Strengthening Instrumental Extinction to Prevent Smoking Relapse

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Purpose of the Study

The central objective of the project is to evaluate the effect of incorporating smoking related contexts into very low nicotine content (VLNC) cigarette extinction trials on clinically relevant, smoking-related outcomes. We will evaluate the effects of multiple context exposure (MCE) on pre-quit nicotine dependence and smoking behavior and smoking cessation outcomes. It is postulated that greater compliance with, and response to smoking VLNCs and greater decreases in craving across the course of MCE and in the cue-reactivity assessment will be associated with better smoking cessation outcomes.

Background & Significance

Each year in the U.S., smoking leads to over 400,000 premature deaths and $190 billion in annual costs due to smoking-related illness and lost productivity. Whereas the majority of smokers wish to quit, only a small percent of attempts are successful. The proposed project can have significant impact on knowledge of basic learning processes, treatment development, and policy.

Smoking VLNCs has been shown to reduce nicotine dependence, decrease smoking behavior, and decrease brain reactivity to smoking cues. In clinical trials, smoking VLNCs with or without concomitant nicotine patch has shown some promise in improving cessation outcomes. However, despite this promise, very little research has sought to directly enhance or strengthen the effects of smoking VLNCs on clinically relevant smoking outcomes.

MCE—in which participants smoke VLNCs while viewing contexts associated with smoking—can potentially increase the efficacy of smoking VLNCs by strengthening and generalizing extinction learning. If MCE increases the effects of VLNC smoking, this would further support the hypothesis that instrumental extinction is responsible for the observed effects. In regards to treatment development, VLNCs have shown promise as a component of smoking cessation intervention; to the degree that MCE can increase the effects of VLNCs, the proposed work will have significant clinical impact. MCE-based therapies could potentially be made portable and inexpensive to distribute via internet/mobile technology; this further increases the possible future impact of the study.

Design & Procedures

We propose to obtain consent from 300 adult smokers interested in quitting smoking. Of those who give consent we expect to identify 80 participants who meet all inclusion and exclusion criteria with the aim of identifying 68 participants who provide useable data. During a phone screening interview, the study will be described in detail and preliminary participant characteristics (e.g. age, number of cigarettes per day) will be assessed. Those participants who meet criteria for participation will be invited to our offices for an informed consent and screening visit. Potential participants will be instructed to bring a valid government issued photo ID to the screening session to confirm age and identity. Identifying

information from the phone screen for the participants who do not meet inclusion criteria will be kept until recruitment for this study is completed.

Screening Session: During the screening session all aspects of the study will be described to subjects and informed consent will be obtained. A standardized PowerPoint presentation will be used to discuss the procedures, risks and benefits with the participant as well as their rights as a research participant. If consent is given we will collect breath and saliva samples in order to verify smoking status and blood alcohol level (BAL). Questionnaires on smoking history, family smoking history, nicotine dependence, and mood will be collected. Participants will also be asked about medical history and complete the Brief Medical History Questionnaire and the Patient Health Questionnaire. Indicating certain items, such as suicidal ideation, significant depression, significant anxiety, or eating disorder, on the Patient Health Questionnaire will trigger medical review by the study physician and emergency referral to psychiatric services if necessary. Research staff will refer to the PrimeMD Evaluation Form when reviewing responses on the Patient Health Questionnaire. Physiological measures such as heart rate, blood pressure, weight, and height will also be measured to assess general health.

Urine samples will be obtained in order to screen for illicit drug use and to assess pregnancy status. Use of illegal drugs will be exclusion criteria. Marijuana use will not be exclusionary, but participants must agree to not use marijuana 24 hours prior to sessions and may not mix their marijuana with tobacco (i.e. blunts). Females who test positive for pregnancy will be excluded from the study and be given options for smoking cessation programs. Participants will also be interviewed regarding their smoking behavior including an assessment of contexts (places) in which they smoke.

Among females, pregnancy at screening as measured by a urine test will be exclusionary. The QuickVue One-Step hCG Urine Test will be used and performed by research staff who have completed competency training from the Duke Office of Clinical Research. Females of child bearing potential must agree to use appropriate contraception during the course of the study. They must further agree to notify the study staff if they become pregnant during the study.

At the end of the screening session participants will complete a computer task where they will look at cigarette point of sale displays and indicate whether they would purchase an item in the display. We will collect eye tracking data using a Tobii X2-60 eyetracker.

Training Session: Participants have the opportunity to complete the training session on the same day as the screening session or they may schedule the session for a separate day. Participants will be required to schedule the training session within 30 days of their screening visit. If a participant still wants to be in the study after 30 days, he or she will need to be re-screened.

At the beginning of the training session participants will be instructed to smoke a usual brand cigarette in order to standardize the time of last cigarette before the task. Following the smoke break, a breath CO sample and BAL will be collected. For all visits breath alcohol levels will be assessed and participants must record a BAL of 0.0. Participants who test positive for alcohol will be excluded from participation that day. Participants testing positive for alcohol on more than one occasion will be excluded from the experiment. Blood pressure and weight will also be collected at this visit.

Participants will complete a baseline assessment of cue-reactivity. Participants will view blocks of smoking and non-smoking environment and proximal cues and will complete craving assessments. During the task, heart rate and respiration will be measured using a BIOPAC system. Mood and withdrawal will be assessed at the end of the task.

Participants will be introduced to the digital camera that they will use to capture images of their personal environments and will be given specific guidelines to follow while taking pictures. All information regarding the recording of events, picture taking, and camera operation (e.g. recharging, storage) will be reviewed. Any questions from participants regarding the use of the camera will be discussed. Participants will also be allowed to take pictures with their own personal devices and email them to study staff. If participants choose to take pictures with a device other than the lab camera provided, the camera on the device must have a photo resolution of at least 72 dpi. All participants will be given 2 disposable lighters with stickers attached reminding them to take pictures of smoking locations. Participants will be asked to take the pictures over the course of 1-2 weeks in order to obtain enough useable photographs before returning to the lab for the camera return session.

Camera Return Session/Randomization: Once participants have collected photographs of personal smoking environments they will return to the lab with the camera 1-2 weeks after the training session. The information from the camera will be uploaded, examined, and reviewed with the participant to ensure enough useable pictures were taken. If the images are acceptable for use then they will continue with the visit. If the pictures do not follow the guidelines for acceptable photographs or if there are not enough pictures the RA will review the guidelines for acceptable pictures with the participant and schedule the camera return session for the following week.

Once the camera is returned with acceptable pictures, all participants will complete a brief task during which they will view a subset of the MCE- images in order to increase the familiarity of the images. Craving will be assessed before and after the task. After dismissal from the camera return session, participants will then be randomized to the EXT/MCE+ or EXT/MCE- group. Individuals in the MCE+ group will view smoking-related environments during the MCE sessions (see below); whereas individuals in the MCE- group will view control images.

Group Assignment/Experimental Period: During the three-week treatment period, half of the sample (n=40) will be randomly assigned to undergo six, 60-minute sessions of multiple context extinction (MCE+) during which they will view smoking-related environments and smoke their assigned cigarettes. The remaining 40 participants will undergo control MCE (MCE-) and smoke their assigned cigarettes. Participants will be provided with packs of VLNC cigarettes matching on menthol preference (SPECTRUM cigarettes NCR-200/NRC-201) and Nicoderm CQ® nicotine patches (EXT) and we will obtain physiological measures. Nicotine patches will be obtained from local drugstores. Participants smoking ≥ 10 cig/day and participants smoking < 10 cig/day will be provided with 21 mg/d and 14 mg/d nicotine patches, respectively. They will be instructed to smoke the same number of VLNCs as they smoked of their usual brand and to only smoke the VLNC cigarettes for the next three weeks. At the first MCE session, instructions regarding cigarette and patch use will be discussed and participants will apply a nicotine patch prior to completing the MCE task.

Women of child-bearing potential will undergo urine pregnancy testing again prior to applying the patch.

MCE Sessions: Participants will be asked to smoke the assigned cigarettes for the next three weeks. During those three weeks they will come into the lab for 2 visits per week (at least 48 hours apart) to undergo MCE and complete questionnaires. Participants will be instructed to return their remaining product, empty cigarette packs, and used patches at each visit. Additional VLNC cigarettes and nicotine patches will be provided as needed at each visit. Smoking behavior and patch use will be assessed by self-report using the Timeline Follow-Back procedure at each visit. CO, BAL, vitals, and weight will be measured at the beginning of each MCE session. Following physiological measures, participants will be seated in front of a computer monitor. Participants will be video recorded during the session to gather data about their smoking behavior. Heart rate and respiration will be measured using a BIOPAC system at the first and last MCE sessions. Participants will complete baseline craving and mood surveys. Participants will view picture stimuli depicting smoking environments including their personal smoking environments (MCE+ condition) or nature environments (MCE- condition) and will be instructed to imagine they are in the location depicted in each image. There will be a total of 10 blocks of images and participants will indicate their current craving level during the task. Each image will be shown for 15 seconds. After block 5, participants will have a 5 minute break and then resume the task. Participants will be instructed to light and smoke a VLNC cigarette at the beginning of the task and following block 2, the 5 minute break, and block 7 (4 cigarettes total). At the end of the session, CO, vitals, and withdrawal and mood will be assessed.

At the end of the three week treatment period, participants will quit smoking while continuing to wear the nicotine patch.

Post-Quit Test Session: Participants will return to the lab following 24 hour abstinence for a post-quit test session where cue-reactivity and withdrawal will be assessed as done during baseline. Abstinence will be verified by expired breath CO level $\leq$ 6 ppm. If the participant does not meet abstinence criteria, s/he will only receive compensation for completing the visit, not for maintaining abstinence.

Abstinence Period Visits: During a 10 week abstinence period, participants will be followed and will be provided with nicotine patches. Participants will return to the lab 1 week, 3 weeks, 6 weeks, and 10 weeks following the quit day. Participants wearing a 21 mg/d patch prior to quitting will step-down to a 14 mg/d patch at 6 weeks post-quit and step-down again to a 7 mg/d patch at 8 weeks post-quit. Participants wearing a 14 mg/d patch prior to quitting will step-down to a 7 mg/d patch at 6 weeks post-quit and continue this treatment for the duration of the study. Physiological measures will be collected and participants will complete questionnaires at each visit. Smoking behavior will be assessed by self-report using the Timeline Follow-Back procedure at each visit to establish whether and when relapse has occurred and patch adherence. At the last visit, the PI or study staff will complete a brief exit interview with the participant to gain insight into their overall study experience and how the study may have changed their smoking behavior or thoughts about smoking. Participants will be debriefed and referred to area resources if additional cessation treatment is desired.

6 Month Follow-up Phone Call: Participants will be contacted by phone 6 months after their quit day to complete a brief interview about their current smoking status and nicotine dependence.

Selection of Subjects

In order to participate in this study, participants will be required to meet the following:

Inclusion criteria:

1. generally healthy (i.e. ambulatory, not currently sick)
2. interest in quitting smoking
3. between the ages of 18 and 65
4. smoking of at least 5 cig/day of a brand delivering ≥ 0.5 mg nicotine (FTC method) for > 1 year
5. an expired CO concentration of at least 10 ppm (to confirm inhalation) or urinary cotinine > 1000 ng/mL to confirm daily smoking (NicAlert=6)

Exclusion criteria:

1. inability to attend all required experimental sessions
2. desire to quit smoking prior to the study quit date
3. a quit attempt resulting in greater than 3 days of abstinence in the past 30 days
4. report of significant health problems including but not restricted to (e.g. chronic hypertension, emphysema, seizure disorder, history of significant heart problems, heart disease, heart attack in the past 90 days, irregular heartbeat)
5. unstable psychiatric conditions (any significant change in psychiatric symptoms during the past 3 months as determined by the study physician)
6. schizophrenia and schizoaffective disorder
7. psychiatric medication changes (e.g. new prescriptions, changes in dosages, or discontinuation of medications) in the past 3 months that was a result of negative changes in symptoms
8. use of other tobacco products or e-cigarettes more than 9 days in the past 30 days
9. current alcohol or drug abuse
10. positive toxicology screen for any of the following drugs: cocaine, opiates, methadone, benzodiazepines, barbiturates, amphetamines, methamphetamines, and PCP
    a. marijuana will be tested for but will not be exclusionary
    b. participants with valid prescriptions for opiates, benzodiazepines, barbiturates, amphetamines or methadone will not be excluded
    c. participants failing the toxicology screen will be allowed to re-screen once
11. use of Theophylline for asthma
12. current use of nicotine replacement therapy or other smoking cessation treatment
13. presence of conditions contraindicated for nicotine replacement therapy (e.g., skin allergies)
14. previous participation in a study within the past year involving use of Spectrum cigarettes
15. systolic BP greater than 140 (participants failing for blood pressure will be allowed to rescreen once)

16. diastolic BP greater than 90 (participants failing for blood pressure will be allowed to rescreen once)
17. heart rate greater than 100 (participants failing for heart rate will be allowed to rescreen once)
18. Blood alcohol level >0.0 (participants failing the blood alcohol screen will be allowed to rescreen once)
19. Pregnant, trying to become pregnant, or breastfeeding

Participants will be asked to indicate in the consent form whether they would like to be contacted about future studies. Participants will be informed there is no obligation to participate and their refusal for future contact will in no way affect their participation in this study.

Subject Recruitment & Compensation

Potential participants will be recruited via community advertisements and websites at Duke University Medical Center. Participants will be recruited through flyers, direct mailings, television, radio, newspaper, bus, and on the internet (Craigslist advertisements, trianglesmokingstudies.com, ResearchMatch). Potential subjects can complete an on-line Qualtrics screening survey accessed from our website, after which they will be called to either be told they were not eligible or to complete a phone screen. During a phone screening interview, the study will be described in detail and participants will be asked questions over the phone to determine initial eligibility. If eligible and interested, they will be scheduled for an informed consent and screening visit.

Participants will receive no payment for the phone screening. Participants will receive $10 in cash for completing the screening session, regardless of eligibility as long as they pass the breath alcohol test, drug test criteria, and meet the minimum requirements for breath carbon monoxide levels (or urinary cotinine levels). Individuals who do not pass these tests will be dismissed from the screening session without payment. Participants will receive $25 each for the picture taking training and camera return sessions, $30 for each MCE Session, $25 for the post-quit test session, $50 for meeting criteria for 24 hour abstinence, and $30 for each abstinence period visit. The total amount earned for completing all sessions of the study is $435. The only payments received in cash are the payments dispensed at the screening session ($10) and post-quit test session ($25 for session, $50 for meeting abstinence criteria). All other payment will be received by check after completion of the study. Participants will receive $10 for completing the 6 month follow-up phone call. Total compensation for attending sessions and completing all phone calls is up to $445.

Consent Process

The PI, Research Coordinator, or Research Assistant will obtain consent from each participant. The person obtaining consent provides the participants with a written document explaining the procedures and risks, and reviews the PowerPoint presentation and answers any questions. A signed copy of the informed consent form will be given to each participant. Participants are informed that they may withdraw from participation in the study at any time without penalty.

The consent process will occur at our lab during regular business hours. There will be one participant in a room along with the study staff member obtaining consent. The door is kept closed for privacy.

Participants are given as much time as needed to fully understand what is involved in the study as well as their rights as research participants. Participants are encouraged to ask as many questions as necessary to gain a complete understanding of the study. No one is coerced into the study, we make it very clear that participation is voluntary and they can choose to withdraw at any time.

Risk/Benefit Assessment

Potential risks of participation include:

1. Breach of Confidentiality: The risk of the interview is loss of privacy if other people find out the results.
2. Smoking study cigarettes: Participants may experience some minor adverse health effects such as headaches or experience withdrawal symptoms which are listed below. In addition, due to the altered nicotine levels, there could be a change in their cigarette use including the manner in which they inhale the smoke or increase the number of cigarettes smoked per day. This increased rate of smoking may persist after completing the study. Smoking the study cigarettes does not provide any less risk than their usual brand cigarette and could pose increased health risks. Participants may also experience increases in carbon monoxide, a gas from smoke.
3. Nicotine patch: Insomnia and abnormal dreams are common and expected side effects associated with 24 hour nicotine patches. If a subject complains of disturbed sleep, s/he will be instructed to remove the patch at bedtime and apply a new one the next day at the usual time. Skin irritation may occur, although this will be minimized by changing the site of patch application daily. If a subject develops itching or a rash at the patch site, s/he will be advised to use 1% hydrocortisone cream on the affected area. Symptoms associated with nicotine toxicity include lightheadedness, dizziness, nausea, fainting and vomiting. Symptoms considered moderate to severe in nature will be evaluated by the study medical staff. Upon evaluation, the participant may be given the choice of continuing in the study at a lower dose patch. If it is thought that being in this study is putting the participant's health at risk, they may be asked to stop participating in the study.
4. Smoking Withdrawal: Participants may experience smoking withdrawal symptoms during this study. The symptoms can be uncomfortable but are typically of minimal risk. At each visit, they will be asked how they feel, and if it is thought that being in this study is putting their health at risk, they may be asked to stop participating in the study. Smoking withdrawal symptoms include:
    (a) Anger, irritability, frustration
    (b) Anxiousness, nervousness
    (c) Depressed mood or sadness
    (d) Desire or craving to smoke
    (e) Difficulty concentrating
    (f) Increased appetite, hunger or weight gain
    (g) Insomnia, problems sleeping or awakening at night
    (h) Restlessness
    (i) Impatience

(j) Constipation
(k) Dizziness
(l) Coughing
(m) Dreaming or nightmares
(n) Nausea
(o) Sore Throat

5. Risk to Fetus: To avoid risks to a fetus, pregnant women will be excluded from this study. Risks include miscarriage, preterm delivery, stillbirth, low birth weight, problems with the placenta, birth defects such as cleft palate, sudden infant death syndrome (SIDS), and early childhood behavioral problems. If a participant becomes pregnant during the study she will be withdrawn from the study and referred to area quit resources. Approximately 30 days after being withdrawn, the research staff will contact the participant to confirm her due date. The licensed medical professional will follow-up with the participant after delivery to ask questions about the baby's health.
6. Changes in blood pressure and/or heart rate: Smoking and nicotine can affect the cardiovascular system which may result in changes in blood pressure and/or heart rate. These changes will be monitored and may result in stopping participation (resting heart rate persistently greater than 100 beats per minute).
7. Exacerbation of psychiatric symptoms: Smoking and nicotine can affect a person's mood and emotions and are associated with psychiatric disorders including major depressive disorder, general anxiety disorder, bipolar disorder and eating disorders. Any changes in nicotine or cigarette consumption could adversely affect psychiatric conditions.

A possible benefit from participation in the study is quitting smoking.

Costs to the Subject

There are no costs to participants for taking part in this study. All the study costs, including any procedures related directly to the study, will be paid for by the study. Moreover, there are no immediate benefits from participating in the study.

Data Analysis & Statistical Considerations

The primary aim of this study will evaluate the effects of MCE+ (vs. MCE-) on pre-quit nicotine dependence and smoking behavior, and smoking cessation outcomes. The premise is that the EXT/MCE+ will result in greater decreases in pre-quit nicotine dependence and smoking behavior and better cessation outcomes as compared to the EXT/MCE- group. Secondarily, we will examine reactivity (craving, physiology) in response to a set of standard smoking cues following abstinence and hypothesize less reactivity in the MCE+ group.

With the second aim of the study we will investigate whether among participants in the EXT/MCE+ group, EXT engagement (compliance with smoking VLNCs), EXT response (decrease in smoking behavior), MCE response (decreased craving across MCE sessions), and post-quit cue-reactivity predict smoking cessation outcomes. The proposition is greater compliance with, and response to smoking

VLNCs and greater decreases in craving across the course of MCE and in the cue-reactivity assessment will be associated with better smoking cessation outcomes.

Data & Safety Monitoring

Data capture will occur in several ways. All source documents will be stored in the participant binders. Research materials include questionnaires, expired air samples for analyzing carbon monoxide and breath alcohol levels, and urine samples for drug and pregnancy screens. Research data without identifiers will be maintained in a locked room and on password-protected computers in the research staff workplace, with only numeric codes identifying subjects. Study consent forms and any PHI will be stored in a locked file cabinet in a separate location from the study data. The link between the participants' names and codes will be stored on a password protected spreadsheet on a secure server. All information collected as part of this study will be accessible only to research staff. The Subject Identifier will be a numeric code that will include information about study number and subject ID number.

It will be made clear to participants that all information obtained during assessments is confidential and that no information will be shared with the participants' clinicians unless the participant requests this in writing. All investigators and staff associated with this project have been trained, and new hires will be trained, on human research ethics in accordance with the requirements of the local institutions.

To ensure minimal missing data, the first time that participants complete the questionnaires, the Research Assistants will go over the questionnaires to ensure that participants understand the questions. Questionnaires will be reviewed for completeness while the participant is present. Several biochemical measures (expired breath CO, urine pregnancy and drug screens) will be analyzed immediately, while the participant is present. If necessary (e.g., if the sample volume is insufficient for analysis), the Research Assistant will try to obtain another sample.

A study participant may be discontinued from the study if the medically responsible investigator determines it is the best decision in order to protect the safety of a participant. While participating in the trial, adverse events will be assessed at every study visit. All events will be documented and followed up. Events attributed to study product will be reviewed and followed until appropriate medical resolution. The study physician will review and sign off on all adverse events and problems as they occur. The PI will report these events to the IRB in accordance with HRPP policies. The PI will review and sign off on all adverse events prior to a participant's completion of the study. Monitoring by the PI and study physician will be conducted on an ongoing basis.

Privacy, Data Storage & Confidentiality

Participants will be informed, in their consent forms, of the data storage and confidentiality safeguards, which are practiced according to current HIPAA regulations. Except when required by law, the participant will not be identified by name, social security number, address, telephone number or any other direct personal identifiers in the study records. Dr. Cynthia Conklin at UPMC will be a collaborator for the study. She is listed as outside key personnel and will not have access to any study PHI or identifiable information.

Pictures taken by participants will become property of the Duke Health Behavior Neuroscience Research Program for research purposes. A participant's pictures of any private location, such as a home, will not be shown to any other research participants in this or any other study. Any pictures of public places (bus stop, restaurant, etc.) may be used and shown to participants in future studies. All photographic images acquired by participants will be reviewable by participants prior to upload to the secure server. Data from the server can only be accessed by authorized study staff with a username and password.