ANXIETY SENSITIVITY AND SMOKING TOPOGRAPHY:

A MULTI-METHOD EXPERIMENTAL INVESTIGATION

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A MULTI-METHOD EXPERIMENTAL INVESTIGATION

A Dissertation

Presented to

The Faculty of the Department

of Psychology

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

By

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June 2015

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ABSTRACT

Introduction: Anxiety sensitivity, the tendency to catastrophically interpret the meaning of anxiety-relevant interoceptive sensations, is implicated in the acquisition and maintenance of anxiety symptoms/disorders and aspects of cigarette smoking. Smokers who tend to perceive interoceptive sensations as harmful or dangerous may be more likely to smoke for affect-regulatory purposes. The present study tested an experimental model of negative reinforcement-based smoking motivation by examining the extent to which laboratory-induced physiological arousal impacts smoking urges, craving, smoking topography (puff style), and the moderating role of anxiety sensitivity. **Method:** Adult daily smokers (n = 90; M_{age} = 43.6 [*SD* = 9.7]; average 15.8 cigarettes per day) were recruited to participate in a single-session experimental study. Participants were randomly assigned to complete a biological challenge procedure, used as an experimental emotion-provocation task that consisted of a single vital capacity inhalation of 35% CO_2-enriched air mixture or compressed room air (control condition). Smoking urges and smoking topography (puff behavior) were assessed before and after the challenge. **Results:** Exposure to the 35% CO_2-enriched air experimental condition, relative to room air, elicited significantly higher levels of subjective distress (b = 0.72, p = .013), panic attack symptoms (b = 1.13, p < .0001), heart rate (b = 0.14, p = .002), and respiration rate (b = 0.47, p < .038). All effects were medium to large in size (Cohen's d range = 0.53 – 1.13). Results revealed a main effect of experimental condition in terms of self-report smoking urges post-challenge (b = -81.26, p = .048; d = -0.45), such that smokers exposed to the 35% CO_2-enriched air reported significantly lower smoking urges post-challenge, relative to the room air condition. There was a significant interaction between

anxiety sensitivity and experimental condition (b = -9.96, p = .014; d = -.56), such that high anxiety sensitive smokers exposed to 35% CO_2-enriched air reported significantly lower levels of smoking urges, relative to low anxiety sensitive smokers, and anxiety sensitivity did not differentially impact smoking urges for those exposed to room air. Regarding smoking topography, results revealed a non-significant main effect of experimental condition in terms of latency to smoking initiation or average inter-puff interval post-challenge. There was a significant condition effect for average puff volume (b = -8.11, p = .048) and puff duration (b = -144.39, p = .050), such that exposure to 35% CO_2-enriched air relative to room air, resulted in significantly smaller and shorter puff inhalations while smoking (Cohen's d = -0.43). There were no significant interaction effects of experimental condition by anxiety sensitivity for any of the smoking topography outcomes. **Discussion:** The experience of abrupt physiological distress may immediately result in decreased subjective smoking urges and changes in puff behavior (smaller volume; shorter duration), likely due to intensity of the cardiorespiratory distress experienced from the 35% CO_2-enriched air manipulation. This appeared to be particularly true for smokers high in anxiety sensitivity, at least in the case of subjective smoking urges. Findings are contextualized with the existing literature examining mechanistic factors linking panic attacks and smoking.

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Tobacco Use: Scope of the Problem

Cigarette smoking is the leading cause of preventable death in the United States (Center for Disease Control and Prevention [CDCP], 2002), contributing to over 443,000 deaths each year, or about 1 of every 5 deaths (CDCP, 2002, 2008, 2013). Tobacco use is estimated to cost the United States approximately $193 billion annually in direct medical expenses and lost productivity (CDCP, 2013), and with approximately 21.4% of the adult population smoking cigarettes (CDCP, 2013), nearly 25 million Americans will die prematurely from smoking-related illnesses (CDCP, 1997). Specifically, cigarette smoking is the most important risk factor for the development of lung cancer, accounting for approximately 80% of lung cancer deaths (American Cancer Society [ACS], 2012), and increases risk for other cancers like cancers of the mouth, pharynx, esophagus, stomach, kidney, bladder, uterus, and colon (ACS, 2012). Smoking also increases risk of heart disease, chronic respiratory diseases (e.g., bronchitis, chronic obstruction pulmonary disease). Continued smoking among individuals who have chronic physical conditions (e.g., asthma, diabetes, cancer, human immunodeficiency virus) can lead to the progression of these conditions and can complicate their treatment (ACS, 2012). In addition to the well-documented physical consequences of smoking, tobacco use is also associated with a host of negative psychological outcomes, including lowered self-esteem, increased self-reported anhedonia, anxiety, stress, increased risk of additional

substance use problems, decreased physical activity, and limited coping/problem solving skills (Dodgen, 2005).

Notably, there are marked benefits of smoking cessation (ACS, 2012; U.S. Department of Health and Human Services [USDHHS], 2004). Since around the mid-1960's, the prevalence of cigarette smoking in the United States has steadily declined, from approximately 42.4% in 1965 to 20.6% in 2009, which corresponds to a decrease of 51.4% (American Lung Association, 2011). It is estimated that 1,177,300 cancer deaths were averted from 1991/1992 through 2009, largely as a result of the reduction in tobacco use over the past 50 years (Jemal et al., 2008; Siegel, Naishadham, & Jemal, 2013). Despite the clear benefits of smoking cessation, a large majority of adult smokers repeatedly fail to quit smoking successfully (CDCP, 2011; Dodgen, 2005; USDHHS , 2010), even though more than half of current smokers report a strong motivation to quit smoking (CDCP, 2011). There is wide recognition that certain subgroups of individuals are at an increased risk for early smoking relapse, thus in order to facilitate successful smoking cessation for these individuals, tailored specialized treatments are likely needed (CDCP, 2013; National Institue of Health, 2006;Ziedonis et al., 2008). This matter is of particular importance given nation-wide health initiatives for tobacco prevention and control aimed at eliminating tobacco use as a public health problem in the U.S. (USDHHS, 2013).

Psychological Disorders and Cigarette Smoking

While population-based smoking rates have declined over the past two decades, cigarette use remains high among certain sub-populations – in particular, psychiatrically vulnerable individuals (Goodwin, Perkonigg, Höfler, & Wittchen, 2013; Goodwin,

Zvolensky, Keyes, & Hasin, 2012; Grant, Hasin, Chou, Stinson, & Dawson, 2004; Lasser et al., 2000; McClave, McKnight-Eily, Davis, & Dube, 2010; Morisano, Bacher, Audrain-McGovern, & George, 2009; CDCP, 2013; Morris, Burns, Waxmonsky, & Levinson, 2014). Large, nationally representative studies estimate that current smoking rates are about twice as high among those with a current psychiatric disorder relative to those with no psychiatric disorder (34.3% vs. 16.7%; Morris et al., 2014). In a recent study of smoking and mental illness (broadly defined), the prevalence of current smoking was 36.1% among persons with a history of mental illness, which was significantly higher relative to those without such history (21.4%; CDCP, 2013). In certain psychiatric disorders, smoking prevalence rates are even higher (e.g., > 60% in those with severe mental illness; Lasser et al., 2000; Williams & Ziedonis, 2004). Additionally, it is estimated that 30.9% of all cigarettes smoked by adults between 2009-2011 were smoked by individuals with a history of mental illness (CDCP, 2013).

Data largely suggests that smokers with psychopathology are significantly less likely to quit smoking successfully (Ferguson et al., 2003), despite making attempts to quit (McClave et al., 2010). One recent estimate suggests that among these adults with a history of mental illness, the quit rate was 34.7%, compared with 53.4% among non-psychiatric adults (CDCP, 2013). More specifically, a host of data suggest that various psychological disorders are linked to poor smoking cessation outcomes, including depressive disorders (Brown, Kahler, Niaura, et al., 2001; Hitsman, Borrelli, McChargue, Spring, & Niaura, 2003; Japuntich et al., 2007; Zvolensky, Bakhshaie, Sheffer, Perez, & Goodwin, 2015), schizophrenia (Covey, Hughes, Glassman, Blazer, & Geroge, 1994; Lasser et al., 2000), anxiety disorders (Piper, Cook, Schlam, Jorenby, & Baker, 2011;

Piper et al., 2010), posttraumatic stress disorder (Beckham, Calhoun, Dennis, Wilson, & Dedert, 2013; Zvolensky et al., 2008), and co-morbid substance use problems (Goodwin et al., 2014; Humfleet, Muñoz, Sees, Reus, & Hall, 1999). Data from a large sample of treatment-seeking smokers found that smokers with a current mood or anxiety disorder were significantly less likely to be abstinent eight weeks following a cessation attempt, relative to those with no history of psychopathology (Piper et al., 2010). This same patterning of effects was not seen for smokers with a past (remitted) disorder or current/lifetime substance use disorder. Thus, there appears to be important variability across forms of psychopathology in terms of smoking lapse. Indeed, such heterogeneity across psychological disorders, in addition to the presence of comorbid disorders, adds further complexity to the understanding of the associations between smoking and psychopathology (Cougle, Zvolensky, Fitch, & Sachs-Ericsson, 2010).

It is also worth noting that there is evidence that suggests smoking is associated with increased likelihood of various psychological disorders, including alcohol use disorders, mood/anxiety disorders (Degenhardt & Hall, 2001), and nicotine dependent-smokers (relative to non-dependent) may be at greater odds of having an anxiety disorder, major depressive/affective disorders, and alcohol/substance use disorder (Breslau, 1995; Breslau & Johnson, 2000; John, Meyer, Rumpf, & Hapke, 2004; Nelson & Wittchen, 1998). Thus, smoking and psychopathology appear to bidirectionally impact the development, exacerbation, and maintenance of each other.

Although reasons for the comorbidity of smoking and psychopathology are not fully unclear, there are several possible explanations (Morisano et al., 2009). First, it is possible that there are shared vulnerability factors that pre-dispose individuals with

psychopathology to initiate and maintain smoking (Breslau, Novak, & Kessler, 2004; Jamal, Van der Does, & Penninx, 2015; Leventhal & Zvolensky, 2015; Munafò, Zetteler, & Clark, 2007). Second, smokers with psychopathology may rely on nicotine with attenuated psychological distress or symptoms (or attenuation of negative affective states due to nicotine withdrawal symptoms; Parrott, 1998; Parrott, 1999; Shiffman & Jarvik, 1984). Third, common social and environmental factors may account for the psychopathology-smoking comorbidity (e.g., Lawn, 2005; Spring, Pingitore, & McChargue, 2003). Lastly, it is possible that the consumption of nicotine through smoking may modulate various neuropharmacological systems or brain regions, which may be involved in the pathogenesis of psychopathology (e.g., Brody et al., 2009; Brody et al., 2004; Picciotto, 2003).

Despite a host of data that implicate the interplay between psychopathology and smoking, smoking remains a largely neglected issue in many mental health facilities (Olivier, Lubman, & Fraser, 2007; Zvolensky, Baker, et al., 2005), which is problematic given nicotine can actually interfere with pharmacotherapy treatment and complicate presentation of psychological symptoms (Aubin, Rollema, Svensson, & Winterer, 2012; Olivier et al., 2007; Ziedonis et al., 2008). Interestingly, a recent meta-analysis found that smokers with a mental illness (broadly defined, including serious mental illness), relative to those without, do not differentially receive advice to quit smoking (Mitchell, Vancampfort, De Hert, & Stubbs, 2015). In fact, smokers with non-serious mental illness were more likely to receive smoking cessation advice relative to smokers with no mental illness (Mitchell et al., 2015). Thus, despite receiving feedback from providers about quitting smoking, those with psychopathology still struggle to quit smoking.

Unfortunately, beyond the development of standard smoking cessation treatment programs (Fiore et al., 2008), few clinical trials have specifically tested the efficacy of smoking cessation treatment programs that address unique needs of smokers with psychopathology (Aubin et al., 2012).

Taken together, there is an increasing emphasis to (a) understand factors related to the maintenance of smoking among psychiatrically-vulnerable smokers (Aubin et al., 2012; Morisano et al., 2009) and (b) develop and test the utility of tailored smoking cessation treatment programs that address the unique needs of psychologically-vulnerable smokers (Minichino et al., 2013; Ziedonis et al., 2008).

Panic Attacks as a Broad Marker of Psychopathology

One approach to explicating the nature of the comorbidity between smoking and psychopathology is through panic attacks, as data suggest that panic attacks are a risk marker for a relatively broad range of psychopathological conditions (Baillie & Rapee, 2005; Goodwin, Brook, & Cohen, 2005; Goodwin & Hamilton, 2001; Goodwin et al., 2004). Panic attacks reflect an abrupt autonomic surge of intense discomfort and extreme fear or impending doom accompanied by a strong flight-or-fight action tendency (American Psychiatric Association [APA], 2013). Panic attacks can occur from calm or anxious states – and regardless of preceding anxious states, the peak intensity of fear or discomfort is reached within minutes. That is, panic attacks are discrete in nature (Craske et al., 2010). Panic attack symptoms include various physical and cognitive responses including: palpitations/pounding heart, sweating, trembling or shaking, sensations of smothering or shortness of breath, feelings of choking, chest pain or discomfort, nausea or stomach distress, feelings of dizziness or light-headedness, chills or heat sensations,

paresthesias, derealization or depersonalization, fear of losing control or 'going crazy', or fear of dying (APA, 2013). Psychophysiological data suggest that panic attacks are indeed reflected by abrupt surges of arousal, typically cardiorespiratory activation/instability that reaches a peak within minutes and subsides within minutes (Craske et al., 2010; Meuret & Ritz, 2010).

It is estimated that approximately 28% of the general US population has experienced a panic attack (clinical or non-clinical) at some point in their life, with 23% experiencing panic attacks without ever meeting criteria for panic disorder and/or Agoraphobia (Kessler, Chiu, Demler, & Walters, 2005). Panic attacks are associated with an increased risk of panic disorder as well as other anxiety disorders (Baillie & Rapee, 2005; Reed & Wittchen, 1998), major depressive disorder (Bittner et al., 2004; Bovasso & Eaton, 1999; Hayward, Killen, Kraemer, & Taylor, 2000), substance use disorders (Baillie & Rapee, 2005), personality disorders (Goodwin et al., 2005) and severe mental illness (Goodwin et al., 2004). Other work has indicated that individuals with non-clinical panic attacks (i.e., panic attacks but not panic disorder) or limited-symptom panic attacks are also at an increased likelihood of having psychological comorbidity (Pané-Farré et al., 2013). Panic attacks are also associated with physical illness, poorer quality of life, and disability (Bovasso & Eaton, 1999; Goodwin, Pine, & Hoven, 2003; Kinley, Cox, Clara, Goodwin, & Sareen, 2009). While specific mechanisms linking panic attacks to psychological and physical symptoms are not fully clear, panic attacks may enhance negative emotional learning in relation to various sources of interoceptive and exteroceptive cues and stressors, especially physical sensations (Bouton, Mineka, & Barlow, 2001).

Panic Attacks and Smoking

There is a growing recognition that cigarette smoking and panic attacks frequently co-occur (Bernstein, Zvolensky, Schmidt, & Sachs-Ericcson, 2007; Cosci, Knuts, Abrams, Griez, & Schruers, 2010; Zvolensky, Feldner, Leen-Feldner, & McLeish, 2005; Zvolensky, Schmidt, & Stewart, 2003). Integrative models of smoking and panic posit that smoking and panic pathologies operate in a bidirectional manner (Zvolensky & Bernstein, 2005): smoking is a risk factor for, and may serve to maintain, panic psychopathology (Breslau et al., 2004; Lasser et al., 2000; McFall et al., 2005; Zvolensky, Feldner, Leen-Feldner, & McLeish, 2005) and pre-morbid panic vulnerability is related to coping-oriented smoking motives and perhaps the maintenance of smoking behavior (Zvolensky, Feldner, Leen-Feldner, & McLeish, 2005).

Recent research converges, in particular, on the observation that panic attacks are associated with various aspects of smoking behavior. For example, smokers with a history of panic attacks relative to those without, report higher levels of nicotine dependence (Piper et al., 2011; Vujanovic, Marshall, Gibson, & Zvolensky, 2010), less self-efficacy for remaining abstinent (Zvolensky, Lejuez, Kahler, & Brown, 2004), and increased negative affect and affect-regulatory smoking motivations (Farris, Zvolensky, Blalock, & Schmidt, 2014). Elevated anxiety-related withdrawal symptoms (e.g., anxiety, restlessness) have been uniquely documented in vulnerable smokers with a history of non-clinical panic attacks (Zvolensky, Lejuez, et al., 2004) in comparison to those without. Other work has found panic attacks are associated with greater quit-day negative affect and nicotine dependence (Marshall, Johnson, Bergman, Gibson, & Zvolensky, 2009; Piper et al., 2010) and less self-efficacy for remaining abstinent (Zvolensky,

Schmidt, et al., 2005).

In regard to smoking cessation, epidemiological data suggest that the prevalence of smoking is significantly higher among those with past-month panic attacks (46.4%) relative to the general non-psychiatric population (22.5%), and smoking cessation rates are significantly lower (29.8% versus 42.5%; Lasser et al., 2000). Within a community, non-clinical sample of daily smokers, those with a history of panic attacks averaged significantly shorter duration of lifetime quit attempts relative to those without a panic attack history (Zvolensky, Lejuez, et al., 2004). Prospective studies also suggest that panic attacks are related to impaired smoking cessation success (Hapke et al., 2005; Sonntag, Wittchen, Höfler, Kessler, & Stein, 2000; Ziedonis et al., 2008), despite the evidence of high levels of motivation to quit among such smokers (Zvolensky & Bernstein, 2005). For example, a large smoking cessation clinical trial found smokers with a history of panic attacks, compared to those without such a history, were significantly less likely to be abstinent at six-month following pharmacotherapy for smoking cessation (Piper et al., 2011).

In summary, empirical research suggest that panic attacks are related to smoking-relevant processes including (1) smoking to manage negative emotional experiences; (2) greater degrees of acute nicotine withdrawal and negative affect upon quitting; and (3) greater difficulties with quitting smoking.

Biological Challenge Methodology to Study Panic-Smoking Interplay

Experimental, laboratory-based methodologies have been used to examine the interplay between smoking and panic-related processes (Abrams, Schruers, Cosci, & Sawtell, 2008). Biological challenge paradigms have been utilized in experimental

psychopathology research (typically in panic disorder research) to produce physiological sensations associated with anxiety/panic-like symptoms (e.g. chest discomfort, dizziness, sweating, shortness of breath; Zvolensky & Eifert, 2001). While many different biological challenge paradigms have been utilized to model panic in the laboratory (e.g., voluntary hyperventilation, breath holding, stimulant administration), one of the most widely used procedures is carbon dioxide (CO_2)-enriched air breathing challenges (Abrams, Schruers, et al., 2008). The popularity in using CO_2 biological challenges is perhaps due to the production of physiological arousal similar to naturally occurring panic attacks (i.e., similar symptoms, duration, severity; Griez, Lousberg, & Van den Hout, 1987; Perna et al., 1994; Van den Hout et al., 1987). The procedure is also reliable (e.g., good test-retest; Coryell & Arndt, 1999; Perna et al., 1994; Verburg, Pols, de Leeuw, & Griez, 1998), non-invasive, and medically safe (Van den Hout et al., 1987).

Several forms of CO_2 breathing challenges have been used, including (a) continuous breathing of CO_2 at low concentration (e.g., 5-7%) for a fixed period of time (10 or 20 minutes) or until panic onset (Sanderson & Wetzler, 1990); (b) rebreathing of CO_2 at low concentrations (e.g., 5-7% CO_2) via a closed system for 5 minutes (Gorman et al., 1988) that produces 2-3% increases in CO_2 by challenge end (Abrams, Zvolensky, et al., 2008); or (c) single or double vital capacity inhalations of 35% CO_2 gas mixture to produce highest exposure but briefest duration (Zandbergen, Pols, de Loof, Lousberg, & Griez, 1989). The latter approach is thought to be one of the most reliable approaches, is easy to administer, safe, and produces abrupt somatic arousal that is characteristic of the onset of naturally occurring panic attacks (Vickers, Jafarpour, Mofidi, Rafat, & Woznica, 2012). Additionally, repeated exposure to high-dose CO_2 in individuals with no history of

panic attacks does not increase risk for subsequent panic attacks – thus, this procedure is safe for use even in non-clinical individuals (Prenoveau, Forsyth, Kelly, & Barrios, 2006).

Biological Challenges and Panic Attacks

Extant data suggest that panic-vulnerable individuals typically respond with greater emotional reactivity to panic-relevant bodily sensations elicited by biological challenge paradigms (Feldner, Zvolensky, Stickle, Bonn-Miller, & Leen-Feldner, 2006; Gonzalez, Zvolensky, Hogan, McLeish, & Weibust, 2011; Kutz, Marshall, Bernstein, & Zvolensky, 2010; Perna, Romano, Caldirola, Cucchi, & Bellodi, 2003; Schmidt & Richey, 2008; Telch, Harrington, Smits, & Powers, 2011; Zvolensky, Eifert, & Lejuez, 2001; Zvolensky, Eifert, Lejuez, & McNeil, 1999). Specifically, individuals with panic disorder and their first-degree relatives respond with greater anxiety/fear to CO_2 challenges, relative to non-clinical control individuals (Papp, Klein, & Gorman, 1993; Perna, Bertani, Caldirola, & Bellodi, 1996). Additionally, CO_2-induced panic attacks are more common in panic-prone individuals relative to non-clinical individuals (Antony, Brown, & Barlow, 1997). Moreover, in healthy volunteers, the typical response to a CO_2 challenge is increased self-reported anxiety and fleeting bodily sensations (Griez & Schruers, 2003). Prospective data also indicate that, in non-clinical individuals, responding with greater subjective distress to a 20 second 20% CO_2 biological challenge is predictive of the development of spontaneous panic attacks during a two year follow-up (Schmidt & Zvolensky, 2007).

Biological Challenges and Smoking

More recent studies have started to evaluate emotional reactivity to bodily sensations among *smokers* in response to a biological challenge (Abrams, Schruers, et al., 2008), which have included breath-holding challenges (Brown, Lejuez, Kahler, & Strong, 2002; Brown et al., 2009; Cosci, Bertoli, & Abrams, 2013; Zvolensky, Feldner, Eifert, & Brown, 2001) and voluntary hyperventilation tasks (Feldner, Vujanovic, Gibson, & Zvolensky, 2008; Marshall et al., 2009; Marshall et al., 2008; Zvolensky, Feldner, Leen-Feldner, Gibson, et al., 2005; Zvolensky, Leen-Feldner, et al., 2004). At least 13 studies have utilized CO_2 biological challenges in smokers. These studies are summarized in Table 1 and reviewed below.

Arousal-relevant outcomes. Smokers exposed to CO_2-enriched air, relative to room air, demonstrate increases in blood pressure, heart rate, state anxiety, and negative affect (Attwood, Ataya, Bailey, Lightman, & Munafò, 2014), which is consistent with literature on CO_2 reactivity in non-smoking studies. Smokers, relative to non-smokers, respond with greater panic attack symptoms (Abrams, Zvolensky, et al., 2008) and urges to escape (Abrams, Schlosser, et al., 2011) during a 5-minute 5% CO_2 re-breathing challenge (c.f. Attwood et al., 2014 experiment 1). In a sample of individuals with panic disorder, those who were smokers, relative to non-smokers, reported greater panic attack symptoms following a single-inhalation 35% CO_2 challenge (Knuts et al., 2010). Other studies have found that among daily smokers, greater post-challenge subjective distress in response to a 4-minute 10% CO_2 challenge is predicted by panic disorder status (Leyro & Zvolensky, 2013) and posttraumatic stress symptom severity (Vujanovic, Marshall-Berenz, Beckham, Bernstein, & Zvolensky, 2010). In non-smokers, nicotine (via

transdermal nicotine patch), relative to placebo, is associated with greater heart rate and pre-challenge anxiety, but not challenge reactivity (Cosci, Abrams, Schruers, Rickelt, & Griez, 2006), suggesting that nicotine may contribute to physiological activation, but not differences in reactivity seen in smokers and non-smokers.

Studies have also examined the use of CO_2 reactivity as processes relevant to smoking cessation. One study found that heavy smokers unable to quit smoking for at least 7 days, relative to those who were able to quit for 7 or more days, responded with greater anxiety and somatic arousal and lower emotional control following a 25 second 20% CO_2 inhalation challenge (Zvolensky, Feldner, Eifert, & Stewart, 2001). In contrast, a different study found that immediate relapsers (smokers who have failed to quit for >24 hours) and delayed relapsers (smokers who have quit for $\geq$ 3months) did not differ in terms of self-reported changes in dysphoria post-CO_2 challenge (three administrations of 20% CO_2 for 3 seconds; Brown et al., 2002). Thus, initial data suggest that responding to panic-relevant sensations may be related to the duration of past quit attempts, although it may not be sensitive in terms of longer (delayed relapse) cessation attempts.

Additionally, several studies have examined the nature of nicotine withdrawal in terms of panic reactivity to a biological challenge based on the expectations that acute nicotine deprivation would amplify affective responding to CO_2 (Brown, Lejuez, Kahler, Strong, & Zvolensky, 2005; Zvolensky & Bernstein, 2005). Empirical findings are mixed. Some studies have found that smokers randomized to 12-hour nicotine deprivation versus smoking as usual do not differ in terms of challenge reactivity (e.g., urge to escape, panic attack symptoms, state anxiety, negative affect, dysphoria) to a 5-minute 5% CO_2 re-breathing challenge (Abrams, Leger, et al., 2011), 7.5% CO_2 single

inhalation challenge (Attwood et al., 2014), or three administrations of 20% CO_2 inhaled for 25 seconds (Brown et al., 2002). Similarly, among smokers with and without panic disorder exposed to a 4-minute 10% CO_2 continuous breathing challenge, 12-hour nicotine deprivation versus smoking as usual did not differentially impact post-challenge subjective distress (Leyro & Zvolensky, 2013). In fact, smoking as usual, relative to 12-hour nicotine deprivation, is associated with *greater* subjective distress during a 4-minute 10% CO_2 continuous breathing challenge (Vujanovic & Zvolensky, 2009) and increased state anxiety and negative affect post single inhalation of 7.5% CO_2-enriched air (Attwood et al., 2014).

However, severity of subjective nicotine withdrawal symptoms, regardless of randomized condition, appears to be associated with (and perhaps a better predictor of) greater post-challenge subjective distress (Leyro & Zvolensky, 2013), panic attack symptoms, and urges to escape (Abrams, Schlosser, et al., 2011). Moreover, after adjusting for withdrawal condition and panic disorder status, one study found that greater subjective reactivity to a 4-minute 10% CO_2 continuous breathing challenge was associated with more severe panic attack symptoms post-challenge (Farris, Zvolensky, Otto, & Leyro, in press).

Smoking relevant-outcomes. Fewer studies have examined smoking-related outcomes as a result of a CO_2 challenge. A within-subject experimental study found that smokers did not report differences in subjective smoking urges after exposure to 7.5% CO_2-enriched air relative to room air (Attwood et al., 2014). Similarly, exposure to three 25 second inhalations of 20% CO_2 did not differentially impact pre-post challenge changes in smoking urges (Brown et al., 2002). However, among smokers deprived for

12-hours versus those smoking as usual, non-abstinent smokers reported greater increases in smoking urges after exposure to a single-inhalation of 7.5% CO_2 relative to room air; no differences by gas manipulation were observed for nicotine deprived smokers (Attwood et al., 2014). In a sample of smokers with and without panic disorder (randomized to smoking as usual or 12-hours nicotine withdrawal), after adjusting for panic disorder status and withdrawal condition, greater subjective reactivity to a 4-minute 10% CO_2 continuous breathing challenge was associated with greater increase in nicotine withdrawal symptom severity post-challenge (Farris et al., in press). Finally, one study found that longer (relative to shorter) persistence of breathing 20% CO_2-enriched air is predictive of lower risk in smoking lapse among smokers undergoing a self-guided quit attempt (Brown et al., 2009).

Collectively, data generally support that: (1) CO_2 challenges increase somatic arousal and subjective distress among smokers; (2) the subjective experience of nicotine withdrawal symptoms may amplify anxious responding to a CO_2 challenge; (3) limited studies have examined smoking-relevant processes post-CO_2 challenge, however preliminary data indicate that CO_2 exposure may impact smoking craving (in some instances) and subjective experience of nicotine withdrawal symptoms; and (4) Individual difference factors likely play an important role in understanding reactivity to CO_2 challenges (Abrams, Schlosser, et al., 2011; Abrams, Zvolensky, et al., 2008; Farris et al., in press; Vujanovic & Zvolensky, 2009).

Anxiety Sensitivity: A Transdiagnostic Construct

Based on the aforementioned relations between panic attacks and smoking, scholarly efforts have focused on explicating factors that underlie the smoking-panic

attack co-occurrence in order to isolate possible therapeutic targets and mechanisms that can be addressed in smoking cessation treatment. Numerous factors in this context have been examined (e.g., severity of nicotine dependence, age of smoking onset, tendency to experience negative mood in general; Zvolensky & Bernstein, 2005) with relatively little success. Yet, one cognitive-based mechanism that has thus far yielded some of the strongest and most consistent evidence is anxiety sensitivity (Bernstein, Zvolensky, Vujanovic, & Moos, 2009).

Anxiety sensitivity is defined as the extent to which individuals believe anxiety and anxiety-related sensations have *harmful consequences* (McNally, 2002; Reiss & McNally, 1985; Taylor, 1995; Taylor, Koch, McNally, & Crockett, 1992). The expectancy model of fear posits that, in the context of personal threat, anxiety sensitivity marks the extent to which one attends to, and perceives, anxiety-relevant sensations as harmful, dangerous, and indicative of catastrophic consequences across several different domains (physical, social, and cognitive consequences; Reiss & McNally, 1985) – thus anxiety sensitivity is conceptualized as a multidimensional construct (Taylor et al., 2007). Similar to other fears, like heights or spiders, anxiety sensitivity, simply put, is a fear of *anxiety or physiological sensations* that accompany anxiety (McNally, 2002). As an illustrative example, individuals high in anxiety sensitivity may interpret heart palpitations (a panic-relevant sensation) as indicative of a heart attack (cognitive distortion), whereas individuals low in anxiety sensitivity may interpret these same sensations as an annoyance or not attend at all to the sensations. Notably, anxiety sensitivity is *not* an index of general trait anxiety (i.e., the tendency to respond with

anxiety in the face of stressors), but is the tendency to respond with fear/anxiety when experiencing anxiety *sensations* (McNally, 2002).

Anxiety Sensitivity and Panic Psychopathology

Anxiety sensitivity is a risk factor for the acquisition and maintenance of psychopathology, primarily anxiety and mood disorders (Olatunji & Wolitzky-Taylor, 2009). Prospective studies with healthy adults (Li & Zinbarg, 2007; Schmidt, Lerew, & Jackson, 1999; Schmidt, Zvolensky, & Maner, 2006) and adolescents (Hayward, Killen, Kraemer, & Taylor, 2000) indicate higher levels of anxiety sensitivity predict the future occurrence of anxiety symptoms and panic attacks, after controlling for trait anxiety and neuroticism (propensity to experience trait negative affect). Anxiety sensitivity also predicts the maintenance of panic disorder among untreated patients, the prospective emergence of panic attacks among infrequent (non-clinical) panickers, and the onset of panic symptoms among individuals free from a history of panic attacks (Ehlers, 1995). Laboratory data bolter these prospective findings (e.g., Brown, Smits, Powers, & Telch, 2003; Carter, Suchday, & Gore, 2001; Rapee & Medoro, 1994; Zinbarg, Brown, Barlow, & Rapee, 2001; Zvolensky, Feldner, Eifert, & Stewart, 2001), indicating that anxiety sensitivity increases the risk for more intense anxiety symptoms and anxiety psychopathology, including panic attacks and panic disorder. Specifically, anxiety sensitivity appears to explain, at least in part, responsitivity to biological challenges (e.g., Clark, 1993; Rapee, 1995; Eifert, Zvolensky, Sorrell, Hopko, & Lejeuz, 1999). For example, after controlling for trait levels of negative affectivity, higher levels of anxiety sensitivity are predictive of greater cognitive and physical panic attacks symptoms following a 4-minute 10% CO_2 continuous breathing biological challenge (Kutz,

Marshall, Bernstein, & Zvolensky, 2010) and post-challenge behavioral avoidance (Gregor & Zvolensky, 2008). Additionally, in a non-clinical sample, the combination of high anxiety sensitivity and high subjective distress following a 20 second 20% CO_2 biological challenge was predictive of spontaneous panic attacks two years later (Schmidt & Zvolensky, 2007). Importantly, anxiety sensitivity is conceptualized as a relatively stable, but malleable, construct and serves as an explanatory mechanism in the treatment of anxiety psychopathology, like panic disorder (e.g., Schmidt, Capron, Raines, & Allen, 2015; Smits, Berry, Rosenfield, et al., 2008; Smits, Berry, Tart, & Powers, 2008).

Anxiety Sensitivity and Smoking Processes

Whereas past work has explored anxiety sensitivity in relation to anxiety psychopathology, research over the past decade has convincingly indicated that this construct may serve as a central explanatory mechanism in cigarette smoking (Leventhal & Zvolensky, 2015). Theoretically, the anxiety sensitivity-smoking association is based on negative-reinforcement models of substance use (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Zvolensky, Schmidt, et al., 2003), as motivation to avoid the experience of discomfort and negative affective is one of the strongest drivers of maladaptive drug use (McCarthy, Curtin, Piper, & Baker, 2010). For example, smokers are more likely to lapse and relapse to smoking after a cessation attempt in the context of experiencing high levels of negative affect (see review by Shiffman, 2005), which is thought to be due to (in part) *perceptions* that smoking will have affect-regulatory effects (i.e., smoking will help me relax and feel less tense; Brandon & Baker, 1991; Kassel, Stroud, & Paronis, 2003). Indeed, *cognitive processes* are thought to explain the link between the experience of negative affect and continued drug use (Curtin, McCarthy, Piper, & Baker, 2006; Kassel,

Wardle, Heinz, & Greenstein, 2010), based on the theoretical understanding that one's interpretation and appraisal of thoughts can impact the frequency and form of negative affect and behavioral responding (e.g., Nosen & Woody, 2009). Naturally, anxiety sensitivity is a logical vulnerability factor that could importantly impact the maintenance of cigarette smoking.

Cross-Sectional Data. Cross-sectional data indicate that anxiety sensitivity is positively associated with negative affect reduction smoking motives (Battista et al., 2008; Comeau, Stewart, & Loba, 2001; Farris, Leventhal, Schmidt, & Zvolensky, 2015; Johnson, Farris, Schmidt, Smits, & Zvolensky, 2013; Leyro, Zvolensky, Vujanovic, & Bernstein, 2008; Novak, Burgess, Clark, Zvolensky, & Brown, 2003; Zvolensky et al., 2006) and beliefs (expectancies) that smoking will reduce negative affect (Brown, Kahler, Zvolensky, Lejuez, & Ramsey, 2001; Farris, Leventhal, et al., 2015; Gregor, Zvolensky, McLeish, Bernstein, & Morissette, 2008). In fact, one study found that anxiety sensitivity was linked to smoking maintenance/reliance indirectly via affect-regulatory smoking expectancies and motives (Farris, Leventhal, et al., 2015).

Related lines of research indicate that anxiety sensitivity is associated with psychological inflexibility in the context of distressing smoking-relevant contexts (Zvolensky, Farris, Schmidt, & Smits, 2014), the tendency to act impulsively when experiencing negative affect (Guillot, Pang, & Leventhal, 2014), and greater expectancies of interoceptive distress during acute smoking abstinence (Farris, Langdon, DiBello, & Zvolensky, 2015). Additionally, smokers high in anxiety sensitivity perceive the prospect of quitting as both a more difficult and personally threatening experience (Zvolensky et al., 2007) possibly due to a hypersensitivity to aversive internal sensations such as

nicotine withdrawal symptoms (Zvolensky, Baker, et al., 2004) or elevated state anxiety (Johnson et al., 2013).

Importantly, anxiety sensitivity appears to be incrementally associated with smoking-relevant processes after adjusting for the presence of panic attacks, trait-negative affect, psychological disorders, problematic substance use, participant sex, medical problems, and smoking rate (Farris, Leventhal, et al., 2015; Johnson et al., 2013; Zvolensky, Farris, Leventhal, & Schmidt, 2014; Zvolensky, Farris, Schmidt, et al., 2014). In fact, one cross-sectional study found that among treatment-seeking smokers, the presence of past-year emotional disorders (anxiety/depressive disorders) was associated with greater levels of nicotine dependence, greater perceived barriers to cessation, and greater severity of problematic symptoms during prior quit attempts, which was indirectly predicted (explained) by anxiety sensitivity (Zvolensky, Farris, Leventhal, et al., 2014), which provides empirical data (albeit cross-sectional) to support that anxiety sensitivity may be a mechanism related to the maintenance of smoking among individuals with certain emotional disorders.

Prospective Data. Regarding smoking cessation, anxiety sensitivity appears to be positively associated with increased motivation to quit smoking, especially among females (Dahne, Hoffman, & MacPherson, 2015), perhaps owing to more concern about the health consequences of smoking (e.g., heart disease, respiratory illnesses). However, higher levels of anxiety sensitivity are associated with greater odds of early lapse (Brown, Kahler, Zvolensky, et al., 2001) and relapse during quit attempts (Assayag, Bernstein, Zvolensky, Steeves, & Stewart, 2012; Zvolensky, Stewart, Vujanovic, Gavric, & Steeves, 2009); these effects are not explained by smoking rate or nicotine

dependence, nicotine withdrawal symptoms, or trait-like negative mood propensity. Thus, despite motivation to quit smoking, high anxiety sensitive smokers appear to struggle to quit successfully.

One reason for smoking cessation difficulties may be use to greater subjective experiences of nicotine withdrawal symptoms. For example, smokers with higher anxiety sensitivity experience more intense nicotine withdrawal symptoms during in early phases of quitting (Johnson, Stewart, Rosenfield, Steeves, & Zvolensky, 2012; Langdon et al., 2013), but not necessarily withdrawal in later phases of quitting (Mullane et al., 2008). Theoretically, high anxiety sensitive smokers may be more 'tuned in' to physiological distress associated with nicotine withdrawal and catastrophically attend to and interpret these sensations as unmanageable (Brown et al., 2005). Importantly though, reductions in anxiety sensitivity are associated with increased odds of cessation success and reductions in cigarette consumption (Feldner, Zvolensky, Babson, Leen-Feldner, & Schmidt, 2008) and smoking cessation is associated with reductions in anxiety sensitivity and nicotine withdrawal (Zvolensky, Bogiaizian, Salazar, Farris, & Bakhshaie, 2014).

Experimental Data. Few experimental studies have examined the interplay between anxiety sensitivity and smoking processes. At least three studies have examined the role of anxiety sensitivity in predicting affective reactivity to a biological challenge. Among smokers and non-smokers exposed to a 5-minute 5% CO_2 rebreathing biological challenge, smokers responded with greater with post-challenge panic attacks symptoms, especially smokers high in anxiety sensitivity (specifically, cognitive concerns about the meaning of internal bodily sensations; Abrams, Schlosser, et al., 2011). Another study utilizing a 4-minute 10% CO_2 continuous breathing biological challenge found that

among adult daily smokers, anxiety sensitivity was positively associated with peri-challenge subjective anxiety ratings (Vujanovic & Zvolensky, 2009), which is consistent with a 3-minute voluntary hyperventilation biological challenge study that found that higher anxiety sensitivity was associated with greater likelihood of having a panic attack during the challenge among 12-hour nicotine deprived smokers (Marshall et al., 2009).

The interplay between anxiety sensitivity and nicotine withdrawal has also been examined in at least four experimental studies. Among heavy smokers randomized to 12-hour deprivation versus smoking as usual, anxiety sensitivity did not conditionally impact the effect of withdrawal group on anxious responding to a 5-minute 5% CO_2 rebreathing biological challenge (Abrams, Schlosser, et al., 2011). In contrast, another study of daily smokers randomized to 12-hour deprivation versus smoking as usual found that higher anxiety sensitivity predicted greater peri-challenge anxious responding among the smoking as usual group (Vujanovic & Zvolensky, 2009). Thus, there is some evidence (albeit mixed) that anxiety sensitivity and smoking recency may interplay to impact responding to distressing somatic states. Relatedly, two experimental studies provide experimental data that suggest that anxiety sensitivity is associated with greater deprivation-induced subjective nicotine withdrawal symptom severity (Marshall et al., 2009; Zvolensky, Farris, Guillot, & Leventhal, 2014) and smoking urges (Zvolensky, Farris, Guillot, et al., 2014).

Additionally, anxiety sensitivity has been examined as a predictor of responding to a laboratory relapse analogue task, where participants are monetarily rewarded to (a) delay initiation of smoking and (b) smoke fewer cigarettes when given the opportunity to smoke (McKee, Krishnan-Sarin, Shi, Mase, & O'Malley, 2006). Here, anxiety sensitivity

indirectly predicted shorter latency to smoking initiation during a relapse analogue task through deprivation-induced smoking urges and nicotine withdrawal symptom severity (Zvolensky, Farris, Guillot, et al., 2014). Of note, anxiety sensitivity was not a *direct* predictor of latency to smoking during the relapse analogue task. Moreover, anxiety sensitivity did not directly or indirectly predict increases in the *number of cigarettes smoked* when deprived during the relapse analogue task (Zvolensky, Farris, Guillot, et al., 2014). Another study found that anxiety sensitivity was not associated with self-efficacy to resist smoking in various situations or changes in smoking rate one week following a smoking cue exposure task (Rogojanski, Vettese, & Antony, 2011). Specifically, smokers randomly assigned to engage in mindfulness (accept arising thoughts/feelings in a mindful way) versus suppression (distance self from experience by avoiding thoughts/feelings) were exposed to a 20-minute cue exposure task and followed-up one week after. Findings indicated a non-significant condition by anxiety sensitivity effect (Rogojanski et al., 2011), although the main effect of anxiety sensitivity was not reported.

In an ad-lib smoking study, a within-subjects experimental test found that high anxiety sensitive smokers exposed to a stressful task (giving a stressful speech) reported greater reductions in state anxiety after smoking of a cigarette, relative to low anxiety sensitive smokers (Evatt & Kassel, 2010). Interestingly, after exposure to a no-speech condition (no stress), high and low anxiety sensitive smokers did not differ in terms of post-smoking reductions in state anxiety (Evatt & Kassel, 2010). This suggests that the impact of anxiety sensitivity in terms of post-smoking negative affect may be conditional upon exposure to a stressor (in this case, social stressor). Another within-subjects test utilizing five different mood induction strategies (speech preparation task, overnight

deprivation, computer challenge, negative mood pictures, and a neutral mood control) examined the role of anxiety sensitivity in predicting smoking reinforcement (average puff volume), smoking reward (liking of cigarette), and negative/positive affect after taking (a) four standardized puffs from a cigarette and then (b) ad-lib smoking during the mood induction (Perkins, Karelitz, Giedgowd, Conklin, & Sayette, 2010). Anxiety sensitivity was not associated ad-lib smoking reinforcement (puff volume) during the mood induction tasks, however higher anxiety sensitivity relative to lower, was associated with greater cigarette liking, specifically during one mood induction task (stressful speech preparation; Perkins, Karelitz, Giedgowd, et al., 2010). In terms of affect, state anxiety and stress/arousal significantly decreased following ad-lib smoking for high anxiety sensitive smokers, but not low, only after exposure to the speech preparation mood induction (not other mood induction tasks; Perkins, Karelitz, Giedgowd, et al., 2010), which is consistent with other findings (Evatt & Kassel, 2010). Additionally, high anxiety sensitivity smokers, relative to low, reported greater increases in positive affect after smoking four standardized puffs, only after overnight abstinence (Perkins, Karelitz, Giedgowd, et al., 2010). This same effect was not seen during other mood indication tasks or after ad-lib smoking, and was only significant for one of two measures of positive affect. One other study found that anxiety sensitivity positively predicted increased positive affect post-cigarette smoking, relative to pre-cigarette smoking (Wong et al., 2013). Anxiety sensitivity was also positively associated with post-smoking cigarette/smoking satisfaction (e.g., “Did it taste good?”, “Was it satisfying?”), enjoyment of sensations in throat/chest, and psychological reward (e.g.,

"Did it calm you down?", "Make you less irritable?"). Notably, anxiety sensitivity was not associated with reduced craving post-smoking (Wong et al., 2013).

Smoking Reinforcement and Smoking Topography

Integrative theories of panic-smoking comorbidity (Zvolensky & Bernstein, 2005), in conjunction with emotion regulation research (Tice & Bratslavsky, 2000), indicate that (a) emotion regulation is a priority for psychologically vulnerable individuals, (b) negative mood states (e.g., panic attacks) can decrease the capacity for adaptive emotion regulation, and (c) ineffective efforts to control negative affective states can contribute to a worsening of negative mood. In the case of anxiety sensitivity, higher anxiety sensitive smokers may struggle to maintain smoking abstinence due to reliance on cigarettes for management (down-regulation) of negative emotional states and somatic arousal. Thus, in the context of distressing somatic states (e.g., like a panic attack), cigarette smokers (and higher anxiety sensitive smokers in particular) may be especially likely to rely on cigarettes (nicotine). However, empirical studies focused on the panic attack and smoking comorbidity have limitedly examined the actual *reinforcing value* of smoking in the context of panic-relevant states.

Reinforcing Value of Nicotine

Nicotine is the key psychoactive ingredient in tobacco that produces the pleasurable psychoactive effects of smoking that promotes nicotine dependence (Schachter, 1978). There are two unique characteristics of cigarette smoking that robustly impact the reinforcing effect of this behavior. First, the speed in which nicotine reaches the brain when smoke is inhaled is rapid – less than 20 seconds (Perkins, Conklin, & Levine, 2008). Importantly, the speed by which a product delivers pleasurable

psychoactive effects to the brain is posited as one of the most important determinants of a drug's addictive potential. For example, alternative forms of tobacco (e.g., smokeless tobacco, nicotine replacement treatments) have a lower dependence likelihood given the slower absorption of nicotine. Second, this pattern of rapid delivery of nicotine to the brain occurs with *each puff* of a cigarette. Consider the implications of this: Smoking one cigarette typically involves taking an average of 10-12 puffs; at a rate of 20 cigarettes per day (one pack), a smoker would receive about 200 "hits" of nicotine per day (Perkins et al., 2008).

Given these two facets of cigarette smoking, one important measurement of tobacco motivation is examining *how* one smokes a cigarette. Smokers can control the timing and to a large extent, the amount/dose of nicotine they consume. These adaptations can be achieved by simply altering the depth, speed, and/or frequency of each cigarette puff. For example, increased levels of nicotine are absorbed from taking more frequent and deeper/longer puffs (i.e., shorter inter-puff intervals and greater puff volume/duration. Empirical data convincingly indicate that smokers will change (compensate) how they smoke to maintain stable levels of nicotine (Ashton & Watson, 1970; Kumar, Cooke, Lader, & Russell, 1977; Sutton, Feyerabend, Cole, & Russell, 1978). For example, smokers take more puffs, longer puffs, and shorter inter-puff intervals when provided with low-nicotine relative to high-nicotine cigarettes (e.g., Epstein, Ossip, Coleman, Hughes, & Wiist, 1981).

It is perhaps not surprising that, when armed with such a flexible and adaptive means of consuming nicotine, a smoker may quickly learn to not only rely smoking as an affective-regulatory aid but to also tailor *how* he/she smokes (puffs/inhales) as a means to

increase the (negative) reinforcing value of a cigarette. That is, attempts to regulate negative affect states may logically be displayed in altered puffing behavior (i.e., one way self-regulate administration of nicotine).

Measurement and Definitions of Topographical Components

Style of puffing behavior (topography) has been of interest for decades (e.g., Frederiksen, Miller, & Peterson, 1977), initially as one form of controlling smoking. Patterns of puffing behavior are suggested to reflect total smoke exposure more accurately than the number of cigarettes smoked per day, and are more closely associated with the relative health risk of smoking (Benowitz, Jacob, Kozlowski, & Yu, 1986; Hatsukami, Morgan, Pickens, & Hughes, 1987). Smoking topography has also been used to comprehensively examine factors that may maintain regulator tobacco use, and to understand individual aspects of nicotine regulation (Burling, Stitzer, Bigelow, & Mead, 1985; Frederiksen et al., 1977). Puffing behavior also provides a behavioral index of the value of smoking reinforcement (Perkins, Karelitz, Conklin, Sayette, & Giedgowd, 2010), is stable across trials and can be experimentally manipulated (Frederiksen et al., 1977). Several topographical aspects of smoking behavior have been operationally defined and measured: *puff duration* (time in milliseconds a smoker inhaled during puff), *puff volume* (among of carbon monoxide, in milliliters, smoker inhaled), *inter-puff interval* (time in between successive puffs, in seconds), and *number of puffs per cigarette.*

Early studies of smoking topography utilized observational methods (via direct observation or video recording) to measure puffing behavior, which required trained raters to code individuals' smoking behavior, which while could be done reliably, was a time consuming procedure (Burling et al., 1985). To facilitate measurement accuracy,

objectivity, and convenience, specialized smoking devices were developed to assess smoking topography, including pneumotachographs (i.e., device that records rate of airflow to and from the lungs; Adams, Lee, Rawbone, & Guz, 1983), pocket calculators (Henningfield, Yingling, ths, & Pickens, 1980), and flow meter designs (Puustinen, Olkkonen, Kolonen, & Tuomisto, 1987). Most recently, mouthpiece-based devices have been developed (e.g., Clinical Research Support System (CReSS) that feature a specialized mouthpiece to most closely model natural smoking behavior, while sampling puff characteristics via pressure transducer. Here, specialized software is used to convert signals to airflow (ml/s) and data are integrated over time. Both computer-connected (CReSS desktop) and portable (CReSS pocket) devices have been created to permit collection of data in and outside the laboratory. Methodological comparisons of topography systems indicate that mouth-piece based devices are acceptable and reliable (Blank, Disharoon, & Eissenberg, 2009). Additionally, while in-laboratory assessment of smoking topography permits for a high degree of internal validity and experimental control, it is advantageous to assess ad-lib smoking in a real-world smoking setting (i.e., outdoors) in order to facilitate generalization of data (Lee, Malson, Waters, Moolchan, & Pickworth, 2003); however, the majority of topography measurement studies exclusively utilized in-laboratory assessment.

Psychological Vulnerability and Smoking Topography

Psychological factors appear to impact smoking reinforcement. The bulk of studies to date have examined topographical components of smoking in smokers with and with psychotic-spectrum disorders. Data suggest that smokers with schizophrenia and schizoaffective disorders naturally take more total puffs per cigarette, shorter inter-puff

intervals, and larger puff volumes relative to non-psychiatric smokers (Tidey, Rohsenow, Kaplan, & Swift, 2005; Williams, Gandhi, Lu, Steinberg, & Benowitz, 2013). Experimental studies further document that smokers with schizophrenia, relative to those without, respond to neuropharmacologic manipulations with greater smoking reinforcement, implicating certain neural factors that may identify smoking reliance in psychiatric smokers (Hitsman et al., 2005; McKee, Weinberger, Harrison, Coppola, & George, 2009). These same differences in smoking reinforcement may not be evidenced in smokers with other psychotic-spectrum symptoms or disorders. For example, one study found that smokers with schizotypy symptoms relative to those without had significantly higher daily rates of smoking and nicotine dependence, but did not differ in terms of smoking topography (Stewart, Vinci, Adams, Cohen, & Copeland, 2013). Additionally, data suggest that smokers with bipolar disorder, relative to those with no psychological disorder, have shorter inter-puff intervals and metabolize nicotine more quickly; although these effects are non-significant after adjusting for use of psychotropic medications (Williams, Gandhi, Lu, Steinberg, & Benowitz, 2012).

A few studies have examined the impact of negative affective states in terms of smoking reinforcement. Laboratory studies indicate that individuals are less able to resist smoking, take more puffs, and smoke more intensely (shorter inter-puff intervals) after laboratory-manipulated stress paradigms versus neutral/relating states (McKee et al., 2011; Rose, Ananda, & Jarvik, 1983). Although some data suggest that depressed and non-depressed smokers do not differ in terms of smoking topography (Malpass & Higgs, 2007), other data indicate that depressive symptoms are associated with greater smoking reinforcement (Perkins, Karelitz, Giedgowd, et al., 2010). One study of smokers with and

without PTSD found that smokers with PTSD had larger puff volumes and exhibited more stable inter-puff intervals even after exposure to trauma-cues (McClernon et al., 2005), suggesting that smokers with PTSD may perpetually smoke to maximize reinforcement regardless of negative-affective provocation. Lastly, anxiety and depressive symptoms both appear to moderate the *course* of self-regulated nicotine administration during ad-lib smoking of a single cigarette in adolescent smokers (Veilleux et al., 2011).

Although few studies have examined psychological processes related to smoking reinforcement, anxiety sensitivity may be *indirectly* associated with shorter time to smoking lapse, but not increased cigarette consumption (Zvolensky, Farris, Guillot, et al., 2014) or smoking reinforcement after mood induction (puff volume; Perkins, Karelitz, Giedgowd, et al., 2010). For more detail, see 'Anxiety Sensitivity and Smoking Processes, Experimental data' (above). Interestingly though, Perkins and colleagues (2010) found that distress intolerance, defined as one's perceived or actual inability to withstand aversive psychological or physiological distress, a related construct to anxiety sensitivity, is associated with greater smoking reinforcement following mood induction. No additional studies (to date) have examined the impact of anxiety sensitivity or related construct in terms of smoking reinforcement.

Summary and Current Limitations

To summarize, compelling data indicate that: (a) panic attacks are linked to reliance/maintenance of smoking, (b) anxiety sensitivity may be an individual difference factor that impacts the panic attack and smoking co-occurrence, (c) CO_2 biological challenge paradigms facilitate controlled, experimental study of the interplay between

panic attacks and smoking, and (d) existing experimental studies on anxiety sensitivity and smoking bolster cross-sectional and prospective findings. This line of research is current limited in several ways: (1) Cross-sectional data cannot provide a controlled test of the interplay between panic attacks and smoking; (2) There have been no laboratory investigations of the role of abrupt physiological arousal (e.g., laboratory model of panic attacks) in terms of smoking urges or smoking reinforcement; (3) Individuals difference factors that may impact smoking reinforcement have been explored (e.g., Perkins, Karelitz, Giedgowd, et al., 2010), but not in the context of panic-relevant states; and (4) Smoking topography studies typically utilize controlled in-laboratory procedures for ad-lib smoking, however this limits real-world generalizability (Collins et al., 2010).

To address these gaps in knowledge, it would be ideal to use an experimental psychopathology approach (via CO_2 biological challenge) to test whether smokers with higher anxiety sensitivity are more reactive to abrupt panic-relevant somatic sensations in terms of smoking urges, latency to smoking initiation, and smoking topography (i.e., reinforcing value of cigarette). Such an investigation would, first, aid in refining integrated theoretical models of emotion and tobacco use. Second, it would inform treatment efforts by providing empirical data regarding the affective, cognitive, and situational antecedents of tobacco use, which can be used to improve tobacco cessation treatments, especially among vulnerable populations such as those with psychological vulnerabilities. Additionally, such an approach would provide collection of multi-method data in both laboratory and real-world environments, and minimization of retrospective recall bias via real-time assessment of emotional processing and drug-use behavior. Together, directly examining the psychopathological processes and mechanisms involved

in panic-smoking relations would provide critical information for treatment development purposes among both psychiatric and non-psychiatric smokers (Zvolensky, Lejuez, Stuart, & Curtin, 2001).

Current Study

The current study examined the main and interactive effect of laboratory-induced abrupt, panic-relevant bodily sensations and anxiety sensitivity in terms of smoking urges, latency to smoking initiation, and smoking topography, as measured through a multi-method approach. To specifically provocative *physiological arousal* in the laboratory (relative to other negative mood states less relevant to panic attacks; Evatt & Kassel, 2010; Perkins, Karelitz, Giedgowd, et al., 2010), a CO_2 biological challenge task was employed. Specifically, the current study utilized a between-subject design of a single vital capacity breath of 35% CO_2-enriched air (counter balanced with 65% O_2) versus compressed room air (normal air composition). Smoking reinforcement was measured by self-reported smoking urges, and behaviorally measured latency to smoking initiation and smoking topography via data collected from an ecologically-valid methodology (mouthpiece-based portable computerized device; Clinical Research Support System [CReSS]).

Two specific aims were tested:

(1) Main effect of abrupt physiological arousal on smoking reinforcement indices. It was hypothesized that smokers in the CO_2 condition, relative to the room air condition, would demonstrate increased smoking reinforcement, as indexed by: (1.a.) greater self-reported smoking urges, (1.b.) shorter latency to smoking/first puff (measured in seconds), (1.c.) larger puff volume (mL), (1.d.) longer puff duration (ms),

and (1.e.) shorter inter-puff intervals (amount of time between puffs; ms), during the course of ad-lib smoking.

(2) Conditional effect of abrupt physiological arousal on smoking reinforcement indices, via anxiety sensitivity. It was hypothesized that, relative to room air condition, the effect of the CO_2 condition on smoking reinforcement indices would be moderated by anxiety sensitivity, such that smokers higher in anxiety sensitivity would respond to the CO_2 task with greater smoking reinforcement, relative to those low in anxiety sensitivity, as indexed by: (2.a.) greater smoking urges, (2.b) shorter latency to first puff, (2.c.) larger puff volume, (2.d.) longer puff duration, and (2.e) shorter inter-puff intervals, during the course of ad-lib smoking.

Method

Participants

Adult daily smokers were be recruited via flyers posted in community areas and college campuses, newspaper advertisements, webpage announcements (e.g., university website, Craigslist.com), and via word-of-mouth. Inclusion criteria for the current study included: (1) between ages 18 to 65 years; (2) a daily smoker for at least the past year; (3) reported smoking an average of ≥ 10 cigarettes; (4) provided biochemical verification of smoking status per expired carbon monoxide (CO) sample ≥ 10ppm[1]; (4) reported smoking first cigarette of day within at least the first 30 minutes of waking (≥ 2 on the FTND item 1)[2]; and (5) had not decreased the number of daily cigarettes smoked by more than half in the past 6 months.

Participants were excluded from the current study based on evidence of: (1) potentially contraindicated medical condition with biological challenge (e.g., coronary

heart disease, chronic obstructive pulmonary disease); (2) limited mental competency and/or the inability to give informed, voluntary, written consent to participate; (3) pregnancy or current nursing per self-report; (4) current psychotropic medication use[3]; (5) current suicidal ideation/intent assessed via diagnostic assessment; (6) current non-nicotine substance use disorder or psychotic spectrum disorder assessed via diagnostic assessment (i.e., bipolar disorder, psychosis); (7) current use of any pharmacotherapy or psychotherapy for smoking cessation; and (8) insufficient command of the English language (i.e., cannot carry on a conversation with an interviewer in the English language or read text). Additionally, due to computerized nature of the study assessment and procedures, participants were also excluded on the basis of self-reported low computer literacy. [4] See Appendix A for study checklist document.

The CONSORT diagram for the current study is presented in Figure 2. A total of 139 participants were assessed for potential inclusion in the study, of which 40 were excluded due to not meeting the abovementioned inclusion/exclusion criteria. The most common reasons for ineligibility were: a current (past year; active) comorbid substance use disorder, smoking < 10 cigarettes per day, and having expired CO levels < 10ppm at baseline. Other reasons for exclusion are detailed in Figure 2. Of the 99 participants randomized at part of the experimental trial, the data from 9 cases were excluded due to: equipment malfunction/pilot participant (n = 5) and invalid self-report data provided at baseline (n = 4).

Thus, 90 participants (M_{age} = 43.6, SD = 9.7; 48.9% female) were included in analyses, with equal randomization to experimental condition (n = 45; 50% CO_2 condition). The sample comprised primarily of smokers who identified race as

Black/African-American (61.1%), white (32.3%), American Indian (1.1%), Asian (1.1%) or other (4.4%); 5.6% identified ethnicity as Hispanic. The majority of participants reported being never married (48.9%), divorced (33.3%), married/co-habitating (10.0%), widowed (5.6%), and separated (2.2%). Regarding educational attainment, participants reported achieving: less than high school (2.2%), part high school (4.4%), completing high school/GED (38.9%), some undergraduate college (32.3%), graduation from 2 year college (5.6%), graduation from 4 year college (15.6%), or professional/doctoral degree (1.1%). Occupational status was primarily reported as unemployed (35.6%), working full-time (25.6%) or part-time (20.0%), disability (8.9%), student (6.7%), retired (2.2%), and homemaker (1.1%).

Measures

Baseline Assessment

A standardized *phone-screening questionnaire* was used to collect standard demographic information (age, gender, race/ethnicity, level of education, income). Mental competency and command of the English language were assessed via caller's understanding of screening questionnaire items.

Medical History Form (MHF). Health conditions and current medication use were assessed with a self-report checklist of medical problems. The checklist was reviewed by the research assistant in order to determine the presence of chronic medical conditions and psychotropic medication use that might be contraindicated for study participation. The principal investigator was consulted in any case of possible contraindication. Female participants were asked, "Are you currently nursing or pregnant, or expecting to become pregnant in the near future?" in order to assess pregnancy status.

Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991). The FTND is a 6-item scale that assesses gradations in tobacco dependence. Scores range from 0-10, with higher scores reflecting higher levels of physiological dependence on nicotine. The FTND has adequate internal consistency, positive relations with key smoking variables (e.g., saliva cotinine), and high test-retest reliability (Heatherton et al., 1991; Pomerleau, Carton, Lutzke, Flessland, & Pomerleau, 1994). Internal consistency of the FTND items in the current study was $\alpha = 0.39$. Respondents also report on their usual cigarette brand, and indicate specific properties of their preference cigarette (e.g., filtered, menthol, exc). See Appendix B for FTND measure. In the current study, participants used their usual brand of cigarettes to complete the standardized smoking trials (detailed below in the *Procedures* section). The research assistant reviewed the FTND form to ensure the reported brand matched the cigarette brand the participant brought to the laboratory appointment.

Nicotine levels differ by cigarette brand and puff topography has been show to significantly differ between menthol versus non-mental cigarettes (Ahijevych & Garrett, 2004). In light of this issue, cigarette characteristics (menthol) were examined as potential relevant covariates in the primary topography outcomes.

Smoking History Questionnaire (SHQ; Brown et al., 2002). The SHQ is a 30-item self-report measure that includes items pertaining to smoking rate, age of initiation, years of being a regular smoker, etc. The SHQ was used to gather information about smoking history in order to establish pattern of cigarette use per eligibility criteria (e.g., daily use). See Appendix C for SHQ measure.

Timeline Follow-Back Interview (TLFB; Sobell & Sobell, 1992). The TLFB is a calendar-based assessment of substance use, in which data are collected using clinician-guided retrospective recall. Participants are encouraged to use notable events (e.g., birthdays, holidays, special events) and patterns of use (e.g., weekends versus week days, locations, time of day) to complete the calendar. The TLFB was used to document frequency, quantity, and patterns of tobacco, alcohol, and illicit drug use in the past 30 days. This form of data collection has been found to have very strong psychometric properties up to 90-days, including excellent inter-rater reliability, test-retest reliability, and strong convergent validity based on collateral interviews (Carey, 1997; Maisto, Sobell, Cooper, & Sobell, 1982). These data were used, in combination with other assessment, to determine presence of regular smoking patterns in the past month, and identify use of other substances that might have been contraindicated for study participation. Internal consistency between TLFB days (7 days in past week) was $\alpha = 0.95$. See Appendix D for TLFB measure.

Carbon Monoxide (CO) Analysis. A Vitalograph Breath Co carbon monoxide monitor was used to measure the amount of carbon monoxide (in parts per million [ppm]) in an expired breath sample, which is an indirect, noninvasive measure of blood carboxyhaemoglobin. Levels of CO typically range from 0-10ppm (non-smoker), 11-20 (light smoker), 21-100 (heavy smoker). To provide a breath sample, the hand-held device prompts the participant to complete a 15 second breath-hold before exhaling completely into a single-use disposable cardboard mouthpiece. For the present study, a CO sample of ≥ 10 ppm was required for study inclusion.

Structured Clinical Interview for DSM-IV Disorders-Non-Patient Version (SCID-I/NP; First, Spitzer, Gibbon, & Williams, 2007). The SCID-I/NP is a clinician-administered semi-structured diagnostic assessment of Axis I psychopathology based on the DSM-IV-TR diagnostic guidelines. Diagnostic assessments were conducted by highly-trained post-baccalaureate research assistants. All research assistants completed a 6-session training conducted by the principal investigator and two additional doctoral-level graduate students, shadowed administration of three assessment cases with a doctoral-level graduate student, completed two live-supervised assessments, and demonstrated diagnostic accuracy on three test cases, prior to being 'signed off' as SCID-trained. In the current study, all diagnostic assessments were audio-recorded and 100% of cases were supervised by the study principal investigator for diagnostic accuracy. A random 20% of recordings were subjected to blinded inter-rater reliability review by a doctoral-level clinical psychology graduate student. No cases of diagnostic disagreement were noted (100% accuracy). The SCID-I/NP was used to assess if any psychological exclusionary criteria were met (e.g., psychotic-spectrum or non-nicotine substance use disorders, suicidality). See Appendix E for SCID-I/NP diagnostic summary page.

Pre-Challenge Measures

Anxiety Sensitivity Index-3 (ASI-3; Taylor et al., 2007). The ASI-3 is an 18-item psychometrically-sound self-report measure in which respondents indicate the extent to which they are concerned about possible negative consequences of anxiety-related symptoms (e.g., "It scares me when my heart beats rapidly"). Responses are rated on a 5-point Likert scale ranging from 0 (*very little*) to 4 (*very much*) and summed to create a total score. The ASI-3 items have strong and improved psychometric properties relative

to previous measure items of the construct (Taylor et al., 2007). The ASI-3 yields three lower-order sub-factors, including concerns about the physical consequences, social consequences, and cognitive consequences of anxiety-relevant sensations. The ASI-3 factors have strong documented psychometric properties in daily cigarette smokers, including factor stability, strong reliability (test-retest, internal consistency), known-group validity, and convergent, discriminant, and predictive validity with key affective and smoking-relevant processes (Farris, DiBello, et al., 2015). Internal consistency of the ASI-3 items in the current study was $\alpha = 0.93$. See Appendix F for ASI-3 measure.

Positive and Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988). The PANAS is a self-report measure that requires participants to rate the extent to which they experience 20 different feelings and emotions (e.g., nervous, interested) based on a Likert scale that ranges from 1 ("*Very slightly or not at all*") to 5 ("*Extremely*"). The measure yields two factors (10 items each), negative and positive affect, and has strong documented psychometric properties (Watson et al., 1988). The negative affectivity subscale was examined as a potentially relevant covariate in analyses. Internal consistency of the PANAS-NA subscales items was $\alpha = 0.93$.

Biological Challenge Measures

Subjective Units of Distress Scale (SUDs; Wolpe, 1968). The SUDs rating scale is a self-reported measure of the extent to which a respondent is currently experiencing 'distress, discomfort, anxiety, or fear', rated from 0 (*none*) to 100 (*extreme*), which was completed immediately before and after the biological challenge task. See Appendix G for SUDS measure.

Diagnostic Sensations Questionnaire (DSQ; Sanderson, Rapee, & Barlow, 1988). The DSQ a 17-item self-report measure of panic attack symptom severity, rated on a 3-point Likert-type scale (0 = *absent* to 3 = *severe)* that was completed immediately before and after the biological challenge task. The DSQ was modified for the current study in two ways. First, while not a DSM-defined panic attack sensation, 'headache' was added an additional symptom, to gauge the extent to which smokers reported pain as a result of the biological challenge. Second, based on pilot testing, the DSQ response options were transformed into a check-box format ("Please CHECK BOX if you are currently experiencing any of the following…") rather than a severity-style likert-scale. This adaptation was implemented to increase simplicity and decrease time to complete the self-report ratings pre/post biological challenge. Thus, the modified-DSQ yielded a symptom count ranging from 0-18 sensations. The total count variable was utilized as a check of the manipulation for panic-specific arousal. See Appendix G for DSQ measure.

Physiological Monitoring. A wireless physiological monitoring device that digitally records data was used to assess heart rate and respiration rate during the 3-minute adaptation period (prior to the biological challenge) and 2-minute recovery period (after the biological challenge). Data were recorded and displayed using the MP150 BIOPAC Systems bioamplifier (BIOPAC Systems, Inc.) and AcqKnowledge III data acquisition software (version 3.8.2) sampling at 1000 Hz. Data output were used to score average heart rate and respiration rate during recording periods.

End-tidal partial pressure CO_2 in exhaled air ($etpCO_2$). As a manipulation check, $etpCO_2$ was sampled during the breathing challenge using the flow volume sensor (RSS100HR; Hans Rudolph, Inc.). Typical levels of expired CO_2 when breathing normal

room air is approximately 5.0%. From breathing 35% CO_2-enriched air, the expected expired CO_2 would be roughly 35.0%, although this value may be higher or lower depending on the depth/duration of the vital capacity breath. The peak etpCO_2 level recorded after the manipulated breath was utilized as a manipulation check. This measurement provides data that allows the experimenter to verify that the desired level of CO_2 was administered.

Dependent Measures

Questionnaire of Smoking Urges-Brief (QSU-B; Cox, Tiffany, & Christen, 2001). The QSU-B is a 10-item self-reported, psychometrically sound assessment of urges for cigarettes. The QSU-B was completed before and after the biological challenge task via pencil/paper. The QSU-B items are rated on a 0-100 scale, with higher ratings indicative of greater agreement with the item. Item responses are scored to yield a total sum score to reflect overall smoking urges. This measure also yields two subscale scores (5 items each), which index desire/craving to smoke (e.g., "I have a desire for a cigarette right now"; "If it were possible, I would probably smoke now") and urges to smoke for negative affect relief (e.g., "I could control things better right now if I could smoke"; "Smoking would make me less depressed"). Two additional items were included for this specific study to assess urges to smoke to relieve anxiety ("Smoking would make me less anxious"; "Smoking would make me less nervous") given the relevance to the current study and due to the lack of specific inquiry about anxiety states in current items in the negative affect relief subscale, although these two items were not included in scoring of QSU-B total or subscales scores. Internal consistency of the QSU-B items was $\alpha = .97$ at pre-challenge. See Appendix G for QSU-B measure.

Clinical Research Support System (CReSS; Plowshare Technologies, Borgwaldt KC, Inc., Virginia). The portable CReSS pocket has a sterilized flow meter mouthpiece that is connected to a pressure transducer, which converts pressure into a digital signal that is sampled at 1,000Hz. CReSS computer software transforms the signal to a flow rate (mL/s), from which puff topography data are computed. The reliability and acceptability of use of the portable CReSS device is well documented (Blank et al., 2009; Perkins, Karelitz, Giedgowd, & Conklin, 2012), and is recommended over direct observation (Blank et al., 2009). Puff topography data included: puff volume (volume of CO taken in during each puff), puff duration (length of time for each puff), and inter-puff interval (amount of time between puffs). Latency to first cigarette puff (milliseconds) was computed as a behavioral measure of craving. Puff level data were averaged to compute mean topography variables for each participant. See Appendix H for CReSS Pocket device instruction.

Procedure

A visual depiction of the study design is provided in Figure 3. Interested callers responding to study recruitment methods completed a *telephone assessment* with a trained research assistant. Potentially eligible participants were read a standardized script describing the research study, informed that the in-person visit would last approximately 3-4 hours in length. A research assistant would address questions, and interested individuals were scheduled for a single-session appointment. Individuals were instructed to bring their usual brand of cigarettes (at least 2 full cigarettes) to their in-person laboratory appointment. Scheduled participants received two telephone reminder calls 72 and 24 hours prior to the scheduled visit to (a) bolster retention rates, (b) provide any

necessary clarification of protocol, and (c) to remind participants to bring their usual brand of cigarettes to the laboratory visit. Participants were also asked whether they were experiencing any cold or flu-like symptoms to avoid risk of potentially contaminating biological challenge breathing equipment.

Upon arrival, participants provided written *informed consent*. A trained post-baccalaureate level research assistant explained the details of the study, potential benefits and risks of participation, and the procedures the participant would undergo if he/she chooses to participate. If the participant signed the informed consent form, he/she was informed that there would be several tasks completed during the course of the study.

First, the *Baseline Assessment* was completed to determine study eligibility. The assessment included a diagnostic assessment (per the SCID-I/NP), the research-assisted Timeline Follow-Back (TLFB) to assess past-30 day use of cigarettes and other substance use, a series of self-report assessments (including the ASI-3), and provided a CO analysis of expired breath.

Next, all participants completed an ad-lib *Smoking Trial (#1)* at a standardized point during the Baseline Assessment. Participants were told they could have a 'smoke break' during which they were oriented to the portable CReSS device and shown how to use it. Then, the experimenter accompanied the participant outdoors, alongside the laboratory, and informed the participant that he/she would have the opportunity to smoke one cigarette using the device. The participant was told to smoking as usual, and was given as much time as desired. Participants were instructed to not talk on or use their telephones, or engage in conversation with others during their smoke break. This smoking period served two important purposes: (1) to familiarize participants with the

use of the CReSS device and (2) to standardize participant recency of last-cigarette. Importantly, outdoor smoking during the smoking trials was designed to create comparable conditions to those where smoking would typically occur (e.g., natural outdoor environment; Perkins et al., 2012), thereby increasing ecological validity without compromising the integrity of the smoking topography data. Additionally, participants smoked using their own brand of cigarettes in order to further increase ecological validity based on targeted outcomes (i.e., *in vivo* smoking behavior). While some experimental topography studies have provided standardized cigarettes or blind participants to cigarette brand, this can alter puffing behavior and may be perceived as artificial or unacceptable and decrease reliability (Perkins et al., 2001; Trtchounian, Williams, & Talbot, 2010; Williams & Talbot, 2011).

Next, as an *Adaptation Period* post-smoking, participants returned inside the laboratory, and completed approximately 60 minutes of additional self-report assessments, which were broken up by two scheduled snack/water breaks (no smoking was permitted). Eligibility status for randomization was determined based on baseline data. Participants continued to the experimental portion of the visit (if eligible), or were dismissed (if ineligible). Ineligible participants were provided $25 compensation for their time and offered psychiatric or smoking cessation referrals if desired.

Eligible participants next completed the *Biological Challenge task.* Participants were randomized to one of two experimental conditions (35% CO_2-enriched air or compressed normal room air) using a computerized randomizer, designed to stratify condition assignment to be equivalent by participant sex. Only the study principal investigator was un-blinded to experimental condition (for purposes of administering the

protocol). The participant and research assistant working with the participant were blinded to experiential condition. The biological challenge task was a single vital capacity breath of CO_2-enried air mixture or compressed room air. The 35% concentration of CO_2 was specifically chosen for its ability to uniquely induce *abrupt changes* in bodily arousal with a single vital capacity inhalation, in comparison to other lower gas concentrations delivered over a longer period of time (e.g., 10% for 4 minutes; Prenoveau et al., 2006).

After completion of the biological challenge, the research assistant instructed the participant that he/she had the opportunity to take another 'smoke break'. The post-challenge ad-lib *Smoking Trial (#2)* was completed via identical procedures to the first smoking trial. After, the research assistant escorted the participant back into the laboratory. The participant was provided compensation ($50), *debriefed* regarding the nature of the study (and were "unblinded" to manipulation condition), and were given smoking cessation and/or psychiatric referrals if requested. See Appendix I for debriefing form text. A final CO monoxide breath sample was collected prior to participant dismissal.

Experimental Manipulation

Experimental sessions were completed in an 8 x 10 ft. sound attenuated room, with adjacent (experimenter/control) room. The participant room contained a desk, chair, computer monitor, video camera, and breathing mask apparatus (detailed below). The adjacent experimenter room ("control room") was fitted with a one-way mirror and video recording monitor to observe the laboratory challenge, an intercom to allow communication between the subject and experimenter, and a Dell PC desktop computer.

The experimenter room also contained two 9in. (diameter) x 51in. (height) high-pressure steel cylinder gas tanks (Praxair gas, Inc.) filled with compressed gas (Active tank: 35% CO_2, 65% O_2; Control tank: 21% O_2, 79% N).

Participants were oriented to the experimental room, fitted with a respiration band and heart rate monitor, and then informed of the challenge procedures. Participants were read the following standardized instructions by the study principal investigator:

> *"You are seated in the experiment room. To your right is a one-way mirror and in front of you, there is a closed-circuit video camera. These allow the researcher to monitor you during the breath task. There is also an intercom that allows for communication between you and the researcher. Now I will fit you with a monitor to measure your breathing."* [Fit respiration band]. "*Now I will attach two sensors to your forearm. These will be used to monitor your heart rate. You will not feel anything while this is monitoring you."* [Fit two sensors]. "*Next, to orient you, the mask in front of you connects to a bag filled with gas. This gas, depending on what you were randomly assigned to contains either 35% carbon dioxide - 65% oxygen or normal compressed room air. As a reminder, you may experience various physical feelings such as breathlessness, racing heart, dizziness, dry mouth, feeling sweaty, feeling faint, and the possibility of having a panic attack. You may also notice a difference in taste when you inhale. Taking a breath of these gases is not harmful and has no long-term consequences. Now I will fit you with the mask. You will only be able to breath from your mouth. Please do not remove the mask."* [Ensure participant understands mouth breathing / attach mask].

Before leaving the room, the principal investigator made sure the participant was comfortable and said:

> *"Now you are ready to learn the breathing task. Turn you attention to the computer monitor in front of you. This will instruct you on how to complete the task. Until it begins, just breathe normally from your mouth. You will only breathing room air during the practice."*

Next, the participant was shown a computerized instructional set. The computerized instruction informed the participant on how to complete *two* vital capacity breaths and allowed practice/follow-along with the instructional prompt. The first vital capacity inhalation was used to clear air from lungs (upon forceful exhale) to prepare for the second vital capacity inhalation (with the manipulated air on randomization). This two-breath combination was completed twice. The first set was to estimate vital breath capacity of the participant; the second set for the actual manipulation. Cross-verification of the inhalation volume between the first and second set of breaths was checked for instructional adherence. The principal investigator monitored the participant from the closed-circuit monitor in the adjacent room during the practice. The principal investigator communicated via intercom if the participant indicated having questions.

Then, the participant was instructed to complete a self-report rating card via pencil/paper, which included the SUDS, modified-DSQ, and QSU-B. After completion of pre-challenge ratings, the participant was instructed to breathe normally and rest until otherwise instructed. This period (timed for 3 minutes) served as a neutral adaptation period. Following this period, the participant completed the biological challenge task. Immediately following, the participant was instructed to complete the second self-report

card via pencil/paper (SUDS, modified-DSQ, and QSU-B), and then completed a recovery period of normal breathing (2 minutes) before the principal investigator re-entered the experimental room to unmask and unhook the physiological monitoring sensors.

Breathing Apparatus

Breathing apparatus and software were engineered and built by Hans Rudolph, Inc. Each gas tank was equipped with a valve regulator (set at about 20 psi) and flow control value, which allowed for control of gas. The gas tanks had a quick-connect fitting mounted to the regulator so that the valve could be easily moved from one tank to the other. Tubing connected from the gas tank to the bottom of the non-diffusing gas bag, which allowed the bag to be filled with gas. The gasbag also had a stopcock valve inserted into a port. Attached was 35mm tubing that was fed through a window from the experimenter "control" room to the experimental "subject" room. This tubing connected to a two-way non-rebreathing valve, which connected to a 22mm port of the Y-shaped balloon valve. The second port was not fitted with tubing, which allowed for breathing of normal air versus the test gas. Both ports were attached to a balloon valve controller. The tail of the Y-shaped balloon valve contained a common port that was fitted with an 18-inch 22mm tube that connected to a pneumotach, which was calibrated to measure tidal flow volume of 3000 mL/s. To this, a flexible silicone mask was attached from which the participant would breathe. Data were continuously recorded to a control box that contained a CO_2 sensor (tests amount of expired CO_2) and the flow volume sensor (RSS100HR), which was attached by encased wire to the pneumotach. The custom software recorded breathing data collected from the tidal flow and CO_2 sensor, and

automatically operated the balloon valves that control the delivery of test gas versus normal air. The data were sampled and recorded every second. The software also provided a graphical user interface to help the principal investigator monitor the participant and record the selected data. See Appendix J for a schematic of the breathing apparatus set-up.

Data Analytic Procedures

Analyses were conducted in SAS 9.0. First, data were screened for data entry errors or illogical inconsistencies. Any identified errors were corrected based on original data. Second, internal consistencies of measure items were examined. Table 2 includes tests for means/standard deviations, internal consistency, observed and possible range for each variable, and test-retest correlations for repeated outcome variables. Next, the frequency distributions, indices of skewness and kurtosis, and tests of normality (via Kolmogorov-Smirnov test statistic; Shapiro-Wilk test statistic) were examined to determine the underlying distribution of study variables.

Next, the equivalence of the random assignment based on key baseline characteristics and pre-challenge smoking-relevant variables was assessed. Any variables in which groups differed were considered for potential include as model covariates in the primary outcome analyses (e.g., key demographics, psychological disorder comorbidity, level of nicotine dependence, used of menthol cigarettes).

Manipulation Check

To ensure the biological challenge method adequately elicited panic-relevant symptoms, a series of regression analyses were conducted to examine differences between the experimental groups in terms of four indices: (1) self-reported SUDs; (2)

number of panic symptoms reported on the modified-DSQ, (3) physiologically-measured heart rate, and (4) physiologically-measured respiration rate. In each analysis, experimental condition (coded 0 = room air; 1 = 35%-CO_2 enriched air) and pre-challenge score was regressed onto the respective post-challenge score. Depending on data distribution, PROC GLM (if normally distributed), PROC GENMOD (with *negbin* distribution; if non-normally distributed), or PROC COUNTREG (for count variable) statements were used in SAS. Biologically measured $eptCO_2$ after the manipulated breath was also examined for between-group differences (PROC TTEST) as an equipment-check to ensure the gas was administered.

Effect sizes were calculated for significant *t* values, using Cohen's *d* ($d = 2t/\sqrt{df}$). According to Cohen (1988), *d* values of .2, .5, and .8 can be considered small, medium, and large, respectively. It was expected that participants who received 35%-CO_2 would report significantly greater subjective distress (SUDS), panic symptoms (per number of DSQ items endorsed), and physiological arousal (heart rate and respiration rate), relative to participants in the room air condition.

Analytic Overview for Test of Aims

The tests of the study aims are visually presented in Figure 1b. Consistent with past research (Blank et al., 2009; Perkins et al., 2012), separate models were constructed for predicting each of the dependent variables. To ensure acceptability of this approach, the inter-correlations between the dependent variables (self-reported urges, latency to first puff, and puff topography variables) were examined.

To address the effect of the panic-relevant sensations on smoking reinforcement indices (Aims 1a through 1e) and moderating effect of anxiety sensitivity (Aims 2a

through 2e), five regression models were conducted. Past-week average number of cigarettes per day (per the TLFB) and pre-challenge anxiety (SUDs) were entered as covariates (in addition to any other variable in which groups differed at baseline). These variables were mean-centered prior to entry into the model. The pre-challenge value of the outcome variable was entered to adjust for baseline levels (i.e., to test unique changes due to the challenge). Experimental condition (dummy coded; 0 = room air, 1 = CO_2-enriched air) and mean-centered anxiety sensitivity (ASI-3) were entered to test main effects. To test the moderating role of anxiety sensitivity, the interaction term (Experimental Condition*ASI-3) was entered.[5]

Dependent variables were (a) self-reported smoking urges (QSU-B total and subscales); (b) latency to first puff; (c) average puff volume, (d) average puff duration; and (e) average inter-puff interval. Analyses were conducted in SAS using the PROC GLM statement (and with 2,500 bootstrapped sampling to accommodate non-normal distributions of any outcome variables). Significant interactions were subjected to probe of the simple slopes at high and low values of the continuous moderator (+/- 1 SD on the ASI-3 total), and the form of the interactions were visually plotted for interpretation of effects.

Results

Descriptive Overview of Sample Characteristics

Demographic characteristics, smoking history variables, and psychological factors are reported in Table 3, for the total sample, and by experimental condition. Regarding smoking history, the average age of smoking initiation was at age 16.0 (*SD* = 6.7) years. Participants indicated smoking for an average of 23.9 years (*SD* = 10.2) in duration, and

smoked an average of 15.8 (*SD* = 5.9) cigarettes per day in the 7-days prior to the laboratory visit. Based on targeted study sampling, the majority of participants reported smoking the first cigarette of the day with 5 minutes (56.7%) and moderate levels of nicotine dependence were reported per the FTND (*M* = 4.8; *SD* = 1.4). Slightly more than half of the sample reported smoking menthol cigarettes (58.9%).

In terms of current (past 12-month) psychological disorders, 33.3% of the sample met criteria for a DSM-IV defined Axis I disorder (of which, 46.7% had more than one diagnosis; range 1-4), which included: posttraumatic stress disorder (11.1%), major depressive disorder (8.9%), specific phobia (8.9%), social anxiety disorder (6.7%), substance use disorder (early/sustained full remission; 5.6%), panic disorder with or without agoraphobia (4.4%), Bipolar Disorder I or II (full remission; 3.3%), eating disorder (3.3%), dysthymic disorder (2.2%), generalized anxiety disorder (2.2%), and alcohol use disorder (early/sustained full remission; 2.2%). Additionally, 26.7% of the sample had a lifetime history of panic attacks (either cued or uncued). The average ASI-3 score 12.7 (*SD* = 12.8) is indicative of overall, low to moderate levels of anxiety sensitivity.

Bivariate Associations Between Study Variables

The inter-correlations between outcome variables were examined (see Table 4) to test whether multivariate analyses should be considered (in the event all outcome variables were highly inter-correlated). Smoking urges and latency to first puff were not significantly correlated with any other outcome variable. Three puff characteristics were inter-related. Puff volume and duration were correlated ($r = .64$, $p < .01$), and both were correlated with average inter-puff interval (r's range .23-.32, p's < .05), although these

associations were moderate in size, thus univariate tests of study aims were conducted (using five separate regression models; one for each outcome variable).

Additionally, while not displayed in Table 4, number of cigarettes per day was correlated with post-challenge smoking urges ($r = .35$, $p < .01$), but not latency to smoking initiation or smoking topography variables (average puff duration, volume, or inter-puff interval). Nicotine dependence (FTND total score) was significantly associated with shorter inter-puff intervals ($r = .23$, $p < .05$). Similarly, anxiety sensitivity was correlated at a bivariate level with post-challenge smoking urges ($r = .30$, $p < .01$) but not post-challenge latency to first puff or any of the three topography variables. Participants sex, age, race, and smoking menthol cigarettes were not associated with any outcome variables. Based on theoretical relevance and to maintain consistency with other CO_2-smoking studies, cigarettes per day was included as a covariate despite non-significant bivariate associations. This measure was utilized as a covariate instead of nicotine dependence based on the low internal consistency of FTND items.

Anxiety sensitivity was not associated with participant sex, age, cigarettes per day, nicotine dependence, or smoking menthol cigarettes (Table 5). Anxiety sensitivity was significantly and moderately correlated with pre-challenge distress (SUDS and DSQ), trait negative affectivity, and presence of any Axis I psychological disorder (r's = .63, p's < .01). To maintain consistency with past CO_2 studies of anxiety sensitivity, trait negative affectivity and state-levels of distress (pre-challenge SUDS) were included as covariates (Kutz et al., 2010; Richey, Schmidt, Hofmann, & Timpano, 2010).

Randomization Check

Experimental groups were compared in terms of baseline smoking and affective characteristics (Table 3). Chi-square and t-test analyses indicated no statistically significant group differences on any of the examined baseline characteristics. As indicated in Table 6, there were significant group differences on pre-challenges levels of subjective distress (SUDS), thus this variable was adjusted for in all main analyses. By controlling for this variable, the unique effects of anxiety sensitivity above state-levels of distress were also tested.

Manipulation Check

Means and standard deviations for all manipulation check variables are presented in Table 6, by experimental condition. Results from test of manipulations are presented in Table 7, and summarized below.

Subjective Distress. Inspection of data distribution, skewness (.75), kurtosis (-.63), and the Kolmogorov-Smirnov (.17, $p < .0001$) and Shapiro-Wilk (.87, $p < .0001$) test statistics indicated a non-normal distribution for post-challenge SUDS, thus PROC GENMOD (with *negbin* distribution) was used in SAS. After adjusting for pre-challenge SUDS, experimental condition was significantly predictive of post-challenge SUDS ($b = 0.72$, $p = .013$), such that participants exposed to CO_2-enriched air reported significantly higher post-challenge SUDS relative to those exposed to room air only (Cohen's $d = 0.53$; medium-sized effect).

Panic Attack Symptoms. The modified-DSQ was summed to create a total count of panic attacks symptoms experienced pre- and post-challenge. Given the count nature of the variable, PROC COUNTREG was used in SAS. Based on inspection of data

distribution, skewness (1.79), kurtosis (2.78), and the Kolmogorov-Smirnov (.28, $p <$ .0001) and Shapiro-Wilk (.73, $p < .0001$) test statistics, it was determined that this variable was non-normally distributed, thus a *negbin* distribution was specified in SAS. After adjusting for pre-challenge DSQ, experimental condition was significantly predictive of post-challenge DSQ ($b = 1.13$, $p < .0001$). Participants exposed to CO_2-enriched air reported significantly more post-challenge symptoms on the DSQ relative to those exposed to room air only (Cohen's $d = 1.00$; large-sized effect).

Heart Rate. Inspection of histogram, skewness (.93), kurtosis (-.36), and Kolmogorov-Smirnov (.20, $p < .0001$) and Shapiro-Wilk (.87, $p < .0001$) test statistics indicated a non-normal distribution for post-challenge heart rate data, thus PROC GENMOD (with *negbin* distribution) was used in SAS. After adjusting for heart rate during the adaptation phase, experimental condition significantly predicted increased heart rate during the recovery phase ($b = 0.14$, $p = .002$), such that heart rate was significantly higher for participants exposed to CO_2-enriched air relative to those exposed to room air only (Cohen's $d = 0.68$; large-sized effect).

Respiration Rate. Inspection of histogram, skewness (.-.39), kurtosis (.11), and non-significant Kolmogorov-Smirnov (.07, $p = .200$) and Shapiro-Wilk (.98, $p = .103$) test statistics indicated a normal distribution for post-challenge respiration rate, thus PROC GLM was used in SAS. After adjusting for heart rate during the adaptation phase, experimental condition was significantly predictive of heart rate during the recovery phase ($b = 0.47$, $p < .038$), such that respiration rate was significantly higher for participants exposed to CO_2-enriched air relative to those exposed to room air only (Cohen's $d = 0.76$; large-sized effect).

Expired etpCO₂. Inspection of data distribution, skewness (.21), kurtosis (-1.78), and Kolmogorov-Smirnov (.27, $p < .0001$) and Shapiro-Wilk (.794, $p < .0001$) test statistics indicated a non-normal distribution for expired $etpCO_2$. Expired $etpCO_2$was only sampled once (after manipulated breath), thus PROC TTEST was used in SAS. The Satterthwaite degrees of freedom were used to adjust for unequal group variances. Here, mean expired $etpCO_2$ values significantly differed by experimental condition ($t = -29.17$, $p < .0001$), with higher values recorded in the CO_2-enriched air relative to room air condition.

Test of Main and Interaction Effects

In all models, covariates included (mean-centered) pre-challenge SUDS, pre-challenge value of the outcome variable, average cigarettes per day (per TLFB), and trait negative affectivity (per PANAS-NA). The main effects included the dummy-coded condition variable and mean-centered ASI-3. The interaction term (ASI-3*Condition) was also entered to examine conditional effects.

Smoking Urges (QSU-B)

Inspection of data distribution, skewness (.602), kurtosis (-1.10), and the Kolmogorov-Smirnov (.18, $p < .0001$) and Shapiro-Wilk (.86, $p < .0001$) test statistics indicated a non-normal distribution for post-challenge QSU-B, thus PROC GLM with bootstrapping was used in SAS. Results are presented in Table 8.

After adjusting for model covariates, results indicated a significant main effect of experimental condition on post-challenge QSU-B ($b = -81.26$, $p = .048$). The size of the effect was small to medium (Cohen's $d = -0.45$). There was a non-significant main effect of anxiety sensitivity ($b = 3.15$, $p = .363$). The effect of the interaction (condition*ASI-3)

was significant (b = -9.96, p = .014). The size of the effect was medium (Cohen's d = -0.56). Test of the simple slopes revealed a significant effect for experimental condition when anxiety sensitivity was high (b = -208.99, p = .011), but not low (b = 46.47, p = .0.30). The form of the interaction was such that high anxiety sensitive smokers exposed to CO_2-enriched air reported significantly lower levels of smoking urges, relative to low anxiety sensitive smokers. In contrast, anxiety sensitivity did not differentially impact smoking urges for those exposed to room air.

Follow-up post-hoc tests were conducted to examine the QSU-B subscales (QSU-Craving/Desire and QSU-Negative affect relief). Consistent with finding from the total score, the interaction term was significant for both subscales (see Figure 4 for plot of the interaction effects). For QSU-Desire, the interaction was significant (b = -5.20, SE = 2.26; $CI_{95\%}$ = -9.81, -0.85; z = -2.30; p = .021), which was a medium sized effect (Cohen's d = -0.53). Test of the simple slopes indicated that the condition effect of experimental condition on QSU-Craving/Desire was significant when anxiety sensitivity was high (b = -53.20, p = .027), but not low (b = 13.50, p = .628). For QSU-Negative Affect relief, the interaction was significant (b = -4.79, SE = 1.97; $CI_{95\%}$ = -8.69, -0.95; z = -2.42; p = .015); a medium sized effect (Cohen's d = -0.55). Test of the simple slopes indicated that the condition effect of experimental condition on QSU-Negative Affect relief was significant when anxiety sensitivity was high (b = -89.21, p = .027) but not low (b = -33.46, p = .119).

Latency to First Puff

Inspection of data distribution, skewness (1.67), kurtosis (2.39), and the Kolmogorov-Smirnov (.20, p < .0001) and Shapiro-Wilk (.80, p < .0001) test statistics

indicated a non-normal distribution for latency to first puff post-challenge, thus PROC GLM with bootstrapping was used in SAS. Results from regression model are presented in Table 8. This model revealed so significant covariate, main, or interactive effects.

Average Puff Volume

Inspection of data distribution, skewness (1.75), kurtosis (4.19), and the Kolmogorov-Smirnov (.15, $p < .0001$) and Shapiro-Wilk (.86, $p < .0001$) test statistics indicated a non-normal distribution for average puff volume post-challenge, thus PROC GLM with bootstrapping was used in SAS. Results from regression model are presented in Table 9. There was a significant main effect for experimental condition ($b = -8.11$, $p = .048$), such that exposure to CO_2-enriched air was associated with significant reductions in average puff volume post-challenge, relative to exposure to room air. This was a small to medium-sized effect (Cohen's $d = -0.43$). There was no significant main effect of anxiety sensitivity, nor was there was significant interaction effect.

Average Puff Duration

Inspection of data distribution, skewness (1.03), kurtosis (1.34), and the Kolmogorov-Smirnov (.10, $p = .044$) and Shapiro-Wilk (.94, $p < .0001$) test statistics indicated a non-normal distribution for average puff duration, thus PROC GLM with bootstrapping was used in SAS. Results from regression model are presented in Table 9. There was a significant main effect for experimental condition ($b = -144.39$, $p = .050$), such that exposure to CO_2-enriched air was associated with significant reductions in average puff duration post-challenge, relative to exposure to room air. This was a small to medium-sized effect (Cohen's $d = -0.43$). There was no significant main effect of anxiety sensitivity, nor was there was significant interaction effect.

Average Inter-Puff Interval

Inspection of data distribution, skewness (1.18), kurtosis (1.71), and the Kolmogorov-Smirnov (.11, $p = .007$) and Shapiro-Wilk (.92, $p < .0001$) test statistics indicated a non-normal distribution for average inter-puff interval post-challenge, thus PROC GLM with bootstrapping was used in SAS. Results from regression model are presented in Table 9. This model revealed so significant covariate, main, or interactive effects.

Discussion

The current study experimentally examined the impact of panic arousal on smoking reinforcement, and anxiety sensitivity as a possible cognitive-affective individual difference mechanic factor. Several keys findings were observed:

First, among daily cigarette smokers, a 35% CO_2-enriched air biological challenge (via a single vital capacity breath) produced significant increases in post-challenge self-reported anxiety/distress and panic attacks symptoms, and heart rate and respiration rate, relative to exposure to room air. Medium to large effect sizes were observed for the manipulation (across subjective and physiological measures of anxiety and arousal), thus this paradigm and CO_2 dosing appears to be efficacious for provicating panic-relevant sensations in cigarette smokers, relative to room air. This extends a biological challenge study that examined use of this dosing in smokers and non-smokers (Knuts et al., 2010) and other clinical/non-clinical samples for panic- and stress-provocation research (Vickers et al., 2012).

Second, the current study is unique in its primary focus on the effect of the CO_2 challenge on *smoking-relevant* outcome variables (relative to panic). Aside from at least

two studies that have examined the role of a biological challenge on smoking craving (Attwood et al., 2014) and subjective nicotine withdrawal symptom severity (Farris et al., in press), other investigations have exclusively focused on explicating the nature of *anxious responding* to somatic provocation among smokers versus non-smokers (Abrams, Zvolensky, et al., 2008), or among smokers in nicotine deprivation or not (Abrams, Leger, et al., 2011; Leyro & Zvolensky, 2013; Vujanovic & Zvolensky, 2009). Specifically, the current study examined five specific smoking-relevant outcomes, associated with aspects of smoking reinforcement: post-challenge self-reported smoking urges, latency to smoking initiation, average puff volume, average puff duration, and average inter-puff interval.

Smoking Urges

Partially consistent with expectations, there was a significant main effect of CO_2-enriched air in terms of post-challenge smoking urges, although the effect was in the opposite direction as hypothesized. Specifically, smokers exposed to 35% CO_2-enriched air, relative to room air, reported significantly *lower* post-challenge smoking urges immediately following the biological challenge. While initially counterintuitive, there are two factors that, in combination, likely account for this finding. First, the assessment of smoking urges occurred within 10 seconds following the manipulated vital capacity breath, consistent with the other prior study of a biological challenge and smoking craving (Attwood et al., 2014). However, when considering the timing of assessment, in combination with the *intensity* of effects of the CO_2 gas concentration, it is likely that severe acute cardiorespiratory distress during the post-challenge self-report period was aversive, resulting in lower desire to smoking in that moment. Interestingly, Attwood et

al. (2014) found that, in a within-subjects test, following a single vital capacity breath of 7.5% CO_2 (relative to room air) there was no main effect of gas condition in terms of post-challenge smoking craving, which further supports the dose-response explanation.

Findings also indicated that high anxiety sensitive smokers (relative to low anxiety sensitive) exposed to CO_2-enriched air had lower self-reported smoking urges. The conditional effect of anxiety sensitivity was non-significant for smokers exposed to the room air condition. Again, the form of the interaction was in the opposite direction however this patterning of effects makes conceptual sense if indeed smokers in the CO_2 condition experienced "CO_2 aversion". That is, given high anxiety sensitive individuals have a greater trait-like propensity towards misinterpreting the meaning of distressing somatic sensations, it logically follows that high anxiety sensitive smokers exposed to CO_2 would respond with decreased smoking urges, due to fear that smoking would may further amplify cardiorespiratory distress, relative to lower anxiety sensitive smokers. Cigarette smoking may only actually be perceived as negatively-reinforcing in the context of lower arousal states or post-panic attack arousal surges.

After natural recovery (decreased arousal) from the CO_2 exposure, it is possible that CO_2-exposed smokers (and high anxiety sensitive smokers) may have had delayed increases in smoking urges. The current protocol did not include repeated assessment of smoking urges during the recovery period or prior to ad-lid smoking. Future experimental challenge paradigms should consider repeated assessment of any post-challenge data to ensure comprehensive documentation of subjective effects, especially after use of high-dose CO_2. Additionally, while the current study utilized a brief psychometrically-valid assessment of smoking urges (10 items per the QSU-B), repeated completion of these 10

items may not be feasible. As one potential alternative, research protocols could instead include a single-item assessment of smoking urge/craving (e.g., *How strong is your desire for a cigarette right now?*) rated on a visual analogue scale (Attwood et al., 2014), which are often used in experimental research.

Latency to Smoking Initiation

Latency to smoking initiation has been conceptualized as a behavioral indicator of craving (McKee et al., 2006), with shorter latency to initiation indicative of strong craving for smoking. It was hypothesized that experimentally induced panic attack sensations would be associated with shorter latency to smoking initiation, and that this would be particularly true for high anxiety sensitivity smokers. Contrary to the hypothesis, there was no main effect of experimental condition on latency to smoking initiation. There was also no main or conditional effect of anxiety sensitivity. This non-significant finding is perhaps surprising given that one study found the anxiety sensitivity was associated with shorter time to smoking initiation after 12-hours of deprivation, relative to smoking as usual, although the effect of anxiety sensitivity only occurred *indirectly* through abstinence-induced subjective smoking urges and nicotine withdrawal symptom severity (Zvolensky, Farris, Guillot, et al., 2014). Thus, the lack of a direct effect of anxiety sensitivity in terms of latency to smoking initiation in the current study is consistent with findings from Zvolensky and colleagues. It is likely that anxiety sensitivity may only impact latency to smoking initiation indirectly through other variables that were not modeled here.

It is also likely that measurement of latency to smoking initiation was subject to several confounding factors in the current study. First, based on study design, all smokers

were taken outside to smoke after about 8 minutes following exposure to the manipulated gas from the biological challenge. Therefore, for all participants, latency to smoking initiation was measured once individuals were outside. This procedure may have artificially truncated variance in this measurement, as the protocol was designed to have all participants initiate smoking once outside, rather than having participants choose *when they wanted* to go outside to smoke. It would be interesting to test how smokers respond to a standardized relapse analogue task after CO_2 exposure, when delaying of smoking is monetarily rewarded and individuals are able to decide when and how much they want to smoke (McKee et al., 2006).

Second, latency to smoking was measured by the CReSS device, which records the amount of time that lapses from when a cigarette is placed into the mouthpiece of the device to when a smokers first takes a puff. Many factors may have artificially extended this window. For example, once outdoors, the research assistant would fit the participant's cigarette into the CReSS device before handing the device to the participant. A participant then may have asked a question, walked to a bench, or dropped their lighter, all prior to actually initiating smoking. These are non-issues when time to smoking initiation is assessed in a controlled, laboratory setting (e.g., during a relapse analogue task). Thus, the validity of this measurement in the current study is perhaps questionable. This issue of measurement accuracy is especially relevant given the lower inter-correlations between latency to smoking initiation assessed pre- and post-challenge ($r = .25$, $p < .05$) relative to other dependent variables.

Smoking Topography

Three puff topography variables were examined in the current study to explore the role of post-challenge smoking reinforcement: puff volume, puff duration, and inter-puff interval. First, based on inter-correlations, these three components of smoking behaviors appear to capture related, yet unique aspects of puff topography. Partially consistent with hypotheses, there was a significant main effect the biological challenge in terms of post-challenge average puff volume and average puff duration, but not average inter-puff interval. Specifically, smokers exposed to 35% CO_2-enriched air, relative to room air, demonstrated on average smaller puff volumes and shorter puff durations. Although in the opposite direction from initial hypothesis, this is consistent with findings that indicated that CO_2-exposure was associated with lower smoking urges post-challenge, relative to room air. That is, puffing behavior reflected lower smoking reinforcement after exposure to CO_2-enrichd air relative to room air. Smoking may have been perceived as aversive for CO_2-exposed smokers (per smoking urges findings), thus this may have been reflected in smoking topography data (regulating smoking behavior to minimalize further respiratory distress). Other studies utilizing stress-induction tasks have found that individuals take more puffs and smoke more intensely (shorter inter-puff intervals) after laboratory-manipulated stress paradigms versus neutral states (e.g., McKee et al., 2011), but other studies have found non-significant differences (e.g., McClernon et al., 2005). Thus, additional work in needed to further explicate factors that impact smoking reinforcement.

Additionally, contrary to hypotheses, there was no direct or interactive effect of anxiety sensitivity in terms of any smoking topography outcome. This is consistent with a

prior study that found a non-significant of anxiety sensitivity on smoking reinforcement (per average puff volume) following a negative mood induction task (Perkins, Karelitz, Giedgowd, et al., 2010). There may be alternative, more relevant individual-difference factors that are related to smoking topography (e.g., distress tolerance, depression; Perkins, Karelitz, Giedgowd, et al., 2010). It is also important to note that smoking topography variables were averaged across the cigarette smoked, which is consistent with other approaches (e.g., Corrigall, Zack, Eissenberg, Belsito, & Scher, 2001; Kassel et al., 2007; Perkins, Karelitz, Giedgowd, et al., 2010). However, studies have found that puff behavior changes during the course of smoking a single cigarette (e.g., decreases in puff volume and puff duration; increases in inter-puff interval; Collins et al., 2010; Guyatt, Kirkham, Baldry, Dixon, & Cumming, 1989; Kolonen, Tuomisto, Puustinen, & Airaksinen, 1992). For example, one study found that smokers decreased the magnitude of puff volume and puff duration during the course of a single cigarette by 33% and 39%, respectively, and increased inter-puff interval by 75% (Guyatt et al., 1989). Based on linear changes in puffing behavior over the course of smoking a cigarette, it is possible that by averaging topography variables, the current study decreased sensitivity in changes in puffing behavior. By examining puff-level data, it would be possible to examine trajectories in puff behavior during the course of the post-challenge cigarette, which could provide more nuanced and informative information about the effect of smoking reinforcement after exposure to a biological challenge.

It is possible that smokers exposed to the CO_2-enriched air (relative to room air) may evidence greater variability in puff-to-puff behavior during the course of smoking a cigarette, especially during initial puffs of the cigarette (evidencing initial smoking

reinforcement). This type of explanation is based on the observation that anxiety symptoms appear to moderate the course of puff behavior during a single cigarette, at least among adolescents (Veilleux et al., 2011). Along these same conceptual lines, the rate of change in puff volume and duration may occur more quickly for smokers exposed to CO_2-enriched air, which could account for why average shorter average puff volumes and durations were observed. Moreover, while anxiety sensitivity did not appear to impact average smoking topography (consistent wtih Perkins, Karelitz, Giedgowd, et al., 2010), it is possible that by examining puff-level data, a different patterning of effects could emerge. Aligned with initial expectations, high anxiety sensitive smokers may respond with greater smoking reinforcement via increased *initial* puff volume and duration, especially among those exposed to CO_2-enriched air.

It is also possible that the opposite pattern could be observed (i.e., initial puff-level data reflect lesser smoking reinforcement), given self-reported smoking urges were lower among smokers exposure to CO_2-enriched air, relative to room air immediately post-challenge. Certainly, the timing of the assessment of post-challenge smoking urges is likely largely impacted by smokers' immediate aversion to CO_2-enriched air, which might not necessarily be related to topographical components of smoking, given (a) initiation of smoking post-challenge occurred on average about 8 minutes post-challenge and (b) non-significant correlations between post-challenge self-reported urges and topographical components. In sum, there is great potential to further extend the understanding of affective factors that impact smoking topography by examining puff-level data, thus this is a logical next-step.

Other Noteworthy Observations

The majority of the participants in the current sample identified race as Black/African-American (61.1%). While race was not correlated with puffing behavior at a bivariate level, it would be important to consider the role of racial/ethnic factors in terms of the interplay between panic-relevant responding and smoking reinforcement. For example, Black/African-American smokers, relative to white smokers, have higher carbon monoxide increase from pre-to post-cigarettes use (Ahijevych, Weed, & Clarke, 2004) and higher cotinine consumption to cigarettes ratios (Ahijevych & Parsley, 1999), despite generally having lower rates of daily cigarette smoking (CDCP, 2014). These data suggest that Black/African-American smokers may be more 'efficient smokers' per single-cigarette (Ahijevych et al., 2004).

Relatedly, lower levels of educational attainment and personal income are associated with increased likelihood of cigarette use and persistence of nicotine dependence (Goodwin, Keyes, & Hasin, 2009). In the current sample, a large portion of participants reported completing high school or less (45.6%) and being unemployed (35.6%). Such socioeconomic factors should be considered in the subsequent analysis of these data to further understand the nature of these contextual factors on stress reactivity and smoking reinforcement.

The frequency of menthol cigarette use in the sample (58.9%) also warrants attention. Menthol may make cigarettes more reinforcing, via several mechanisms, which may promote smoking maintenance. For example, menthol has cooling and anesthetic physiological effects that may reduce irritating effects of smoking and sooth lungs, which in turn may permit greater inhalation of cigarette smoke (Ahijevych & Garrett, 2004).

Mentholated cigarettes are also typically higher in tar and nicotine (Federal Trade Comission, 2000). Additionally, menthol increases sensations of airflow during respirations (e.g., breathing freely) and has bronchodilating effects, which may permit increased lung exposure to nicotine, tar, and tobacco constituents; this may further increase addiction and toxicity potential in smokers who use mentholated cigarettes (Ahijevych & Garrett, 2004). Importantly, data suggest that Black/African-American smokers are more likely to smoke mentholated cigarettes (69%) relative to white smokers (23%; Giovino et al., 2004), which is important given the large percentage of Black/African-American smokers in the current sample. In fact, in the current sample, 89.1% of African-American smokers, relative to 10.3% of white smokers, reported smoking mentholated cigarettes. Given the unique respiratory effects of mentholated cigarettes, it would be informative to examine the interplay between cardiorespiratory distress experienced during a CO_2 biological challenge and smoking behavior among smokers who use menthol cigarettes. This type of approach may provide more nuanced information about how respiratory distress, panic arousal, and smoking behavior inter-relate.

Limitations

There are several limitations that warrant comment. First, it is well-documented that levels of CO increase throughout the day as incrementally more cigarettes are smoked (Burling et al., 1985). The procedures utilized in the current study did not include standardization of smoking behavior prior to the experimental laboratory visit or timing of study appointments (e.g., participants were seen in the morning and afternoon for the experiment). These factors could have impacted observable puffing behavior, if

individuals were already 'satiated' in terms of nicotine. However, based on initial expired CO breath samples (*M* = 24.0 ppm, *SD* = 10.9), data suggest that smokers likely had smoked within the past 12-24 hours suggesting they were not arriving to the appointment in nicotine deprivation, and may rule-out the possibility that smokers were sated (based on lack of an extremely high mean expired CO value). Further, by design, all participants smoked one cigarette approximately 60-90 minutes prior to the biological challenge, in an attempt to standardize recency of smoking behavior (and to document baseline [non-manipulated] smoking topography).

Second, while random assignment into experimental condition was utilized, smokers randomized to CO_2-enriched air versus room air reported significantly higher levels of pre-challenge subjective distress (SUDS). This pre-existing difference potentially indicates that smokers exposed to CO_2-enriched air were experiencing greater anticipatory distress pre-exposure, relative to smokers exposed to room air. It could be argued that this pre-manipulation difference confounds findings. However, based on lack of group differences on other pre-challenge measures, consistent patterning of manipulation effects across subjective and physiological measures, medium to large effect sizes, and significant effects above controlling for this variable all analyses, the impact of this pre-group difference may be negligible.

Third, despite targeted efforts to recruit more heavily nicotine dependent smokers, FTND scores indicate that, on average, smokers reported moderate levels of physiological dependence (*M* = 4.8, *SD* = 1.4). However, 97.8% of the sample reported initiating smoking within the first 30 minutes upon waking (56.7% in the first five minutes), which is often considered a stronger indicator of nicotine dependence.

Additionally, the internal consistency of the FTND items was low ($\alpha = 0.39$). This is an issue often apparent with this measure (Korte, Capron, Zvolensky, & Schmidt, 2013). Regardless, it is possible that among a more nicotine dependent sample (of heavier smokers; e.g., > 20 cigarettes/day; Abrams, Leger, et al., 2011), a CO_2 biological challenge may differentially impact the panic responding and smoking behavior. It is also worth noting, however, the changing characteristics of smokers in the U.S. (CDCP, 2014), which documents the declining overall smoking rates in the U.S. Thus, while examination of these processes in more nicotine dependent sample may provide additional insight into these important relations, it is also possible that this current sample is representative to the current demographic of smokers, at least in terms of smoking behavior/rate, especially ethnic/racial minority smokers who tend to smoke on average, fewer cigarettes per day (CDCP, 2014).

Fourth, while anxiety sensitivity is often considered an *amplifier* of negative affective states (e.g., Zvolensky, Farris, Guillot, et al., 2014), it is also conceptualized as an underlying explanatory mechanism that *accounts for* the link between panic attacks (or psychopathology more broadly) and smoking maintenance (Zvolensky, Farris, Leventhal, et al., 2014). Thus, it would be warranted to model anxiety sensitivity as a statistical mediator of the effect of the experimental manipulation on smoking reinforcement. Here, the effects of CO_2-expsoure would be expected to impact smoking reinforcement indirectly via the effect of anxiety sensitivity.

Lastly, many individual factors impact responding to a CO_2 biological challenge, including sleep deprivation (Babson, Feldner, Trainor, & Smith, 2009), trauma-exposure (Hawks, Blumenthal, Feldner, Leen-Feldner, & Jones, 2011; Vujanovic, Marshall-

Berenz, et al., 2010), extent of cannabis use (Bonn-Miller & Zvolensky, 2009), exercise (e.g., Esquivel et al., 2012), caffeine use (e.g., Nardi et al., 2007), and among females, menstrual cycle phase (Nillni, Rohan, & Zvolensky, 2012). These individual difference factors were not considered here, but could meaningfully inform smoking reinforcement post-challenge, thus warrant empirical consideration in future studies.

Integrative Summary and Implications

The current findings add experimental data to the emerging body of literature on the interplay between panic attacks and aspects of cigarette smoking. Findings confirm that high (relative to low) anxiety sensitive daily cigarette smokers are sensitive to cardiorespiratory provocation (akin to panic attack sensations). Immediate subjective and cardiorespiratory distress appears to promote immediate decreases in smoking urges and puff behavior (volume, duration), which adds additional unique data to the literature to support that smokers alter *how they smoke* based on *arousal states*. These data aid in refinement of integrated models of panic attacks and smoking (Zvolensky & Bernstein, 2005), and generally inform negative reinforcement models of drug addiction (McCarthy et al., 2010). Specifically, data indicate that the intensity (not just the presence) of physiological arousal likely impacts smoking motivation and reinforcement.

Although historically rich, there are many avenues for extension in the smoking topography literature. A logical first-step would be to conduct a systematic review of the literature on smoking topography (especially as it relates to psychological/affective distress), as this is presently lacking. Such a synthesis could potentially facilitate (a) development of methodological standards for examining topography data (e.g., puff-level

data), (b) summarize points of overlap and divergence across study findings, and (c) delineate areas for future study.

Additionally, it is important to understand individual difference factors that contribute to smoking reinforcement. Here, anxiety sensitivity was examined as one of many possible factors that may amplify smoking reinforcement post-biological challenge, although various psychological factors impact affective responding to a biological challenge (Zvolensky & Eifert, 2001). For example, data indicate that avoidance-based coping (Spira, Zvolensky, Eifert, & Feldner, 2004), discomfort intolerance (Bonn-Miller, Zvolensky, & Bernstein, 2009), and experiential avoidance (Feldner, Zvolensky, Eifert, & Spira, 2003; Karekla, Forsyth, & Kelly, 2004) impact challenge responding, thus could be considered as alternative factors that could impact links between panic attacks and smoking reinforcement.

Regarding smoking cessation, the predictive validity of puff topography components has also not been explored. For example, among smokers undergoing a smoking cessation attempt, it is unknown how smoking behavior is associated with smoking cessation outcomes. Theoretically, smoking reinforcement would be associated with poorer quit outcomes (e.g., earlier lapse/relapse), however this has not been empirically examined. Relatedly, exploring factors that are associated with changes (reductions) in smoking reinforcement would be meaningful and informative from an intervention perspective. For instance, one study found that moderate physical activity (via brisk walking) relative to passive sitting, was associated with reductions in aspects of smoking topography (Faulkner, Arbour-Nicitopoulos, & Hsin, 2010). Moreover, the clinical utility of smoking topographical 'profiles' has not yet been explored. While

controlled puffing has been historically used to facilitate smoking cessation (Frederiksen et al., 1977), it is possible that personal smoking topography data could be usefully summarized to smokers, as a form of tailored feedback regarding smoking reinforcement behavior. Emerging research suggests that use of a personal CO monitor to provide regular biochemical feedback may assist in smoking cessation (Beard & West, 2012). Puffing behavior feedback may be useful for smokers attempt to quit, especially if smoking reduction and or scheduled smoking is part of a smoking cessation intervention, to ensure that smokers are attending to *how* they are smoking, not exclusively *when* or *how much*.

Overall, the present findings empirically document the importance of further exploring the associations between panic-relevant arousal and smoking reinforcement, and individual risk factors that may amply risk for smoking maintenance. When considered in the larger context of other research (Piper et al., 2011), the present findings underscore that there may be a need for specialized smoking cessation interventions for smokers with panic attacks (Zvolensky, Lejuez, Kahler, & Brown, 2003), and more generally for smokers with psychological disorders (Ziedonis et al., 2008). Data suggest that self-regulation of smoking behavior is impacted by subjective distress and physiological arousal, and psychological distress more broadly (e.g., McKee et al., 2011; Veilleux et al., 2011). Thus, tailed interventions for psychologically-vulnerable smokers would ideally (a) identify emotional and situational antecedents to smoking behavior, (b) provide psychoeducation about the role of self-regulated puffing behavior as a mechanism for affect-regulation (and how such accommodations may maintain smoking

behavior, and (c) teach skills to manage and tolerate physiological arousal and negative emotional states, without smoking (or altering smoking style).

Footnotes

[1]Due to sensitivity of expired CO to recency of smoking, three participants were included in the study despite CO levels < 10. These participants had CO levels ≥ 6. These participants reported smoking ≥ 20 cigarettes per day on the Timeline Follow-Back (TLFB).

[2]The original study included criterion required participants to score ≥ 5 on the Fagerström Test for Nicotine Dependence (FTND). Due to difficulties with recruitment with this relatively stringent cutoff, participants were instead included on the basis reporting smoking their first cigarette within at least the first 30 minutes of waking (≥ 2 on the FTND item 1). Two participants reported smoking greater than 30 minutes of waking but were included based on self-reported smoking of ≥ 10 cigarettes per day and expired CO levels of ≥ 10ppm at baseline.

[3]In order to facilitate timely study recruitment, this inclusion criteria was 'loosened' such that smokers reporting use of stable psychotropic medication use (unchanged medication dose for ≥8 weeks) and non-use of PRN medications, were deemed eligible for study participation; 9 participants were included who reported stable use of psychotropic medications (most frequently SSRI, SNRI).

[4]This exclusion criterion was included after study initiation based on a high number of participants who reported being unable to use a computer, thus not being able to initiate or complete computerized study assessments.

[5]Moderation describes a situation in which the effect of X on Y varies as a function of a third variable, M (the moderator variable). Moderated effects are typically modeled statistically as an interaction between X and M, and derived by computing the product of

X and M (Hayes, 2009). In the present study, anxiety sensitivity was conceptualized on an *a priori* basis as a variable that would affect the relation between exposure to panic-relevant sensations and smoking (moderator); not conceptualized as a factor that accounts for or explains the relation between panic-sensations and smoking motivation (i.e., mediator; Hayes, 2009).

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Table 1. Summary of studies utilizing a CO_2 biological challenge with smokers

Study	CO_2 Type	Sample	Findings
Abrams et al., 2008[1]	5-minute 5% CO_2 rebreathing	24 heavy smokers in 12-hour withdrawal vs. 24 non-smokers	Smokers reported greater increases in cognitive and somatic panic symptoms, however lower respiration (minute ventilation) during the challenge; heart rate did not differ between groups.
Abrams et al., 2011a[1]	5-minute 5% CO_2 rebreathing	27 heavy smokers in 12-hour withdrawal vs. 27 smokers smoking as usual	After adjusting for group status, nicotine withdrawal symptom severity predicted greater post-challenge panic attack symptoms and urge to escape
Abrams et al., 2011b[1]	5-minute 5% CO_2 rebreathing	28 heavy smokers in 12-hour withdrawal vs. 30 heavy smokers smoking as usual vs. 27 non-smokers	Withdrawal condition among smokers was not associated with challenge reactivity (urge to escape/panic attack symptoms). Smokers responded with greater urge to escape, relative to non-smokers. Anxiety sensitivity x smoking status predicted increased panic attack symptoms, and high anxiety sensitivity smokers not in withdrawal reported greatest panic attack symptoms
Attwood et al., 2014	7.5% CO_2 vs. room air	Ex1: 12 smokers and 12 non-smokers; within-subject design Ex2: 24 smokers randomized to smoking as usual or 12-hours deprivation	Ex1: CO_2 relative to room air increased blood pressure, heart rate, state anxiety and negative affect; smoking status interacted with CO_2 to predict greater increases in blood pressure in non-smokers. Within smokers, exposure to CO_2 versus air did not differentially impact smoking urges. Ex2: CO_2 relative to room air increased blood pressure, state anxiety and negative affect, and decreases in positive affect; no significant effect for heart rate. Deprivation condition interacted with state anxiety and negative affect, with smoking as usual associated with greater reactivity when exposed to CO_2 relative to room air. There was a significant deprivation condition x gas interaction for smoking craving, such that non-abstinent smokers reported greater increases in craving when exposed to CO2 relative to room air, but no differences for abstinent smokers.
Vujanovic & Zvolensky, 2009[2]	10% CO_2 continuous breathing for 4 min.	90 daily smokers randomly assigned to 12-hour withdrawal or smoking as usual	Group x AS interaction for subjective anxiety at 1 and 2 minutes, but not 3 and 4 minutes during challenge. High AS smokers in the smoking as usual condition reported highest peri-challenge anxiety
Vujanovic et al., 2010[2]	10% CO_2 continuous breathing for 4 min.	63 daily smokers who reported exposure to $\geq$ 1 traumatic events; 12-hour withdrawal or smoking as usual	PTSD severity x group predicted peri-challenge anxiety at minutes 3 and 4 of challenge but not minutes 1 and 2. Form of interaction was for smoking as usual condition x higher PTSD predictive of greater peri-challenge anxiety.
Leyro & Zvolensky, 2013[3]	10% CO_2 continuous breathing for 4 min.	58 daily smokers with and without panic disorder; randomized to 12-hour withdrawal or smoking as usual	Smokers with panic disorder and higher levels of nicotine withdrawal (regardless of condition) had greater post-challenge panic attack symptoms but not subjective distress. There was a main effect of withdrawal predicting greater subjective distress during challenge, and interaction of panic disorder x time, such that panic disordered smokers had quicker initial decrease in anxiety following the challenge, although rate of recovery decelerated over time.
Farris et al., in press[3]	10% CO_2 continuous breathing for 4 min.	54 daily smokers with and without panic disorder; randomized to 12-hour withdrawal or smoking as usual	After adjusting for panic disorders status and randomization condition, greater subjective reactivity to challenge was associated with greater post-challenge panic attack symptoms and nicotine withdrawal symptom severity. Perceived distress

			intolerance predicted greater subjective distress to challenge, which indirectly accounted for the effects for greater panic attacks symptoms and nicotine withdrawal post-challenge.
Zvolensky et al., 2001	20% CO_2 continuous breathing for 25s.	22 heavy smokers who were split into those who were able to quit $\geq$ 7 days (n=10) vs. < 7 days (n=12)	Smokers with < 7 day quit history reported significantly greater subjective anxiety, bodily arousal, emotionally aversive, and reported less emotional control; groups did not differ in terms of heart rate.
Brown et al., 2002	15 mins; three 20% CO_2 presentations at 5min (25s), 10min (25s), and 15min ($\leq$30s)	16 smokers quit attempts < 24hr vs.16 smokers with history of quit attempt $\geq$3m; within-subject test of smoking as usual vs. 12-hour deprivation	Post-challenge dysphoria increased after CO_2 exposure, but not differentially for smokers with an immediate relapse versus delayed relapse history. There was no effect of CO_2 manipulation of changes in pre-post smoking urges.
Brown et al., 2009	15 min; two 20% CO_2 presentations at 7min (25s) and 12 min ($\leq$ 60s).	81 daily smokers motivated to quit smoking enrolled in a self-guided quit attempt study	Longer duration until self-termination of breathing CO_2-enriched air during the second presentation was associated with significantly reduced likelihood of smoking lapse.
Cosci et al., 2006	Single vital capacity breath of 35% CO_2	33 non-smokers in a within-subject test of nicotine patch vs placebo patch	Nicotine patch increased heart rate and panic attack symptoms pre-challenge, but not reactivity to challenge.
Knuts et al., 2010	Single vital capacity breath of 35% CO_2	92 participants (46 smokers and 46 non-smokers) with panic disorder	Smokers evidenced greater challenge reactivity relative to non-smokers in terms of self-reported panic symptoms, but rates of panic attacks did not differ between smokers and non-smokers.

Note: Superscript number denotes overlapping samples.

Table 2. Internal consistencies, means and standard deviations, range, and inter-correlations for study variables

Baseline Variable	Alpha	Items	Mean (SD)	Possible Range	Observed Range
ASI-3 Total	0.93	18	12.7 (12.8)	0-72	0-50
ASI-3 Physical	0.88	6	3.7 (4.7)	0-24	0-23
ASI-3 Cognitive	0.88	6	2.9 (4.4)	0-24	0-20
ASI-3 Social	0.86	6	6.2 (5.6)	0-24	0-22
FTND total	0.39	6	4.8 (1.4)	0-10	0-8
PANAS-NA	0.93	10	18.0 (8.4)	10-50	10-47
CPD/7 days	0.95	7	15.8 (5.9)	--	6.4-34.3
Outcome Variable	**Alpha**	**Items**	**Mean (SD)**	**Observed Range**	***r***
PRE-QSU total	0.97	10	348.3 (321.8)	0-1000	.798**
POST-QSU total	0.96	10	322.1 (317.9)	0-1000	
PRE-Latency Puff	--	--	8930.7 (5571.7)	2962-27397	.246*
POST-Latency Puff	--	--	9553.6 (6888.9)	2095-31351	
PRE-Puff Volume	--	--	67.4 (30.8)	25.7-227.7	.650**
POST-Puff Volume	--	--	64.8 (24.2)	30.4-158.9	
PRE-Puff Duration	--	--	1780.6 (681.7)	631-3980	.881**
POST-Puff Duration	--	--	1662.4 (670.1)	639-4070	
PRE-IPI	--	--	13221.2 (5575.6)	2605-32328	.818**
POST-IPI	--	--	12519.0 (6584.7)	2265-36036	

** $p < .05$; ** $p < .01$*

Table 3. Sample demographics, smoking and psychological history

	Total (n = 90)		**CO_2-Enriched Air (n = 45)**		**Room Air (n = 45)**		
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	**X^2 or t**
Demographics							
Sex							
Male	46	51.1	23	51.1	23	51.1	0.00
Female	44	48.9	22	48.9	22	48.9	
Age	43.6	9.7	42.5	9.4	44.7	9.9	1.08
Race							
White	29	32.2	16	35.6	13	28.9	0.47
Black	55	61.1	26	57.8	29	64.4	
Other	6	6.7	3	6.7	3	6.7	
Education							
High School or less	41	45.6	23	51.1	18	40.0	1.12
At least part college	49	54.4	22	48.9	27	60.0	
Marital Status							
Never married	44	48.9	25	55.6	19	42.2	3.92
Divorced/Separated	32	35.6	15	33.3	17	37.8	
Married	9	10.0	2	4.4	7	15.6	
Widowed	5	5.6	3	6.7	2	4.4	
Employment Status							
Full-Time	23	25.6	13	28.9	10	22.2	1.46
Part-Time	18	20.0	7	15.6	11	24.4	
Unemployed	32	35.6	17	37.8	15	33.3	
Other	17	18.9	8	17.8	9	20.0	
Smoking History							
Age smoke initiation	16.0	6.7	15.0	4.4	17.0	8.3	1.48
Years/smoker	23.9	10.2	23.3	10.4	24.4	10.1	0.54
Cigarettes per day	15.8	5.9	16.1	6.4	15.5	5.3	-0.52
FTND total score	4.8	1.4	4.7	1.5	4.9	1.3	0.81
Expired CO at BL	24.0	10.9	24.7	11.5	23.3	10.3	-0.62
FTND Item 1							
Within 5 minutes	51	56.7	27	60.0	24	53.3	0.41
Greater 5 minutes	39	43.3	18	40.0	21	46.7	
Menthol cigarettes							
Yes	53	58.9	24	53.3	29	64.4	1.15
No	37	41.1	21	46.7	16	35.6	
Psychological History							
Psychological Dx							
Yes	30	33.3	19	42.2	11	24.4	3.20
No	60	66.7	26	57.8	34	75.6	
History/panic attack							
Yes	24	26.7	14	31.1	10	22.2	0.91
No	66	73.3	31	68.9	35	77.8	

Table 4. Inter-correlations between study outcome variables

Outcome Variable	2.	3.	4.	5.
1. QSU-Total	.03	.08	.12	-.18
2. Latency to first puff	--	-.12	-.09	.15
3. Average puff duration		--	.64**	.32**
4. Average puff volume			--	.23*
5. Average inter-puff interval				--

** p < .05; ** p < .01; QSU-Total = Questionnaire of Smoking Urges; all variables assessed post-challenge.*

Table 5. Bivariate associations between anxiety sensitivity and baseline characteristics.

Variable	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**	**10.**
1. Anxiety Sensitivity	.09	-.03	.04	.07	.06	.54**	.61**	.45**	.49**
2. Sex (female)	--	-.19	-.05	-.15	.05	.11	.07	.01	.01
3. Age		--	.16	-.07	-.11	-.15	-.24*	-.25*	-.12
4. Race (white)			--	.19	-.46**	.06	.13	-.06	.10
5. BL Cigarettes/day				--	-.16	.14	.11	.07	-.01
6. Menthol (Yes)					--	.06	-.17	.11	.09
7. Any DX (Yes)						--	.47**	.36**	.37**
8. BL Negative Affect							--	.31**	.45**
9. Pre-SUDS								--	.64**
10. Pre-DSQ									--

** p < .05; ** p < .01; Note: Anxiety sensitivity = Anxiety Sensitivity Index-3 (Total score); Sex (0 = male; 1 = female); Race (0 = non-white; 1 = white); BL Cigarettes/day = Baseline cigarettes per day; Menthol Cig (0 = no; 1 = yes); Any Disorder = Baseline psychological disorder (0 = no disorder; 1 = past-year disorder); BL Negative Affect = Baseline negative affectivity per the Positive and Negative Affect Scale (Negative affect subscale); PRE SUDS = Pre-challenge levels of subjective distress; PRE DSQ = Pre-challenge number of panic attacks symptoms.*

Table 6. Means and standard deviations for manipulation check variables

	Room Air		CO_2	
Variable	***Mean***	***SD***	***Mean***	***SD***
SUDS Pre-Challenge*	15.09	23.09	33.27	29.83
SUDS Post-Challenge	18.09	24.07	42.58	31.92
DSQ Pre-Challenge	0.40	0.99	0.91	1.55
DSQ Post-Challenge	0.56	0.56	2.38	2.37
HR Pre-Challenge	89.38	27.90	94.29	33.61
HR Post-Challenge	88.33	27.55	105.28	37.47
RES Pre-Challenge	17.84	1.14	17.70	1.30
RES Post-Challenge	17.85	0.96	18.27	1.17
Expired $etpCO_2$	7.51	1.87	42.95	7.93

*Note: SUDS = Subjective Units of Distress; DSQ = modified-Diagnostic Symptom Questionnaire (number of panic attack symptoms); HR = Heart rate; RES = Respiration rate; Expired $etpCO_2$ = Expired end-tidal peak CO_2. *Pre-manipulation group differences were observed on this variable.*

Table 7. Tests of manipulation effects

	Experimental Condition		Effect Size
Outcome Variable	***b***	***SE***	***d***
SUDS Post-Challenge	0.721*	0.289	0.527
DSQ Post-Challenge	1.128***	0.238	1.002
HR Post-Challenge	0.141**	0.046	0.682
RES Post-Challenge	0.468*	0.222	0.800

** p < .05; ** p < .01; ***p < .001; Note: SUDS = Subjective Units of Distress; DSQ = modified-Diagnostic Symptom Questionnaire (number of panic attack symptoms); HR = Heart rate; RES = Respiration rate. All analyses were conducted controlling for pre-challenge values on the outcome variable.*

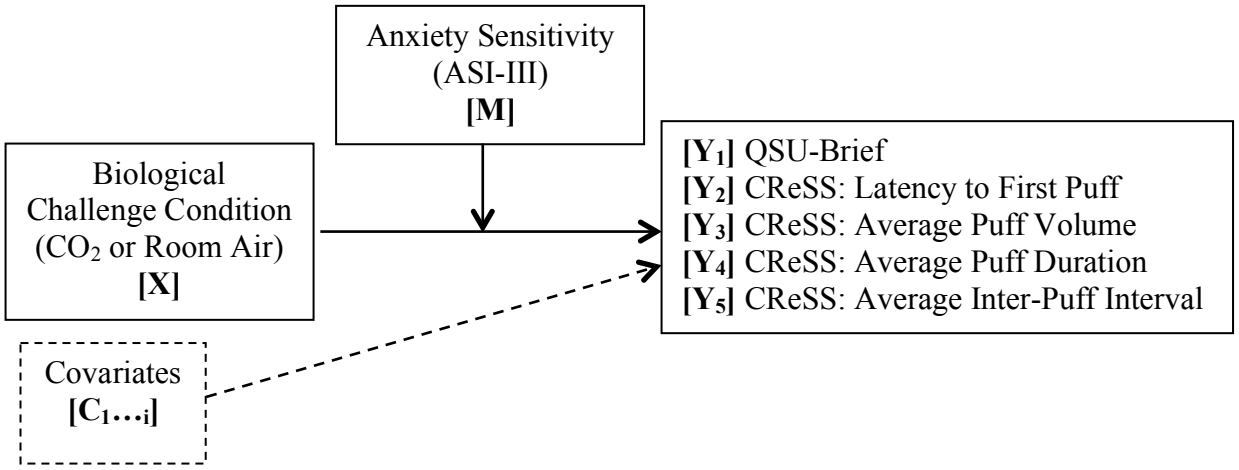
Table 8. Results for main and interaction effects for smoking urges and latency to first puff

Outcome: Post-Challenge Smoking Urges (QSU-B)						
Predictor	**b**	**SE**	**CI Low**	**CI High**	**Z value**	**p**
Intercept	93.10	40.12	7.19	163.27	2.32	.020
CPD	1.66	2.80	-4.14	6.95	0.59	.555
Trait Negative Affect	6.99	4.24	-1.43	15.35	1.65	.099
Pre-Challenges SUDS	0.03	0.88	-1.80	1.73	0.04	.968
Pre-Challenge QSU	0.81	0.09	0.63	0.99	8.66	.000
Condition	-81.26	40.99	-164.18	-4.25	-1.98	.048
ASI-3	3.15	3.46	-4.10	9.27	0.91	.363
Condition x ASI-3	-9.96	4.07	-17.93	-2.08	-2.45	.014
Outcome: Latency to First Puff Post-Challenge (ms)						
Predictor	**b**	**SE**	**Low**	**High**	**Z value**	**p**
Intercept	8798.11	991.94	5086.31	880.02	8.87	.000
CPD	-44.4	138.22	-308.72	230.97	-0.32	.749
Trait Negative Affect	5.25	106.31	-183.84	249.01	0.05	.960
Pre-Challenges SUDS	23.85	36.3	-47.65	93.08	0.66	.509
Pre-Challenge Latency	0.26	0.16	-0.05	0.58	1.63	.103
Condition	-2854.69	1767.12	-6422.11	547.61	-1.62	.105
ASI-3	66.47	121.34	-177.82	301.49	0.55	.582
Condition x ASI-3	-40.73	160.98	-346.68	272.52	-0.25	.803

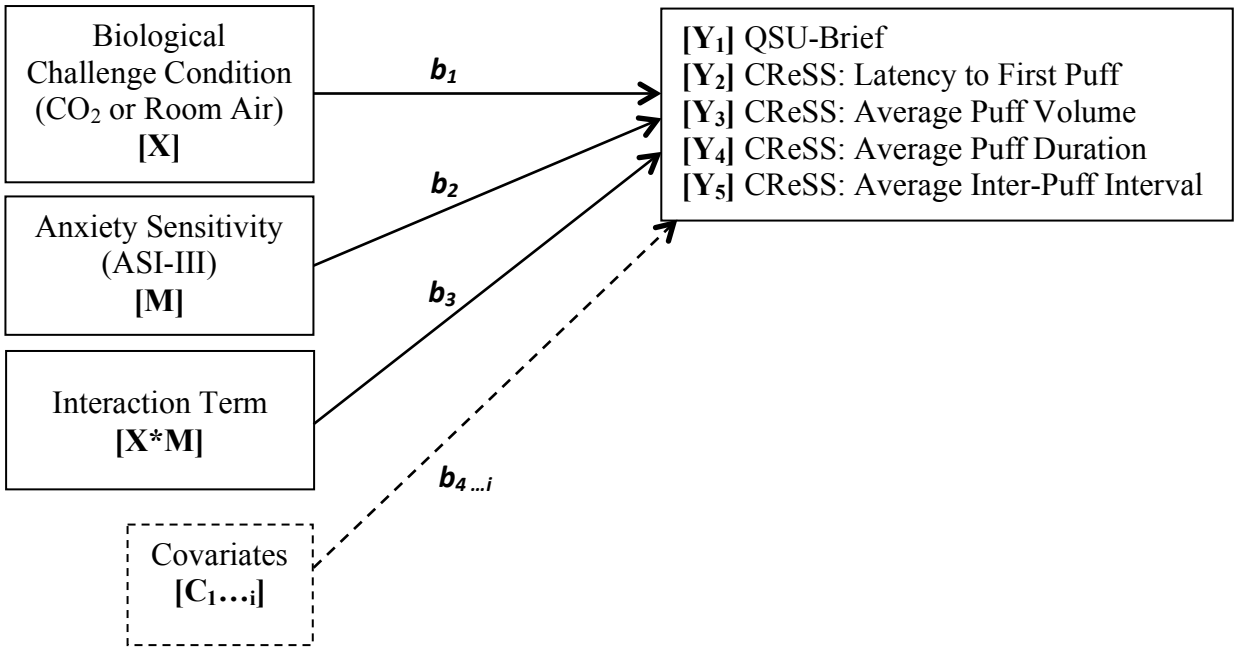
Table 9. Results for main and interaction effects for inter-puff interval, puff duration, and puff volume

Outcome: Average Inter-Puff interval (ms)						
Predictor	**b**	**SE**	**Low**	**High**	**Z value**	**p**
Intercept	-240.87	129.85	-2361.99	2033.80	-1.85	.064
CPD	123.64	68.62	-1.15	266.68	1.80	.072
Trait Negative Affect	38.91	72.15	-98.40	184.25	0.54	.589
Pre-Challenges SUDS	-4.71	20.81	-47.02	35.39	-0.23	.818
Pre-Challenge IPI	0.98	0.08	0.82	1.12	12.30	.000
Condition	-650.96	888.96	-2383.77	1065.73	-0.73	.465
ASI-3	17.08	44.54	-74.09	101.86	0.38	.704
Condition x ASI-3	-76.40	55.58	-186.74	39.24	-1.37	.171
Outcome: Average Puff Volume (mL)						
Predictor	**b**	**SE**	**Low**	**High**	**Z value**	**p**
Intercept	30.71	12.28	0.17	48.42	2.50	.012
CPD	-0.12	0.26	-0.68	0.40	-0.47	.639
Trait Negative Affect	-0.17	0.35	-0.92	0.53	-0.47	.639
Pre-Challenges SUDS	-0.01	0.08	-0.16	0.14	-0.07	.944
Pre-Challenge Volume	0.56	0.19	0.31	1.04	3.01	.003
Condition	-8.11	4.12	-16.82	-0.61	-1.97	.049
ASI-3	0.06	0.41	-0.71	0.92	0.15	.883
Condition x ASI-3	-0.10	0.34	-0.81	0.54	-0.30	.764
Outcome: Average Puff Duration (ms)						
Predictor	**b**	**SE**	**Low**	**High**	**Z value**	**p**
Intercept	165.275	123.859	-60.61	414.209	1.33	.182
CPD	7.645	5.504	-2.343	19.438	1.39	.165
Trait Negative Affect	-1.721	4.9	-10.759	8.479	-0.35	.725
Pre-Challenges SUDS	-1.051	1.511	-4.005	1.89	-0.70	.487
Pre-Challenge Duration	0.886	0.069	0.752	1.021	12.84	.000
Condition	-144.393	73.987	-293.164	-3.988	-1.95	.050
ASI-3	6.679	5.066	-2.994	17.163	1.32	.187
Condition x ASI-3	-8.734	6.035	-20.943	2.895	-1.45	.148

Figure 1. Conceptual (a) and Statistical (b) Models



(a) Conceptual Model



(b) Statistical Model

Figure 2. CONSORT diagram

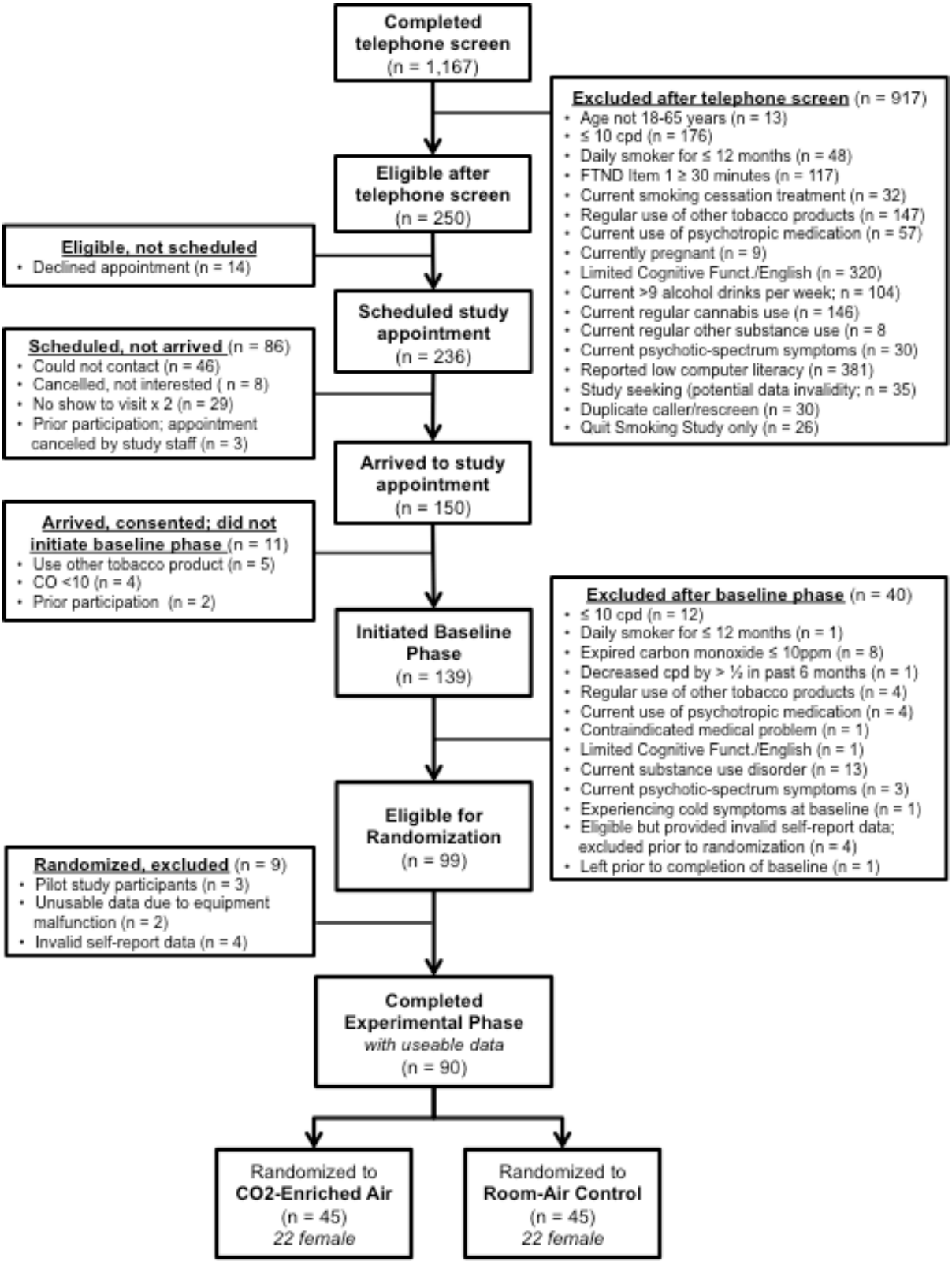


Figure 3. Visualization of study procedures

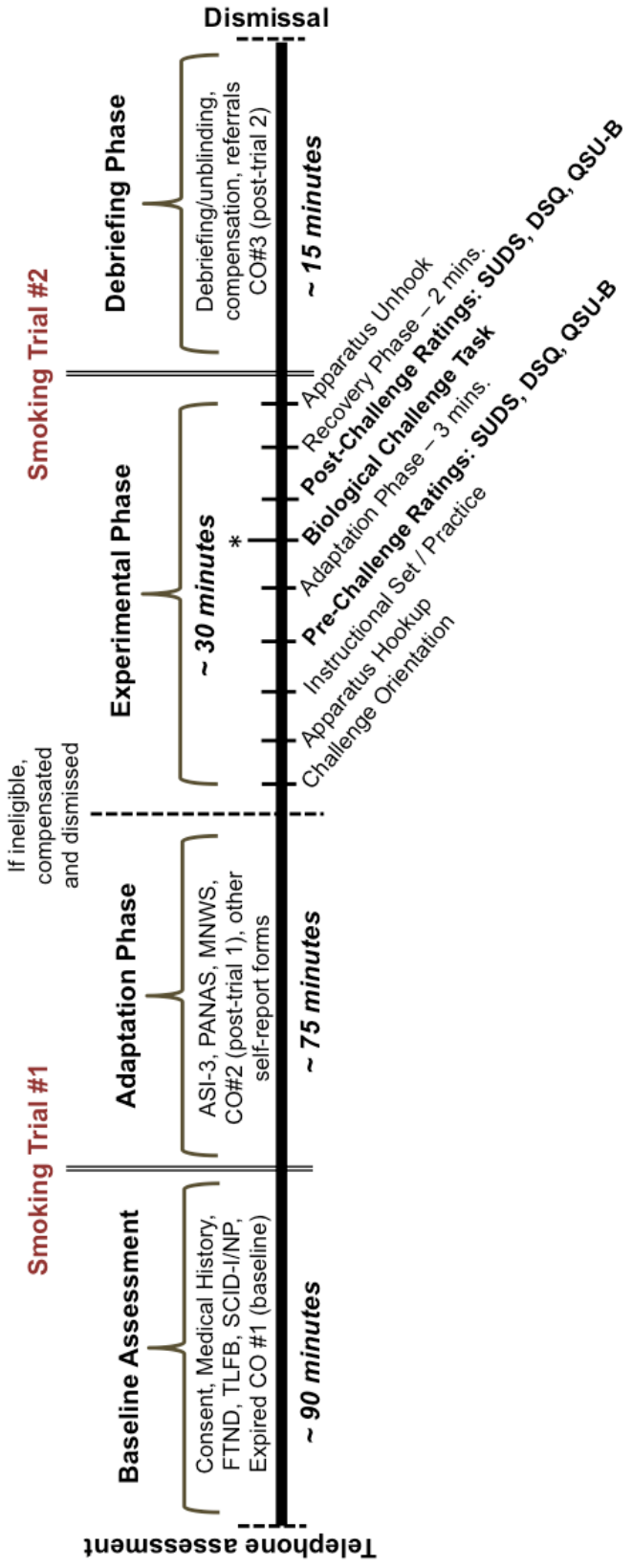
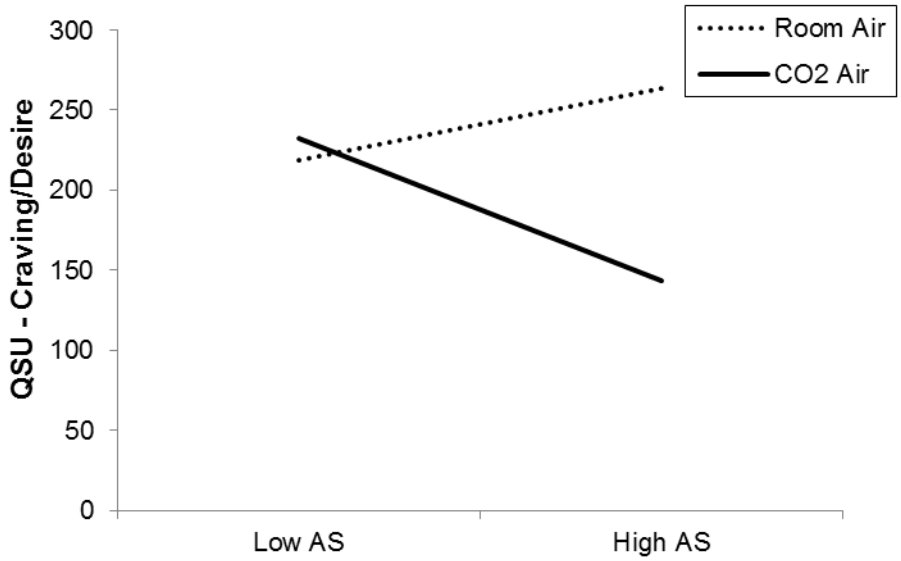
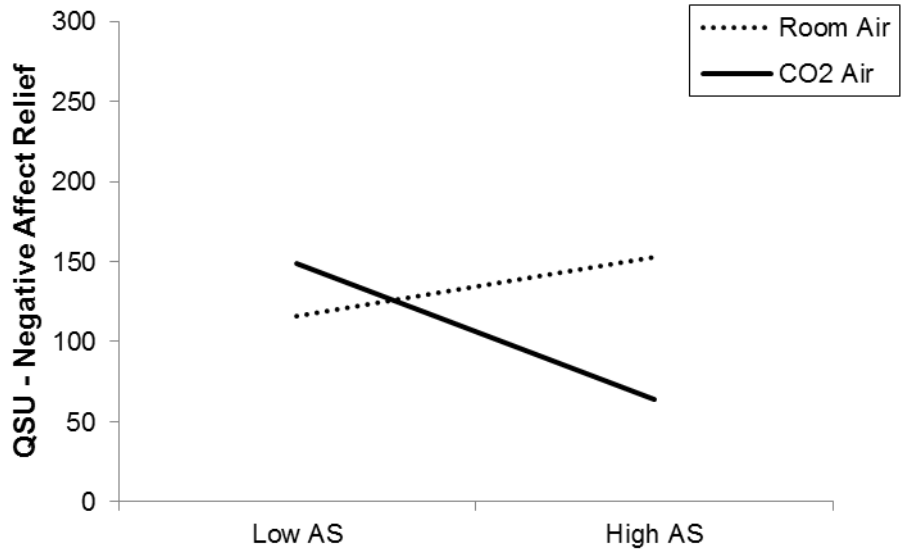


Figure 4. Interaction of experimental condition and anxiety sensitivity in predicting smoking urges subscales

(a) Interaction for QSU-Craving/Desire subscale



(b) Interaction for QSU-Negative Affect relief subscale



Appendix A

Eligibility Checklist

Date Triage: _____ **RA:** _____ (Initials)

Date Baseline: _____@____am/pm **CC1/CC2:** ____/____ (Initials)

Date Rescheduled: _____@___am/pm **CC1/CC2:** ____/____ (Initials)

ID#: _____ **Check for Quit Study Eligibility: Yes No**

I. Inclusion Criteria:	**Yes**	**No**
I1. Age 18-65	____	____
I2. ≥ 10 cigarettes per day	____	____
I3. Daily smoker for ≥ 12 months	____	____
I4. FTND- Item 1 ≤ 30 minutes	____	____
I5. C0 ≥ 10 at BL	____	____

E. Exclusion Criteria:	**Yes**	**No**
E1. Decreased the number of cigarettes per day by more than ½ in the last 6 months	____	____
E2. Current smoking cessation treatment	____	____
E3. Regular use of other tobacco products	____	____
E4. Current use of psychotropic medication	____	____
E5. Chronic medical problem	____	____
E6. Currently pregnant	____	____
E7. Limited mental competency and inability to provide informed, voluntary, written consent	____	____
E8. Planning on moving within the next month	____	____
E9. Insufficient command of the English lang.	____	____
E10. Current substance use disorder	____	____
E11. Current suicidal ideation	____	____
E12. Current psychotic-spectrum symptoms	____	____
E13. Could not contact	____	____
E14. Cancelled visit, no longer interested	____	____
E15. No show to study visit	____	____
E16. Already participated	____	____
E17. Equipment failure (internal error)	____	____
E18. Invalid Self-report assessments	____	____

Eligibility Status: Eligible ↓ Ineligible: _____ ↓

Randomization: **Yes** **No** N/A

If No, why: _____

PI Approval: _____ Date:_____

Appendix B

Fagerström Test for Nicotine Dependence (FTND)

1. How many minutes after you wake do you smoke your first cigarette? _____(min.)

2. How many cigarettes a day do you smoke? _____(#cig.)

For questions 3-6 please use the provided scale and write the number of your answer on the blank line to the right.

0 = No, never
1 = Sometimes
2 = Most of the time
3 = Yes, always

3. Do you find it difficult to refrain from smoking in places where it is forbidden; e.g., in church, at the library, in cinemas, etc.? _____

4. Do you smoke more during the first 2 hours of your day than during the rest of the day? _____

5. Do you smoke if you are so ill that you are in bed most of the day? _____

6. When you are smoking, do you inhale? _____

For questions 7-8, please write your answer on the blank line below each question.

7. Which cigarette of the day would you most hate to give up?
   (please be specific)_____

8. a. What is you usual brand of cigarettes?
   Brand: _____

   b. Check off all the following that apply to your brand:

_____regular	_____menthol	_____hard pack
_____nonfiltered	_____lights	_____nonmenthol
_____soft pack	_____filtered	_____ultralights
_____kings	_____100's	_____120's

Appendix C

Smoking History Questionnaire (SHQ)

For each question below, please write the number of the answer on the blank line(s) to the right of each item.

1. How old were you when you **first** smoked a cigarette? (years) _____
2. How old were you when you started regular daily cigarette smoking? (years) _____
3. For how many years, altogether, have you been a regular daily smoker? _____
4. Since you started regular daily smoking, what is the average number of cigarettes you smoked per day? _____
5. Think about your smoking during the **last week**, how many cigarettes did you smoke in an average day? _____
6. Do you currently use:
   a. Cigars 1 = YES 0 = NO _____
   b. Smokeless tobacco 1 = YES 0 = NO _____
   c. Pipe tobacco 1 = YES 0 = NO _____
7. When were you smoking the **heaviest**? (year) _____
8. When smoking the heaviest, how many cigarettes did you smoke per day? _____
9. How many times in your life have you made a serious attempt to quit smoking? _____
10. As best as you can remember, how long ago did you make your first attempt to quit smoking? (years) _____
11. How many years have you smoked? (total number of years) _____
12. How many different times in you life have you made an attempt to quit smoking where you have stayed off cigarettes for 12 or more hours? (Do not include time sleeping) _____
13. Since you started smoking regularly, have you ever quit for a period of at least 24 hours? 1 = YES 0 = NO _____
14. Since you first started smoking, what was the **longest** period of time that you were able to stay off cigarettes? (If less than 1 day, do not include time sleeping)

Years _____ Months _____ Days _____ Hours _____

15. Please give us some information about your most recent attempts to quit smoking. Begin with the most **recent** date. Write answers on the lines below.

When did it occur?	**How long did you quit?**
Days abstinent	Hours abstinent
_____ date	_____ days and/or _____ hours
_____ date	_____ days and/or _____ hours
_____ date	_____ days and/or _____ hours

16. In your attempts to quit smoking, what methods have you used?

	1 = YES	**0 = NO**
a. Cold turkey		_____
b. Smoke-enders		_____
c. Behavior modification		_____

d. American Cancer Society / Lung Association Program _____
e. Hypnosis _____
f. Acupuncture _____
g. With friends, relatives, etc. . . _____
h. Gradual reduction _____
i. Telephone Counseling _____
j. Substitute other tobacco product _____
k. Nicotine Patch _____
l. Nicotine Gum _____
m. Other _____ (please specify) _____

17. While trying to quit, how serious have each of the following problems been for you?

1	2	3	4	5
Not at all	A little	Moderately	Very	Extremely

a. Weight gain _____
b. Increased eating _____
c. Digestive problems _____
d. Nausea _____
e. Headaches _____
f. Drowsiness _____
g. Depression or low mood _____
h. Fatigue _____
i. Insomnia _____
j. Difficulty concentrating _____
k. Heart pounding, or sweating _____
l. Decreased heart rate _____
m. Irritability _____
n. Restlessness _____
o. Anxiety _____
p. Craving for tobacco _____
q. Other _____ _____

18. Have you in the **past** had a disease or illness you believe was caused or aggravated by your smoking? 1 = YES 0 = NO _____

19. Do you have any symptoms **now** that you believe are caused by your smoking? 1 = YES 0 = NO _____

20. Do you have a disease or illness **now** that you believe is caused by or aggravated by your smoking? 1 = YES 0 = NO _____

21. Has a doctor ever told you to stop smoking?
1 = YES 0 = NO _____

22. Were you smoking 12 months ago?
1 = YES 0 = NO _____

23. Where you smoking 6 months ago?
1 = YES 0 = NO _____

24. Have you reduced the number of cigarettes you smoke in the last month?
1 = YES 0 = NO _____
If **YES**, by how many cigarettes? _____

25. Did you switch brands in the last month?
1 = YES 0 = NO _____
If **YES**, what was your old brand _____

26. Does your desire for a cigarette ever disrupt the activities you are involved in? 1 = YES 0 = NO _____

27. In what situations DON'T you smoke?
0 = No, I never smoke . . .
1 = Yes, I sometimes/once in while smoke . . .
N/A = Not applicable

a. In public _____
b. At work _____
c. At home _____
d. In presence of certain relative (e.g., parents, in-laws) _____
e. In presence of my children _____
f. At meetings _____
g. Inside the home of non-smokers _____
h. In my car when non-smokers are with me _____
i. In other people's car(s) _____
j. In restaurants _____
k. In airplanes _____
l. Other _____ (please specify) _____

28. To the best of your knowledge, categorize the use of cigarettes by the following people in your life. Please use the following scale and place the number answer on the line to the right.

1 = Smoker 2 = Ex-smoker
3 = Never smoked 4 = Don't know 5 = Not applicable

Biological Father _____
Biological Grandmother (father's side) _____
Biological Mother _____
Biological Grandmother (mother's side) _____
Biological Grandfather (father's side) _____
Biological Grandfather (mother's side) _____

29. How many biological brother and sisters do (did) you have? _____
30. How many of them had ever smoked cigarettes? _____

Appendix D

Timeline Follow-Back (TLFB)

Directions: Please complete the attached calendar by filling in any substance(s) you have used during the past 30 days. Please do not leave spaces blank unless you have not used that substance in the past 30 days. For substances that have been used in the past 30 days, place a zero (0) on all days that the substance was not used. Below, please find a standard measurement for each substance:

ALC = Alcohol TOB = Tobacco MAR = Marijuana
OTH1 = Other Drug 1 OTH2 = Other Drug 2

CIGARETTES:

One Standard Cigarette is Equal to:

ALCOHOL:

One Standard Drink is Equal to:

One 12 oz can/bottle of beer

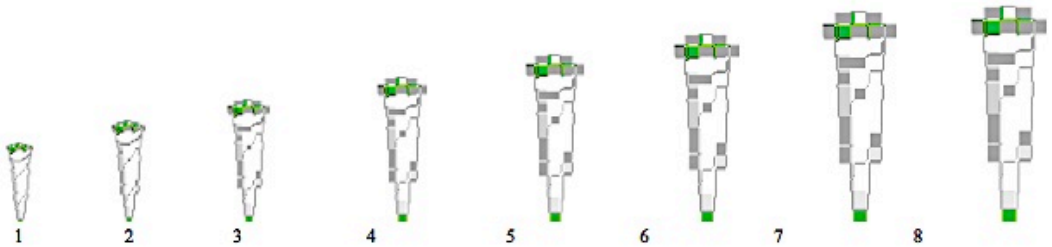
One 5 oz glass of regular (12%) wine

1 ½ oz of hard liquor (e.g. rum, vodka, whiskey)

1 mixed or straight drink with 1 ½ oz hard liquor

MARIJUANA AND OHER SUBSTANCES:

Use the Following Examples to Describe the Amount of your Current Use:



OHER SUBSTANCES INCLUDE:

____ **Sedatives-hypnotics-anxiolytics:** Quaalude, barbiturates, valium, xanax, klonapin, ativan, lunesta, ambien, or other
____ **Stimulants:** Amphetamine, speed, metamphetamine, dextroamphetamine, methylphenidate, prescription diet pills, or other
____ **Opioids:** Heroin, morphine, opium, methadone, codeine, oxycodone, hydrocodone, gentanyl, meperidine, hydromorphone
____ **Cocaine:** Snorting, IV, freebase, crack, speedball, or other
____ **Hallucinogens/PCP:** LSD (acid), mescaline, peyote, mushrooms, MDMA, PCP, ketamine, or other
____ **Other:** Steroids, solvenets, gases, nitrites, over-the-counter sleep or diet pills

Timeline Follow-Back (TLFB)

MONDAY			TUESDAY			WEDNESDAY			THURSDAY			FRIDAY			SATURDAY			SUNDAY		
Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount
ALC			ALC			ALC			ALC			ALC			ALC			ALC		
TOB			TOB			TOB			TOB			TOB			TOB			TOB		
MAR			MAR			MAR			MAR			MAR			MAR			MAR		
OTH1			OTH1			OTH1			OTH1			OTH1			OTH1			OTH1		
OTH2			OTH2			OTH2			OTH2			OTH2			OTH2			OTH2		
Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount
ALC			ALC			ALC			ALC			ALC			ALC			ALC		
TOB			TOB			TOB			TOB			TOB			TOB			TOB		
MAR			MAR			MAR			MAR			MAR			MAR			MAR		
OTH1			OTH1			OTH1			OTH1			OTH1			OTH1			OTH1		
OTH2			OTH2			OTH2			OTH2			OTH2			OTH2			OTH2		
Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount
ALC			ALC			ALC			ALC			ALC			ALC			ALC		
TOB			TOB			TOB			TOB			TOB			TOB			TOB		
MAR			MAR			MAR			MAR			MAR			MAR			MAR		
OTH1			OTH1			OTH1			OTH1			OTH1			OTH1			OTH1		
OTH2			OTH2			OTH2			OTH2			OTH2			OTH2			OTH2		
Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount
ALC			ALC			ALC			ALC			ALC			ALC			ALC		
TOB			TOB			TOB			TOB			TOB			TOB			TOB		
MAR			MAR			MAR			MAR			MAR			MAR			MAR		
OTH1			OTH1			OTH1			OTH1			OTH1			OTH1			OTH1		
OTH2			OTH2			OTH2			OTH2			OTH2			OTH2			OTH2		
Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount	Sub	Freq.	Amount
ALC			ALC			ALC			ALC			ALC			ALC			ALC		
TOB			TOB			TOB			TOB			TOB			TOB			TOB		
MAR			MAR			MAR			MAR			MAR			MAR			MAR		
OTH1			OTH1			OTH1			OTH1			OTH1			OTH1			OTH1		
OTH2			OTH2			OTH2			OTH2			OTH2			OTH2			OTH2		

Appendix E

Structural Clinical Interview of DSM-IV-TR Disorders (SCID-I/NP) Summary Page

SCID-I/NP (for DSM-IV-TR) (First et al., 2007) Modified Summary Diagnostic Sheet i

Clinicians Ratings and Diagnoses

ABSENT		MILD		MODERATE		SEVERE		VERY SEVERE
0----------	1	---------2---------	3	---------4---------	5	---------6---------	7	----------8
None		Slightly disturbing/not really disabling		Definitely disturbing/ disabling		Markedly disturbing/ Disabling		Very severely disturbing/ disabling

CURRENT DSM-IV DIAGNOSES

	PRINCIPAL DIAGNOSIS	SEVERITY RATING	AGE OF ONSET	ADDITIONAL DIAGNOSES	SEVERITY RATING	AGE OF ONSET
AXIS I:						
	Panic Attack History? (F1a) Yes No	Age at first PA				
	Uncued Panic Attack? (F1) Yes No					
	Criterion A trauma? (F103a) Yes No					
	Number of different trauma types? #____ List:					
AXIS II:				Age at Time of Trauma		
AXIS III:						
AXIS IV:	Acute:		Enduring:			
	Number of Stressors (from box below):					
GAF:	Present:					
CGI-S:	Present:					

DSM-IV Axis IV: Psychosocial and Environmental Problems

Check:

___ **Problems with primary support group (childhood, adult, parent-child).** Specify: _____

___ **Problems related to the social environment.** Specify: _____

___ **Educational problems.** Specify: _____

___ **Occupational problems.** Specify: _____

___ **Housing problems.** Specify: _____

___ **Economic problems.** Specify: _____

___ **Problems with access to health care services.** Specify: _____

___ **Problems related to interaction with the legal system/crime.** Specify: _____

___ **Other psychosocial problems.** Specify: _____

Structural Clinical Interview of DSM-IV-TR Disorders (SCID-I/NP) Summary Page

SCID-I/NP (for DSM-IV-TR) (First et al., 2007) Modified Summary Diagnostic Sheet ii

DSM-IV Axis V: Global Assessment of Functioning Scale

Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment in functioning due to physical (or environmental) limitations

CODE (**Note:** Use intermediate codes when appropriate, e.g., 45, 68, 72).

NP105

100 | 91 **Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his/her many positive qualities. No symptoms.**

90 | 81 **Absent or minimal symptoms** (e.g., mild anxiety before an exam); **good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns** (e.g., an occasional argument with family members).

80 | 71 **If symptoms are present, they are transient and expectable reactions to psychosocial stressors** (e.g., difficulty concentrating after family argument); **no more than slight impairment in social, occupational, or school functioning** (e.g., temporarily falling behind in school work).

70 | 61 **Some mild symptoms** (e.g., depressed mood and mild insomnia) **OR some difficulty in social, occupational, or school functioning** (e.g., occasional truancy, or theft within the household), **but generally functioning pretty well, has some meaningful interpersonal relationships.**

60 | 51 **Moderate symptoms** (e.g., flat affect and circumstantial speech, occasional panic attacks) **OR moderate difficulty in social, occupational, or school functioning** (e.g., few friends, conflicts with peers or coworkers).

50 | 41 **Serious symptoms** (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) **OR any serious impairment in social, occupational, or school functioning** (e.g., no friends, unable to keep a job).

40 | 31 **Some impairment in reality testing or communication** (e.g., speech is at times illogical, obscure, or irrelevant) **OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood** (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school).

30 | 21 **Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment** (e.g., sometimes incoherent, acts grossly inappropriate, suicidal preoccupation) **OR inability to function in almost all areas** (e.g., stays in bed all day; no job, home, or friends).

20 | 11 **Some danger of hurting self or others** (e.g., suicide attempts without clear expectation of death, frequently violent, manic excitement) **OR occasionally fails to maintain minimal personal hygiene** (e.g., smears feces) **OR gross impairment in communication (e.g., largely incoherent or mute).**

10 | 1 **Persistent danger of severely hurting self or others** (e.g., recurrent violence) **OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death.**

0 **Inadequate information.**

Clinical Global Impression Scale (Severity)

SEVERITY OF ILLNESS

Considering your total clinical experience with this particular population, how mentally ill is this participant at this time?

0 = Not assessed
1 = Normal, Not At All Ill
2 = Borderline Mentally Ill
3 = Mildy Ill
4 = Moderately Ill
5 = Markedly Ill
6 = Severely Ill
7 = Among the Most Extremely Ill Participants

Appendix F

Anxiety Sensitivity Index-3 (ASI-3)

Please circle the number that best corresponds to how much you agree with each item. If any items concern something that you have never experiences (e.g. fainting in public) answer on the basis of how you think you might feel *if you had* such an experience. Otherwise, answer all items on the basis of your own experience. Be careful to circle only one number for each item and please answer all items.

		Very little	A little	Some	Much	Very much
1.	It is important for me not to appear nervous.	0	1	2	3	4
2.	When I cannot keep my mind on a task, I worry that I might be going crazy.	0	1	2	3	4
3.	It scares me when my heart beats rapidly.	0	1	2	3	4
4.	When my stomach is upset, I worry that I might be seriously ill.	0	1	2	3	4
5.	It scares me when I am unable to keep my mind on a task.	0	1	2	3	4
6.	When I tremble in the presence of others, I fear what people might think of me.	0	1	2	3	4
7.	When my chest feels tight, I get scared that I won't be able to breathe properly.	0	1	2	3	4
8.	When I feel pain in my chest, I worry that I'm going to have a heart attack.	0	1	2	3	4
9.	I worry that other people will notice my anxiety.	0	1	2	3	4
10.	When I feel "spacey" or spaced out I worry that I may be mentally ill.	0	1	2	3	4
11.	It scares me when I blush in front of people.	0	1	2	3	4
12.	When I notice my heart skipping a beat, I worry that there is something seriously wrong with me.	0	1	2	3	4
13.	When I begin to sweat in a social situation, I fear people will think negatively of me.	0	1	2	3	4
14.	When my thoughts seem to speed up, I worry that I might be going crazy.	0	1	2	3	4
15.	When my throat feels tight, I worry that I could choke to death.	0	1	2	3	4
16.	When I have trouble thinking clearly, I worry that there is something wrong with me.	0	1	2	3	4
17.	I think it would be horrible for me to faint in public.	0	1	2	3	4
18.	When my mind goes blank, I worry there is something terribly wrong with me.	0	1	2	3	4

Appendix G

Pre and Post-Challenge Self-Report Form

***Includes*:**
Subjective Units of Distress (SUDS) *[top left]*
Diagnostic Symptom Questionnaire, Modified (DSQ) *[right column]*
Questionnaire of Smoking Urges – Brief (QSU-B) *[bottom left]*

What level of distress, discomfort, anxiety, or fear are you experiencing CURRENTLY?

☐ 0 (none) – 100 (extreme)

Please rate the extent to which you CURRENTLY agree/disagree with each statement:

0 (not at all) – 100 (Completely)

___ I have an urge for a cigarette
___ A cigarette would taste good now
___ All I want right now is a cigarette
___ Smoking would make me less nervous
___ I am going to smoke as soon as possible
___ I have a desire for a cigarette right now
___ Smoking would make me less depressed
___ I would do almost anything for a cigarette now
___ If it were possible, I probably would smoke now
___ Smoking would make me less anxious
___ Nothing would be better than smoking a cigarette right now
___ I could control things better right now if I could smoke

Please CHECK BOX if you are CURRENTLY experiencing any of the following:

☐ Chest tightness or chest pain
☐ Faintness
☐ Dizziness, lightheadedness, unsteadiness
☐ Choking
☐ Breathlessness or smothering sensations
☐ Sweating
☐ Numbness or tingling in face or extremities
☐ Hot flushes or cold chills
☐ Fear of dying
☐ Feeling unreal or in a dream
☐ Fear of losing control
☐ Fear of going crazy
☐ Sensation of panic or fear
☐ Pounding or racing heart
☐ Trembling or shaking
☐ Nausea or abdominal distress
☐ Headache
☐ Panic attack

ID#: _____
Card ___ of ___

Note: On the QSU-B, two items were added to tap anxiety-related urges ("Smoking would make me less nervous" and "Smoking would make me less anxious"). On the DSQ, items were coded as Yes/No versus severity, and two one item was added to tap pain-related symptoms ("Headache").

Appendix H

Smoking Topography Instruction for Clinical Research Support System (CReSS) Pocket

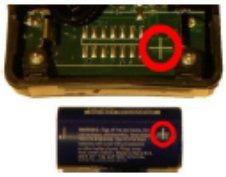
CReSS Pocket Quick Reference Guide

Install/Replace Battery:

1. Remove cover from Battery Compartment.

2. Insert Battery.

   Ensure the battery is fully inserted and the polarity is correct.



3. Replace cover on Battery Compartment.

Insert Disposable Mouthpiece:

1. Remove mouthpiece from protective wrapping.
2. Press mouthpiece onto CReSS Pocket.

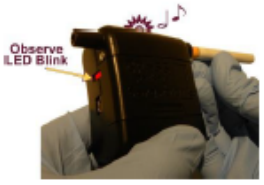
   Ensure snug fit.

P/N: 10937011

CReSS Pocket Quick Reference Guide (Continued)

Insert Cigarette:

1. Insert Cigarette fully into the nozzle.
2. Listen for one long beep and one short higher pitched beep.
3. Watch for red LED blink.



CReSS Pocket beeps and indicators:

- **Inserting Cigarette:** Long beep followed by a short, Higher pitched beep and red LED blink indicates the cigarette has been recognized in the nozzle.
- **Puffing on Cigarette:** Green LED lights while a puff is being detected.
- **Removing Cigarette:** Long beep followed by a short, lower pitched beep and orange LED blink indicates the cigarette is confirmed to have been removed and the cigarette information has been saved.
- **Error Condition:** One long low beep together with a red LED blink indicates an error has occurred. Try a fresh battery.
- **Contact the study administrator** if an error condition continues to occur, or if any other condition not mentioned above occurs.

Warning!

- Do not use the device while driving or operating machinery.
- Do not drop the device.
- Do not get the device wet.
- Do not share the device with other smokers.
- Do not open the device or battery cover (Unless the battery has become dislodged or needs replacing).
- Do not put out cigarettes while they are in the device.

Appendix I

Debriefing Form

PANIC-RELEVANT SITUATIONAL ANXIETY AND SMOKING MOTIVATION
DEBRIEFING FORM – Room Air (Control condition)

The purpose of this research study is to learn how daily smokers exposed to laboratory-induced abrupt physical sensations (e.g., rapid heart rate, sweaty palms, and lightheadedness) will respond in regards to smoking behavior. In this study, there was a 50% of being randomly assigned to take one single vital capacity breath of either (1) 35% carbon dioxide-enriched air, or (2) compressed room air.
You were randomly assigned to the ROOM AIR CONDITION. This means, when completing the single inhalation of gas mixture, you took a breath of regular room air. This compressed room air consists of oxygen (21%) and nitrogen (79%). Breathing in the room air does not result in any different physical feelings besides those you might normally experience after taking a full breath.

This research project is conducted by Samantha G. Farris, M.A. and Michael J. Zvolensky, Ph.D. from the Department of Psychology at the University of Houston. This is a student-based doctoral research project that is being conducted under the supervision of Michael Zvolensky, Ph.D. If you have any questions, please feel free to contact Samantha Farris at 713-743-8056 or Dr. Zvolensky at 713-743-8595.

PANIC-RELEVANT SITUATIONAL ANXIETY AND SMOKING MOTIVATION
DEBRIEFING FORM – Carbon Dioxide-Enriched Air (Active condition)

The purpose of this research study is to learn how daily smokers exposed to laboratory-induced abrupt physical sensations (e.g., rapid heart rate, sweaty palms, and lightheadedness) will respond in regards to smoking behavior. In this study, there was a 50% of being randomly assigned to take one single vital capacity breath of either (1) 35% carbon dioxide-enriched air, or (2) compressed room air.
You were randomly assigned to the CARBON DIOXIDE-ENRICHED AIR CONDITION. This means, when completing the single inhalation of gas mixture, you took a breath of gas mixture that contained a greater concentration of CO_2 than usual room air. This compressed gas mixture consisted of carbon dioxide (35%) and oxygen (65%). During and after the procedure, you may have experienced breathlessness, mild tachycardia, dizziness, dry mouth, feeling sweaty, fainting, and/or a panic attack. These sensations are simply indicators of physiological arousal, and are likely sensations you have experienced before in your life. For example, during exercise, it is common to experience many of these same sensations. Just like when exercising, there are no long-term adverse effects from taking a single inhalation of CO_2-enriched air. In fact, this is a standardized procedure that has been used successfully and safely with thousands of participants.

This research project is conducted by Samantha G. Farris, M.A. and Michael J. Zvolensky, Ph.D. from the Department of Psychology at the University of Houston. This is a student-based doctoral research project that is being conducted under the supervision of Michael Zvolensky, Ph.D. If you have any questions, please feel free to contact Samantha Farris at 713-743-8056 or Dr. Zvolensky at 713-743-8595.

Appendix J

Breathing Apparatus Schematic