Introduction

The overarching aim of the present investigation was to delineate empirical linkages and interactive effects between a cognitive risk factor for panic disorder (PD), anxiety sensitivity (AS; fear of anxiety), and acute (12-hour) nicotine withdrawal in order to better understand the etiology of panic vulnerability processes. To provide a framework for the current study and contextualize the relevance of AS and nicotine withdrawal in terms of panic vulnerability, the present document reviews the theoretical and empirical literature related to the following domains: (1) clinical significance of panic-related psychopathology; (2) clinical significance of smoking; (3) co-occurrence of smoking and panic psychopathology; (4) associations between smoking and onset and concurrence of panic psychopathology; (5) AS and smoking; (6) nicotine withdrawal and panic vulnerability; and (7) nicotine withdrawal and AS.

Background and Significance

Panic-Spectrum Psychopathology: Clinical Significance

Panic attacks. Panic attacks are a subjective sense of extreme fear or impending doom accompanied by an autonomic nervous system surge and a strong flight-or-fight action tendency (Barlow, Brown, & Craske, 1994). Recent estimates of unexpected ("out of the blue") panic attacks in representative samples suggest that approximately 20% of individuals experience such attacks at one point in their lives and 11.2% have experienced such attacks in the past 12 months (Kessler, Chiu, Jin, Ruscio, Shear, & Walters, 2006), indicating that it is a relatively common psychological experience. These findings are generally consistent with earlier investigations using non-representative samples (e.g., Craske, Brown, Meadows, & Barlow, 1995). Many people experience panic attacks without necessarily developing PD (i.e., nonclinical panic attacks; Norton, Cox, & Malan, 1992). Typically, individuals who experience nonclinical

panic attacks do not experience these attacks as “spontaneous” or “uncued” as is generally the case in PD, but rather in certain contexts such as stressful or threatening social situations (Norton, 1989). Such panic attacks can occur among those with and without other types of psychopathology (i.e., Bryant & Panasetis, 2005). Even when not accompanied by PD, panic attacks can be associated with increased rates of disability and role impairment (Kessler et al., 2006). Panic attack onset tends to first occur between the ages of 12-13 years (Hayward et al., 1992; Macaulay & Kleinknecht, 1989; Warren & Zgourides, 1988). Important interpretative caveats to these investigations, however, are that they have focused almost exclusively on youth. These rates of onset should thus be considered useful guides for estimating onset but as of yet cannot be viewed as definitive.

Panic disorder (PD). PD involves recurrent, unexpected panic attacks *and* anxious apprehension about the possibility of experiencing future panic episodes (American Psychiatric Association [APA], 2000). Lifetime estimates of PD with agoraphobia and PD without agoraphobia are 1.1% and 3.7%, respectively (Kessler et al., 2006). Twelve-month estimates for PD (with or without agoraphobia) are approximately 2.8% (Kessler et al., 2006). Thus, PD is a relatively common psychiatric disorder when considered from both lifetime and 12-month prevalence rates. This clinical condition is generally regarded as a disorder of adulthood with a median age of onset of 24 years (Burke, Burke, Regier, & Rae, 1990), although some emerging research has noted that another possible “peak onset period” may be between ages 45-54 years (Burke et al., 1990). PD with and without agoraphobia is associated with a chronic, fluctuating course, high rates of healthcare utilization, and high rates of both psychiatric comorbidity and substance use disorders (Brown & Barlow, 1992; Zvolensky, Bernstein, Marshall, & Feldner, 2006).

Agoraphobia. Individuals with PD often show some signs of avoidance of potentially threatening situations (Feldner, Zvolensky, & Leen-Feldner, 2004), although not all persons with this disorder will meet diagnostic criteria for agoraphobia. Agoraphobia often reflects a pattern of behavior characterized by consistent avoidance of threatening situations where a panic attack, or high levels of anxiety, is perceived to be likely to occur (e.g., limited options to escape); or the experience of marked emotional distress when in such situations. Avoidance behavior can be multifaceted, ranging from certain physical environments to more specific stimuli (e.g., certain substances like caffeine; Rapee, Craske, & Barlow, 1995). Although agoraphobia does not necessarily require the presence of panic attacks or PD (Fava, Grandi, & Canestrari, 1988), many researchers conceptualize agoraphobia as a complication of (severe) PD (Barlow, 2002). Agoraphobia with or without PD often is related to higher rates of clinically significant life impairment and severity of illness (Kessler et al., 2006). The onset of agoraphobia with or without PD is not as firmly established as that of panic attacks and PD, although some research suggests it may occur later in life (Lindesay, 1991).

Smoking: Clinical Significance

Cigarette smoking is the most popular form of tobacco use (Windle & Windle, 1999), and it is a leading preventable cause of death and disability in the United States ([U.S.], Centers for Disease Control and Prevention [CDC], 1994). Smoking is a major causal or complicating factor in various types of medical illness, including heart disease, a variety of pulmonary diseases (e.g., chronic obstructive pulmonary disease), and several types of cancer (U.S. Department of Health and Human Services, 2000). Moreover, smoking is responsible for approximately 31% of all cancer-related deaths in the U.S. (American Cancer Society, 2006). Although smoking increases one's risk for developing a variety of lethal medical diseases, quitting smoking decreases the risk of

developing such problems and may increase the survival time among those persons who have already developed medical problems (Samet, 1992).

Despite a reduction in smoking prevalence over the past 25 years, approximately 45 million to 48 million (approximately 22% to 25%) adults in the U.S. currently smoke (CDC, 1996). In addition, research has shown that approximately 64% of adolescents report having smoked cigarettes and 14% report smoking in the past month (i.e., 20 out of the past 30 days; CDC, 2002), evidencing the maintained prevalence of smoking among youth. Though approximately 70% of current smokers report motivation to quit smoking (CDC, 1999), 90% to 95% of smokers who quit smoking on their own (Garvey, 1988) and 60% to 80% of those who attend smoking cessation treatment programs relapse to smoking (Brown & Emmons, 1991).

Co-occurrence of Smoking and Panic Psychopathology

Both community-based and representative studies have examined the extent of the co-occurrence between smoking and panic psychopathology. Investigations have consistently found a positive association between smoking and a history of panic attacks and PD (Amering et al., 1999; Degenhardt, Hall, & Lynskey, 2001; Glassman et al., 1990; Hughes, Hatsukami, Mitchell, & Dahlgren, 1986; Pohl, Yeragani, Balon, Lycaki, & McBride, 1992; Tilley, 1987).

Studies of treatment-seeking adults. Among treatment-seeking adults, several studies have reported that, among patients with panic psychopathology (either PD or agoraphobia or both), rates of current daily smoking ranged from 19% (Baker-Morissette, Gulliver, Wiegel, & Barlow, 2004) to 57% (Himle, Thyer, & Fischer, 1988), with the majority of investigations finding rates between 30% to 50% (Amering et al., 1999; Lopes et al., 2002; McCabe et al., 2004; Pohl et al., 1992). These rates of smoking are generally higher than among comparison groups of individuals without

psychiatric problems and typically higher — or as high as — rates among individuals with other anxiety or mood disorders (McCabe et al., 2004). These data collectively suggest that smoking is relatively common among treatment-seeking individuals with panic psychopathology.

Community-based studies. Two studies examining prevalence rates of smoking and panic psychopathology using community-based samples have been conducted to date (Hayward, Killen, & Taylor, 1989; Valentiner, Mounts, & Deacon, 2004). Hayward et al. (1989) examined 95 ninth grade public school students, while Valentiner et al. (2004) examined 337 college students. Both investigations found that individuals with panic attacks, but not necessarily those with PD or agoraphobia, reported higher rates of regular smoking (Hayward et al., 1989; Valentiner et al., 2004). For example, Hayward et al. (1989) reported that 77% of individuals with a lifetime history of panic attacks had engaged in "experimental" or "regular" smoking compared to only 48% of adolescents without a lifetime history of panic attacks. These findings generally parallel those noted in studies of treatment-seeking individuals with panic psychopathology.

Studies using representative samples. Several studies have utilized representative sampling to examine smoking rates among those with panic psychopathology (Covey, Hughes, Glassman, Blazer, & George, 1994; Farrell et al., 2001; Lasser et al., 2000), and conversely, to examine rates of panic psychopathology among smokers (Black, Zimmerman, & Coryell, 1999; Breslau, Kilbey, & Andreski, 1991; Goodwin, Zvolensky, & Keyes, 2007; Nelson & Wittchen, 1998). In the most comprehensive representative study, based on data from the National Comorbidity Survey (NCS), a nationally-based study that used structured clinical interviews to document prevalence rates of psychopathology (Kessler et al., 1994), Lasser et al.

(2000) examined smoking rates corresponding to psychiatric diagnoses. Participants were 4,411 individuals, aged 15 to 54 years, residing in the U.S. Lasser et al. (2000) reported that rates of smoking were highest among individuals with panic-related problems (i.e., history of panic attacks, PD, and agoraphobia) and other anxiety disorders where panic attacks are common (i.e., posttraumatic stress disorder; Lasser et al., 2000). Among individuals diagnosed with panic attacks, PD, and agoraphobia in their lifetime, 38%, 35%, and 38% were current smokers, respectively. These rates were significantly greater than rates of current smoking among individuals without mental illness (22%). By comparison, 36% of individuals with a lifetime history of major depression and 49% of individuals with a lifetime diagnosis of drug abuse or dependence were current smokers. Rates of lifetime smoking among persons with a lifetime history of panic psychopathology (i.e., panic attacks, PD, or agoraphobia) ranged from 58% to 61%. When diagnostic status in the past month was used as the grouping variable, current rates of smoking were 46% among persons with panic attacks, 42% among persons with PD, and 48.1% among persons with agoraphobia. It is noteworthy that as number of mental diagnoses increased (ranging from 0 to 4 or more), the percentage of heavy (i.e., peak consumption exceeding 24 cigarettes a day) compared to relatively lighter (i.e., peak consumption less than 24 cigarettes per day) smokers increased. Overall, these data suggest that smoking occurs at relatively higher rates among those with panic psychopathology compared to those with no mental illness; and that heavier smoking may be associated with more severe psychopathology (i.e., higher number of comorbid diagnoses).

Other investigations have sought to evaluate rates of panic psychopathology among smokers (Black et al., 1999; Breslau et al., 1991; Goodwin et al., 2007; Nelson & Wittchen, 1998). All of these investigations except that by Black and colleagues (1999),

which reported community-based recruitment, involved some sort of representative sampling strategy. In contrast to the studies reviewed earlier, these investigations attempted to understand panic within the context of tobacco dependence and severity. Here, across studies, results indicated that among those persons meeting criteria for more addictive use of cigarettes (e.g., nicotine dependence), there is a greater prevalence of panic psychopathology (Breslau et al., 1991). For example, Breslau and colleagues (1991) found that 6.6% of persons meeting criteria for moderate nicotine dependence, 4.8% of those with mild nicotine dependence, and 2.4% of those with no nicotine dependence had a lifetime diagnosis of PD. Nelson and Wittchen (1998) similarly found that, among participants endorsing a lifetime history of smoking (yes/no), 7.6% met lifetime diagnostic criteria for panic attacks, 2% for PD, and 4.4% for agoraphobia. These rates of panic psychopathology were significantly greater than those reported among nonsmokers of whom 2.4% had a panic attack history, 0.7% had PD, and 1.6% had agoraphobia. Smokers with a lifetime nicotine dependence diagnosis, compared to smokers without such a diagnosis, evidenced greater rates of panic attacks (11.3% versus 4.0%), PD (2.2% versus 1.8%), and agoraphobia (6.4% versus 2.5%). It should be noted that a similar, albeit not uniform, pattern of findings was apparent for individuals with other psychiatric disorders (e.g., alcohol dependence, drug dependence). Overall, the extant literature suggests that heavier rates of smoking (greater degrees of dependence) are associated with a greater rate of comorbidity with panic psychopathology.

Smoking: Association with Onset of and Concurrence with Panic Problems

Developmental course. The onset of daily smoking typically occurs between the ages of 15 and 20 and rarely after age 25 (Breslau, Johnson, Hiripi, & Kessler, 2001). For example, the CDC reports that in the U.S., approximately 3,900 adolescents

between the ages of 12 and 17 years initiate cigarette smoking each day (CDC, 2004), and an additional 1,500 become daily cigarette smokers each day (Substance Abuse and Mental Health Services Administration, 2006).

While the median age of onset for PD is approximately 24 years of age (Burke et al., 1990), the typical age of onset for panic attacks is between the ages of 12 to 13 years (Goodwin & Gotlib, 2004; Hayward et al., 1992; Warren & Zgourides, 1988). For example, Goodwin and Gotlib (2004) reported that the mean age of panic attack onset was 13.4 years (*n* = 1,285; age range: 9 – 17 years). Other studies based on community or school samples have found similar results, with the modal age of onset of panic attacks being age 12 (Hayward et al., 1992; Warren & Zgourides, 1988); clinical samples report a slightly younger age of panic attack onset (Alessi & Magen, 1988; Black & Robbins, 1990). These data suggest that smoking initiation may typically precede the onset of PD. However, one important interpretative caveat to these investigations is that they focus exclusively on youth and expressly do not sample from a larger age range. Thus, it is possible that the "average" age of onset of panic attacks may be different if the sampling strategy incorporated adults.

In fact, reports of smokers with "active panic problems" are not entirely consistent with this perspective. For example, Amering and colleagues (1999) examined 102 consecutive PD patients with or without agoraphobia attending an academic treatment clinic in Austria. Participants were diagnosed using a structured clinical interview and queried about their smoking status. Individuals presenting with "severe somatic illness" and comorbid depression and other psychiatric illnesses were excluded from the study. Amering and colleagues (1999) reported that the onset of smoking preceded the onset of PD (cf. panic attacks) by 12.3 years (*SD* = 9.4) in a community sample of individuals with the condition (*n* = 102). Furthermore, Bernstein, Zvolensky, Schmidt, and Sachs-

Ericsson (2007) directly evaluated onset patterns among 4,409 adults (M_{age} = 33.1, *SD* = 10.7, women = 2,221) from the NCS (Kessler et al., 1997). Results indicated that, among individuals with a lifetime history of comorbid daily smoking and panic attacks (*n* = 167), the onset of daily smoking (*M* = 16.0 years, *SD* = 3.0) preceded the onset of panic attacks (*M* = 27.8 years, *SD* = 7.6) in the majority, but not among all, of the individuals reporting co-occurring smoking and panic psychopathology (63.7%, *n* = 106). A relatively large minority of comorbid cases (33%; *n* = 55) reported that panic attacks (*M* = 11.4 years, *SD* = 5.2) *preceded* the onset of daily smoking (*M* = 18.2 years, *SD* = 4.7). The concurrent (same year) onset of these two problems appeared rarely (3.3%, *n* = 6). Also, as the pattern of ages of onset above illustrates, daily smoking demonstrated a relatively consistent mean age of onset (middle to late adolescence) across comorbid sub-samples and the uni-morbid sub-sample of smokers (age 18.5 years). In contrast, the mean ages of onset of panic attacks differed markedly between the comorbid sub-samples and the uni-morbid sub-sample of nonsmokers with panic attacks (age 20.3 years).

Prospective studies. Prospective studies offer unique insight into the nature of the observed relations over time, and by extension, the order or temporal sequence of the associations. Researchers have evaluated the association between smoking and risk of panic psychopathology in a number of studies. Breslau and Klein (1999) tested the association between daily smoking and risk for panic attacks and PD. Participants were drawn from two separate epidemiologically-defined data sets. Across both data sets, results indicated that there was a significant lifetime and prospective association between daily smoking and onset of panic attacks and PD; daily smokers were almost 4 times more likely to experience panic attacks and 13 times more likely to develop PD after controlling for major depression and gender. Additionally, among individuals who

continued to smoke, compared to those who had quit, there was a significantly increased risk for experiencing a panic attack and PD. Furthermore, Johnson et al. (2000) investigated the longitudinal association between cigarette smoking and anxiety disorders among 688 youth. Heavy smoking (≥ 20 cigarettes per day) during adolescence was associated with a higher risk of developing PD and agoraphobia during early adulthood, even after controlling for a variety of theoretically-relevant factors (e.g., alcohol and other drug use, parental history of psychopathology, temperament, socioeconomic status). Additionally, smoking did not increase the risk of developing other anxiety disorders such as obsessive-compulsive disorder, thus indexing specificity with respect to panic-related problems. There also was no evidence that PD or another anxiety disorder during adolescence was associated with an increased risk of chronic cigarette use in young adulthood.

In another prospective study recently completed in Germany, 2,500 participants (ages 14-24 years at baseline) were evaluated over 4 years (Isensee, Wittchen, Stein, Höfler, & Lieb, 2003). Compared with all other levels of smoking, dependent regular smokers at baseline were significantly more likely to develop panic attacks and PD, and a similar pattern was observed for agoraphobia. Similarly, Breslau, Novak, and Kessler (2004) evaluated daily smoking and the subsequent onset of psychiatric disorders. Results indicated that the onsets of PD (odds ratio = 2.6) and agoraphobia (odds ratio = 4.4) were associated with pre-existing daily smoking after controlling for age, gender, ethnicity, and educational level. Additionally, after controlling for pre-existing psychiatric disorders and sociodemographic characteristics, current nicotine dependent smokers were significantly more likely to meet diagnostic criteria for PD compared to current non-dependent smokers and former smokers. Importantly, the likelihood of PD and agoraphobia was significantly reduced with increased time since quitting; and these

effects were specific to these conditions and not other psychiatric disorders. More recently, Goodwin, Lewinsohn, and Seeley (2005) replicated the results of Breslau and Klein (1999), Johnson et al. (2000), and Isensee et al. (2003) by finding that daily smoking during adolescence was associated with an increased risk for panic attacks and PD in young adulthood. Moreover, the observed effects were no longer evident after controlling for parental smoking and anxiety disorder status, suggesting that these family history characteristics may be formative in the linkages between smoking and panic psychopathology.

While data focused expressly on developmental course and smoking-panic psychopathology is limited, extant studies suggest that the majority of cases may involve smoking preceding panic attacks and PD. Taken together, it seems that smoking is associated with increased risk for developing panic psychopathology (Breslau & Klein, 1999; Isensee et al., 2003; see Zvolensky, Feldner, Leen-Feldner, & McLeish, 2005, for a review). These same studies (e.g., Lasser et al., 2000) suggest that the observed association between smoking and panic psychopathology is not due to sociodemographic characteristics (e.g., gender), other psychiatric conditions (e.g., major depressive disorder, alcohol use), or symptom overlap in diagnostic criteria for anxiety disorders and nicotine dependence (Zvolensky, Schmidt, & Stewart, 2003).

Smoking and maintenance of panic psychopathology. It is important to briefly note that smoking might still theoretically contribute to maintenance processes relevant to comorbidity among individuals who meet criteria for two or more disorders (Zvolensky, Schmidt, & Stewart, 2003); though there is little empirical work on this topic. Furthermore, there is some limited work suggesting that smoking among those with panic attacks or PD is associated with more severe panic problems (Zvolensky, Forsyth, Fuse, Feldner, & Leen-Feldner, 2002; Zvolensky, Schmidt, & McCreary, 2003). Although

these studies are not solely focused on the etiology of PD per se, they provide further evidence of a smoking-panic association. For example, Zvolensky, Schmidt, and McCreary (2003) found that treatment-seeking smokers with PD compared to nonsmokers with PD reported more severe and intense anxiety symptoms, greater interview-based overall severity ratings of panic symptoms, and more social impairment. In these investigations, effects did not vary by gender, age, or other forms of substance use. Moreover, there is emerging evidence that these types of effects are relatively specific to PD and psychopathology that frequently co-occurs with panic (e.g., posttraumatic stress disorder; Feldner, Babson, & Zvolensky, 2007). For example, Morissette, Brown, Kamholz, and Gulliver (2006) found that smokers with anxiety disorders, as compared to their non-smoking counterparts, reported higher levels of AS (i.e., fear of anxiety and bodily-related sensations; McNally, 2002; reviewed below), anxiety symptoms, and agoraphobic avoidance. However, this association was specific to PD and not evident for any of the other studied anxiety disorders, which did not include posttraumatic stress disorder (Morissette et al., 2006).

Laboratory studies have yielded similar results. As one illustrative example, Zvolensky, Leen-Feldner et al. (2004) employed a voluntary hyperventilation paradigm to examine associations between smoking and fearful responding to bodily sensations among 61 adults from the community (40 women; M_{age} was 24.8 [SD = 7.8]). One-third of the sample met diagnostic criteria for current PD (primary diagnosis) and consisted of regular smokers; one-third met only the diagnostic criteria for current PD (primary diagnosis) but was comprised of non-smokers; and the final third consisted of regular smokers who did not meet criteria for PD or any other type of psychopathology. Results indicated that smokers with PD reported greater levels of anxiety, as compared to smokers without PD, at baseline and showed greater increases in anxiety during the

post-challenge assessment and recovery period relative to baseline. Additionally, there was a significant time by group interaction for the panic groups; specifically, the linear decrease in anxiety during recovery was significantly steeper for nonsmokers with PD than for smokers with PD. This finding suggests a slower reduction in anxiety among smokers with PD as compared to nonsmokers with PD. Together, smoking among those with panic psychopathology seems to be associated with more severe panic symptoms.

Summary of Smoking and Panic Literature

Overall, research suggests that (1) smoking is more common among those with panic attacks and PD compared to the general population and vice versa (Breslau et al., 1991; Goodwin et al., 2007; Lasser et al., 2000); (2) smoking typically precedes the onset of PD; (3) smoking increases the risk for developing panic problems (Johnson et al., 2000); and (4) smoking is associated with more severe panic symptoms among those with the disorder (Zvolensky, Leen-Feldner et al., 2004). These four lines of research suggest that daily smokers are an "at risk" group for panic problems and prompt psychopathologists to explore the mechanisms underlying these associations.

Anxiety Sensitivity and Smoking

Anxiety sensitivity (AS). Arguably, the most important individual difference factor relevant to the etiology of PD is AS, which reflects the fear of anxiety and anxiety-related sensations (Reiss & McNally, 1985). AS is a dispositional, trait-like cognitive characteristic that is unique from the temperamental variables of trait anxiety (McNally, 1996). This cognitive factor is theorized to predispose individuals to the development of panic problems (Reiss & Havercamp, 1996). For example, if a person perceives bodily sensations associated with autonomic arousal as a sign of imminent personal harm, this "high AS" individual is theorized to experience elevated levels of anxiety and to be at an increased risk for a panic attack. Research has strongly supported this line of theorizing:

(1) prospective studies with adolescents and adults indicate that AS predicts the future occurrence of panic attacks and worry about the future occurrence of such attacks (Schmidt, Lerew, & Jackson, 1997, 1999; Schmidt, Zvolensky, & Maner, 2006; Weems, Hayward, Killen, & Taylor, 2002); (2) AS is a significant predictor of responses to panic provocation procedures in the laboratory, even after controlling for negative affectivity (Zinbarg, Brown, Barlow, & Rapee, 2001); (3) AS is elevated among persons with a history of PD compared to those without the disorder (Taylor, Koch, & McNally, 1992); and (4) AS decreases with remission of panic psychopathology through intervention (Telch et al., 1993), and unlike many other panic risk factors (e.g., family history of PD), can therefore easily be targeted for therapeutic change in future intervention work.

AS and smoking. Several studies have examined the potential moderating role of AS in terms of the link between smoking and panic-relevant psychopathology, such that higher levels of AS may strengthen—or exacerbate—this association. In one study of epidemiologically-defined (i.e., representative) adult residents of Moscow (n = 95 daily smokers from a larger sample of about 400 persons; Zvolensky, Kotov, Antipova, & Schmidt, 2003), AS moderated the effects of cigarettes smoked per day (M = 15) on level of agoraphobic avoidance. This significant interaction accounted for approximately 10% of unique variance after controlling for their respective main effects and the theoretically-relevant factors of problematic alcohol use and negative affectivity. No interaction, however, was found for panic attacks, potentially due to the fact that assessment of this factor was restricted to the past (most recent) week to enhance the validity of panic reports (but probably truncating variability). Overall, these findings suggest smokers are not a homogeneous group in regard to their risk for panic problems and individual differences in AS may be key factors in accounting for such differences.

Moderating effects for AS also have been evident in between-group tests involving smokers and nonsmokers. For example, the combination of high levels of AS and a positive current smoking status predicted panic symptoms and somatic complaints, but not depressive symptoms in a biological challenge test (Leen-Feldner et al., 2007). Again, such findings suggest that AS (and possibly other factors) may moderate the relation between smoking and prototypical panic psychopathology variables (panic attacks and somatic complaints), even after controlling for gender and negative affectivity. Moreover, these associations are specific to panic-relevant processes. In a re-analysis of the Russian epidemiological study reported earlier, Zvolensky and colleagues extended this smoking and AS effect (Zvolensky, Kotov, Bonn-Miller, Schmidt, & Antipova, 2008). Here, AS again moderated the association of smoking status with indices of anxiety symptoms; effects were evident after controlling for the variance accounted for by alcohol use problems, environmental stress (past month), and gender.

Prospective tests examining moderating factors in the tobacco use-panic relation are very limited. In the only study to date on this topic, McLeish, Zvolensky, and Bucossi (2007) evaluated the moderating role of AS in the relation between smoking rate and panic vulnerability variables among a community-based sample of 125 daily smokers (60 women; M_{age} = 26.02 years). Findings indicate that the interaction between AS and smoking rate significantly predicted concurrent agoraphobic avoidance (3.2% of unique variance) and change in levels of anticipatory anxiety about bodily sensations during the 3-month follow-up period (4.7% unique variance). Smokers high in AS who also smoked at greater rates reported the highest levels of avoidance and greatest increase in anticipatory anxiety. These data, in accord with cross-sectional findings (Leen-Feldner et al., 2007; Zvolensky, Kotov et al., 2003), once again, suggest that AS is an important

individual difference factor that, when coupled with higher rates of smoking, is associated with greater levels of avoidance and anticipatory anxiety among daily smokers, both of which contribute to the development of panic psychopathology.

AS and smoking cessation. In the earliest study in this domain, Brown, Kahler, Zvolensky, Lejuez, and Ramsey (2001) examined a subset of data from a randomized controlled clinical trial comparing standard smoking cessation treatment versus standard smoking cessation plus cognitive-behavioral treatment for depression in smokers with past major depressive disorder. In this investigation, the association between AS and relapse during the early stages of a quit attempt (e.g., first week), when individuals are most apt to experience symptoms of anxiety (Hughes, Higgins, & Hatsukami, 1990), was examined. AS was significantly associated with increased odds of lapsing during the first week after quit day (odds ratio = 2.0). Subsequent work has conceptually replicated and extended the results of Brown and colleagues (2001). For example, Zvolensky, Bonn-Miller, Bernstein, and Marshall (2006) found AS was significantly associated with increased risk of early smoking relapse among a community sample of daily smokers; these effects were evident above and beyond smoking rate and negative affectivity. Such work has recently been extended to low-level smokers from Mexico, adding cross-national empirical support (Zvolensky, Bernstein, Jurado, Colotla, Marshall, & Feldner, 2007). Collectively, there is a growing amount of empirical evidence suggesting that panic psychopathology or pre-morbid panic-relevant variables, such as elevated AS, is related to early relapse problems, and possibly, lower rates of overall success in quitting.

A closely related line of inquiry has suggested that AS is related to motivation to quit, barriers to quitting, and reasons for quitting. For example, Zvolensky, Baker, and colleagues (2004) found AS was related to higher levels of current motivation to quit smoking among adult daily smokers (M_{age} = 20.4, $M_{cigarettes\ per\ day}$ = 10.2), and these

effects were not attributable to other theoretically-relevant factors (e.g., gender, smoking rate). These findings may at first seem counterintuitive in that it seems logical that individuals with high levels of AS would be *less* likely to express interest or motivation in quitting due to the feared negative consequences related to quitting (e.g., withdrawal symptoms, emotional dyscontrol). Yet, related work suggests that smokers who worry about the negative health-related effects of smoking may engage in more quitting behavior (Dijkstra & Brosschot, 2003). From this perspective, high AS smokers may be more apt to perceive a personal vulnerability to the negative effects of smoking (e.g., health risks), and as such, express greater *motivation* to quit (Zvolensky & Bernstein, 2005) despite their greater difficulty in successfully doing so (Brown et al., 2001). In line with this reasoning, Zvolensky, Vujanovic, and colleagues (2007) more recently examined the relations between AS and (1) motivation to quit smoking, (2) barriers to smoking cessation, and (3) reasons for quitting smoking among 329 (160 women; M_{age} = 26.08 years, *SD* = 10.92) adult daily smokers. After covarying for theoretically-relevant variables (negative affectivity, gender, axis I psychopathology, non-clinical panic attack history, number of cigarettes smoked per day, and current levels of alcohol consumption), AS was significantly incrementally related to level of motivation to quit smoking, as well as perceived barriers to quitting smoking. Additionally, after accounting for the variance explained by other theoretically relevant variables, AS was significantly associated with self-control reasons for quitting smoking (intrinsic factors), as well as immediate reinforcement and social influence reasons for quitting (extrinsic factors). These results provide empirical evidence that AS is uniquely related to level of motivation to quit smoking, perceived barriers to quitting, and certain intrinsic and extrinsic reasons for quitting.

AS and smoking motives. Another facet of evidence in support of a smoking-

panic relation is apparent from motivational and outcome expectancy research. In regard to smoking-related motivational processes, there is a large empirical literature documenting that smokers often attribute their smoking, at least in part, to its mood-regulating functions and believe that smoking will reduce negative affect states (Parrott, 1999). Due to their affective vulnerability, smokers with panic-relevant vulnerabilities (i.e., high AS) may be particularly motivated to smoke to escape from emotional distress elicited by acute nicotine withdrawal or non-withdrawal states (e.g., anticipatory anxiety; Zvolensky & Bernstein, 2005). A number of cross-sectional studies support this theory. Specifically, studies have indicated that AS is associated with coping-oriented smoking motives among young adults without a history of psychopathology (Novak, Burgess, Clark, Zvolensky, & Brown, 2003; Stewart, Karp, Pihl, & Peterson, 1997; Zvolensky, Bonn-Miller et al., 2006), adult clinical samples (Leyro, Zvolensky, Vujanovic, & Bernstein, in press), adolescents (Comeau, Stewart, & Loba, 2001), and individuals with a past history of major depression (Brown et al., 2001). Zvolensky, Feldner, Leen-Feldner et al. (2004) reported conceptually similar findings for relations between AS and negative-reinforcement outcome expectancies for smoking. Furthermore, more recent studies have extended this work via the examination of the incremental validity of AS, examined concurrently with other theoretically-relevant cognitive and affective factors (i.e., perceived control, discomfort intolerance), in relation to coping-oriented smoking motives and negative reinforcement outcome expectancies (Gregor et al., in press; Leyro et al., in press). The Comeau et al. (2001) investigation, in particular, is noteworthy in that AS moderated the relation between trait anxiety (i.e., frequency of anxiety symptoms) and use of cigarettes to cope with affective distress, reporting a stronger relationship between anxiety and use of cigarettes to cope with negative emotions among high AS, compared with low AS, youth. Using a sample of PD patients,

Zvolensky, Feldner, Leen-Feldner, and colleagues (2005) also found that smokers with PD reported higher levels of smoking to reduce negative affect than their counterparts without such a history. These cross-sectional studies are not capable of elucidating the direction of the effects. Theoretically, coping-oriented smoking motives may have bi-directional effects, influencing, and being influenced by, affective vulnerability. An initial investigation exploring this possibility was consistent with such an account (Gregor, Zvolensky, Bernstein, Marshall, & Yartz, 2007), reporting that coping-oriented motives were incrementally related to a variety of negative affective and cognitive factors.

Nicotine Withdrawal and Panic Vulnerability

One of the most striking aspects of nicotine use is that withdrawal symptoms (i.e., symptoms that emerge from a reduction of a specified drug in the body) are a prominent feature during the course of addictive use, and this has been conceptualized as a potential mechanism linking smoking to panic problems (Zvolensky, Schmidt, & Stewart, 2003). Indeed, a large body of work has sought to explicate withdrawal symptoms across specific periods of time (Pomerleau, Pomerleau, & Marks, 2000) and to clarify the role of withdrawal symptoms in relapse (Hughes, 1992). Although the findings of studies addressing nicotine withdrawal symptoms are voluminous and diverse, it is evident that (1) nicotine deprivation among regular smokers produces a variety of prototypical withdrawal symptoms, including—but not necessarily limited to—irritability, restlessness, headaches, increased appetite, and sleep problems (Hughes, 2007a; Hughes & Hatsukami, 1986; Hughes et al., 1990); (2) negative affect is a central feature of such withdrawal (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Patten & Martin, 1996, Piper & Curtin, 2006); and (3) there is a gradual emergence of withdrawal symptoms, with early signs occurring even after very short periods of time (e.g., minutes after the last cigarette smoked; Jarvik et al., 2000; Schuh & Stitzer, 1995). It is important to

remember in this context that while prolonged periods of withdrawal symptoms may be particularly distressing to individuals, relatively shorter periods of withdrawal (i.e., 60 to 270 minutes) are the most frequent type of withdrawal-based experience in the day-to-day lives of regular smokers (Hughes et al., 1990).

The aversive interoceptive cues that are a hallmark of nicotine withdrawal (both acute and prolonged) may have important implications for the study of panic vulnerability (Zvolensky, Schmidt, & Stewart, 2003). Specifically, the process of withdrawal from nicotine is characterized by an exacerbation of negative affect (e.g., anxiety, irritability) and other interoceptive symptoms (e.g., bodily tension; Hughes et al., 1990). Daily smokers experience repeated withdrawal episodes (varying in intensity and duration) on a daily basis and seemingly countless bouts of withdrawal over the course of their smoking careers. These withdrawal episodes represent potentially formative learning opportunities in the sense that the individual learns to associate internal and external stimuli with decreasing drug levels (O'Brien, 1976). Indeed, regular smokers are attuned to detecting, often in an automatic fashion, even slight changes in drug levels and to associate them with increases in withdrawal symptoms (Baker et al., 2004); this perspective is supported by a large body of basic research on drug learning (Spencer, Yaden & Lal, 1988).

Panic psychopathology or pre-morbid risk factors appear to be related to severity of acute nicotine withdrawal. In an early study in this domain, Breslau et al. (1991) found that tobacco withdrawal symptoms in a sample of young adults were significantly elevated among smokers with "any anxiety disorder" compared to individuals without a history of such disorders; however, specific anxiety diagnoses were not provided, rendering unclear the specificity of such results to panic psychopathology per se. Zvolensky, Baker, and colleagues (2004) found that daily smokers with a history of panic

attacks reported significantly more intense anxiety-related withdrawal symptoms (i.e., anxiety, restlessness, difficulty concentrating, and irritability) compared to smokers without such a history; no differences were evident for the other tobacco withdrawal symptoms (e.g., increased appetite).

Preliminary research utilizing biological challenge paradigms has yielded corroborating empirical evidence. For example, Zvolensky, Feldner, Leen-Feldner et al. (2005) evaluated the incremental validity of acute nicotine withdrawal symptoms (elicited by an average of two hours of nicotine deprivation) relative to negative affectivity, AS, and nicotine dependence in predicting anxious responding to a three-minute voluntary hyperventilation. The sample consisted of 90 regular smokers (46 females), as defined by smoking ≥ 10 cigarettes per day for at least one year, recruited through the general community. Consistent with prediction, greater levels of pre-challenge nicotine withdrawal symptoms uniquely predicted post-challenge intensity of panic symptoms and anxiety relative to other established factors.

More recently, Abrams and colleagues (in press) examined 24 adult heavy smokers (10 females) in 12-hour nicotine withdrawal and 24 adult non-smokers (12 females) on subjective and physiological reactivity to a 4-minute carbon dioxide (CO_2) re-breathing challenge. Results indicate that, despite decreased respiration during the challenge, smokers experienced a significantly greater increase in self-reported panic symptoms than non-smokers. Additionally, smokers reported significantly greater trait levels of suffocation fear prior to the challenge.

Extrapolating from this research, interoceptive cues produced by nicotine withdrawal may serve to amplify anxious responding to evocative cues, particularly among highly anxiety sensitive individuals. This perspective is supported by numerous biological challenge studies which have shown that pre-challenge anxiety levels are a

consistent predictor of post-challenge anxiety and panic attack symptoms in the laboratory across different procedures and populations (Coplan et al., 1998). Additionally, if withdrawal symptoms are particularly strong, bodily sensations might be misappraised as personally dangerous (e.g., “I’m losing control”), leading to a further intensification of anxiety symptoms and perhaps culminating in a panic attack. Through repeated withdrawal-specific learning experiences, certain smokers might develop hypervigilance to, and anxiety about, aversive interoceptive sensations.

Conceptual Model: Integrating Research on Nicotine Withdrawal and AS

Given that smoking-based withdrawal symptoms can elicit greater emotional vulnerability to fear-relevant stimuli (i.e., bodily sensations), it is logical to wonder why individuals would smoke if it increases their risk for such aversive anxiety experiences in the short-term and emotion-based psychopathology over the long-term (Johnson et el., 2000). The partial answer to this question is likely related to the fact that smokers often use tobacco as a means of regulating their mood and coping with stress. Indeed, smokers tend to attribute their smoking to its alleged anxiolytic properties (Frith, 1971); reliably report higher frequencies of smoking behavior when anxious or emotionally distressed (Shiffman, 1993); and expect that smoking will help to reduce negative affect (Copeland, Brandon, & Quinn, 1995). Although smokers tend to perceive smoking behavior as an emotion regulatory strategy by which to reduce and manage negative affect, research findings do not necessarily support this perception (Baker et al., 2004). In fact, the perceived anxiolytic effects of smoking described by regular smokers seem to be reductions in acute nicotine withdrawal symptomatology (Parrot, 1999). A key finding that has emerged from this literature is that the effects of smoking on anxiety-related states are highly dependent on other factors related to affective processing (Kassel, 1997). Specifically, research suggests that smoking-related effects associated with

emotional processing are largely indirect, as the variability in such effects is influenced by individual difference factors (Kassel, Stroud, & Paronis, 2003), such as AS.

AS and nicotine withdrawal. AS also may be critically important to PD vulnerability among smokers by serving to moderate the role of nicotine withdrawal on the development of panic-related processes. As described above, nicotine withdrawal elicits aversive interoceptive sensations. In this context, it is worth explicitly noting that: (1) individuals who regularly use drugs often cite unfavorable withdrawal experiences with such substances, which may serve as setting events for panic attacks (Aronson & Craig, 1986); and (2) among regular smokers, nicotine withdrawal (acute or prolonged), specifically, results in a variety of prototypical aversive internal cues that gradually emerge, and hence, are dynamic symptoms (Hughes & Hatsukami, 1986). These interoceptive stimuli may be perceived as personally threatening and unexpected among vulnerable persons, such as those high in AS. In particular, smoking-related withdrawal sensations may provide an opportunity for individuals to learn that physical sensations and other internal cues may be aversive and anxiety-provoking, and when coupled with individual differences in AS, contribute to a specific vulnerability to develop panic attacks and PD. Specifically, persons with high levels of AS should perceive interoceptive sensations as personally threatening and anxiety provoking. Therefore, the high AS individual experiencing bodily sensations related to nicotine withdrawal would be exposed to more frequent and intense aversive interoceptive learning trials. In this manner, smoking-related withdrawal cues are more likely to become phobic stimuli among individuals with elevated levels of AS (Bouton, Mineka, & Barlow, 2001). In contrast, individuals low in AS may be less susceptible to the panic-related effects of withdrawal because they are less fearful of internal sensations.

In regard to panic vulnerability, what is perhaps most clinically significant is that the combination of high AS and greater levels of acute nicotine withdrawal may place the individual at increased risk for anxious and fearful responding to internal cues (e.g., bodily sensations). That is, AS may increase the chance that more intense nicotine withdrawal symptoms will promote anxious and fearful responding to internal cues such as bodily sensations (please see Figure 1). In contrast, nicotine withdrawal may be less problematic for panic-relevant responding among low AS individuals. Thus, when a high AS smoker experiencing nicotine withdrawal symptoms is exposed to some evocative event that elicits bodily cues (whether expected or unexpected), he/she may be more apt to react to them in a panic-relevant fashion. Individual differences in AS may therefore moderate the intensity of nicotine withdrawal in regard to responding to internal cues with anxiety and fear. Theoretically, the moderator (i.e., AS) identifies the type of circumstances under which nicotine withdrawal has an effect on the panic outcome (Baron & Kenny, 1986). By contrast, AS would not be a mediator, as it does not necessarily explain why nicotine withdrawal affects panic symptoms.

As reviewed above, in the only relevant study to date, Zvolensky, Baker et al. (2004) found that AS predicted the intensity of nicotine withdrawal during the first week of a most recent quit attempt among 127 regular smokers. Another prospective investigation found AS was related to elevated state anxiety during a quit attempt among adult daily smokers by one-month following cessation (Mullane, Stewart, Rhyno, Steeves, Watt, & Eisner, in press). These findings suggest that smokers high, relative to low, in AS are more likely to perceive interoceptive sensations that occur during nicotine deprivation (e.g., restlessness, anxiety, difficulty concentrating) as personally dangerous (e.g., “I’m going crazy”) or threatening (e.g., “I’m losing control”). Although this investigation did not test a moderating hypothesis per se, it does highlight an association

between AS and nicotine withdrawal, a pre-requisite to the above model. Given existing theory and these data, it is important to conduct a rigorous test of an AS moderator hypothesis in relation to the association of nicotine withdrawal to panic relevant responding, using a controlled laboratory paradigm.

Overall Significance

Data addressing anxiety-related individual difference variables among smokers that may relate to increased risk for developing PD are very limited. The absence of such information critically hinders efforts to: (1) understand the nature of the processes affecting the smoking-panic association; (2) better identify smokers with the highest susceptibility to panic-related problems; and thus (3) develop specialized prevention programs that can meaningfully target smoking and other panic risk factors. The present research has begun to fill these important gaps in the literature by examining the extent to which AS moderates the relation between level of nicotine withdrawal and fear responding to bodily sensations.

Present Study: Aims and Hypotheses

This investigation links theory and research on cognitive vulnerability for PD with smoking research on acute nicotine withdrawal to test the hypothesis that hypersensitivity to panic-relevant interoceptive cues (i.e., AS) moderates the role of nicotine withdrawal in relation to panic-relevant responding to a CO_2 challenge among daily smokers. The CO_2 challenge paradigm was selected for the present investigation because it can reliably produce bodily arousal and psychological symptoms relevant to panic states in both nonclinical and clinical samples (e.g., Zvolensky & Eifert, 2000). The specific aims of the present study were thus to test the hypothesis that AS moderates the relation between pre-challenge nicotine withdrawal states (i.e., random group assignment to Nicotine Deprivation, not smoking for 12 hours, or Non-Nicotine

Deprivation, smoking 'as usual') and responding to a CO_2 procedure (controlling for anticipatory anxiety, gender, number of axis I diagnoses, negative affectivity, and average daily smoking rate) as indexed by: (1) level of post-challenge anxiety focused on bodily sensations and intensity of panic attack symptoms; (2) skin conductance reactivity; and (3) level of behavioral avoidance of a future challenge. Based upon the conceptual model delineated above, it was expected that individuals reporting higher levels of AS and undergoing nicotine deprivation (i.e., higher levels of nicotine withdrawal) would demonstrate the greatest levels of anxiety, panic-relevant responding, and skin conductance reactivity to the CO_2 procedure as well as greater behavioral avoidance of a future challenge.

Research Design and Methods

Participants

A total of 90 current (daily) smokers (35 women; M_{age} = 28.87, *SD* = 12.12, *Range* = 18-60 years) were examined for purposes of the current study. A total of 116 participants provided informed consent to participate in the study and attended the first of two study appointments (please see Procedure: Overview section below). Of these 116 participants, 3 participants reported quitting smoking immediately following the first appointment and were thus excluded from further participation; 3 participants were excluded on the basis of current or past psychotic-spectrum psychopathology; 1 participant was excluded due to having decreased the number of daily cigarettes smoked by more than half in the past 6 months (please see inclusion/exclusion criteria below); 2 participants were excluded at the second session due to not passing biochemical verification tests of smoking status (carbon monoxide analysis of breath samples > 10 ppm; please see inclusion/exclusion criteria below); and 17 participants did not return for the second appointment and were not reachable by phone. Therefore,

a total of 26 participants did not complete participation in the entire study.

A series of tests were conducted to assess differences between participants who did and did not complete participation in the study due to exclusion or self-discontinuation. A chi square test was conducted, and the groups did not significantly differ in terms of gender [X^2 (1, N = 116) = 1.85, p = .17]. A series of independent samples t-tests were then conducted, and the groups did not significantly differ on several key variables,[1] including age [t(114) = -.34, p = .73], education level [t(111) = 1.76, p = .08], marital status [t(111) = -1.54, p = .12], number of cigarettes smoked per day [t(112) = -1.33, p =.18], or number of smoking years [t(113) = -1.06, p = .28]. All the following information is based on the 90 participants who completed both sessions of the study.

The racial composition of the sample was consistent with that of the state of Vermont population (State of Vermont Department of Health, 2007): approximately 93.3% of the sample identified as white/Caucasian, 2.2% identified as black/African-American, 2.2% identified as Hispanic/Latino, and 2.2% identified as "other." In terms of educational status, 2.2% of participants received less than a high school education, 32.2% of participants completed high school or passed a General Educational Development (G.E.D.) test, 47.8% of participants completed some college or were currently enrolled in college, 13.3% of participants completed college, 3.3% of participants completed some graduate coursework, and 1.1% of participants (n = 1) held a graduate degree. With regard to current marital status, 78.9% of participants reported being single, 6.7% reported being married, 5.6% reported being divorced, 7.8% reported being separated from their spouse/partner, and 1.1% reported being widowed.

At the first appointment, smoking status was verified using carbon monoxide (CO) analysis of breath samples, and participants evidenced a mean rating of 18.10 (*SD*

= 12.09), indicating regular smoking (CO ppm >10). Participants reported smoking an average of 15.67 (*SD* = 8.22) cigarettes per day and smoking for an average of 11.16 (*SD* = 10.88) years. Participants reported initiating daily smoking at a mean age of 17.47 (*SD* = 5.20) years. A mean low to moderate level of nicotine dependence was reported (*M* = 3.40, *SD* = 1.93). In terms of cessation, participants reported an average of 2.53 (*SD* = 2.40) quit attempts, with a mean of 3.86 (*SD* = 6.39) occasions of at least 12-hour abstinence.

Approximately 77.7% of participants reported drinking alcohol, and on average, these individuals endorsed drinking 2 to 4 times per month and consuming 3 or 4 drinks on occasion. More specifically, approximately 18.9% of participants endorsed drinking alcohol at the frequency of monthly or less, 16.7% endorsed drinking 2 to 4 times per month, 28.9% reported drinking 2 to 3 times per week, and 13.3% reported drinking 4 or more times per week. Participants scored a mean of 9.91 (*SD* = 7.04) on the Alcohol Use Disorders Identification Test (AUDIT; Babor, De La Fuente, Saunders, & Grant, 1989, 1992), with 54.4% of participants meeting criteria for at least moderate alcohol problems, as indexed by a score of 8 or higher on the AUDIT. In terms of marijuana use, approximately 51.1% of participants reported using marijuana on at least one occasion in the past 30 days. Approximately 41.1% of the sample reported using marijuana at least weekly during the past month, and specifically, 10% of participants endorsed using marijuana on 1 to 3 occasions in the past month, 21.1% endorsed using marijuana on 4 to 7 occasions in the past month, and 20.0% reported using marijuana more than once per day.

In regard to axis I psychiatric diagnoses -- excluding substance use disorders which were not assessed -- 32.2% of participants met criteria for current (past month) *Diagnostic and Statistical Manual of Mental Disorders – 4th Edition, Text Revision* (*DSM-*

IV) axis I psychopathology. Of participants with current axis I psychopathology, 13.3% met criteria for one axis I diagnosis, 11.1% met criteria for two axis I diagnoses, and 7.8% met criteria for three axis I diagnoses. A total of 15 participants met criteria for generalized anxiety disorder, 12 participants met criteria for major depressive disorder, 8 participants met criteria for social phobia, 7 participants met criteria for specific phobia, 6 participants met criteria for panic disorder with or without agoraphobia, 2 participants met criteria for posttraumatic stress disorder, 1 participant met criteria for obsessive compulsive disorder, 1 participant met criteria for agoraphobia, 1 participant met criteria for dysthymia, and 2 participants met criteria for bipolar disorder.

Adult regular smokers interested in the investigation were screened by phone for study eligibility. For inclusion in the study, participants (1) were between 18 and 65 years of age; (2) were daily smokers for at least the past year; (3) were currently (past month) smoking at least 10 cigarettes per day; (4) had not decreased the number of cigarettes smoked per day by more than half in the past 6 months; and (5) reported a willingness to abstain from smoking for a 12-hour period, as determined by CO analysis of breath samples (10 ppm cutoff; Cocores, 1993). Participants were excluded from the study based on evidence of: (1) limited mental competency and the inability to give informed, voluntary, written consent to participate; (2) current or past psychotic-spectrum symptomatology; (3) current (past week) suicidal intent; (4) for women, the possibility of being pregnant (by self-report); and (5) current or past chronic illness (e.g., heart disease, chronic obstructive pulmonary disease). Individuals with a history of panic attacks and PD were not excluded, since nicotine withdrawal may exacerbate panic-relevant responding even among individuals with panic attacks and PD, thus serving to maintain the panic-related conditions over time. These screening criteria were successfully used in previous studies involving CO_2 administration (Zvolensky, Eifert, &

Lejuez, 2001) and were assessed by a validated medical history screening interview developed explicitly for this purpose (Forsyth & Eifert, 1998). Upon request, all individuals meeting psychiatric exclusionary criteria were referred to the department clinic that is housed in the same building as our laboratory.

Procedure: Overview

Data collection for the study was conducted over a period of 12 months.

Participant retention, differential dropout, and follow-up. The study consisted of two appointments, averaging 2 hours and 45 minutes in length, respectively. The mean duration of time between appointments was 6 days (*SD* = 3.93, *Range* = 1-19 days). Participants were compensated a total of $35 for participating in the entire study and were paid based on their length of involvement in the study. To reduce attrition, participant payments were back-loaded such that participants received $10 at the completion of the first session and $25 at the conclusion of the second session. Only participants who met eligibility requirements, as determined by the interview screening at the first session, were scheduled for the second session. This compensation schedule was intended to decrease the probability of attrition by offering adequate reward incentives for the completion of both phases of the study. In addition, eligible participants received telephone reminders 24 hours prior to their second scheduled appointment to confirm appointment times and to provide any necessary clarification of protocol (i.e., 12-hour abstinence from smoking for the nicotine deprivation – CO_2 group). Please see Figure 2 for an outline of the study procedure.

Screening and group assignment. Smokers were recruited through newspaper advertisements and flyers posted in local businesses and on community bulletin boards***.*** Recruitment ads stated, “Are you a smoker? Would you be willing to stop smoking for 12 hours?” Persons responding to study advertisements were first contacted via telephone,

screened to ensure that basic inclusionary criteria were met (see above), and scheduled for a visit, if deemed appropriate. Potentially eligible persons (e.g., smoking ≥ 10 cigarettes per day) were invited to the laboratory to complete the baseline assessment session.

At the baseline session, participants completed informed verbal and written consent and then were administered a complete diagnostic interview, a validated medical screening interview, and CO analysis of breath samples. If eligible after these procedures, stratified random assignment procedures were utilized to assign participants to either the (1) Nicotine Deprivation – CO_2 or (2) Non-Nicotine Deprivation – CO_2 condition (i.e., smoking as usual). Eligible participants were given a battery of self-report questionnaires to complete between appointments and return at the second session. The second session was scheduled at the conclusion of the baseline session for a date *within* 2 weeks of the baseline assessment. At the end of the first visit, participants were compensated $10.

At the conclusion of the first appointment, participants were informed as to whether or not to refrain from smoking for 12 hours prior to their next scheduled appointment. All participants were instructed to not use any form of nicotine replacement therapy for the duration of their involvement in the study; and this information was verbally verified at both study appointments. Specifically, participants in the Nicotine Deprivation group were asked to refrain from smoking for 12 consecutive hours prior to their second scheduled appointment, which consisted of the CO_2 administration component. The 12-hour nicotine deprivation interval was standardized so that all participants were instructed to refrain from smoking for 12 hours overnight; second session visits were scheduled during the morning hours relevant to the participants' stated 12-hour deprivation interval (i.e., individuals scheduled their appointments for

morning time slots that reflected their particular 12-hour overnight deprivation schedule). The 12-hour period of deprivation and its standardization were based upon past work that has suggested (1) it produces meaningful variability in symptom level and profiles (Hughes et al., 1990); (2) it is a common experience for acute withdrawal and hence a good model for the present study; and (3) it is feasible at a practical level for carrying out this protocol. For example, in a recent study, a 12-hour period of smoking abstinence was used to elicit nicotine withdrawal symptoms among 45 daily smokers (M. J. Zvolensky, personal communication, January 15, 2005). In all cases, it is expected that future work can build upon this study and extend the withdrawal deprivation to greater periods of time. Individuals in the Non-Nicotine Deprivation group were told to smoke as normal, and information on their actual use of nicotine during this 12-hour interval was obtained via self-report and CO analysis of breath samples.

Trained research assistants placed phone calls to all participants 24 hours prior to their second appointments to ensure (1) that participants were reminded of their appointments, and (2) that participants in the Nicotine Deprivation group remembered to abstain from smoking for 12 hours prior to their scheduled session. Upon arrival to the laboratory for the second session, participants in the Nicotine Deprivation group again completed CO analysis of breath samples to biochemically verify smoking abstinence. Participants assigned to this group who had not refrained from smoking did not complete the laboratory session; they were dropped/replaced from the study. Participants in the Non-Nicotine Deprivation group were asked to smoke “as usual” prior to returning to the laboratory for a second appointment to undergo the CO_2 challenge. Upon returning to the laboratory, they were asked to smoke one cigarette 15 minutes prior to the laboratory session, which was visually verified by a trained research assistant, to ensure an absence of nicotine deprivation. Participants in this group also were asked to

biochemically verify smoking status (i.e., non-abstinence) via completion of CO analysis of breath samples. Since the current investigation examined the effects of nicotine withdrawal rather than the effects of nicotine exposure, nicotine exposure standardization (i.e., use of standardized cigarettes) relevant to the Non-Nicotine Deprivation group was not warranted.

Pre-Challenge Measures

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Diagnostic assessments were conducted using the SCID-I-NP (non-patient version; First, Spitzer, Gibbon, & Williams, 1995). The SCID-I-NP version was used because participants in the study were not identified as psychiatric patients. Consistent with past work in this domain, only the mood, psychosis, and anxiety sections of the SCID-I-NP were administered for purposes of the present study (e.g., McLeish et al., 2007). The *DSM-IV* version of the SCID-I has been shown to have good reliability (inter-rater Kappa = .63 – 1.0, Zanarini et al., 2000; test-retest Kappa = .44 - .78, Zanarini et al., 2000) and good to excellent validity (Basco et al., 2000); and the SCID-I is generally regarded as the "gold standard" in diagnostic interviewing (Shear et al., 2000). All SCID-I interviews (100%) were administered by the Principal Investigator of this project and supervised by the faculty advisor. Interviews were audio-taped and the reliability of a random selection of 20.6% of interviews (n = 24) was determined and checked for accuracy by a doctoral-level independent rater; no cases of (diagnostic coding) disagreement were noted.

Anxiety Sensitivity Index (ASI). To assess sensitivity to, and discomfort with, anxious arousal, the 16-item ASI (Reiss, Peterson, Gursky, & McNally, 1986) was employed. The ASI is a self-report measure on which respondents indicate, on a 5-point Likert-style scale (0 = *very little* to 4 = *very much*), the degree to which they fear the potential negative consequences of anxiety-related symptoms and sensations. The ASI

is scored as a single sum across all items, and the total score may range from 0 to 64. The ASI has high internal consistency, ranging from .84 for a sample of college students with arachnophobia (i.e., fear of spiders) to .88 -.90 for a clinical sample of anxiety-disordered patients (Reiss et al., 1986). The ASI has demonstrated good test-retest reliability (kappa = .75) as well as excellent convergent validity (r > .70) with other established anxiety-relevant measures (Peterson & Reiss, 1992; Zinbarg, Mohlman, & Hong, 1999). The ASI is unique from, and demonstrates incremental predictive validity to, trait anxiety (McNally, 1996). The ASI is made up of one higher-order factor (ASI Total Score) and three lower-order factors: Physical, Psychological, and Social Concerns (Zinbarg, Barlow, & Brown, 1997). In the present investigation, as in past work (Zvolensky, Kotov et al., 2003), the total ASI score was utilized, as it represents the global AS factor and therefore reflects the different types of lower-order fears.

Positive Affect Negative Affect Scale (PANAS). The PANAS (Watson, Clark, & Tellegen, 1988) is a 20-item measure on which respondents indicate, on a 5-point Likert-type scale (1 = *Very slightly or not at all* to 5 = *Extremely*), the extent to which they generally feel different feelings and emotions (e.g., “Hostile”). The PANAS is a well-established measure commonly used in psychopathology research (Watson et al., 1988). Factor analysis indicates that it assesses two global dimensions of affect: negative and positive. Both subscales of the PANAS have demonstrated good convergent and discriminant validity. Additionally, both the negative affectivity and the positive affectivity scales of the PANAS have demonstrated high levels of internal consistency across a range of populations, including cross-national samples (range of alpha coefficients: .83 - .90 and .85 - .93, respectively; see Watson, 2000). The PANAS has also demonstrated good reliability (r = .71) (Watson et al., 1988). Only the negative affectivity scale (PANAS-NA) was used in the present study.

Smoking History Questionnaire (SHQ). Smoking history and pattern were assessed with the well-established SHQ, which includes items pertaining to smoking rate, age of onset, and years of regular smoking. The SHQ has been successfully used in previous studies as a descriptive measure of smoking history (Brown, Lejuez, Kahler, & Strong, 2002; Zvolensky, Lejuez, Kahler, & Brown, 2004). In the present study, the SHQ was used to determine all smoking-relevant history characteristics (e.g., daily smoking rate, number of past quit attempts). Since the SHQ is a descriptive measure, information regarding its psychometric properties is not relevant or available.

Fagerstrom Test for Nicotine Dependence (FTND). The FTND is a 6-item scale designed to assess gradations in tobacco dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). Two items are rated on a four-point Likert-style scale (0-3); and four items are rated dichotomously (yes/no). Sample items include, "How soon after you wake up do you smoke your first cigarette?" and "Do you find it hard to refrain from smoking in places where it is forbidden?" The FTND is a revision of the Fagerstrom Tolerance Questionnaire (FTQ; Fagerstrom, 1978). The FTND has shown good internal consistency, positive relations with key smoking variables (e.g., saliva cotinine; Heatherton et al., 1991; Payne, Smith, McCracken, McSherry, & Antony, 1994), and high degrees of test-retest reliability (Pomerleau, Carton, Lutzke, Flessland, & Pomerleau, 1994).

Minnesota Nicotine Withdrawal Scale (MWS). The MWS (Hughes & Hatsukami, 1986) is a reliable and sensitive 7-item self-report scale that was utilized to measure current nicotine withdrawal symptoms. On the MWS, participants are asked to rate their nicotine withdrawal symptoms on a 4-point Likert-type scale (0 = *not present* to 3 = *severe*). As recommended by Hughes and Hatsukami (1998), only *DSM-IV* withdrawal symptom items were included in the computation of the MWS total score.

The MWS was administered at the second session at three distinct time-points, spaced approximately 8-10 minutes apart: pre-challenge (immediately upon arrival to the laboratory), minute 9 of pre-challenge baseline, and post-challenge (approximately at minute 3 post-challenge). Pre-challenge ratings, indexed upon arrival to the laboratory, were used to verify group differences in withdrawal symptoms as per the between-group manipulation check.

Alcohol Use Disorders Identification Test (AUDIT*;* Babor et al., 1989, 1992*).* The AUDIT is a 10-item self-report screening measure developed by the World Health Organization to identify individuals with alcohol problems (Babor et al., 1989, 1992). There is a large body of literature attesting to the validity of the AUDIT (Saunders, Aasland, Babor, De La Fuente, & Grant, 1993). In the present study, the total score was computed to measure alcohol use problems (Babor et al., 1989, 1992), and the frequency and quantity of use items were used to determine patterns of alcohol use among the sample.

Marijuana Smoking History Questionnaire *(MSHQ;* Bonn-Miller & Zvolensky, 2005*).* The MSHQ was used to assess marijuana use history and pattern. The MSHQ is a self-report instrument that includes items pertaining to marijuana smoking rate (lifetime and past 30 days), age of onset at initiation, years of being a regular marijuana user, and other descriptive information. The MSHQ has been employed successfully in past research (e.g., Bonn-Miller, Zvolensky, Leen-Feldner, Feldner, & Yartz, 2005; Zvolensky, Bonn-Miller, Bernstein, McLeish, Feldner, & Leen-Feldner, 2006). In the present study, the item relevant to past 30-day marijuana use was utilized to determine patterns of recent marijuana use among the sample. Since the MSHQ is a descriptive measure, information regarding its psychometric properties is not relevant or available.

Carbon Monoxide (CO) Analysis. A noninvasive biochemical verification of smoking history was completed by CO analysis of breath samples (10 ppm cutoff; Cocores, 1993). Expired air CO levels were assessed using a CMD/CO Carbon Monoxide Monitor (Model 3110; Spirometrics, Inc.).

Challenge Measures

Subjective Units of Distress Scale (SUDS). SUDS ratings (Wolpe, 1958) were used to index self-reported anxiety focused on bodily sensations. This Likert-type scale ranges from 0 (*no anxiety*) to 100 (*extreme anxiety*). Participants completed these scales before the challenge procedure as an index of anticipatory anxiety, during the challenge procedure (at one-minute intervals), and immediately after the challenge as an index of maximum anxiety focused on bodily sensations.

Diagnostic Sensations Questionnaire (DSQ). The DSQ (Sanderson, Rapee, & Barlow, 1988, 1989) was used to assess *DSM-IV* panic attack symptoms immediately post-challenge. This measure is frequently employed in challenge work (Zinbarg et al., 2001; Zvolensky, Eifert, Lejuez, & McNeil, 1999). Ratings for the DSQ are made on a 9-point Likert-type scale (0 = *not at all* to 8 = *very strongly felt*). The DSQ, specifically, lists *DSM-IV* panic symptoms and yields composite scores for a mean intensity level for cognitive (e.g., fear of going crazy) and physical (e.g., breathlessness or smothering sensations) symptoms. Past work has used these symptom composites in laboratory challenge studies (Forsyth, Eifert, & Canna, 2000; Schmidt, Forsyth, Santiago, & Trakowski, 2002); the panic symptom composites (i.e., physical symptoms, cognitive symptoms) shared only 30% of variance with one another, indicating that they were tapping distinct but related aspects of panic-related symptoms (Zvolensky, Leen-Feldner et al., 2004).

Post-Challenge Avoidance Measure. In order to index behavioral avoidance post-challenge, participants' willingness to participate in another CO_2 administration was evaluated by a one-item self-report questionnaire. This item asked participants to rate their *levels* of willingness to participate in another CO_2 administration study. Specifically, participants were told that other CO_2 studies will be recruiting individuals for participation within the next 2 weeks. Then, participants were asked to indicate their willingness to participate 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 (Eifert & Heffner, 2003).

Laboratory Challenge Methodology

For purposes of this study, the CO_2-inhalation paradigm (Forsyth & Eifert, 1998; Zvolensky & Eifert, 2000; Zvolensky, Eifert et al., 1999) 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 (see Zvolensky & Eifert, 2000, for a review). Moreover, it has been safely and effectively used in previous work with adults across numerous research sites without adverse incident for decades (e.g., Gorman et al., 2001). The advantages of using this challenge tactic are several and include: (1) its ability to produce reliable psychological and autonomic responses that resemble those seen clinically in patients with PD; (2) the ability to safely and carefully control its administration (i.e., timing and duration); (3) the fact that it is a noninvasive, reliable, and well-investigated provocation, with known parameters; and (4) that it functions effectively to produce clinically-relevant responses that escalate rapidly within several seconds and that remit quickly.

Laboratory procedure. At the second scheduled session, each participant was introduced to a controlled laboratory setting with intercom and auditory communication with the experimenter in the adjacent room. Via a television monitor that was connected to two cameras in the experiment room, the experimenter maintained audio-visual monitoring of each participant. The Principal Investigator or a trained research assistant attached psychophysiological monitoring electrodes and a C-Pap respiratory mask to each participant. Participants listened to a standardized audio-taped description of the challenge procedure, successfully used in past work to equate expectancy effects (Feldner, Zvolensky, Eifert, & Spira, 2003; Spira, Zvolensky, Eifert, & Feldner, 2004). The audio-taped directions informed participants that breathing CO_2-enriched air might produce several transitory sensations (e.g., dizziness), but no adverse long-term effects (Harrington, Schmidt, & Telch, 1996). During the session, participants sat alone in the experiment room. The description of the procedure was as follows:

> *"During the study, you will receive several inhalations of CO_2-enriched air that may produce physical and mental sensations associated with bodily arousal. You may feel your heart racing, your palms might be sweaty, you might feel dizzy, and you might have some breathing problems. However, there will be no adverse long-term effects resulting from the inhalations."*

There were three main recording phases during the challenge. The first phase consisted of a 10-minute pre-challenge baseline. The second phase involved a computer automated CO_2 biological challenge (see Lejuez, Forsyth, & Eifert, 1998), a commonly employed tactic that effectively elicits fear responses (Zvolensky & Eifert, 2000). For both the Nicotine Deprivation and Non-Nicotine Deprivation groups, the challenge paradigm consisted of a single 4-minute 10% CO_2-enriched air provocation. The third phase consisted of a 5-minute post-challenge recovery period; and participants

completed a set of self-report measures (see above). Then, participants were debriefed and compensated $25.

Laboratory physiological measures. 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. Skin conductance reactivity data, which has been shown to effectively discriminate high and low AS individuals in past stress induction challenge work (e.g., Stewart & Pihl, 1994), was assessed in micromhos by using a Coulbourn S71-23 isolated skin conductance coupler. Disposable Ag/AgCl electrodes were placed in a standard bilateral configuration on the palmar side of each wrist and on the first fingers of the non-dominant hand. Respiration rate (breaths-per-minute) was sampled using a Pnemograph sensor cable with two elastic PS-2 sensors filled with conductive fluid. Stretching across the sensors causes a voltage change, thereby providing a measure of excursion of the chest during respiration. Physiological responsiveness was assessed continuously throughout all study phases.

Apparatus. Experimental sessions were completed in an 8 ft. x 10 ft. sound attenuated room, containing a chair, desk, Pentium-III microcomputer, SVGA color monitor, mouse, and keyboard, located in the Department of Psychology at the University of Vermont. Audio-visual monitoring allowed participants to communicate with the experimenter in the adjacent room. The experimenter room contains 10% CO_2 compressed air enclosed in a 40-cylinder gas tank, a one-way mirror, and a Coulbourn Modular recording device read through a Pentium microcomputer. A one-way mirror and video camera allowed experimenters to directly observe session events. The challenge was a single 4-minute administration of 10% CO_2-enriched air (10% CO_2, 21% O_2, 69% N_2); this time period has previously been successfully employed (Feldner et al., 2004).

The 10% CO_2 is a validated dosage, as indexed by pCO_2, arousal indices, and self-reported distress (Zvolensky & Eifert, 2000). Participants were equipped with a continuous positive pressure Downs C-Pap Mask. The CO_2 is stored in a 101 cm cylinder and fed through a 5 cm X 5 cm hole via aerosol tubing from the experimenter room to a positive-pressure downs C-Pap mask worn by participants. An automated and well-established apparatus, fully described in Lejuez et al. (1998), was used for CO_2 delivery.

Data Analysis

Overview

The main and interactive relations between AS and nicotine withdrawal were evaluated in relation to responding to the CO_2 challenge using a hierarchical multiple regression procedure (Cohen & Cohen, 1983). Squared semi-partial correlations (sr^2) were used as indices of effect size in all models and were tested at a two-tailed alpha of .05 (Tabachnick & Fidell, 2007). Main effect variables were mean-centered prior to computing product terms (Aiken & West, 1991). Consistent with past research in this area (Schmidt, Lerew, & Joiner, 2000), separate models were constructed for predicting each of the dependent variables. Alpha level was corrected using a Bonferroni procedure to control for family-wise error, and since a total of four hierarchical regression analyses were proposed, alpha was set to .0125 (.05/4 = .0125). This analytic approach provided a test of incremental validity and ensured that any observed effects for the interaction term are separable from the variance accounted for by the other theoretically-relevant factors at levels one or two in the equation (Cohen & Cohen, 1983). Based on recommendations of Cohen (1988), the form of significant interactions, if applicable, was examined by inserting specific values for each predictor variable (one standard deviation

above and below the mean for AS) into the regression equations associated with the described analysis.

It is noteworthy that AS was conceptualized on an *a priori* basis as a variable that would affect the relation between nicotine withdrawal and panic responsivity (i.e., a moderator variable), rather than account for the relation (i.e., mediator variable; Holmbeck, 1997). That is, given evidence of a direct association between nicotine withdrawal and panic responsivity (Zvolensky, Baker, et al., 2004), AS was hypothesized to maintain a significant association with panic vulnerability even after accounting for variance attributable to nicotine withdrawal and panic symptoms. Therefore, AS was not conceptualized as a mediator in this particular study (Baron & Kenny, 1986).

Hypothesis Testing

Hypothesis 1. To address hypothesis 1, two hierarchical multiple regression analyses were performed. For these analyses, predictor variables were divided into three levels in the hierarchy: (1) anticipatory anxiety (baseline SUDS rating; recorded at minute 9 of pre-challenge baseline), gender, number of axis I diagnoses, negative affectivity, and average daily smoking rate were entered at level one; (2) mean-centered main effect for AS (ASI total score) and withdrawal group status (Nicotine Deprivation vs. Non-Nicotine Deprivation; dichotomous variable) were simultaneously entered into the model as a set at level two; and (3) the interaction term for AS (mean-centered) and withdrawal group status were entered at level three. The dependent variable for the first hierarchical multiple regression analysis was level of anxiety focused on bodily sensations (post-challenge SUDS ratings; recorded during minute 1 post-challenge), and the dependent variable for the second analysis was intensity of panic attack symptoms (DSQ total composite score). The DSQ composite score was used, as it includes both physical and cognitive symptoms and therefore is a robust index of panic-relevant

responding and the most inclusive way to examine associations with panic-related symptom intensity reporting (Zvolensky & Eifert, 2000). Based upon this conceptual model, it was expected that those individuals reporting higher levels of AS and randomly stratified to the Nicotine Deprivation group would demonstrate the greatest level of panic-relevant responding to the CO_2 procedure.

Hypothesis 2. To address hypothesis 2, one hierarchical multiple regression analysis was performed; the dependent measure was a composite (average) physiological variable of skin conductance reactivity readings taken at one-minute intervals during the CO_2 challenge. As previously discussed, skin conductance levels have effectively discriminated high and low AS individuals in past stress-induction challenge work (e.g., Stewart & Pihl, 1994). At level one, anticipatory anxiety (baseline skin conductance level; recorded at minute 9 of pre-challenge baseline), gender, number of axis I diagnoses, negative affectivity, and average daily smoking rate were entered at level one as covariates. At level two, the mean-centered main effect for AS (ASI total score) and withdrawal group status (Nicotine Deprivation vs. Non-Nicotine Deprivation; dichotomous variable) were simultaneously entered. At level three, the mean-centered interaction term for AS and withdrawal group status was entered. Based upon the conceptual model, it was expected that individuals reporting higher levels of AS and randomly stratified to the Nicotine Deprivation group would demonstrate the greatest level of skin conductance reactivity (i.e., change from baseline to overall levels during the challenge). This approach to data analysis of physiological variables is consistent with past challenge work on anxiety (Zvolensky & Eifert, 2000).

Hypothesis 3. To address hypothesis 3, one hierarchical multiple regression analysis was performed. For this analysis, predictor variables were divided into three levels in the hierarchy in a manner identical to that proposed for hypothesis 1. The

dependent variable for the regression analysis was level of avoidance of a future CO_2 procedure (Post-Challenge Avoidance Measure). Based upon the conceptual model, it was expected that individuals reporting higher levels of AS and randomly stratified to the Nicotine Deprivation group would demonstrate the greatest level of avoidance of a future challenge (i.e., least amount of interest in completing another CO_2 procedure in the future).

Results

Descriptive Analyses

Please see Table 1 for a summary of participant characteristics as a function of withdrawal group status (Nicotine Deprivation vs. Non-Nicotine Deprivation). Two chi-square analyses (dichotomous variables: gender and psychotropic medication use) and a series of independent samples *t*-tests were conducted to assess differences between the nicotine deprivation conditions, and groups were compared in terms of characteristics including gender, psychotropic medication use, age, education level, number of axis I diagnoses (SCID-I-NP), negative affectivity (PANAS), average daily smoking rate (SHQ), daily smoking rate during the past week (SHQ), age onset of daily smoking (SHQ), number of daily smoking years (SHQ), nicotine dependence level (FTND-total), alcohol use problems (AUDIT-total), past 30-day marijuana use, AS (ASI-total), anticipatory anxiety (pre-challenge SUDS ratings, recorded at minute 9 of pre-challenge baseline/1 minute pre-challenge), peri-challenge anxiety (SUDS ratings recorded at one-minute intervals during the challenge), post-challenge anxiety (SUDS ratings recorded during minute 1 post-challenge), and latency to mask pulling (minutes) and discontinuation of challenge procedure.[2]

Significant differences between groups were found in terms of age, number of daily smoking years, and nicotine withdrawal symptoms (pre-challenge). The Non-

Nicotine Deprivation group was significantly older [$t(88) = -2.29$, $p < .05$] and reported smoking for a higher number of years [$t(87) = -2.53$, $p < .05$] than the Nicotine Deprivation group. As expected, the Nicotine Deprivation group endorsed significantly higher levels of nicotine withdrawal symptoms than the Non-Nicotine Deprivation group [$t(87) = 2.66$, $p = .009$].

Data Reduction Approach and Manipulation Checks of Challenge Paradigm

After screening for outliers due to sampling error (e.g., participant movement), the integrity of the 10% CO_2 – enriched air laboratory challenge paradigm was examined. Standard data reduction strategies employed in past biological challenge work were employed for the physiological data screening and reduction process (Zvolensky, Lejuez, & Eifert, 1998); specifically, any non-readable data (e.g., missing data due to human error, such as an electrode falling off a participant) were eliminated. The data also were inspected for falling within an expected range, per the recommendations of Venables and Christie (1980). If data were at an extreme (e.g., heart rate greater than 230 beats per minute), they were removed due to the likelihood of containing a potential sampling error.

Please see Table 2 for descriptive data and group comparisons in terms of dependent measures pre- (minute 9 of pre-challenge baseline) to post-challenge (minute 1 post-challenge). Within the total sample, SUDS anxiety ratings, skin conductance level, heart rate, and respiration rate all significantly increased from pre- to post-challenge. When the Nicotine Deprivation and Non-Nicotine Deprivation groups were examined independently, this pattern was maintained with one notable exception: The Nicotine Deprivation group did not report significantly greater levels of anxiety (SUDS anxiety ratings) at post-challenge, as compared to pre-challenge.

Zero-Order Correlations

Please see Table 3 for a summary of all zero-order correlations and descriptive data for all theoretically-relevant variables.

Correlations among covariates. The SUDS anticipatory anxiety variable was significantly associated with number of axis I diagnoses (r = .31, p < .01) and daily smoking rate (r = .25, p < .05). Gender was significantly associated with anticipatory anxiety – skin conductance reactivity (pre-challenge minute 9) (r = -.21, p < .05), with men manifesting greater levels of pre-challenge skin conductance reactivity than women. Finally, number of axis I diagnoses was significantly correlated with negative affectivity (r = .50, p < .01).

Correlations between covariates and dependent variables. As expected, the SUDS anticipatory anxiety variable was significantly correlated with post-challenge SUDS anxiety ratings (r = .37, p < .01); and anticipatory anxiety – skin conductance reactivity was significantly associated with the skin conductance reactivity composite variable (average of challenge minutes 1-4) (r = .76, p < .01). Furthermore, gender was significantly associated with DSQ total score (r = .27, p < .01), with women reporting higher levels of panic-relevant responding than men. Number of axis I diagnoses was significantly correlated with post-challenge SUDS anxiety ratings (r = .32, p < .01).

Correlations between covariates and predictor variables. The SUDS anticipatory anxiety variable (r = .23, p < .05), number of axis I diagnoses (r = .45, p < .01), and negative affectivity (r = .62, p < .01) were each significantly associated with AS.

Correlations between predictor and dependent variables. Contrary to expectation, none of the predictor variables was significantly associated with any of the dependent variables.

Hierarchical Regression Analyses[3, 4, 5]

Table 4 presents a summary of the regression analyses.

Self-reported anxiety, panic attack symptoms, and avoidance outcomes. In terms of post-challenge SUDS anxiety ratings, step one of the model accounted for a significant 17% of variance [$F(5, 75) = 3.24$, $p = .01$]. Pre-challenge SUDS anxiety ratings ($\beta = .23$, $sr^2 = .05$, $p < .05$) and number of axis I diagnoses ($\beta = .30$, $sr^2 = .06$, $p < .05$) were the only significant predictors. Contrary to hypothesis, steps two [$F(2, 73) = .10$, $p = .90$] and three [$F(1, 72) = .88$, $p = .34$] of the model did not account for significant portions of the model variance, and no significant predictors were noted at the level of main or interactive effects.

With regard to panic attack symptoms (DSQ total score),[6] the overall model, including steps one [$F(5, 77) = 1.97$, $p = .09$], two [$F(2, 75) = 1.17$, $p = .31$], and three [$F(1, 74) = .23$, $p = .63$], did not contribute any unique variance. Only gender was a significant predictor ($\beta = .26$, $sr^2 = .07$, $p < .05$). No other significant predictors were noted at the level of main or interactive effects.

In terms of behavioral avoidance of a future challenge, the overall model, including steps one [$F(5, 74) = 1.80$, $p = .12$], two [$F(2, 72) = .72$, $p = .49$], and three [$F(1, 71) = .72$, $p = .39$], did not contribute any unique variance. Both number of axis I diagnoses ($\beta = -.37$, $sr^2 = .08$, $p < .01$) and negative affectivity ($\beta = .27$, $sr^2 = .05$, $p < .05$) were significant predictors. No other significant predictors were noted at the level of main or interactive effects.

Physiological outcomes.[7] In terms of skin conductance reactivity, step one of the model accounted for a significant 73% of variance [$F(5, 69) = 37.79$, $p < .001$]. Only pre-challenge skin conductance (recorded at minute 9 of pre-challenge baseline) was significantly predictive of skin conductance reactivity during the challenge ($\beta = .84$, $sr^2 = .70$, $p < .001$). No other significant predictors were noted at the level of main or

interactive effects, and neither steps two [$F(2, 67) = .22$, $p = .80$] nor three [$F(1, 66) = .19$, $p = .66$] accounted for significant portions of variance.

Post Hoc Tests: Introduction

Due to the lack of empirical support for the hypotheses, a series of theoretically-driven *post hoc* tests were completed. As with any *post hoc* exploration, caution is needed to interpret the findings. It is perhaps most prudent to utilize these additional analyses as a theory-generating tactic for future work focused on panic vulnerability processes among daily smokers; this type of information therefore should not be viewed as offering a 'definitive conclusion.'

Post Hoc Tests: First Series

Post hoc tests were conducted, using the same models as described in the *a priori* Hypothesis Testing section, to examine the main and interactive relations between AS and withdrawal group status (Nicotine Deprivation vs. Non-Nicotine Deprivation; dichotomous variable) in relation to SUDS anxiety ratings *during the challenge procedure* (minutes 1-3 of the challenge). Repeated measures analysis of variance (ANOVA) procedures were conducted, as the dependent variable consists of a measure administered over 3 consecutive one-minute intervals (Tabachnick & Fidell, 2007). The partial eta squared (η^2) coefficients were used as estimates of effect size (Tabachnick & Fidell, 2007). In the *a priori* tests, the SUDS dependent variable was recorded during the first minute *post-challenge*, as this has been the standard method of indexing panic-relevant responding in the laboratory (Zvolensky et al., 1998).

Consistent with the *a priori* tests, predictor variables were: (1) anticipatory anxiety (baseline SUDS rating, recorded at minute 9 of pre-challenge baseline), gender, number of axis I diagnoses, negative affectivity, and average daily smoking rate; (2) mean-centered main effect for AS (ASI total score) and withdrawal group status (Nicotine

Deprivation vs. Non-Nicotine Deprivation; dichotomous variable); and (3) the interaction term for AS (mean-centered) and withdrawal group status. Peri-challenge SUDS anxiety ratings were obtained by asking participants to complete a SUDS questionnaire at minutes one, two, and three during the challenge procedure. This approach allows for more accurate testing of participants' anxiety levels during the CO_2 challenge procedure, as participants provided ratings in real time during the challenge.

Primarily, it was hypothesized that the interaction of AS (mean-centered) and withdrawal group status would significantly predict peri-challenge SUDS anxiety ratings, above and beyond the variance accounted for by the covariates and main effect terms. Specifically, it was expected that those individuals reporting higher levels of AS and randomly stratified to the Nicotine Deprivation Group would demonstrate the greatest level of anxious responding during the CO_2 challenge procedure. Secondarily, follow-up univariate ANOVA tests were planned, if a significant interactive effect was determined in the repeated measures ANOVA test, so as to isolate the time-points of the AS by withdrawal group status interactions. Here, it was hypothesized that the AS (mean-centered) by withdrawal group status interactive effect would significantly predict anxious responding during minutes one and two of the challenge; these effects were not expected for minute three of the challenge. That is, it was expected that individuals with higher levels of AS and randomly stratified to the Nicotine Deprivation group would exhibit the highest levels of anxiety at the first two minutes of the challenge procedure. This interactive effect was not expected for challenge minute 3 because habituation was expected to occur beyond the second minute of the challenge (Beck, Shipherd, & Zebb, 1997). The follow-up analyses would follow a model (covariates, main effects, interactive term) identical to that for the repeated measures ANOVA. A Bonferonni correction (.05/2

= .025) would be applied to the follow-up analyses to control for family-wise error rate (Tabachnick & Fidell, 2007).

Repeated measures ANOVA. A 2 (withdrawal group status: Nicotine Deprivation vs. Non-Nicotine Deprivation) x 3 (SUDS assessment: minutes 1-3) repeated measures ANOVA was conducted, and the between-subjects effects were evaluated in terms of the predictive validity of each of the covariates, main effects, and interaction term (AS x withdrawal group status) on the SUDS within-subjects variable. Please see Figure 3 for a depiction of SUDS ratings over time by group. Please see Table 5 for a summary of results.

According to Mauchly's Test for sphericity, the sphericity assumption was violated [Mauchly's W = .88, Approximate X^2 = 7.85, p = .02]. Therefore, the Huynh-Feldt statistic, a significance test adjusted for violation of the sphericity assumption (Tabachnick & Fidell, 2007), was used to interpret the test of within-subjects effects [F(2.00, 132.00) = 3.69, p < .05, partial η^2 = .05]. In terms of between-subjects effects, pre-challenge SUDS anxiety ratings (minute 9 of pre-challenge baseline) were significant predictors of peri-challenge SUDS anxiety ratings [F(1, 66) = 4.46, p < .05, partial η^2 = .06]. No other covariates were significant predictors. Furthermore, the main effect of AS [F(1, 66) = 4.69, p < .05, partial η^2 = .32] was a significant predictor of peri-challenge SUDS anxiety ratings; while the main effect of withdrawal group status was not a significant predictor. Finally, the interactive effect of AS by withdrawal group status was significantly incrementally predictive of peri-challenge SUDS anxiety ratings [F(1, 66) = 5.53, p < .05, partial η^2 = .07].

Follow-up analyses. Two univariate ANOVAs were then performed to examine the time points at which significant AS by withdrawal group interactive effects were noted. Please see Table 5 for a summary of results. In terms of Challenge Minute 1 –

SUDS anxiety ratings, anticipatory anxiety (SUDS anxiety ratings, minute 9 of pre-challenge baseline) [$F(1, 70) = 8.08$, $p = .006$, partial $\eta^2 = .10$] and average daily smoking rate [$F(1, 70) = 4.03$, $p = .04$, partial $\eta^2 = .05$] were the only significant covariate predictors.

At the level of main effects, AS was a significant predictor [$F(1, 70) = 5.20$, $p = .02$, partial $\eta^2 = .06$] of Challenge Minute 1 – SUDS anxiety ratings; withdrawal group status was not a significant predictor. As predicted, a significant AS by withdrawal group interactive effect was noted [$F(1, 70) = 5.70$, $p = .02$, partial $\eta^2 = .07$].

With regard to Challenge Minute 2 – SUDS anxiety ratings, none of the covariates were significant predictors. Neither of the main effect variables yielded significant predictive effects. However, as expected, a significant AS by withdrawal group interactive effect was noted [$F(1, 78) = 8.92$, $p = .004$, partial $\eta^2 = .11$].

It might be noted that, as hypothesized, the AS by withdrawal group interaction did not significantly predict Challenge Minute 3 – SUDS anxiety. Negative affectivity [$F(1, 66) = 5.07$, $p = .02$, partial $\eta^2 = .07$] and AS [$F(1, 66) = 4.90$, $p = .03$, partial $\eta^2 = .06$] were the only significant predictors.

Mapping the forms of the significant interactions. Based on the recommendations of Cohen and Cohen (1983), the forms of the significant interactions were examined by inserting specific values for each predictor variable into the equations associated with the described analysis (one standard deviation above and below the mean for AS). As can be seen in Figure 4, the forms of the significant interactions varied between Challenge Minute 1 and Minute 2. The effects at Minute 2 were consistent with hypothesis, while the effects at Minute 1 were inconsistent with hypothesis.

At Challenge Minute 1, the highest levels of SUDS anxiety ratings were evidenced first by individuals in the Non-Nicotine Deprivation Group reporting high levels

of AS (*n* = 6); second by individuals in the Nicotine Deprivation Group reporting high levels of AS (*n* = 7); third by individuals in the Non-Nicotine Deprivation Group reporting low levels of AS (*n* = 11); and fourth by individuals in the Nicotine Deprivation Group reporting low levels of AS (*n* = 4). Therefore, the effects at Minute 1 were not consistent with hypotheses.

At Challenge Minute 2, the highest levels of SUDS anxiety ratings were reported first by individuals in the Nicotine Deprivation Group reporting high levels of AS (*n* = 6); second by individuals in the Non-Nicotine Deprivation Group reporting high levels of AS (*n* = 6); third by individuals in the Non-Nicotine Deprivation Group reporting low levels of AS (*n* = 9); and fourth by individuals in the Nicotine Deprivation Group reporting low levels of AS (*n* = 3). The effects at Minute 2 were consistent with hypotheses.

Post Hoc Tests: Second Series

Due to the inconsistent findings for the AS by withdrawal group status interactive effects at SUDS – Minute 1 and SUDS – Minute 2 post-challenge, nicotine withdrawal symptoms (MWS total score) were examined (by withdrawal group status) at two distinct time-points during the challenge procedure (minute 9 of pre-challenge baseline; post-challenge) to determine whether group differences in self-reported nicotine withdrawal symptoms were indeed maintained over time. As per the *a priori* group comparisons and manipulation checks, the groups significantly differed at pre-challenge (please see Table 1), and therefore, this time-point was not included in these *post hoc* tests. It was hypothesized that the Nicotine Deprivation group, as compared to the Non-Nicotine Deprivation group, maintained significantly higher levels of self-reported nicotine withdrawal symptoms over the course of the challenge procedure.

A repeated measures ANOVA procedure was conducted, as the dependent variable consists of a measure administered over 2 time-points, with an (approximate) 8-

10 minute interval between administrations (Tabachnick & Fidell, 2007). The partial eta squared (η^2) coefficients were used as estimates of effect size (Tabachnick & Fidell, 2007). Specifically, a 2 (withdrawal group status: Nicotine Deprivation vs. Non-Nicotine Deprivation) x 2 (MWS assessment: minute 9 of pre-challenge baseline, post-challenge) repeated measures ANOVA was conducted, and the between-subjects effects were evaluated in terms of the MWS within-subjects variable. Please see Figure 5 for a depiction of MWS ratings over time by group.

Since the within-subjects variable (MWS total score at 2 time-points) has only two levels, the issue of sphericity is not applicable (Tabachnick & Fidell, 2007). In terms of between-subjects effects, withdrawal group status did not significantly predict MWS symptoms over time [$F(1, 77) = .57$, $p = .45$], indicating that groups did not significantly differ in terms of nicotine withdrawal symptoms beyond the first pre-challenge baseline time-point.

Discussion

The overarching aim of the present investigation was to delineate empirical associations and interactive effects between AS, a cognitive risk factor for PD, and acute (12-hour) nicotine withdrawal in order to better understand the etiology of panic vulnerability processes. Linking theory and research on panic vulnerability and smoking processes, this study provided a novel test of the interplay between AS and nicotine withdrawal (group status) -- using an experimental CO_2-enriched air laboratory paradigm -- in predicting anxious, panic-relevant responding as indexed by: (1) level of post-challenge anxiety focused on bodily sensations and intensity of panic attack symptoms; (2) skin conductance reactivity; and (3) level of behavioral avoidance of a future challenge. *Post hoc* tests were also conducted to examine the interactive effects of AS

and nicotine withdrawal group status on peri-challenge anxiety ratings (minutes 1-3 of the challenge).

Interactive Effects

A priori tests. Contrary to hypothesis, the interactive effect of AS by nicotine withdrawal (group status) did not significantly predict post-challenge anxiety (SUDS) ratings, intensity of panic attack symptoms, skin conductance reactivity, or level of avoidance of a future challenge. Furthermore, there was no association with this interactive variable and any other physiological factor, including heart rate reactivity or respiration rate. This pattern of findings was not attributable to the definition of 'nicotine withdrawal,' since results were consistent even when withdrawal was defined continuously using all participants' pre-challenge MWS total scores (please see Footnote 5). Furthermore, this pattern of findings was not attributable to the definition of panic attack intensity (DSQ), since the results were consistent when either of the DSQ subscales (Physical Concerns or Cognitive Concerns) were examined as dependent variables and when the DSQ was scored, according to *DSM-IV* criteria, to index panic attacks (yes/no; dichotomously) or number of panic attack symptoms continuously (please see Footnote 6). Therefore, AS and nicotine withdrawal did not demonstrate a synergistic effect in terms of the *a priori* defined aspects of panic vulnerability (self-report or physiological). It is unlikely that these findings are attributable to statistical power, since the sample consisted of 90 individuals; a sample size consistent with the planned power analysis, which was based on past work (Abrams et al., in press; Zvolensky, Feldner, Leen-Feldner et al., 2005). Furthermore, no trends toward statistical significance were noted for any of the interactive effects, underscoring the lack of an apparent interactive effect in terms of these dependent variables. The null findings relevant to the *a priori* hypotheses are broadly consistent with a related study by Piper

and Curtin (2006), which found that nicotine deprivation did not affect emotional response intensity and emotion regulation success in response to experimental manipulation of affect (via presentation of a series of neutral and negatively-valenced photographs) among 48 nicotine dependent smokers, assigned to either continued smoking or 24-hour nicotine deprivation. Yet, several methodological and sample limitations may have confounded these findings, and these potential caveats are discussed below (please see Methodological Limitations and Sample Limitations sections below).

Post hoc tests. A series of *post hoc* tests were conducted to test whether AS moderated the effect of nicotine withdrawal (group status) and peri-challenge responding, as indexed by SUDS anxiety ratings taken at minutes 1-3 during the challenge. First, the interactive effect of AS by withdrawal group significantly predicted Challenge Minute 1 – SUDS anxiety ratings, with a small effect size ($\eta^2 = .07$). However, the forms of the significant effects were *inconsistent* with hypotheses. At minute 1 of the challenge, individuals high in AS and in the Non-Nicotine Deprivation group reported the highest levels of anxiety, followed by the high AS individuals in the Nicotine Deprivation group. Second, as expected, AS moderated the association between nicotine withdrawal (group status) and Challenge Minute 2 - SUDS anxiety ratings, with a small – moderate effect size ($\eta^2 = .11$). Here, the forms of the interactions were consistent with hypotheses and individuals in the Nicotine Deprivation group with high levels of AS indexed the highest levels of anxious responding, followed by high AS individuals in the Non-Nicotine Deprivation group. Third, as predicted, no significant interactive effects were noted at the third minute of the challenge, possibly due to habituation effects (Beck et al., 1997).

These findings are novel in at least three significant ways. First, no studies to date have attempted to experimentally manipulate nicotine withdrawal and to examine its

interactive effect with AS in predicting panic responding. Second, this was the first study to date to index nicotine withdrawal symptoms during the course of a challenge procedure to assess changes in self-reported withdrawal symptoms over time by nicotine deprivation group. Third, this was the first study to date in this literature to also index anxiety ratings during the challenge, in addition to the more traditional post-challenge ratings, and to use peri-challenge anxiety ratings as dependent variables in a test of interactive effects.

The results may be informed by several theoretical accounts of smoking-anxiety interplay (Zvolensky & Bernstein, 2005). First, the significant interaction of AS by Non-Nicotine Deprivation (smoking as usual) in predicting anxious responding during minute 1 of the challenge is broadly consistent with past work using cross-sectional approaches that has indexed similar interactive effects (McLeish et al., 2007). It also is consistent with laboratory work that has documented higher levels of challenge-relevant panic reactivity among smokers (Zvolensky, Leen-Feldner et al., 2004). Therefore, it may suggest that smoking as usual (and immediately pre-challenge) may uniquely interact with AS to predict an escalation of anxiety symptoms in the context of increased physiological arousal.

Theoretically, this type of account may be attributed to at least three factors, which are worthy of further empirical exploration. First, it is possible that recent smoking in a group of daily smokers (Non-Nicotine Deprivation group) may cause increases in acute shortness of breath or perceived shortness of breath that may be attenuated by even 12 hours of smoking abstinence (Nicotine Deprivation group). These types of respiratory difficulties may be exacerbated by wearing a C-Pap mask, and this effect therefore might have contributed to the higher levels of anxiety at pre-challenge, challenge minute 1, and challenge minute 3 reported by those in the Non-Nicotine

Deprivation group. This possibility is informed by the work of Abrams et al. (in press), which found that smokers, as compared to non-smokers, manifested significantly greater trait levels of suffocation fear. Future work might index these potential respiratory effects using more sensitive psychophysiological equipment than that used in the present study as well as specialized self-report measures to index respiratory problems. Second, although there is a dearth of empirical evidence relevant to the acute biological effects of smoking, it is possible that a variety of neurobiological effects elicited by recent nicotine use might be linked to greater anxious responding to the induction of physiological arousal via the challenge paradigm. For example, smoking behavior has been associated with acute, mild-moderate increases in the neurotransmitter dopamine and elevated dopamine levels have been linked to increased anxiety-relevant symptoms, such as hyperarousal (Barrett, Boileau, Okker, Pihl, & Dagher, 2004; Brody et al., 2004; Hughes, 2007b; Takahashi et al., 2007). Therefore, from a psychobiological perspective, it is possible that individuals in the Non-Nicotine Deprivation group reported higher anxiety symptoms as a result of acute surges in dopamine, a result of recent nicotine administration (smoking prior to the challenge). Future research in this area is needed to further investigate the psychobiological effects of smoking, using positron emission topography (PET) scans, magnetic resonance imaging (MRI), and/or computerized axial tomography (CT) scans, for example; and how such effects might interplay with cognitive or affective factors in eliciting anxiety symptoms. Finally, since the onset of nicotine withdrawal symptoms may occur within minutes of smoking (Jarvik et al., 2000; Schuh & Stitzer, 1995), it is possible that (relatively low) nicotine withdrawal symptoms in both groups were partially accounting for the anxiety effects. This theoretical possibility is discussed further below (please see p. 58).

Second, the significant moderating effect of AS in terms of the association between the Nicotine Deprivation group and anxious responding at Challenge – Minute 2 is consonant with *a priori* postulation and past work documenting the effect of nicotine withdrawal symptoms in eliciting panic responsivity among smokers (Zvolensky & Bernstein, 2005). Therefore, it may be that smoking as usual (and just minutes before the challenge) is just as potent as nicotine withdrawal symptoms in eliciting panic-relevant anxiety symptoms but at differing stages (minutes 1 and 2, respectively) of the onset of panic-relevant sensations. Thus, the mechanism by which smoking and panic-spectrum psychopathology are linked may be more complex than initially anticipated, and future work is necessary to replicate and extend the current findings.

However, it should be noted that, as suggested by the second series of *post hoc* tests, nicotine withdrawal symptoms increased for individuals in the Non-Nicotine Deprivation group over the course of the challenge protocol. Although the Nicotine Deprivation group, as compared to the Non-Nicotine Deprivation group, reported significantly higher levels of nicotine withdrawal symptoms at the first pre-challenge time-point, these significant group differences diminished by minute 9 of the pre-challenge baseline period and were not evident at post-challenge either (please see Figure 5). In addition, the Non-Nicotine Deprivation group evidenced a consistent increase in withdrawal symptoms over the three time-points, while the Nicotine Deprivation group indexed a drop in nicotine withdrawal symptoms at minute 9 of pre-challenge baseline, perhaps due to habituation to anticipatory anxiety (Beck et al., 1997), and another increase in symptoms at post-challenge, possibly related to increased anxiety during the challenge. Furthermore, it might be noted that the findings may be due to flaws inherent in the manipulation of nicotine withdrawal (please see Methodological Limitations section), which may have yielded inadvertently erroneous effects.

Third, as depicted in Figure 4, patterns of anxiety ratings between groups (over the course of the challenge) are worthy of note. Differences between high AS and low AS individuals – regardless of group status – are apparent at pre- and post-challenge time-points. High AS individuals reported significantly higher levels of anxiety ratings than the low AS individuals, regardless of group. That is, high AS individuals in the Non-Nicotine Deprivation and Nicotine Deprivation groups reported relatively similar levels of SUDS anxiety ratings at pre- and post-challenge. At Challenge Minute 1, high AS individuals in the Non-Nicotine Deprivation group (M = 83.33, SD = 20.41) reported the highest levels of anxiety ratings, but the mean difference in anxiety ratings with the high AS – Nicotine Deprivation group (M = 78.57, SD = 17.25) is small. At Challenge Minute 2, the effect is reversed with high AS individuals in the Nicotine Deprivation group (M = 83.33, SD = 12.90) reporting the highest levels of anxiety; but again the difference with the high AS - Non-Nicotine Deprivation group (M = 75.00, SD = 31.62) is rather small. At Challenge Minute 3, the high AS individuals in the Non-Nicotine Deprivation group reported the highest anxiety ratings (M = 87.50, SD = 20.91), while the high AS individuals in the Nicotine Deprivation group (M = 66.66, SD = 25.81) reported the same levels of anxiety as the low AS individuals in the Non-Nicotine Deprivation group (M = 66.66, SD = 21.65). At post-challenge, high AS individuals in either group reported approximately equivalent anxiety ratings, which suggests that anticipatory anxiety and recovery processes might be the same for all high AS smokers following physiological evocation, regardless of nicotine deprivation schedules. Yet, due to the preliminary nature of this study and the small sample size of high AS individuals (n = 13; high AS defined as one standard deviation above the mean) in the current study, replication and extension of this work is necessary prior to further theoretical extrapolation.

Furthermore, low AS individuals reported significantly lower levels of anxiety ratings than the high AS individuals from pre- to post-challenge, regardless of group. Interestingly, at Challenge Minute 1, low AS individuals in the Non-Nicotine Deprivation group (*M* = 58.00, *SD* = 31.64) reported higher levels of anxiety than individuals in the low AS – Nicotine Deprivation group (*M* = 41.66, *SD* = 28.86). These group differences among low AS individuals continued through minutes 2 and 3 of the challenge. This may suggest that, for low AS individuals, recent smoking (smoking as usual) may be more associated with panic-relevant anxiety in response to physiological evocation than 12-hour nicotine deprivation. At pre- and post-challenge, low AS individuals in both groups reported relatively equivalent anxiety ratings (consistent with the pattern of findings for high AS individuals, discussed above), suggesting anticipatory anxiety and recovery processes might be similar for all low AS smokers following physiological evocation, regardless of nicotine deprivation schedules. However, due to the preliminary nature of this study and the very few individuals upon which this is based (low AS individuals in both groups: *n* = 15), the results should be interpreted with caution and further theoretical extrapolation should be postponed until replication of the current work is completed.

Main Effects

Neither AS nor withdrawal group status were significantly incrementally predictive of any of the (*a priori*) dependent measures, including post-challenge anxiety (SUDS) ratings, intensity of panic attack symptoms, skin conductance reactivity, or level of avoidance of a future challenge. AS and nicotine withdrawal (group status) also did not demonstrate significant incremental associations with other physiological variables (please see Footnote 7) or zero-order correlations with these dependent variables. *Post*

hoc tests revealed significant incremental main effects for AS in terms of SUDS anxiety ratings at minutes 1 and 3 of the challenge.

AS. Contrary to extensive empirical work citing significant associations between AS and panic-relevant responding, using biological challenge approaches (Zinbarg et al., 2001) and longitudinal designs (Schmidt et al., 1997, 1999), the results of this study indicated significant relations between AS and fear responsivity only at minutes 1 and 3 of the challenge. This may be due to at least two key factors. First, the current study did not sample specifically for high AS individuals, and therefore, the higher-end variability in AS was attenuated. Specifically, only 13 individuals reported levels of AS one standard deviation above the mean; and 15 individuals reported levels of AS one standard below the mean. This indicates that, as might be expected, most individuals reported moderate levels of AS (Reiss et al., 1986). However, the relatively normative levels of AS evidenced by the majority of the sample might have significantly limited the possibility of observing AS-anxiety effects.

Second, to be consistent with the bulk of past work in this area, AS was measured continuously/dimensionally, using the total score yielded by the ASI. Recent latent structural research on AS has indicated that the construct may demonstrate a taxonic structure (e.g., Bernstein, Zvolensky, Norton et al, 2007), such that higher-end levels of AS – determined using taxometric methodologies – represent a more valid approach to examining risk for panic-relevant psychopathology (Bernstein & Zvolensky, 2007). Recent work has evidenced that dimensional measures of the construct, such as the ASI total score used in the present investigation, reflect latent taxonic individual differences in the construct (Bernstein et al., 2007) that may be especially useful in models of affective vulnerability. The AS taxon, as compared to the more traditional, dimensional measures of AS, has been associated with higher levels of predictive

validity in terms of panic-relevant outcomes (Bernstein et al., 2007). In the present investigation, AS was evaluated dimensionally; taxometric methods were not employed due to design limitations (i.e., small sample size). Future investigations that are methodologically (e.g., large sample size) and statistically designed to incorporate taxonic and dimensional structures could further evaluate and compare the relations between AS – indexed both as the AS taxon and the AS dimensional variable -- and nicotine withdrawal and panic responding.

Nicotine withdrawal. Nicotine withdrawal group status was not incrementally predictive of any of the studied dependent variables, and no zero-order associations were noted, either. Notably, when the analyses were conducted using a continuous index of nicotine withdrawal (MWS – total score), then nicotine withdrawal symptoms were a significant predictor of panic attack symptoms during the challenge (please see Footnote 5). This finding is consistent with past work that has shown incremental associations between nicotine withdrawal symptoms and panic symptoms (Zvolensky, Feldner, Leen-Feldner et al., 2005).

Given that scores on the MWS may range from 0 – 21, the nicotine withdrawal symptom severity scores endorsed by the Nicotine Deprivation group (M = 5.81, SD = 4.32) were rather low even at the first pre-challenge assessment, with only 7 individuals reporting scores one standard deviation above the mean and only 1 participant endorsing a score above 15. This data is highly significant in terms of offering a potential explanation for the null *a priori* hypotheses, and it underscores the importance of considering the possible flaws in the manipulation of nicotine withdrawal (discussed below in the Methodological Limitations section).

Finally, given the differential patterns of nicotine withdrawal symptoms reported by the Nicotine Deprivation and Non-Nicotine Deprivation groups at the first pre-

challenge time-point, minute 9 of the pre-challenge baseline period, and post-challenge (please see Interactive Effects section above), changes in self-reports of nicotine withdrawal symptoms may have unexpectedly confounded the results. Since the Non-Nicotine Deprivation and Nicotine Deprivation groups were reporting relatively similar levels of nicotine withdrawal symptoms by minute 9 of the pre-challenge baseline period, the theoretical premise for random assignment of participants to withdrawal group (Nicotine Deprivation vs. Non-Nicotine Deprivation) was null prior to the administration of the CO_2-enriched air. This effect may due to (1) habituation or anxiety elicited by the challenge (as discussed in the Interactive Effects section above) or (2) flaws in the experimental manipulation of nicotine 'withdrawal' (please see Methodological Limitations section below).

Other Noteworthy Observations

Anticipatory anxiety. Anticipatory anxiety (pre-challenge SUDS ratings) was significantly associated with post-challenge SUDS ratings and Challenge – Minute 1 SUDS ratings but not with SUDS ratings at minutes 2 or 3 of the challenge. Thus, pre-challenge anxiety appears to be the most relevant for explaining early (minute 1) and later (post-challenge) aspects of anxious responding to bodily perturbation.

Pre-challenge skin conductance was a significant predictor of skin conductance reactivity, accounting for 73% of variance. This finding is consistent with past work, which has found that skin conductance levels pre-challenge account for high levels of variance in skin conductance reactivity during the challenge (e.g., Stewart & Pihl, 1994).

Gender. Gender was the only significant predictor of panic attack symptoms (β = .26, sr2 = .07, $p < .05$), with women reporting significantly higher levels of panic attack symptoms during the challenge than men. This gender effect is consistent with (1) the higher prevalence rates of panic disorder in women than men (APA, 2000), and (2)

laboratory studies that have documented higher rates of challenge-relevant panic responsivity among women as compared to men (Kelly, Forsyth, & Karekla, 2006).

Number of axis I diagnoses. The number of axis I diagnoses was significantly predictive of post-challenge anxiety as well as behavioral avoidance of a future challenge. Although the withdrawal groups did not differ in terms of number of axis I diagnoses, it seems that the presence of more complex psychopathology (indexed by a higher rate of psychiatric comorbidity) was a significant factor in predicting anxious challenge responding among daily smokers. Furthermore, at the zero-order level, number of axis I diagnoses was significantly correlated with anticipatory anxiety (SUDS ratings), negative affectivity, AS, and post-challenge anxiety (SUDS ratings). This finding is consistent with past work, which has documented that clinical samples generally respond more anxiously to panic evocation paradigms than nonclinical samples (Zvolensky & Eifert, 2000). This study also replicates past work that has examined panic-relevant responding among *clinical samples of smokers* and found that smokers with current axis I psychopathology are more apt to respond anxiously to affect evocation paradigms than smokers without current axis I psychopathology (Feldner, Vujanovic, Gibson, & Zvolensky, in press; Zvolensky, Leen-Feldner et al., 2004). It may be important for future work to replicate and extend these findings across clinical samples to document panic-relevant etiology and maintenance processes among other types of psychopathology.

Negative affectivity. Negative affectivity was a significant predictor of post-challenge avoidance and anxiety ratings at minute 3 of the challenge. These findings are broadly consistent with past work that indicates negative affectivity is related to anxiety and distress to bodily sensations (Zvolensky, Feldner, Eifert, & Stewart, 2001). At the zero-order level, negative affectivity was significantly associated with number of axis I

diagnoses and AS. Again, this finding is in line with work highlighting a relation between a temperamental tendency to experience negative affect and a variety of psychiatric conditions (Watson, 2005).

Daily smoking rate. Daily smoking rate was significantly predictive of only anxiety ratings at minute 1 of the challenge. Therefore, in terms of anxiety at minute 1 of the challenge, both daily smoking rate and the interaction of AS by Non-Nicotine Deprivation group (smoking as usual) predicted higher levels of anxiety. Theoretically, daily smoking rate and smoking as usual may be particularly predictive of anxious responding during the onset of panic-relevant physiological arousal. This conclusion is consistent with past work, which has found that daily smoking rate is significantly associated with panic-relevant psychopathology in community samples (Hayward et al., 1989, Valentiner et al., 2004) as well as panic-relevant responding in laboratory studies (Zvolensky, Leen-Feldner et al., 2004). In addition, smokers, as compared to nonsmokers, have been found to evidence higher rates of anxious responding to biological challenge paradigms (e.g., Abrams et al., in press). At the zero-order level, daily smoking rate was significantly correlated with anticipatory anxiety (SUDS ratings), which also suggests that daily smoking rate may contribute to higher levels of (baseline) anxiety. Collectively, these findings add to past research by providing laboratory evidence of a smoking-anxiety linkage to somatic perturbation.

Group differences. Although participants were randomly assigned to withdrawal group (Nicotine Deprivation vs. Non-Nicotine Deprivation), two key between-group differences were nonetheless evident. Specifically, the Non-Nicotine Deprivation group was significantly older and reported (daily) smoking for a greater number of years than the Nicotine Deprivation group. Therefore, it is possible that age and longer smoking

history may have contributed to the higher levels of anxiety reported by the Non-Nicotine Deprivation group at pre-challenge and minutes 1 and 3 of the challenge.

Methodological Limitations

Since many of the findings yielded by the current study are inconsistent with theoretical and empirical precedent, it is important to interpret the findings as preliminary and to contextualize the results within several methodological limitations which may have confounded the effects. First, the manipulation of nicotine withdrawal in the current study was standardized to a 12-hour overnight nicotine deprivation period. Although this manipulation was consistent with theoretical and empirical precedent (Hughes et al., 1990), it is possible that the overnight deprivation may have attenuated the nicotine withdrawal effects. Since some theoretical models of smoking posit that nicotine withdrawal is classically conditioned (Gilbert, 1995), it is possible that the absence of behavioral or environmental cues in the overnight deprivation schedule may have inadvertently decreased the effect of nicotine withdrawal symptoms for smokers in the Nicotine Deprivation group.

Second, all participants were instructed to not use any form of nicotine replacement therapy during their involvement in the study, and this information was only verbally verified at both study appointments. Therefore, it is possible that some participants in either the Nicotine Deprivation or Non-Nicotine Deprivation groups nevertheless elected to use nicotine replacement products, thus potentially confounding their self-reported nicotine withdrawal or affective symptoms as well as their anxious responding to the challenge (e.g., Morissette, Palfai, Gulliver, Spiegel, & Barlow, 2005; Tiffany, Cox, & Elash, 2000). For instance, past work has shown that smokers using transdermal nicotine patches, as compared to smokers using placebo patches, reported lower self-reported smoking urges and lower levels of negative affectivity (Morissette et

al., 2005; Tiffany et al., 2000). Due to the paucity of research examining the effects of nicotine replacement therapies on the cognitive-affective experiences of smokers, it is important for future work to more closely monitor and verify the use of nicotine replacement products in studies of nicotine withdrawal and anxiety.

Third, the challenge paradigm was standardized so that audio-taped instructions (1) directed participants to complete questionnaires at specific times throughout the challenge and (2) signaled the onset and offset of the CO_2-enriched air administration. As shown in Figure 3, both the Nicotine Deprivation and Non-Nicotine Deprivation groups evidenced a drop in SUDS anxiety ratings at post-challenge. Since three of the dependent variables were indexed via post-challenge measures (SUDS, DSQ, Behavioral Avoidance Measure), it is possible that the announcement of the offset of the CO_2 administration was related to collective relief (i.e., lower levels of anxiety) among participants, which confounded the findings relevant to these measures. Thus, future work might manipulate the challenge protocol such that participants are asked to index final panic-relevant ratings either (1) prior to the offset of the CO_2 administration or (2) without an audio-taped offset prompt.

Fourth, although there is evidence of the potency of the current challenge administration in eliciting increases in self-reported anxiety ratings and physiological responding (please see Table 2), the challenge is still a departure from the experience of real-world anxiety or panic symptoms. The CO_2-enriched air experimental paradigms are reliably utilized to elicit panic-relevant symptoms (Zvolensky & Eifert, 2000) and provide a controlled setting in which to study panic-related psychopathology without the biases relevant to retrospective self-report data. However, the limitations inherent to the laboratory setting (e.g., psychophysiological and audio-visual monitoring, breathing via mask, audio-taped instructions, questionnaire completion) should be considered in

interpreting the current data. Future work might use ecological momentary recording devices to facilitate recording of panic-relevant sensations, smoking behavior, and nicotine withdrawal symptoms in real time to monitor individuals' symptoms across a variety of settings and times. This type of methodology would increase generalizability and ecological validity, while reducing the 'artificiality' of effects generated by a laboratory setting.

Fifth, although the challenge protocol was standardized via the use of audio-taped instructions, several interpersonal factors may have affected the results. Primarily, it should be noted that, due to staffing issues, the Principal Investigator met with all participants across both study sessions. By virtue of this design, participants' familiarity and rapport with the Principal Investigator, established during the first session, might have contributed to (1) increases in overall comfort level during the second (experimental) session, (2) increases in social desirability biases in reporting anxiety or nicotine withdrawal symptoms at the second session, and (3) greater levels of perceived safety during the challenge procedure, which might have led to lower reports of anxiety or discomfort during the challenge. Furthermore, the study design did not provide an experimenter script to standardize the interactions between the experimenter and participant at the second session, prior to the audio-taped segment. Therefore, the experimenter interacted with participants in an unstandardized manner for approximately 10 minutes prior to the standardized portion of the session in order to conduct CO analysis of breath sampling, administer pre-challenge questionnaires, and fasten physiological electrodes. Past work has shown that unstandardized interpersonal interaction may inadvertently serve to develop or support rapport, which may confound the findings of challenge methodologies (Rassovsky & Kushner, 2003). Therefore, future work might control for these types of factors by employing different personnel to

administer interviews versus challenge protocols and by standardizing all experimenter-participant interactions at the challenge appointment.

Finally, the one-item Post-Challenge Avoidance Measure employed in the current study indexed participants' willingness to participate in another challenge paradigm within 2 weeks of the second session date. Interpretations of findings related to this measure should be interpreted with caution for at least three significant reasons. The lack of immediacy inherent to the item wording (i.e., 2-week time-frame) might have confounded the results by not indexing immediate fear-related avoidance in real time. Participants' reports of their desire to participate in a future challenge may not be fully in line with their actual behavior, such that participants may report that they would be willing to return but may not actually intend or desire to follow through (and vice versa). It also is possible that this measure of avoidance taps boredom, frustration, social desirability, desire for monetary reward, or related factors rather than 'pure' fear-driven avoidance. Thus, future work should attempt to solidify the current findings through a more rigorous methodology. For example, future work intended to index panic-related avoidance might incorporate a second challenge minutes following the first challenge to more accurately assess willingness to engage in another challenge; and changes in affective responsivity (habituation or lack thereof) could be assessed, as well.

Sample Limitations

Although broad-based community recruitment strategies were utilized, the sample has several limitations worthy of note. First, participants were relatively homogeneous in terms of race/ethnicity, as 93.3% of the sample identified as white/Caucasian. To increase the generalizability of the current findings, future work may wish to sample from more diverse populations. Second, individuals comprising the current sample participated in the study for monetary reward and were not necessarily

interested in quitting smoking at the time of entry into the study. To rule out possible self-selection bias and to increase the ecological validity of the findings, it may be important for future work in this domain to utilize recruitment tactics other than those implemented in the current study (e.g., recruiting smokers with a desire to quit smoking). Not sampling smokers who were attempting smoking cessation may have contributed error to the study, as several motivational and expectancy processes relevant to AS and other pertinent affective processes (e.g., negative affectivity) may not have been relevant to the present sample, thus limiting generalizability (Leyro et al., in press; Zvolensky, Vujanovic et al., 2007). Third, participants in the current study endorsed relatively low levels of nicotine dependence (FTND total score: *M* = 3.40, *SD* = 1.93; FTND possible range: 0-8). Since higher levels of nicotine dependence have been associated with more intense nicotine withdrawal symptoms (Hughes, 2007a), it is possible that nicotine dependence attenuated the effects of withdrawal symptoms on anxious responding in the current study. It will be important for future work to specifically recruit more highly nicotine dependent smokers in order to better understand the role of nicotine dependence in the association between nicotine withdrawal, AS, and panic-relevant responding. Fourth, future work in this domain should recruit and enroll a gender-matched sample in light of the current gender differences in self-reported panic attack symptoms (reported above) and past work documenting women's greater anxious responsivity (Kelly et al., 2006) to rule out any potential gender effects. As the current sample was predominantly male (*n* = 55 of 90), it is possible that this factor may have inadvertently affected the results.

Fifth, a high percentage of the current sample reported being regular marijuana and alcohol users; approximately 20% of the sample reported using marijuana more than once per day, and 54.4% of the sample met criteria for moderate alcohol problems.

Concurrent substance use was not conceptualized *a priori* as a potential confound to the current investigation. There is a relative dearth of literature examining the impact of regular marijuana or alcohol use on nicotine withdrawal symptoms or panic-relevant responding, and therefore, there is the potential that regular use of these substances may have affected either nicotine withdrawal symptoms, self-reported anxious responding to the challenge, or physiological responsivity to the challenge paradigm. On a related note, the presence of *DSM-IV* substance use disorders was not formally assessed in the present study. It is therefore possible that participants met criteria for other substance use disorders (e.g., opiate abuse), and that this type of substance use affected the current results. It may be important for future work in this line of inquiry to more rigorously assess substance use and to exclude individuals who use substances other than nicotine regularly in order to more conclusively delineate linkages between nicotine withdrawal and panic responding.

Clinical Implications

There are at least three key clinical implications of the present work. The interaction of AS by nicotine deprivation as well as AS by non-nicotine deprivation (smoking as usual) in predicting anxiety symptoms during the challenge underscores the important association between AS and panic responsivity among smokers. Primarily therefore, the incorporation of AS reduction techniques (e.g., interoceptive exposure), corresponding cognitive-behavioral skills, and relevant psychoeducation into smoking cessation programs may yield very promising results (Zvolensky & Bernstein, 2005). By learning coping skills relevant to anxiety-relevant bodily sensations, higher AS smokers may be better able to quit smoking because they might develop the skills to substitute more adaptive emotion regulation skills for the (perceived) affect regulatory properties of smoking. Secondarily, PD prevention programs might be developed for high AS smokers

whereby AS reduction techniques (e.g., interoceptive exposure, cognitive-behavioral skills) are combined with standard smoking cessation techniques to prevent the development of PD among this high risk group (via decreasing AS and facilitating smoking cessation; Feldner, Zvolensky, Babson, Leen-Feldner, & Schmidt, in press). Third, as higher levels of AS have been linked to various types of psychological syndromes and conditions (e.g., posttraumatic stress disorder, chronic pain), advancing clinical science relevant to the AS – smoking association in the context of other clinical syndromes may be especially fruitful in terms of informing more specialized smoking cessation intervention programs and possibly developing various specialized prevention programs for high AS smokers (Feldner et al., 2008).

Summary

The current investigation adds uniquely to the extant literature relevant to AS – smoking associations. This study presented an innovative effort to experimentally manipulate nicotine withdrawal, to measure anxiety ratings peri-challenge, and to test the interactive effects of AS by nicotine withdrawal in predicting anxious responding to a CO_2-enriched air laboratory paradigm. At Challenge – Minute 1, AS moderated the association between Non-Nicotine Deprivation (smoking as usual) and anxious responding. At Challenge – Minute 2, AS moderated the association between Nicotine Deprivation and anxious responding. Overall, this study offers a significant stepping stone for future translational research advances to build upon, with the ultimate goal of informing intervention and prevention efforts.

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Footnotes

[1] Group comparisons relevant to AS (Anxiety Sensitivity Index total score; ASI total score) could not be conducted. Participants who were excluded at baseline were not asked to complete the ASI, while participants who self-discontinued participation did not return their completed questionnaire packets. Complete ASI data therefore was not available to conduct meaningful comparisons.

[2] A total of 15 participants (of 90 total participants) pulled their masks during the challenge procedure and requested discontinuation of the CO_2 administration. No significant differences were noted between the Nicotine Deprivation and Non-Nicotine Deprivation groups in terms of (1) number of participants who discontinued the challenge or (2) the latency to discontinuation (please see Table 1 for details). All participants completed the post-challenge questionnaires (SUDS, DSQ, Post-Challenge Avoidance Measure) at the point of CO_2 discontinuation.

[3] Analyses were conducted with only anticipatory anxiety as a covariate, and patterns of main and interactive effects were consistent with those reported here.

[4] Analyses were conducted after all participants with current panic disorder (n = 6; Nicotine Deprivation group: n = 2; Non-Nicotine Deprivation group: n = 4) were removed from the dataset, and patterns of main and interactive effects were consistent with those reported here.

[5] Analyses were conducted, with the same regression models, using nicotine withdrawal symptoms (MWS total score, mean centered; continuous variable) rather than withdrawal group status (dichotomous variable). Overall patterns of findings were consistent with one noted exception: In terms of panic attack symptoms (DSQ total score), nicotine withdrawal symptoms were (marginally) significant predictors [t = 1.93, β = .22, sr^2 = .04, p = .05].

[6] When *post hoc* analyses were run with the DSQ subscales, DSQ – Physical Concerns (measures panic-relevant physical concerns) and DSQ – Cognitive Concerns (measures panic-relevant cognitive concerns), as dependent variables (using the same model), identical patterns of findings emerged. The overall models did not contribute any significant variance. Gender was the only significant predictor in relation to both DSQ – Physical Concerns [β = .25, sr^2 = .06, p = .02] and DSQ – Cognitive Concerns [β = .23, sr^2 = .05, p = .04]. No other significant predictors were noted at the level of main or interactive effects.

Furthermore, the pattern of findings did not change when the DSQ was scored so as to index (a) the number of *DSM-IV* panic attack symptoms (measured continuously; each symptom counted if participant rated it at a level of 4 or greater on the 9-point Likert-style scale) or (b) the endorsement of *DSM-IV* panic attacks (yes/no; quantified according to *DSM-IV* criteria with each symptom counted if participant rated it a level of 4 or greater on the 9-point Likert-style scale) as dependent variables. In terms of the number of *DSM-IV* panic attack symptoms, a hierarchical linear regression was conducted and gender emerged as the only significant predictor [β = .29, sr^2 = .08, p = .009]. With regard to the endorsement of *DSM-IV* panic attacks (yes/no), a logistic regression was conducted and no significant predictors were noted.

[7] In terms of heart rate reactivity, step one of the model accounted for a significant 35.6% of variance, [F(5, 69) = 7.61, p < .001]. Only pre-challenge heart rate (recorded at minute 9 of baseline) was significantly predictive of heart rate reactivity during the challenge (β = .58, sr^2 = .29, p < .001). Daily smoking rate was a marginally significant predictor (β = -.20, sr^2 = .04, p = .06). No other significant predictors were noted at the level of main or interactive effects. Neither steps two [F(2, 67) = .27, p = .76] nor three [F(1, 66) = .16, p = .68] accounted for significant portions of variance.

With regard to respiration rate, the overall model, including steps one [$F(5, 34) = 2.05$, $p = .09$], two [$F(2, 32) = .06$, $p = .94$], and three [$F(1, 31) = .44$, $p = .51$], did not account for any significant variance. Only gender ($\beta = .35$, $sr^2 = .12$, $p < .05$) was significantly predictive of respiration rate during the challenge. No other significant predictors were noted at the level of main or interactive effects.

Table 1. Descriptive Data and Between-Group Comparisons.

Variable	***Nicotine Deprivation[1]***		***Non-Nicotine Deprivation[2]***		***Group Comparisons***
	Male	*Female*	*Male*	*Female*	
Gender[3]	31	14	24	21	$X^2 = 2.29$, $p = .19$
Current Psychotropic Medication Use	$n = 13$		$n = 18$		$X^2 = 1.07$, $p = .30$
	M	*SD*	*M*	*SD*	
Age	26.00	9.75	31.73	13.62	* $t(88) = -2.29$, $p < .05$
Education[4]	2.87	.86	2.87	.86	$t(88) = .00$, $p = 1.0$
Number of Current Axis I Diagnoses	.44	.81	.73	1.09	$t(88) = -1.42$, $p = .15$
Negative Affectivity (PANAS)	20.35	8.15	19.27	7.41	$t(84) = .64$, $p = .52$
Daily Smoking Rate, Since Initiation	16.45	9.86	14.91	6.23	$t(87) = .88$, $p = .37$
Daily Smoking Rate, Past Week	15.37	7.00	13.00	5.83	$t(88) = 1.75$, $p = .08$
Age Onset of Daily Smoking	17.20	5.56	17.75	4.86	$t(88) = -.50$, $p = .61$
Number of Daily Smoking Years	9.32	8.35	15.26	13.25	* $t(87) = -2.53$, $p < .05$
FTND – Total[5]	3.58	1.99	3.23	1.87	$t(84) = .83$, $p = .40$
AUDIT – Total[6]	10.38	6.35	9.41	7.76	$t(83) = .63$, $p = .52$
Past 30 – Day Marijuana Use[7]	4.26	3.36	3.81	3.36	$t(64) = .54$, $p = .58$
ASI – Total[8]	19.13	8.78	17.77	10.04	$t(86) = .67$, $p = .50$
MWS – Total[9]	5.81	4.32	3.40	4.25	** $t(87) = 2.66$, $p = .009$
Anticipatory Anxiety[10]	54.09	28.04	50.04	28.22	$t(87) = .67$, $p = .49$
Peri-Challenge Anxiety, Minute 1[11]	60.11	30.91	69.46	24.96	$t(83) = -1.53$, $p = .12$
Peri-Challenge Anxiety, Minute 2[12]	65.12	29.81	70.73	27.85	$t(78) = -0.86$, $p = .38$
Peri-Challenge Anxiety, Minute 3[13]	61.28	32.62	78.90	22.62	** $t(78) = -2.81$, $p = .006$
Post-Challenge Anxiety[14]	54.65	33.29	64.41	30.20	$t(84) = -1.42$, $p = .15$
Latency to Mask Pulling (minutes)[15]	1.68 ($n = 7$)	.78	2.02 ($n = 8$)	1.22	$t(13) = -.62$, $p = .54$

Note. N = 90 (n = 45 per group); * $p < .05$; ** $p < .01$; *** $p < .001$. [1]Nicotine Deprivation Group (no smoking for 12 hours prior to challenge); [2]Non-Nicotine Deprivation Group (smoking as usual and 15 minutes prior to challenge); [3]Gender (1 = male; 2 = female); [4]Education Levels: 1 = less than high school; 2 = high school/GED; 3 = some college; 4 = college graduate; 5 = some graduate work; 6 = graduate degree; [5]Fagerstrom Test for Nicotine Dependence – Total score; [6]Alcohol Use Disorders Identification Test – Total score; [7]Frequency of Past 30-Day Marijuana Use, Marijuana Smoking History Questionnaire; [8]Anxiety Sensitivity Index – Total score; [9]Minnesota Nicotine Withdrawal Scale – Total score, pre-challenge; [10]Pre-Challenge Subjective Units of Distress Scale Ratings (SUDS at minute 9 pre-challenge); [11]Peri-Challenge Subjective Units of Distress Scale Ratings, Minute 1 (SUDS at minute 1 peri-challenge); [12]Peri-Challenge Subjective Units of Distress Scale Ratings, Minute 2 (SUDS at minute 2 peri-challenge); [13]Peri-Challenge Subjective Units of Distress Scale Ratings, Minute 3 (SUDS at minute 3 peri-challenge); [14]Post-Challenge Subjective Units of Distress Scale Ratings (SUDS during minute 1 post-challenge); [15]Latency to mask pulling and discontinuation of challenge procedure among participants (in minutes) – a total of 15 participants (of 90 participants total) removed the mask and requested discontinuation

Table 2. Manipulation Checks: Pre- to Post-Challenge Comparisons

Variable	***Group***	***Pre-Challenge[1] M (SD)***	***Post-Challenge[2] M (SD)***	***Tests of Pre- to Post-Challenge Change***
SUDS Ratings[3]	Total	51.82(28.42)	59.53(31.98)	**t*(85) = -2.11, *p* = .03
	Nicotine Dep.[4]	54.18(28.36)	54.65(33.29)	*t*(42) = -.09, *p* = 0.92
	Non-Nicotine Dep.[5]	49.46(28.62)	64.41(30.20)	***t*(42) = -2.95, *p* = .005
DSQ – Total[6]	Total	n/a	52.19(28.21)	n/a
	Nicotine Dep.	n/a	50.75(29.61)	
	Non-Nicotine Dep.	n/a	53.60(27.04)	
Skin Conductance	Total	1.87(1.75)	4.60(3.86)	****t*(86) = -7.83, *p* < .001
	Nicotine Dep.	1.74(1.37)	4.34(2.88)	****t*(42) = -6.85, *p* < .001
	Non-Nicotine Dep.	1.99(2.05)	4.85(4.65)	****t*(43) = -4.88, *p* < .001
Heart Rate	Total	81.72(12.20)	88.48(15.82)	****t*(86) = -3.94, *p* < .001
	Nicotine Dep.	76.75(11.53)	85.42(15.11)	***t*(42) = -3.38, *p* = .002
	Non-Nicotine Dep.	86.57(10.90)	91.48(16.09)	**t*(43) = -2.14, *p* = .037
Respiration Rate	Total	15.60(3.11)	18.49(3.97)	****t*(49) = -4.40, *p* < .001
	Nicotine Dep.	14.87(2.64)	18.36(3.95)	****t*(25) = -4.24, *p* < .001
	Non-Nicotine Dep.	16.39(3.43)	18.63(4.08)	**t*(23) = -2.15, *p* = .04

Note. *N* = 90 (Nicotine Deprivation Group: n = 45; Non-Nicotine Deprivation Group: n = 45); * *p* < .05, ** *p* < .01, *** *p* < .001; [1]Levels at minute 9 of pre-challenge baseline period; [2]Levels immediately post-challenge (minute 1 of recovery period); [3]Subjective Units of Distress Scale Ratings; [4]Nicotine Deprivation Group (no smoking for 12 hours prior to challenge); [5]Non-Nicotine Deprivation Group (smoking as usual and 15 minutes prior to challenge); [6]Diagnostic Sensations Questionnaire – total score

Table 3. Zero-Order (or Bi-Variate for Dichotomous Variables) Correlations and Descriptive Data for Theoretically-Relevant Variables

Variables	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	***M* (*SD*)**	***Range***
Covariates														
1. Anticipatory Anxiety: SUDS[1]	-	.06	.05	.31**	.19	.25*	.23*	-.02	.37**	.04	.02	.04	35.94 (27.8)	0-100
2. Anticipatory Anxiety: Skin Conductance[2]	-	-	-.21*	-.06	-.12	.16	-.00	.06	.01	-.11	.76**	.21	1.86 (1.7)	1-12.76
3. Gender[3]	-	-	-	-.01	.11	-.16	.03	.16	.18	.27**	-.13	-.12	38.9% female	-
4. Number of Axis I Diagnoses	-	-	-	-	.50**	.20	.45**	.15	.32**	.01	-.11	-.10	0.58 (.97)	0-3
5. Negative Affectivity (PANAS)[4]	-	-	-	-	-	.06	.62**	-.07	.07	.00	-.18	.05	19.80 (7.7)	10-42
6. Daily Smoking Rate, Since Initiation	-	-	-	-	-	-	.04	-.09	.03	-.19	.12	.01	15.67 (8.2)	5-60
Predictors														
7. Anxiety Sensitivity (ASI – Total)[5]	-	-	-	-	-	-	-	-.07	.12	.13	-.06	.09	18.44 (9.4)	2-48
8. Group Status[6]	-	-	-	-	-	-	-	-	.15	.05	.06	.05	50% each	-
Dependent Variables														
9. Post-Challenge Anxiety: SUDS[7]	-	-	-	-	-	-	-	-	-	.43**	.08	-.20	59.53 (31.9)	0-100
10. DSQ – Total[8]	-	-	-	-	-	-	-	-	-	-	.09	-.34**	52.19 (28.2)	6-126
11. Skin Conductance Reactivity-Composite[9]	-	-	-	-	-	-	-	-	-	-	-	.07	3.46 (2.8)	1-15.67
12. Post-Challenge Avoidance[10]	-	-	-	-	-	-	-	-	-	-	-	-	67.47 (33.8)	0-100

Note. *N* = 90 (Nicotine Deprivation Group: n = 45; Non-Nicotine Deprivation Group: n = 45); *$p < .05$, **$p < .01$. [1]Anticipatory Anxiety: Subjective Units of Distress Scale Ratings (minute 9 of pre-challenge baseline); [2]Anticipatory Anxiety: Skin Conductance (minute 9 of pre-challenge baseline); [3]Gender (1 = male; 2 = female); [4]Positive Affect Negative Affect Scale – Negative Affect subscale; [5]Anxiety Sensitivity Index – Total score; [6]Group Status (1 = Nicotine Deprivation Group; 2 = Non-Nicotine Deprivation Group); [7]Post-Challenge Anxiety: Subjective Units of Distress Scale Ratings (first minute post-challenge); [8]Diagnostic Sensations Questionnaire – Total score; [9]Skin Conductance Reactivity - Composite (minutes 1-4 of challenge); [10]Post-Challenge Avoidance Measure – Total Rating of Willingness to Participate in Another Challenge Procedure (0 = *no desire to participate;* 100 = *definite desire to participate*)

Table 4. Hierarchical Linear Regressions: Main and Interactive Effects

	ΔR^2	*t* (each predictor)	β	sr^2	*p*
Dependent Variable: Post-Challenge SUDS Anxiety Ratings[1]					
Step 1	.17				.010
Pre-Challenge SUDS Ratings[5]		2.05	.23	.05	.043
Gender[6]		1.51	.16	.02	.135
Number of Axis I Diagnoses		2.32	.30	.06	.023
Negative Affectivity (PANAS)		-1.03	-.13	.01	.305
Daily Smoking Rate, Since Initiation		-.36	-.04	.00	.714
Step 2	.00				.904
ASI – Total[7]		-.14	-.02	.00	.888
Group Status[8]		.42	.04	.00	.673
Step 3	.01				.349
ASI x Group		-.94	-.34	.01	.349
Dependent Variable: DSQ – Total Score[2]					
Step 1	.11				.091
Pre-Challenge SUDS Ratings		-.01	-.00	.00	.985
Gender		2.43	.26	.07	.017
Number of Axis I Diagnoses		.83	.11	.00	.409
Negative Affectivity (PANAS)		-.76	-.10	.00	.449
Daily Smoking Rate, Since Initiation		-1.48	-.17	.02	.143
Step 2	.02				.316
ASI – Total		1.52	.21	.02	.131
Group Status		-.07	-.00	.00	.945
Step 3	.00				.630
ASI x Group		-.48	-.18	.00	.630
Dependent Variable: Skin Conductance Reactivity (Composite)[3]					
Step 1	.73				< .001
Pre-Challenge SC[9]		12.97	.84	.70	< .001
Gender		1.02	.06	.01	.311
Number of Axis I Diagnoses		-.51	-.04	.00	.607
Negative Affectivity (PANAS)		-.74	-.05	.00	.460
Daily Smoking Rate, Since Initiation		.56	.03	.00	.571
Step 2	.00				.803
ASI – Total		.45	.03	.00	.654
Group Status		-.43	-.03	.00	.662
Step 3	.00				.662
ASI x Group		.44	.09	.00	.662
Dependent Variable: Level of Avoidance of a Future Challenge[4]					
Step 1	.10				.123
Pre-Challenge SUDS Ratings		.83	.09	.00	.409
Gender		-1.43	-.16	.02	.154
Number of Axis I Diagnoses		-2.66	-.37	.08	.009
Negative Affectivity (PANAS)		2.01	.27	.05	.048
Daily Smoking Rate, Since Initiation		.28	.03	.00	.776

Step 2	.01				.490
ASI – Total		.56	.08	.00	.572
Group Status		1.08	.12	.01	.280
Step 3	.00				.397
ASI x Group		-.85	-.32	.01	.397

Note. *N* = 90; [1]Post-Challenge Subjective Units of Distress Scale Ratings (first minute post-challenge); [2]Diagnostic Sensations Questionnaire – Total score (completed immediately post-challenge); [3]Skin Conductance Reactivity – Composite (minutes 1-4 of challenge); [4]Post-Challenge Avoidance Measure; [5]Pre-Challenge Subjective Units of Distress Scale Ratings (minute 9 of pre-challenge baseline); [6]Gender (1 = Male; 2 = Female); [7]Anxiety Sensitivity Index – Total score (mean-centered); [8]Group status (1 = Nicotine Deprivation; 2 = Non-Nicotine Deprivation); [9]Pre-Challenge Skin Conductance (minute 9 of baseline)

Table 5. Post Hoc Tests: ANOVA Results, Between-Subjects Effects

	F	η^2	*p*
Repeated Measures ANOVA			
Dependent Variable: Peri-Challenge Anxiety, Minutes 1-3[1]			
Covariates			
Pre-Challenge SUDS Ratings[5]	4.46	.06	.038
Gender[6]	.99	.01	.321
Number of Axis I Diagnoses	3.11	.04	.082
Negative Affectivity (PANAS)	2.57	.03	.113
Daily Smoking Rate, Since Initiation	2.23	.03	.139
Main Effects			
ASI – Total[7]	4.69	.06	.034
Group Status[8]	1.81	.02	.182
Interactive Effect			
ASI x Group	5.53	.07	.022
Univariate ANOVA			
Dependent Variable: Challenge Anxiety – Minute 1[2]			
Covariates			
Pre-Challenge SUDS Ratings	8.08	.10	.006
Gender	1.74	.02	.191
Number of Axis I Diagnoses	2.02	.02	.160
Negative Affectivity (PANAS)	.57	.00	.449
Daily Smoking Rate, Since Initiation	4.03	.05	.048
Main Effects			
ASI – Total	5.20	.06	.026
Group Status	1.91	.02	.171
Interactive Effect			
ASI x Group	5.70	.07	.020
Dependent Variable: Challenge Anxiety – Minute 2[3]			
Covariates			
Pre-Challenge SUDS Ratings	2.74	.04	.103
Gender	1.11	.01	.295
Number of Axis I Diagnoses	2.90	.04	.093
Negative Affectivity (PANAS)	.89	.01	.347
Daily Smoking Rate, Since Initiation	.50	.00	.480
Main Effects			
ASI – Total	1.79	.02	.184
Group Status	.22	.00	.639
Interactive Effect			
ASI x Group	8.92	.11	.004
Dependent Variable: Challenge Anxiety – Minute 3[4]			
Covariates			
Pre-Challenge SUDS Ratings	1.50	.02	.224
Gender	.26	.00	.610
Number of Axis I Diagnoses	2.08	.03	.153
Negative Affectivity (PANAS)	5.07	.07	.028
Daily Smoking Rate, Since Initiation	1.62	.02	.206

Main Effects			
ASI – Total	4.90	.06	.030
Group Status	3.53	.05	.060
Interactive Effect			
ASI x Group	1.34	.02	.251

Note. *N* = 90; [1]Subjective Units of Distress Scale (SUDS) Anxiety Ratings, Challenge Minutes 1-3; [2]Subjective Units of Distress Scale (SUDS) Anxiety Ratings, Challenge Minute 1; [3]Subjective Units of Distress Scale (SUDS) Anxiety Ratings, Challenge Minute 2; [4]Subjective Units of Distress Scale (SUDS) Anxiety Ratings, Challenge Minute 3; ; [5]Pre-Challenge Subjective Units of Distress Scale Ratings (minute 9 of pre-challenge baseline); [6]Gender (1 = Male; 2 = Female); [7]Anxiety Sensitivity Index – Total score (mean-centered); [8]Group status (1 = Nicotine Deprivation; 2 = Non-Nicotine Deprivation)

Figure 1: Conceptual model: AS as moderator of the association between nicotine withdrawal and panic-relevant responding.

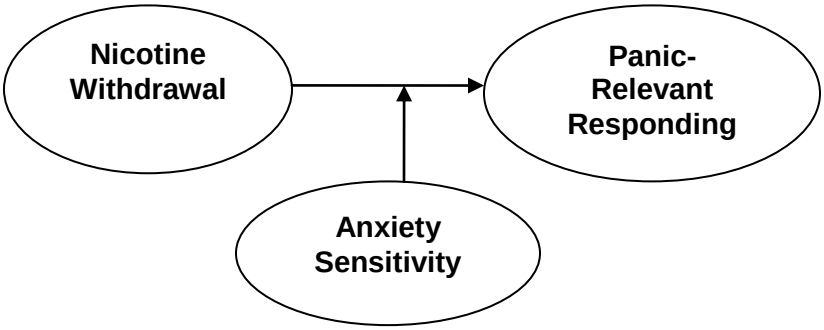

Figure 2: Outline of study procedure

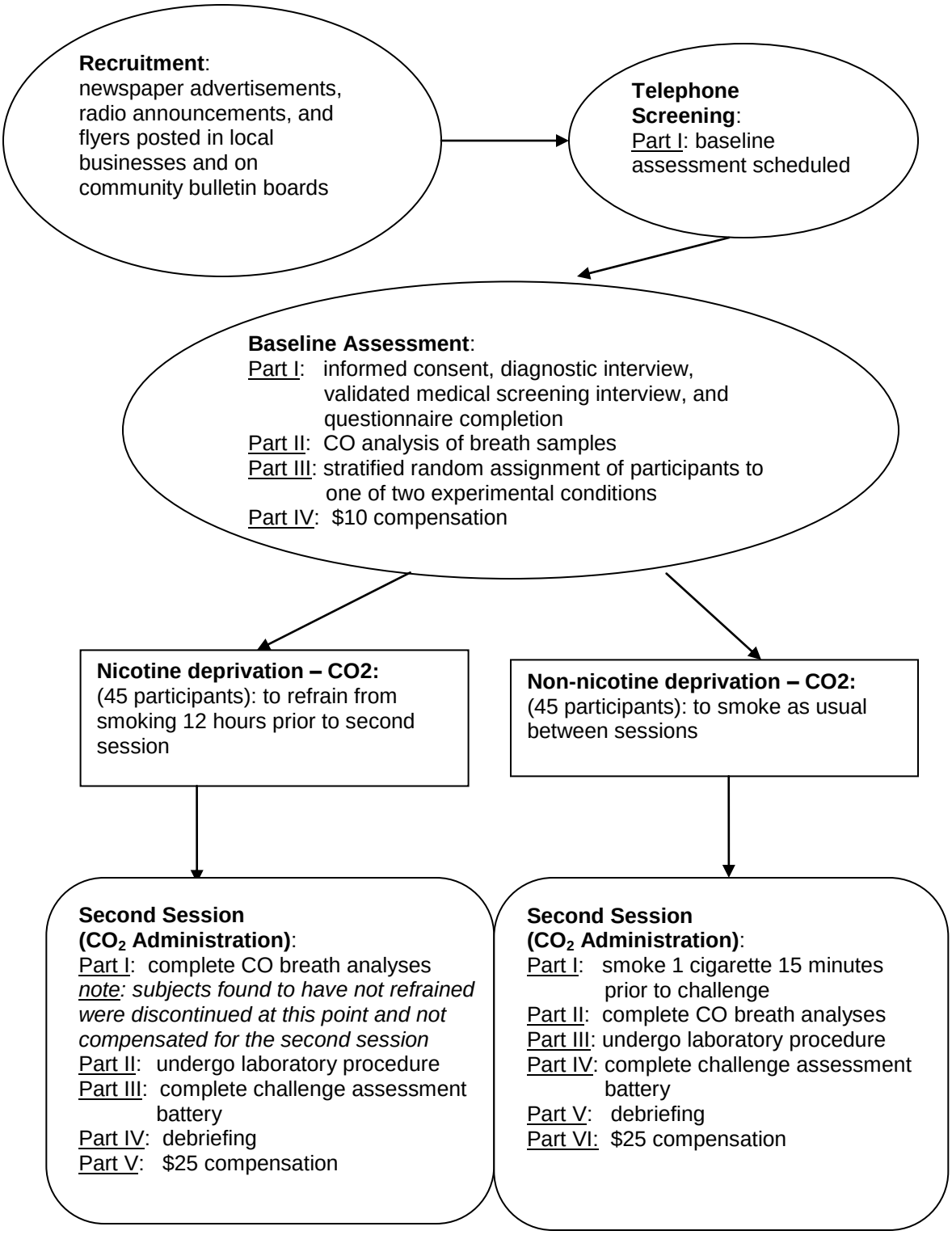

Figure 3: Anxiety ratings over time by withdrawal group

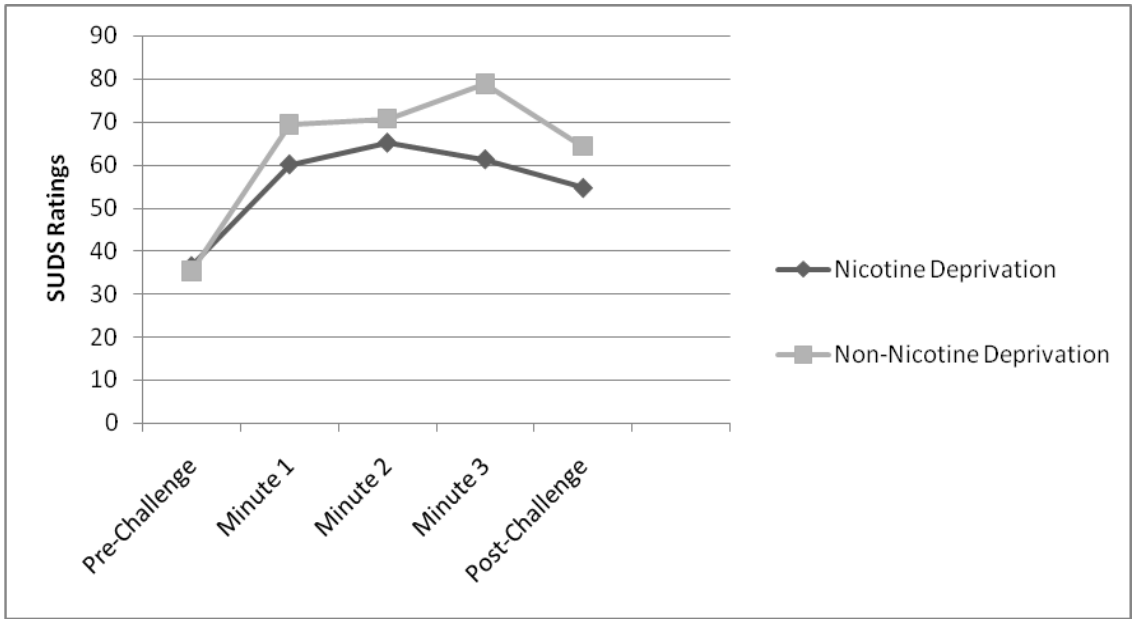

Figure 4: SUDS anxiety ratings: Withdrawal group status by AS interactive effects

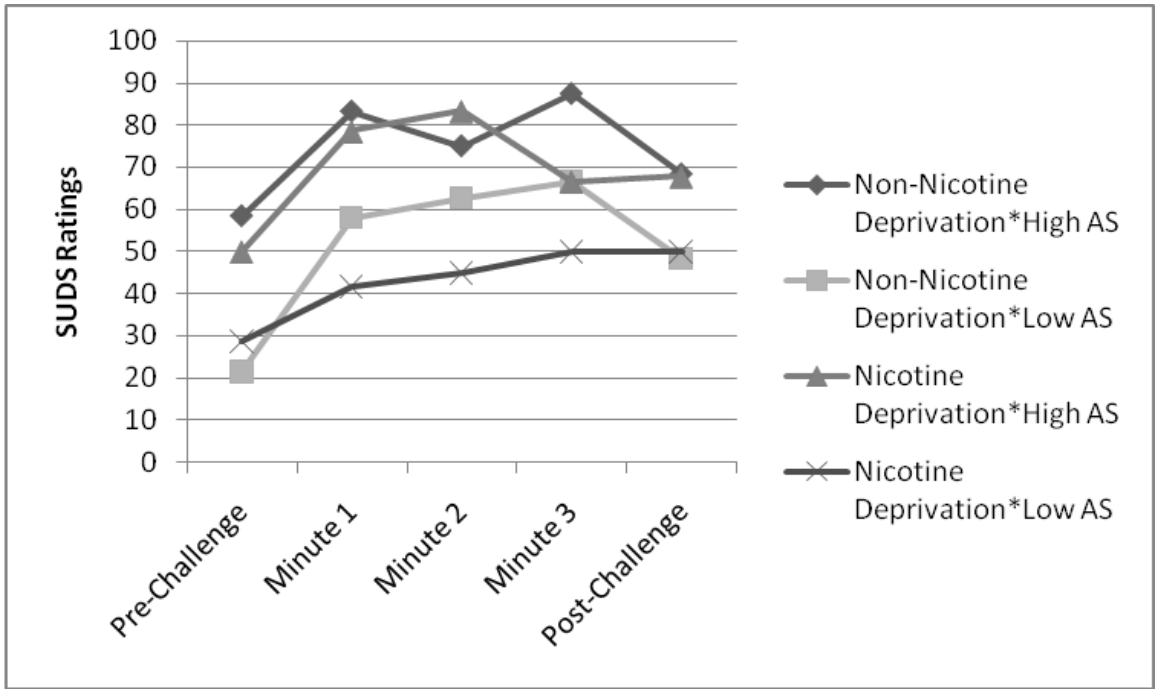

Figure 5: Nicotine withdrawal symptoms over time by withdrawal group