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A Puff Topography Biofeedback Paradigm to Reduce Stress-Precipitated Smoking Reinforcement

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STUDY INFORMATION

- **Title of Project:** Development of a Puff Topography Biofeedback Paradigm to Reduce Smoking Reinforcement

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1.0 Research Design

1.1 Purpose/Specific Aims

A. Objectives

In the **current study** we propose a proof-of-concept experimental test of PTBT and its ability to modify stress-precipitated puff topography, and in turn, acute smoking reinforcement. Specifically, emotionally-distressed daily smokers (*N*=88) will be randomized to either PTBT or Control (Sham) Training. After the training day, participants will complete a stress-precipitated smoking trial where they will undergo an acute laboratory stress induction and smoke using the assigned training. We propose the following specific aims:

Aim 1 (Target Engagement): To evaluate PTBT as a strategy to "engage" (modify) puff topography -- a putative biobehavioral target of smoking reinforcement. Following stress-induction, we hypothesize that PTBT, compared to Control, will result in significant changes in puff topography, namely: (a) smaller average puff volume (mL), (b) shorter average puff duration (sec), and (c) longer inter-puff intervals (sec).

Aim 2 (Acute Clinical Outcomes): To evaluate whether PTBT produces acute clinical changes in stress-precipitated smoking reinforcement. Following stress-precipitated smoking trial, we hypothesize that PTBT, compared to Control, will result in significantly less acute smoking reinforcement, indexed by: (a) greater reductions in expenditures and consumption of hypothetical cigarettes smoked within the same context (e.g., PTBT or ad-lib) and (b) lower self-report cigarette satisfaction/reward (self-report) post-smoking.

Aim 3 (Explore Mechanisms of PTBT). To explore cardiac vagal control (CVC) as a biological mechanism of PTBT. We will explore whether there are differences in CVC (respiratory sinus arrythmia) between smokers in PTBT compared to Control. We hypothesize that PTBT (vs Control), will produce greater reductions in CVC, as compared to baseline CVC, during stress-precipitated smoking.

This is the first study to test whether an integrated theoretically-based biobehavioral paradigm can modify puff topography and subsequent smoking reinforcement. This addresses the need for ***innovative approaches to decrease acute smoking reinforcement***. If associated with reduced smoking reinforcement, this paradigm could inform pre-cessation efforts designed to better prepare emotionally-distressed smokers for quitting.

B. Hypotheses / Research Question(s)

Smoking among adults with emotional distress is a recognized tobacco health disparity. Smokers with emotional distress are particularly vulnerable to **smoking reinforcement** due to various biopsychological factors that contribute to deficits in emotion regulation and reward processing, which undermine cessation efforts. Better preparing smokers for cessation (prior to a quit attempt) is essential to improve outcomes in emotionally-distressed smokers who require additional coping strategies to address affect-driven smoking.

A critical driver of smoking reinforcement is HOW a cigarette is smoked (i.e., puff topography). The timing and intensity of one's puffing can titrate or maximize the cigarette's rewarding effect. Our group has identified **puff topography as a novel biobehavioral "target" mechanism of smoking reinforcement** in emotionally-distressed smokers. We have found that topographical components of puffing (e.g., shorter inter-puff intervals, longer puff durations) are linked to heightened smoking reinforcement in emotionally-distressed smokers, but not in control smokers. Emotionally-distressed smokers also take larger and more rapid *initial* puffs at the start of a cigarette – maximizing immediacy and intensity of reward.

Although largely considered a behavioral phenotype of smoking reinforcement, inherent in puffing behavior are corresponding changes in cardiorespiratory parameters (e.g., cardiac vagal control [CVC])

that may promote self-regulation and reduce craving. We recently proposed an integrated psychophysiological model of emotional distress and smoking, wherein impaired smoker CVC not only implicates physiological homeostasis, but also influences addiction-relevant processes, including impaired higher-order cognitive processes needed for self-regulation and psychological functioning (e.g., reduced anxiety and stress). Yet, under certain time-sensitive contexts (e.g., stress), emotionally-distressed smokers may puff in a way that *enhances* CVC, resulting in acute self-regulatory benefits, and in turn paradoxically amplify the reinforcing value of each puff. Thus, a biobehavioral intervention that could "engage" (modify) puff topography has the strong potential to reduce the reinforcing value of cigarettes in emotionally-distressed smokers.

Informed by our biobehavioral framework, we developed a **Puff Topography Biofeedback Training (PTBT)**, a modified application of heart rate variability biofeedback to change puff topography. PTBT is a 30-min training that teaches smokers to adjust their puffing to a pace that is designed to minimize CVC in order to attenuate acute self-regulatory, emotional, and craving-reductions associated with smoking. Thus, PTBT is a theoretically-informed, well-specified paradigm designed to directly target puff topography – a mechanism of smoking reinforcement, which directly aligns with the NIH's Science of Behavior Change (SOBC) and experimental therapeutics initiatives.

1.2 Research Significance

1. This is the first study to develop and test a **puff topography biofeedback training (PTBT)**. Participants will receive real-time feedback regarding puffing (e.g., when to inhale/exhale, breath duration, and inter-puff interval). PTBT was designed based on an integrated theoretical behavioral and psychophysiological model of smoking reinforcement, and thus aims to address learning-based behavioral aspects of puffing (by promoting extinction learning/new learning), in addition to altering a physiological mechanism of puffing (CVC). Therefore, PTBT is a promising theoretically-based intervention, that if supported by this proposed experimental study, would be well-positioned for progressive translation into intervention efficacy testing, consistent with NIH initiatives.[49–51]

2. There is increasing recognition that preparing smokers for cessation (prior to a quit attempt) is essential to improve outcomes,[52] particularly in smokers with emotional distress who may require additional coping strategies to address affect-driven smoking.[53] If PTBT is associated with reduced smoking reinforcement, this paradigm could inform treatment effects designed to prepare emotionally-distress smokers for quitting.[52] Notably, existing interventions that successfully attenuate *pre-cessation* smoking reinforcement are primarily pharmacological in nature (e.g., nicotine replacement,[54] varenicline[55]), while behavioral interventions targeting smoking reinforcement are generally used during the *post-cessation* period (e.g., contingency management,[56] behavioral activation/behavioral economic-based approaches[57]). Thus, the current study would address a gap in the provision of evidence-based behavioral interventions that target pre-cessation smoking reinforcement, which has the **potential to improve cessation outcomes in vulnerable smokers (emotionally-distressed).**

1.3 Research Design and Methods

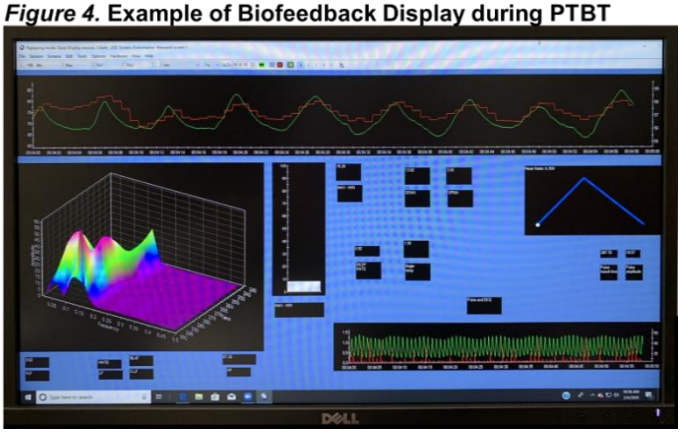
This study is an experimental, between-subjects test of biofeedback puff topography training (relative to sham training) in reducing stress-induced smoking reinforcement. Specifically, combustible cigarettes smokers (n = 80) will be randomized to receive puff topography biofeedback (n = 40) or sham training (n = 40) prior to exposure to a laboratory stressor paradigm. Stress-precipitated smoking behavior will be assessed directly after the stressor task, wherein participants will be given the instructions to smoke utilizing their assigned puff training. Smoking reinforcement will be measured using a multi-method approach, including self-report, psychophysiology, and behavioral indices (see Measures). Outcome variables include: (1) puff topography indices (averages, trajectory) and (2) reinforcer pathology indices (delay reward discounting, cigarette demand, urges, affect, and smoking enjoyment).

A. Research Procedures

See **Figure 3** for an overview of the experimental procedures. Participants will complete a telephone interview to verify key exclusion/inclusion criteria. Participants who appear to be eligible will be scheduled for a remote assessment session. If eligible following the remote session, participants will be scheduled for two in-person visits on consecutive days. For standardization (internal validity), all in-person visits will be scheduled to occur ~4hrs following the estimated time of participants' first cigarette of the day. Participants will be informed that they will smoke their second daily cigarette during the lab visit and instructed to avoid behaviors that may confound CVC (e.g., vigorous physical activity or consumption of caffeine within 2 hr; alcohol use within 12 hr).

Baseline Assessment (Remote Visit): Staff will obtain written informed consent, after which participants will complete an eligibility assessment (see **Table 1**). They will then complete the baseline assessment battery (see **Table 1**).
Training Visit (V1): Participants will be screened for final eligibility criteria (e.g., CO level) upon arrival. Assessment of self-reported affective and smoking related variables will be conducted via self-report at various times throughout the session (see the orange stars on **Figure 3**). Participants will be attached to physiological recording equipment throughout the session, including blood pressure volume, ECG, and respiration. When they smoke (in a ventilated smoking room), smoking topographical indices will be recorded using the handheld *Clinical Research Support System* (CReSS micro; described in **C.7**).
Training Conditions: Eligible participants will then be **randomized** to either the PTBT or Control (Sham Training) and informed that the training will be used in V2. Block randomization will be used with biological sex (female vs. male) as a blocking variable, as sex is a known factors that influences puff topography and reinforcement.[36,58,59] Both trainings will be time-matched.
PTBT: PTBT is designed to decrease puff topography influences on smoking reward informed by heart rate variability biofeedback paradigms. Participants will be taught how to puff in a way that may feel different from their usual puffing behavior. Participants will be hooked up to a respiratory band, electrocardiogram (ECG) electrodes, and a blood volume sensor finger cuff (pulse plethysmograph) while seated in a ventilated smoking room. Following a 5-min adaptation period, they will be introduced to a breathing pacer (EZ-Air Plus; Biofeedback Foundation of Europe), which is integrated with the *Thought Technology* biofeedback interface (**Figure 4**), and taught how to use the pacer to guide the pace of their inhalation and exhalation. Participants will be taught to breathe steadily as a white ball (pacer) proceeds up the incline, and exhale as they follow the ball on the decline. They will first practice breathing normally with the pacer to ensure they understand the procedures. Then, participants will smoke following the pacer while using the CReSS micro device for a 5-min phase. To address reinforcement immediacy and intensity, the pacer will be set to a 2 sec inhalation matched with a 2 sec exhalation, for a 4 sec cycle, such that *puffing* maps onto a respiration pace of 15 breathes/min. This pace should minimize CVC (**Figure 2, right**). To address reinforcement reliability, the inter-puff-interval will vary between 4 secs and 30 secs as the experimenter will instruct the participant when to puff. In an adjacent room, the experimenter will be able to monitor real-time displays of physiological data and observe the session via video

Figure 4. **Example of Biofeedback Display during PTBT**



conferencing system and provide additional training instructions, as needed. Participants will then complete a 5-min rest period.

Control: In the control condition, i.e. sham training, participants will be hooked up to the same physiological monitoring equipment and complete the same 5-min adaptation period. They will then be instructed to smoking with the CreSS device while focusing their attention during a 5-min vanilla task.[66] The task involves attending to a computer screen and counting the number of times a designated color rectangle occupies the screen. Different colored rectangles are presented one at a time, for 500ms every 10 sec, for a total of 5-min. The full color spectrum is reflected and participants are told to make their best guess about color match. Participants are asked at the end to report the number of times the designated color was observed and are not given any feedback or incentive for correct color counts. No instructions will be provided about puffing behavior. Participants will then complete a 5-min rest period.

Stress-Precipitated Smoking Visit (V2). Participants will return to the laboratory on the following day, at the same time, and be provided the same pre-visit instructions. Participants will be hooked up with physiological monitoring assessment while seated in the smoking lab. Next, a new consent will be presented, introducing them to the Trier Social Stress Test (TSST), which has been used in our prior studies (R03DA041556; F31DA043934). The TSST is a well-validated laboratory paradigm that reliably induces psychological and physiological stress,[67–69] including smoking craving.[70,71] While presenting the consent form, the experimenter will explain that they will have to prepare for and deliver a speech about why they are the best candidate for a job of their choosing. To maximize anticipatory stress, participants will be introduced to a male and female confederate who will presumably observe and evaluate the speech.[72] After a 2-min preparation period, they will be shown a video example of a speech where a participant receives negative/neutral feedback from confederates, which serves to provide participants with additional information regarding the stressful nature of the task. In our studies, this preparation/anticipatory period produces medium-large increases in negative affect in smokers (Cohen's *d* = 0.60-1.30). After the preparation period, participants are told that the confederates need additional time to trouble-shoot the camera system, and as a result they will be able to smoke before delivering the speech. Participants will be instructed that they will practice the training they learned (PTBT or Control) while they smoke, and will complete the same 5-min adaptation period pre-smoking and 5-min rest period post-smoking. The stress-precipitated smoking trial will be followed by the post-smoking assessments. Participants will then be unhooked from the physiological monitoring equipment and informed that they do not actually have to give the speech. The research staff will proceed to notify participants that they have completed the study visit. Research staff will thank participants for all of their time and effort, provide them with their respective compensation, and encourage them to contact the study staff via email or phone (contact information listed on the participant's previously provided consent form) should they have any additional questions or concerns regarding their participation.

B. Data Points

Group differences will be examined between biofeedback puffing vs. shame in response to V2 stress-precipitated smoking through measures of: (1) puff topography indices (puff volume, duration, IPI), (2) self-report assessments and (3) physiological indices of emotional distress (cardiac vagal control).

C. Study Duration

This study comprises one remote session of up to two hours, and two in-person visits over the course of two days, with a duration of up to 2 hours for V1 and V2 respectively.

D. Endpoints

The endpoint of the study is post-V2, once participants have completed the experimental design of the second visit (assuming eligibility through V1).

1.4 Preliminary Data

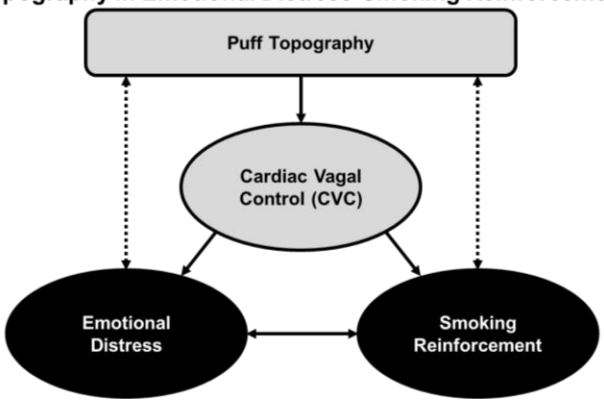
1. Smoking among adults with emotional distress is a recognized tobacco health disparity.[1–3] Despite reductions in the prevalence of smoking over the past fifty years (currently ~15% in US),[4,5] smoking prevalence in individuals with emotional distress (i.e., anxiety and mood disorders) is disproportionally higher (38%-45%)[2,6,7] and has remained relatively stable over recent years.[2] Smokers with emotional distress (vs. those without) are less likely to quit smoking successfully[8–13] in large part because of the **reinforcing effects of cigarettes (i.e., smoking reinforcement).**[14,15] Incentive sensitization theory[30] proposes three core processes that underlie drug reinforcement: liking, wanting, and learning. Smoking is posited to be initially motivated by the *positive* reinforcing effects of cigarettes/nicotine (i.e., "*liking*": pleasure, satisfaction) and in turn, appetitive and urgency ("*wanting":* craving) motivation for cigarettes develops due to the reliable, immediate rewarding effect.[16] Over time, smoking is maintained by the *negative* reinforcing effects (i.e., "*learning*": relief from aversive states and stress).[15,17] Smokers with emotional distress are particularly vulnerable to smoking reinforcement due to various biopsychological factors that contribute to deficits in emotion regulation and heightened reward processing.[18–25] Thus, there is an ongoing need for ***innovative approaches to decrease smoking reinforcement*** to improve cessation success in this vulnerable group.

2. A critical aspect of smoking reinforcement is the reliability, intensity, and immediacy of its rewarding effect.[26] We propose that these aspects of smoking reinforcement are particularly valuable to emotionally-distressed smokers who rely on cigarettes as a go-to "quick fix" strategy during certain time-sensitive contexts (e.g. acute distress, or initial smoking abstinence). For example, modification of WHEN they smoke (e.g., when stressed) and HOW they smoke their cigarette provides smokers with the ability to easily titrate/maximize the timing and intensity of the cigarette's rewarding effect. These aspects of smoking behavior are referred to as "**puff topography**", which can be indexed in many ways including *puff volume* (amount of carbon monoxide [CO] inhaled, mL), *puff duration* (length of time for each inhalation, sec), and *inter-puff interval* (time between inhalations, sec). Indeed, evidence indicates that both trait and state distress are related to alterations in smoking behavior. For example, smokers with emotional distress (compared to those without) smoke in a way that maximizes intensity (e.g., larger inhalations while puffing).[27,28]

3. Puff topography is a novel "target" of smoking reinforcement in emotionally-distressed smokers. Although puff topography has been historically studied in the context of tobacco control (i.e., reducing CO or nicotine exposure),[29–33] we propose ***puff topography as a biobehavioral target*** of smoking reinforcement. We have found that topographical components of puffing (e.g., shorter inter-puff intervals, longer puff durations) are linked to heightened smoking reinforcement (wanting, liking) in emotionally-distressed smokers but not control smokers (small-medium effects).[34] We have also identified several cognitive-affective aspects of emotional distress (e.g., distress intolerance, negative urgency) that are related to alterations in ad-libitum and stress-precipitated puff topography.[35–38] Notably, we have moved beyond the *status quo* in our approach to this work by examining puff-to-puff changes (time-varying) during smoking rather than relying on the established (normative) methods of examining average puff parameters.[28,39,40] This method provides precision in understanding time-sensitive aspects of puff topography. For example, we found that emotionally-distressed smokers (vs. non-distressed) take larger and more rapid initial puffs at the start of a cigarette (i.e., reward immediacy and intensity) and demonstrate more persistent, stable puffs over the course of the cigarette (i.e., reward reliability).[35] Together, our data indicate that puff topography is a well-specified, precise, time-sensitive mechanism of smoking reinforcement. If puff topography can be "engaged" via intervention (modifiable), it would have the strong potential to reduce the reinforcing value of cigarettes in emotionally-distressed smokers.

4. An integrated psychophysiological framework to understanding puff topography (Figure 1).

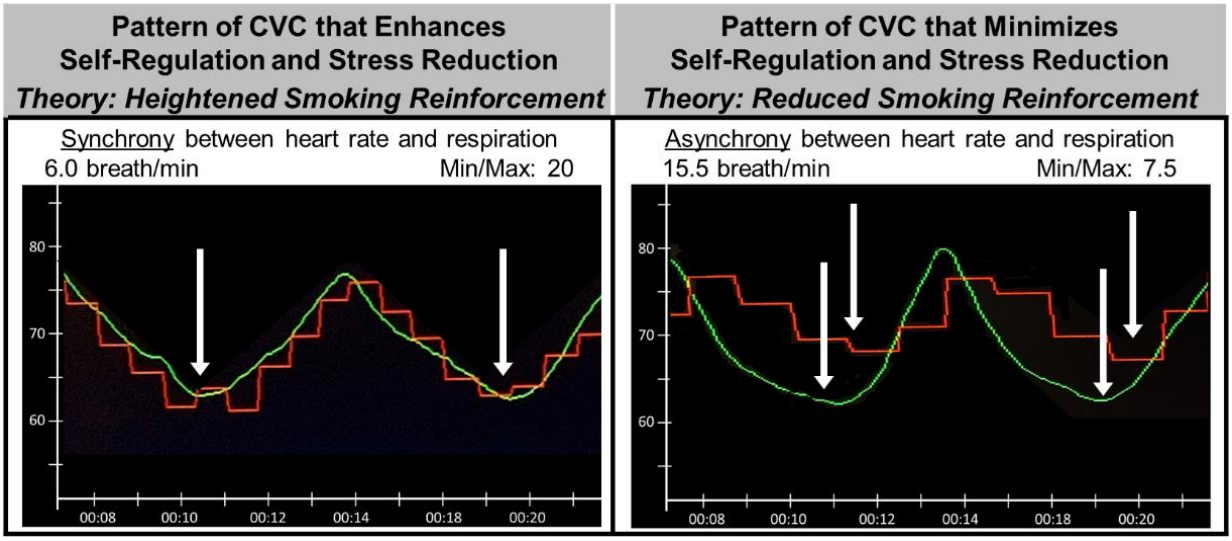
Figure 1. **CVC as a Theorized Mechanism of Puff Topography in Emotional Distress-Smoking Reinforcement**



Inherent in puffing behavior are corresponding changes in cardiorespiratory parameters, such as **cardiac vagal control (CVC),** i.e., vagus nerve mediated regulation of the heart rate. Changes in heart rate that occur during inhalation and exhalation (i.e., respiratory sinus arrhythmia [RSA]) reflect CVC. When breathing is slowed to a pace that maximizes oscillations in heart rate and blood pressure (increased CVC),[41] there are numerous clinical benefits,[42] including improved self-regulation, mediated by changes in prefrontal-subcortical inhibitory circuits.[43,44] Indeed, improved CVC promotes more flexible and adaptive responding to the environment and less hypervigilance to threat.[45] In accord, we recently proposed an integrated psychophysiological model of emotional distress and smoking[46] wherein impaired CVC observed in smokers is not only implicated in physiological homeostasis, but also in addiction-relevant processes, including higher-order cognitive processes needed for self-regulation[46] and psychological functioning (e.g., distress).[43] Although slowed breathing to improve CVC is often leveraged for clinical benefit, we posit that under certain time-sensitive contexts (e.g., stress), emotionally-distressed smokers puff in a style that mimics slowed breathing – maximizing oscillations in cardiorespiratory systems and *acute* self-regulatory benefits – which in turn, paradoxically enhance smoking reinforcement. Thus, we propose that puff topography is not only a behavioral determinant of smoking reinforcement, but is also physiologically-based (CVC), and together drive the reinforcing value of each puff.

5. Puff Topography Biofeedback Training (PTBT) as a novel strategy for "target engagement". CVC's effect on self-regulation has been leveraged in biobehavioral interventions, like heart rate variability biofeedback, which has been used to promote reductions in emotional distress[43] and substance craving.[47]

***Figure 2.* CVC synchrony (left) vs asynchrony (right)**



Heart rate variability biofeedback involves instructing individuals to slow their respiration rate to around 6.0 breaths/minute,[41] by following a breathing pacer and/or viewing real-time respiration and heart rate wave forms, with the goal of achieving wave form *synchrony.* See **Figure 2** for an illustration of how breathing changes can influence CVC (i.e., Min/Max) by creating synchrony vs. asynchrony between heart rate (red)

and respiration (green), and in turn theoretically influence reinforcement. Aligned with our proposed framework, we developed **Puff Topography Biofeedback Training (PTBT)**, a modified application of heart rate variability biofeedback, to change puff topography. Specifically, PTBT involves teaching emotionally-distressed smokers to adjust their puffing to a pace that produces *asynchrony* between heart rate and respiration, in order to *attenuate* CVC and self-regulatory, emotional, and craving-reductions associated with smoking. Aligned with the NIH's Science of Behavior Change inititiave[48] and experimental medicine approach,[49] in the **current study** we propose to test whether the **identified target (i.e., puff topography)** can be **experimentally engaged** via a well-specified intervention (PTBT).

1.5 Sample Size Justification

The effects of PTBT on the outcomes of interest are unclear given that there are no prior data. However, our studies of differences in puff topography in the context of acute stress vs. control produce medium-sized effects (*d*s=0.46-0.54).[36] Thus, we believe a medium size effect is clinically meaningful, and therefore, the sample size was calculated to detect a medium effect size difference across training groups. Mean Difference**.** For linear regression models, a sample size of 58 is sufficient to detect a medium effect size (f^2=.143 [R^2 change/1-cumulative R^2) = .143) with 80% power and alpha of 0.05 via multiple regression analyses with up to 10% variance explained by the main predictor (training group) and up to 5 other covariates (e.g., sex, number of cigarettes per day, depressive/anxiety symptom severity, corresponding baseline values, and CO boost) accounting for up to additional 20% of the anticipated variance. Without any covariates in the model, a sample size of 73 is needed to detect a medium effect size (f^2=.11) across training groups (explaining 10% variance). Mediation (Aim 3). Statistical power for a mediation analysis with a single mediator was estimated using Monte Carlo power analysis for indirect effects.[86] The inclusion of mediation analyses led us to increase our sample size to n=80, which is sufficient for detection of indirect effects with a proportion-mediated effect size of 50%[87] (correlations between predictor, mediators, and outcome, *r* =.40-.43) with 80% power and alpha of 0.05. which we deemed sufficient given the exploratory nature of these analyses. Taken together, to ensure analyses are adequately powered, we propose a sample of 88 (allowing for ~8-10% attrition) with a final intended sample of 80 completers (40 per condition).

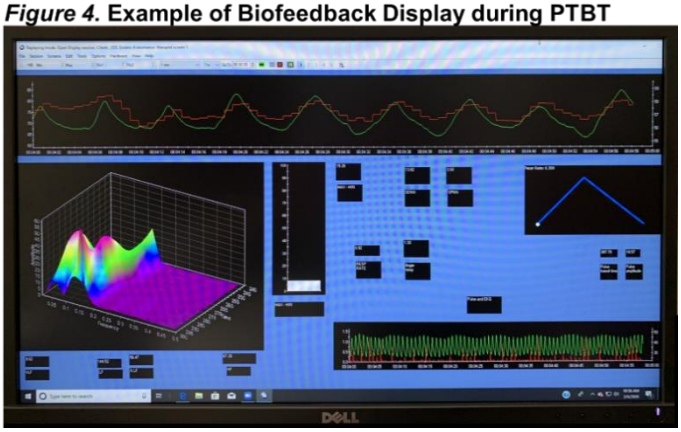
1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables

1. Training Conditions: Eligible participants will then be **randomized** to either the Puff Topography Biofeedback (PTBT) or Control (Sham Training) and informed that the training will be used in V2. Block randomization will be used with biological sex (female vs. male) as a blocking variable, as sex is a known factors that influences puff topography and reinforcement.[36,58,59] Both trainings will be time matched.

PTBT: PTBT is designed to decrease puff topography influences on smoking reward informed by heart rate variability biofeedback paradigms. Participants will be taught how to puff in a way that may feel different from their usual puffing behavior. Participants will be hooked up to a respiratory band, electrocardiogram (ECG) electrodes, and a blood volume sensor finger cuff (pulse plethysmograph) while seated in a ventilated smoking room. Following a 5-min adaptation period, they will be introduced to a breathing pacer (EZ-Air Plus; Biofeedback Foundation of Europe), which is integrated with the *Thought Technology* biofeedback interface (**Figure 4**), and taught how to use the pacer to guide the pace of their inhalation and exhalation.

Figure 4. **Example of Biofeedback Display during PTBT**



Participants will be taught to breathe steadily as a white ball (pacer) proceeds up the incline, and exhale as they follow the ball on the decline. They will first practice breathing normally with the pacer to ensure they understand the procedures. Then, participants will smoke following the pacer while using the CreSS micro device for a 5-min phase. To address reinforcement immediacy and intensity, the pacer will be set to a 2 sec inhalation matched with a 2 sec exhalation, for a 4 sec cycle, such that *puffing* maps onto a respiration pace of 15 breathes/min. This pace should minimize CVC (**Figure 2, right**). To address reinforcement reliability, the inter-puff-interval will vary between 10 secs and 30 secs, as the experimenter will instruct the participant when to puff. In an adjacent room, the experimenter will be able to monitor real-time displays of physiological data and observe the session via video and intercom system and provide additional training instructions, as needed. Participants will then complete a 5-min rest period.

Control: In the control condition, i.e. sham training, participants will be hooked up to the same physiological monitoring equipment and will complete a 5-min adaptation period. They will then be instructed to smoking with the CreSS device while focusing their attention during a 5-min vanilla task.[66] The task involves attending to a computer screen and counting the number of times a designated color rectangle occupies the screen. Different colored rectangles are presented one at a time, for 500ms every 10 sec, for a total of 5-min. The full color spectrum is reflected and participants are told to make their best guess about color match. Participants are asked at the end to report the number of times the designated color was observed and are not given any feedback or incentive for correct color counts. No instructions will be provided about puffing behavior. Participants will then complete a 5-min rest period.

2. Stress-Precipitated Smoking Visit (V2). Participants will return to the laboratory on the following day, at the same time, and be provided the same pre-visit instructions. Participants will be hooked up with physiological monitoring assessment while seated in the smoking lab. Next, a new consent will be presented, introducing them to the Trier Social Stress Test (TSST), which has been used in our prior/ongoing studies (R03DA041556; F31DA043934). The TSST is a well-validated laboratory paradigm that reliably induces psychological and physiological stress,[67–69] including smoking craving.[70,71] While presenting the consent form, the experimenter will explain that they will have to prepare for and deliver a speech about why they are the best candidate for a job of their choosing. To maximize anticipatory stress, participants will be introduced to a male and female confederate who will presumably observe and evaluate the speech.[72] After a 2-min preparation period, they will be shown a video example of a speech where a participant receives negative/neutral feedback from confederates, which serves to provide participants with additional information regarding the stressful nature of the task. In our studies, this preparation/anticipatory period produces medium-large increases in negative affect in smokers (Cohen's d = 0.60-1.30). After the preparation period, participants are told that the confederates need additional time to trouble-shoot the camera system, and as a result they will be able to smoke before delivering the speech. Participants will be instructed that they will practice the training they learned (PTBT or Control) while they smoke and will complete the same 5-min adaptation period pre-smoking and 5-min rest period post-smoking as in V1. The stress-precipitated smoking trial will be followed by the post-smoking assessments. Participants will then be unhooked from the physiological monitoring equipment and informed that they do not actually have to give the speech. The research staff will then proceed to notify participants that they have completed the study visit. Research staff will thank participants for all of their time and effort, provide them with their respective compensation, and encourage them to contact the study staff via email or phone (contact information listed on the participant's previously provided consent form) should they have any additional questions or concerns regarding their participation.

B. Dependent Variables or Outcome Measures

Acute Clinical Outcomes: Smoking Reinforcement.
Short Hypothetical Cigarette Purchase Task (S-CPT)
Modified Cigarette Evaluation Questionnaire (mCEQ)

Target Mechanisms: Cardiac Vagal Control.
Respiratory Sinus Arrythmia (RSA)

Target: Puff Topography (CreSS Micro).
Puff Volume (mL)
Puff Duration (seconds)
Inter-Puff-Interval (IPI; seconds)

C. Eligibility Measures
Medical History Form (MHF)

The Mini International Neuropsychiatric Interview 7.0.0 (MINI) sections C, I, J, and K.
Expired CO Breath Sample
Smoking History Questionnaire (SHQ)
Fagerström Test for Cigarette Dependence (FTCD)

1.7 Drugs/Devices/Biologics
N/A.

1.8 Specimen Collection
N/A.

1.9 Data Collection

A. Primary Data Collection

- **Location**: This project will be conducted at the Rutgers University Affective and Biological Underpinnings of Substance Use and Anxiety (ABUSA) Laboratory located on the 2nd floor of 1 Spring Street, New Brunswick, NJ. The lab space is equipped with two rooms for psychophysiological assessment with adjacent rooms for monitoring, an in-lab smoking room that is ventilated to the outdoors with an adjacent control room for monitoring. Some eligibility and baseline assessments will be conducted remotely, using video-conferencing software (e.g., HIPAA compliant Zoom or Teams platforms) and online survey collection software (e.g., Qualtrics).
- **Process of Data Collection**: Data will be collected by IRB-approved and trained research staff from both labs of the Principal Investigators, in accordance with the procedures described in detail in section 1.3. In brief, combustible cigarettes smokers with emotional distress (N=88) will be randomized to receive puff topography biofeedback (n = 44, 50%) or sham training (n = 44, 50%) prior to exposure to a laboratory stressor paradigm. Stress-precipitated smoking behavior will be assessed directly after the stressor task, wherein participants will be given the instructions to smoke utilizing their assigned puff training. Smoking reinforcement will be measured using a multi-method approach, including self-report, psychophysiology, and behavioral indices
- **Timing and Frequency**: After the initial telephone screening, data collection will occur on one remote occasion and two in-person occasions. The remote session entails one initial assessment to confirm eligibility and collection of baseline data via interview and self-report. For the in-person visits, V1 entails data collection through self-report measures (administered at the starred time points in **Figure 3**), as well as receiving their assigned training condition. V2 will occur on the following day at the same time as V1.
- **Procedures for Audio/Visual Recording**:
  The diagnostic interview during the remote session will be recorded via HIPAA compliant platform (e.g., Zoom, Teams) to be used for supervision purposes as well as to ensure diagnostic fidelity.
- **Study Instruments**:
  Puff topography will be objectively measured with the *CReSS micro* (Plowshare Technologies, Borgwaldt KC, Inc), a hand-held device that 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. Puff indices will be averaged and examined at puff-to-puff level. To index changes in ***CVC*** as a function of condition, continuous ECG and respiration data will be sampled at 1,000Hz, and differences in RSA from the 5-min adaptation period (V1) to the 5-min peri-smoking period (V2) will be derived and scored using cardiopro in accord with established guidelines.[73] ***Smoking reinforcement*** will be assessed with: **(a)** the *Short-Cigarette Purchase Task* (S-CPT),[74] a hypothetical purchase task designed for repeated assessment of cigarette (wanting), modified to purchasing of the *"last cigarette smoked"* to index intensity (*consumption when free*), O_{max} (*maximum expenditure on cigarettes*), and breakpoint (*point at which consumption is zero)* and **(b)** the *Modified Cigarette Evaluation Questionnaire* (mCEQ),[75] which assesses how respondents feel about the "last cigarette smoked" with subscales that tap liking (*cigarette satisfaction*), wanting (*craving reduction*), and learning (*psychological reward*).

- **Subject Identifiers**:
  Data will be de-identified with an arbitrary ID number. Subject identifiers of name, email address, address, and phone number will be stored under lock and key and in password-protected electronic databases, separate from all data.

B. Secondary Data Collection

Additional measures administered and administration time points are included below in **Table 1**. Please refer to **Figure 3** for where these time points fall in the visit procedures. Full measures are attached for review.

Measure	Screening	Baseline (remote session)	0	Adaptation	1 1a, and 1b	Smoking	2	Rest
Phone Screen.	X							
Depression, Anxiety, and Stress Scales, 21 Item Version (DASS-21).		X						
The Mini International Neuropsychiatric Interview 7.0.0 (MINI) sections C, I, J, and K.		X						
Demographic information.		X						
Smoking History Questionnaire.		X						
Medical History Form.		X						
McCarthur Ladder for Subjective Social Status.		X						
Economic Strain Questionnaire.		X						
Fagerstrom Test for Cigarette Dependence.		X						

Mood and Anxiety Symptoms Questionnaire.		X						
Multidimensional Experiential Avoidance Questionnaire.		X						
Anxiety Sensitivity Index.		X						
Distress Tolerance Scale.		X						
Distress Intolerance Index.		X						
Brief WISDM.		X						
Positive And Negative Affect Schedules (PANAS).		X						
Pittsburgh Sleep Quality Index.		X						
Readiness to Quit.		X						
Difficulties in Emotion Regulation Scale.		X						
Avoidance and Inflexibility Scale.		X						
Pre-Session Review Sheet			X					
Modified Cigarette Evaluation Questionnaire.								X
Hypothetical Cigarette Purchase Task.		X		X				X
Visual Analogue Scales of Discrete Affective States.			X		X		X	
Brief Questionnaire of Smoking Urges.			X		X		X	
State Difficulties in Emotion Regulation Scale – modulation subscale.					X (not 1a)			
Expired CO.			X				X	
CReSS topography.						X		
Psychophysiological parameters (e.g., RSA, BVP, Respiration).				X		X		X

2.0 Project Management

2.1 Research Staff and Qualifications

Key Personnel:

Principal Investigators.
Samantha Farris, Ph.D. Dr. Farris is an Assistant Professor in the Department of Psychology at Rutgers University, a licensed clinical psychologist in the Department of Psychology. Dr. Farris has expertise in naturalistic and experimental methods to study smoking reinforcement, including overseeing observational protocols for puff topography with use of technology-aided handheld devices. Dr. Farris also has expertise in the management and processing of puff topography data. Dr. Farris will devote 100% of 1 month's effort (i.e., 13 hours/week, for 12 weeks) to the project to ensure that the project is completed within the one-year period. Specifically, she will be responsible for: a) overall management of the project and IRB; b) training and supervision of puff topography via CReSS micro; c) oversight of assessment of reinforcer pathology; d) oversight of safety, data monitoring, and data processing related to puff topography; and e) statistical analyses.

Teresa Leyro, Ph.D. Dr. Leyro is an Assistant Professor in the Department of Psychology at Rutgers University and a licensed clinical psychologist. Dr. Leyro has expertise in psychophysiological assessment (e.g., heart rate, respiration) and use of biofeedback paradigms in the context of substance use, in addition to expertise in conducting experimental laboratory-based studies in emotion and smoking. Dr. Leyro will also devote 100% of 1 month's effort (i.e., 13 hours/week, for 12 weeks) to this project to ensure that the project is completed within the one-year period. Specifically, she will be responsible for: a) management of study recruitment and retention; b) oversight of assessment of respiratory parameters; c) training and supervision of biofeedback paradigm; and d) oversight of safety, data monitoring, and data processing related to biofeedback paradigm.

Project Coordinators. Danielle Hoyt, M.A. Ms. Hoyt is a graduate student in the Department of Psychology at Rutgers University under the mentorship of PI Leyro. Ms. Hoyt will also attend/participate in weekly study meetings with the MPIs to discuss study progress and problem-solve issues as they arise. **Hannah Brinkman, B.A.** is also a graduate student in the Department of Psychology at Rutgers University under the mentorship of PI Leyro. They will be largely responsible for technical aspects of the study including recruitment, telephone screening, scheduling and appointment reminders, retention, conducting baseline assessments and experimental protocol, maintaining study records/IRB, and overseeing research assistants.

Other Personnel:

Post-Doctoral Researcher. Brianna Altman is a post-doctoral researcher in the Clinical Psychology Rutgers REHAB and ABUSA lab under the supervision of Drs. Leyro and Farris. She completed extensive training in evidence-based smoking cessation treatment and will serve as an independent assessor.

Graduate Student Researchers. Jacqueline Smith, M.A, Mindy Kibbey, B.A., Lilly Derby, B.S., Lauren Davis, B.S., Allison Bond, M.A., and Sonali Singal, B.A. are graduate students in the Clinical Psychology program at Rutgers University, under the supervision of Drs. Leyro and Farris. They have each completed extensive training in evidence-based smoking cessation treatment and will serve as independent assessors.

Research Assistants. Sayaka Carpenter, Dana Steinberg, Isabel Cunha, Gabriela Rivera, and Brittany Keller are post-baccalaureate laboratory managers and project coordinators for Drs. Farris and Leyro and Kathleen Kildosher, Dipabali Jana, Aisha Ghauri, Huong (Valerie) Le, Jason Marum, Lori Khadse, Samantha Stucchi, Annmarie Elgendy, Gabriel Brevet, Helena Beshay, Marcus Shipp, Nidhi Gourabathuni, Rutu Patel, Patricia DiFalco, Priyanka Taribagil, Jorge Rivera, and Long Tran are research assistants under the supervision of Drs. Farris and Leyro. They will assist with subject recruitment, participant visits, data entry and coding, and compiling study materials.

2.2 Research Staff Training

All research personnel will receive, if they have not already, extensive (10-15 hours) training on all study procedures. PIs Dr. Farris and Dr. Leyro will oversee training, which will include verbal description and behavioral demonstration. Staff will then be led through the study's procedures as mock participants, before administering each study task to the PIs or graduate students designated by the PIs to allow for sufficient practice and corrective feedback if necessary. All study staff have previously administered some or all of the aforementioned techniques during prior investigations.

2.3 Resources Available

Research will take place in the Affective and Biological Underpinnings of Substance Use and Anxiety (ABUSA) laboratory in the Department of Psychology on the second floor of One Spring Street, New Brunswick. These facilities include the materials necessary for data collection (e.g., carbon monoxide smokerlyzer, physiological monitoring) and secure storage (e.g., locked file cabinets, password-secure computers).

2.4 Research Sites

The Affective and Biological Underpinnings of Substance Use and Anxiety (ABUSA) laboratory in the Department of Psychology on the second floor of One Spring Street, New Brunswick.

3.0 Multi-Center Research

N/A.

4.0 Subject Considerations

4.1 Subject Selection and Enrollment Considerations

A. Method to Identify Potential Subjects

Participants will be recruited through: (a) free online internet advertisement (e.g., Facebook posts, Craigslist), (b) flyers posted in the community and health-related clinics in the New Brunswick and Central New Jersey area, and (c) paid advertisements through BUMP Digital Marketing and Build Clinical, both online recruitment services used in previous research by both PIs. BUMP and Build Clinical will target daily smokers in the Northern and Central New Jersey areas via targeted advertisements on Facebook, Instagram and other social media sites and websites. Recruitment materials are attached. Any individuals meeting inclusion/exclusion criteria will be provided the opportunity to participate in this study. Individuals interested in participation will undergo a brief phone screen to determine presence of inclusion criteria and absence of exclusion criteria.

B. Recruitment Details

We intend to recruit 180 daily smokers and retain 80 eligible. The study will be conducted at the Affective and Biological Underpinnings of Substance Use and Anxiety (ABUSA) laboratory at Rutgers University, in New Brunswick, NJ. The ABUSA laboratory (directed by MPI Leyro) has a psychophysiological suite and ventilated in-laboratory smoking room. Through our studies (R03DA041556; F31DA024919; R21DA045182; R34DA043751), we have developed effective

strategies to recruit emotionally-distressed smokers from the community at a consistent rate. We will recruit via community fliers and announcements, local tobacco clinics (via Co-Is Steinberg/Delnevo), and both BUMP digital marketing and Build Clinical, online recruitment services.

Subject Screening

Potential participants will be screened via telephone by protocol-approved research staff, trained under the direction of Drs. Leyro and Farris. See section 11.0 Recruitment Materials for the full text of the phone screen.

- **Inclusion Criteria**
- (1) Age 18-55; (2) daily smoking ≥ 8 cigarettes/day verified by carbon monoxide analysis of breath sample ≥ 5 ppm;[64] (3) smoking within 30 min of waking; and (4) English fluency.
- **Exclusion Criteria**
  (1) current smoking cessation treatment; (2) past-month reduction of cigarettes/day by ≥50%; (3) non-nicotine substance use disorder (moderate or severe); (4) past-year psychiatric instability (e.g., psychosis, mania); (5) severe visual, hearing, or cognitive impairments; (6) medical condition that could impact stress reactivity or physiology (e.g., respiratory, cardiovascular, autoimmune, pregnancy, neurodegenerative disorders); and (7) current regular use of medication that could affect CVC (e.g., beta blockers, benzodiazepines; note-use of SSRIs/SNRIs is permitted if dose is stable ≥ 6 wks).

4.2 Secondary Subjects

N/A.

4.3 Number of Subjects

A. Total Number of Subjects

80 total participants are expected to complete the full protocol. In order to have 80 full completers (attendees that remain eligible and complete both visits), 180 are expected to be initially enrolled.

B. Total Number of Subjects If Multicenter Study

N/A.

C. Feasibility

Based on our prior trials, we expect to retain 90% of subjects across the two visits. Financial incentives will also aid in retention: with $20 for completing the remote screening/baseline visit, $30 for completing V1 and $100 for completing V2. We have used this back-loaded schedule of compensation in our prior smoking lab-studies with high retention rates (F31DA024919; F31DA035564). Additionally, with the use of Build Clinical and BUMP Digital Marketing, we expect to be able to consent and enroll 80 completers very feasibly. Prior engagement through both labs with BUMP's recruitment service has yielded up to 12 inquiries per day in prior smoking research, and the eligibility criteria would allow a broad scope of potential participants.

4.4 Consent Procedures

A. Consent Process

- **Location of Consent Process**
  The initial consent process will take place via video conferencing software during the initial remote visit. Consent to the TSST procedures will occur in the laboratory at One Spring Street at the start of V2.
- **Ongoing Consent**

Ongoing consent will be confirmed on the basis of ongoing communication and study participation. In addition, participants will explicitly be reminded of study expectations, limitations, compensation, and right to withdraw. Study staff will attempt to contact participants who miss study appointments or follow-up appointments until they provide verbal or written indication that they no longer wish to participate.

- **Individual Roles for Researchers Involved in Consent**
  All of the research assistants, graduate students, and project manager have been trained and are experienced in prior consent administration and may collect consent from participants through the course of the protocol.
- **Consent Discussion Duration**
  Staff will go over details regarding the procedure, time commitment, payment, risks/benefits, and option to discontinue the study at any time without penalty. We anticipate that it will take participants 5 minutes to read the consent and up to an additional 5 for staff to review relevant information.
- **Coercion or Undue Influence**
  During the consent process, staff will make clear to participants that they will receive full compensation if eligible, and that early termination will result in payment for the portion completed, as detailed in the consent, and will not result in loss of ability to participate in future research.
  Subject Understanding
  Participants will be asked if they require any clarification and must verbally indicate they fully understand all study procedures, in addition to providing written consent.

B. Waiver or Alteration of Consent Process
N/A.

C. Documentation of Consent

- **Documenting Consent**
  All participants will sign the consent form, indicating their consent.
- **Waiver of Documentation Of Consent (i.e., will not obtain subject's signature)**
  N/A.

4.5 Special Consent/Populations

N/A.

4.6 Economic Burden and/or Compensation for Subjects

A. Expenses
Participants may incur costs of transportation to arrive at the study site. Travel and transportation costs will not be reimbursed.

B. Compensation/Incentives
Participants will receive compensation in cash. Participants will receive compensation based on study attendance and continued eligibility. They will receive $30 for the remote screening/baseline session. If eligible to continue, they will receive an additional $70 upon completion of V1. If they return for V2, participants will receive $100 for participating in V2 and a $50 completion bonus. Compensation totals a potential of up to $250 per participant.

C. Compensation Documentation
Participants will sign receipts indicating their receipt of compensation. Compensation will also be logged electronically in a tracking log accessible only to research staff.

4.7 Risks of Harm/Potential for Benefits to Subjects

A. Description of Risks of Harm to Subjects

(1) Phone Screen and Questionnaire Completion: Potential participants may become uncomfortable or distressed when asked certain questions (e.g., regarding illicit substance use; current/past mental health and physical health). However, Drs. Leyro and Farris have many years of experience administering these questionnaires in various study protocols and study personnel will receive extensive training in conducting the Phone Screen. Also, participants will be offered an additional layer of protection via a Certificate of Confidentiality.

(2) PTBT: There are some minimal risks associated with the administration of the proposed breathing interventions. The most often observed risk is discomfort breathing at a pace that is much slower than typical and worry that one is not inhaling adequate air. To address this potential risk, study clinicians will be carefully trained in providing participants with a clear rationale for the procedure, clinical management of distress associated with the intervention, and appropriate adjustments to ensure participants are able to adhere to the protocol.

(3) Physiological Recording: All of our sensors record responses from the surface of the body and are hence noninvasive and should not cause the participants any discomfort or physical harm. Patients may experience mild discomfort with the application and removal of passive electrodes to monitor their physiological parameters. However, we do not anticipate this discomfort to be longstanding. To minimize discomfort, all sensors are placed and removed by study staff that will receive training in appropriate placement and removal.

(4) Assessment Procedures: No risks are associated with self-report or behavioral assessments other than mild distress due to the sensitive nature of questions or induced distress as a function of difficulty or attention demands on some of the behavioral tasks. Study personnel are experienced and sensitive to this issue and will cease testing if a participant displays excessive frustration during behavioral testing, although neither PI has experienced this in her prior research.

B. Procedures which Risk Harm to Embryo, Fetus, and/or Pregnant Subjects

N/A.

C. Risks of Harm to Non-Subjects

N/A.

D. Assessment of Social Behavior Considerations

No risks are associated with self-report or behavioral assessments other than mild distress due to the sensitive nature of questions or induced distress as a function of difficulty or attention demands on some of the behavioral tasks. Study personnel are experienced and sensitive to this issue and will cease testing if a participant displays excessive frustration during behavioral testing, although the PI has never experienced this in her prior research.

E. Minimizing Risks of Harm

Described above in section A and D.

- **Certificate of Confidentiality**

  This research is covered by a Certificate of Confidentiality. Researchers with this Certificate may not disclose or use information or documents that may identify study participants in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless study participants have consented for this use. Information or documents protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child

abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if participants have consented to the disclosure, including for their medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects. A Certificate of Confidentiality does not prevent participants from voluntarily releasing information about themselves or their involvement in this research. If a participant wants their research information released to an insurer, medical care provider, or any other person not connected with the research, they must provide consent to allow the researchers to release it. The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of harm to self or others as well as reports of child and elderly abuse and neglect.

- **Provisions to Protect the Privacy Interests of Subjects**

Our research team employs standard procedures to ensure confidential information about study participation is not disclosed. All data are linked to an arbitrary study ID unrelated to personal information. The file linking participants to their study ID will be stored in a password-protected file, located within a password-protected database on an encrypted computer and maintained separately from de-identified personal data files. Only select trained laboratory personnel will have access to the file. All computer files or printed data used for analysis also will be de-identified. Consent forms and payment forms will be stored in a locked file cabinet separate from data in an office that is locked when not occupied. Participants' confidentiality also is protected by never associating a participant's name with results in any published or otherwise publicly presented report. Demographic information, including information about participants' age, ethnicity, education, marital status and employment status, will be reported using averages and percentages computed over multiple participants and never reported at the level of individual participants.

F. Potential Benefits to Subjects

While no individual benefits for subjects are anticipated, the data obtained through this study may help inform and shape effective interventions for smoking cessation.

5.1 Health Insurance Portability and Accountability Act (HIPAA)

N/A.

5.2 Family Educational Rights and Privacy Act (FERPA)

N/A.

5.3 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

A. Special Populations

N/A.

5.4 General Data Protection Regulation (GDPR)

N/A.

5.5 NJ Access to Medical Research Act (Surrogate Consent)

N/A.

6.0 Data Management Plan

6.1 Data Analysis

Prior to conducting outcome analyses, we will use descriptive statistics and graphical analysis to evaluate the distributional properties of outcome variables. T-tests and $\chi 2$ initial analysis will be used to evaluate the equivalence of the groups on baseline variables (i.e., successful randomization).

Test of Aim 1: First, tests of the effects of puff training on puff topography indices (i.e., puff volumes and duration, and inter-puff intervals) will be conducted using linear regression models. The mean level of each index over the course of the stress-precipitated smoking session will be calculated for each individual to be used as outcomes. The primary independent variable is training group (PTBT vs. Control. Planned covariates include biological sex (0=male, 1=female), number of cigarettes per day, and emotional distress (DASS-21), and the models will be tested with and without covariates. Effect size (d) will also be calculated. In addition, a series of multilevel models will be used to test whether 1) the mean levels and 2) changes in the levels of puff topography (i.e., volume, duration, inter-puff intervals) during stress-precipitated smoking session differ across groups. Levels of puff volumes, durations, and inter-puff intervals for each puff (outcomes), and puff number (level 1) make up the first level of data nested within individuals at the second level. Training group and other baseline characteristics will be entered in the models as level 2 variables. We will examine the effects of PTBT (vs. Control) on the individual mean (i.e., the middle point of the values over time) and the individual trajectory slope (i.e., the rates of changes over time) for each topography index in separate models. A cross-level interaction term between training group (level 2) and puff number (level 1) will be included in each model. Puff number will be centered around the mid-point for each individual so that the intercept reflects the estimated mean level of each topography outcome. Separate quadratic and cubic slopes (squared and cubic puff number) will be included as level 1 predictors if their inclusion improves model fit. Intercepts and slopes will be specified as random if it improves model fit and coefficients varied significantly across individuals. Deviance statistics will be used to compare model fit between two models.[79] Unconditional models will be initially estimated, and then training group will be included as a level-2 variable predicting level-1 intercept and slope coefficients. The models will be fitted with and without level 2 planned covariates (i.e., sex, FTCD, DASS-21, and the baseline average value of the corresponding outcome).

Test of Aim 2: The effects of PTBT vs. Control on acute smoking reinforcement (i.e., cigarette purchase task [S-CPT], cigarette satisfaction/reward [mCEQ]) following stress-precipitated smoking will be estimated using separate linear regression models with group predicting each outcome. Planned covariates include the baseline value of the outcome when relevant (S-CPT), biological sex, number of cigarettes per day, and DASS-21, and the models will be tested with and without covariates. Effect size (d) will also be calculated.

Test of Aim 3 (Exploratory Analyses): Differences in CVC (via RSA) between training groups during the stress-precipitated smoking trial will be tested using linear regression models, controlling for baseline levels. Training group will be used to predicting CVC (outcome). Covariates will be identical to those in prior analyses, and will be tested with and without covariates, and effect size (d) will be calculated.

6.2 Data Security

A master list of names and numbers is kept in a separate location and is used to facilitate the collection of data. Specifically, this Master list will be stored in a password protected excel document stored on Microsoft Teams, which is a secure cloud-based file storage application. Only senior staff will have access to the master list linking names and code numbers. Clinically important assessment data (e.g., suicidal intent) will be made available to clinical staff to more effectively coordinate services. All research staff directly involved with study participants will be fully trained by the PIs and will demonstrate competence in procedures for clinical assessment and appropriate intervention to address psychiatric adverse events. In such cases, research staff will also immediately contact a PI (Dr. Farris or Dr. Leyro) who will be on call at all times. Appropriate clinical action will be taken in such circumstances. Individuals will be provided with a list of referrals for counseling as needed.

All staff will be fully trained in relevant ethical principles and procedures, particularly around confidentiality. All assessment and treatment procedures will be closely supervised by Dr. Farris and Dr. Leyro. No personal participant information will be presented in any publication or presentations resulting from this research.

6.3 Data and Safety Monitoring

A. Data/Safety Monitoring Plan

We believe that potential risks to participants in this study will be minimal. The risks do include the possibility of psychological distress during study screening. All research staff directly involved with study participants will be fully trained by the PIs and will demonstrate competence in procedures for clinical assessment and appropriate intervention to address psychiatric adverse events. In such cases, research staff will also immediately contact a PI (Dr. Farris or Dr. Leyro) who will be on call at all times. Appropriate clinical action will be taken in such circumstances. Individuals will be provided with a list of referrals for counseling as needed.

The principal investigators, Drs. Farris and Leyro, will take ultimate responsibility for safety monitoring in the study. They will be in frequent contact with the study Co-Is and study staff. All adverse events will be promptly reported to the PI. Any incident involving a serious injury, medical hospitalization, or death will be reported to the Rutgers IRB as a Serious Adverse Event (SAE) within 24 hours. SAEs will be reviewed by the full committee of the Rutgers IRB. The report will include whether they were expected or unexpected, a rating of severity of the event, a brief narrative summary of the event, a determination of whether a causal relationship existed between the study procedures and the event, whether the informed consent should be changed as a result of the event and whether all enrolled participants should be notified of the event. Serious and other unexpected adverse events will also be tracked and reported semi-annually to the IRB.

In terms of data monitoring, self-report measures will be entered by participants directly into Qualtrics (a data entry and management program). Data is stored on a secure cloud-based server that will only be accessible to the PI and relevant research team members. Physiological data will be stored electronically in files accessible only to research staff. Data will be reviewed post-collection by the PIs or a graduate researcher for validity and quality of collection.

B. Data/Safety Monitoring Board Details

N/A.

6.4 Reporting Results

A. Individual Subjects' Results

Individual results will not be shared with subjects.

B. Aggregate Results

Aggregate results will not be shared with subjects.

C. Professional Reporting

Results from this study, negative or positive, will be shared with the greater scientific community via manuscripts published in peer-reviewed journals, as well as through posters and presentations at relevant scientific conferences. No individual or identifying data will be presented.

Clinical Trials Registration, Results Reporting and Consent Posting

N/A.

6.5 Secondary Use of the Data

After data have been collected and study results published, de-identified data will be made available to other qualified researchers upon request, on a CD or other electronic means compatible with our systems. The request will be evaluated by the PIs to ensure that it meets reasonable standards of scientific integrity. We have carefully selected standardized and widely-used assessments of affective states, emotional vulnerability, and smoking order to promote data sharing and integration into larger databases and to allow other researchers to analyze the data, including conducting meta-analyses. We may also choose to share de-identified data with colleagues/collaborators at other institutions. We will work on the data dictionary throughout the study. We will submit primary results for publication by the end of the project period, and will have final de-identified datasets and data dictionaries available by the end of the project period.

7.0 Research Repositories – Specimens and/or Data

N/A.

8.0 Approvals/Authorizations

N/A.

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