HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

Measuring Neuroadaptations in Response to Very Low Nicotine Content Cigarettes

Principal Investigator:

Name: Andrea Hobkirk
Department: Psychiatry
Telephone: 717-531-0003 ext. 286415
E-mail Address: ahobkirk@pennstatehealth.psu.edu

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1.0 Objectives

1.1 Study Objectives

The specific aims of the current study are to:

1) Examine the longitudinal effect of very low nicotine content (VLNC) cigarettes on changes in task-related functional neural activation within brain circuitry associated with incentive salience valuation and executive function. We hypothesize that, for the VLNC group compared to the normal nicotine content (NNC) group:

a. Reactivity to smoking vs. pleasant odors within incentive salience circuitry will decrease.
b. Reactivity to monetary rewards within incentive salience circuitry will increase.
c. Activity during decision-making and inhibitory control within executive control circuitry will increase.

2) Assess the longitudinal effect of VLNC cigarettes on changes in effective (directional) connectivity between incentive salience and executive control brain circuitry. We hypothesize that, for the VLNC group compared to the NNC group:

a. The influence of executive control over incentive salience circuitry, measured during task demands that simultaneously engage both processes, will increase.
b. The influence of non-smoking reward salience circuitry over smoking salience circuitry during the odor cue reactivity task will increase.

3) Establish measurable and objective neural outcomes of successful reductions in smoking dependence.

1. We hypothesize that changes in functional activation and effective connectivity over the course of the VLNC intervention will be correlated with reductions in subjective and behavioral assessments of smoking dependence, including the number of cigarettes smoked per day, subjective reports of dependence, craving, and withdrawal.

4) Assess the effect of VLN Cigarettes vs NNC cigarettes on the levels of salivary miRNAs targeting dopamine, glutamate, acetylcholine and GABA-related transcripts over 6-weeks.

1. We hypothesize that the VLNC group will have significantly more changes in miRNA expression than the NNC group. A two-way repeated measures ANOVA will be conducted to compare changes in miRNA expression over three time points for the VLNC and NNC groups.

5) Determine if within-subject changes in miRNA expression are associated with changes in fMRI BOLD signal during smoking cue-reactivity and inhibitory control tasks for the VLNC group over 6-weeks.

1. We hypothesize that salivary levels of miRNAs with putative targets in the nicotine addiction pathway will be associated with decreased corticostriatal cue-reactivity and increased ventromedial and dorsolateral prefrontal cortex engagement during inhibitory control in the VLNC group compared to the NNC group.

1.2 Primary Study Endpoints

Changes in neural reactivity to tobacco odor and changes in smoking dependence.

1.3 Secondary Study Endpoints

N/A

2.0 Background

2.1 Scientific Background and Gaps

Although half of the 37 million adult smokers in the US attempt to quit each year, only an estimated 3% are successful.[1,2] This is why smoking continues to be the leading cause of preventable death in the US, killing nearly half a million people each year from tobacco-related causes.[3] Given that approximately 70% of smokers report a desire to quit, there is a critical need for improved neuropharmacological cessation aids to assist current smokers in quitting and to inform FDA regulations aimed at preventing highly addictive tobacco products from reaching the market.[2]

A key neurobehavioral component that contributes to the development of cigarette addiction is the conditioned associations that form between smoking stimuli and the rewarding dopaminergic effects of nicotine.[4] Associative learning is driven primarily by cellular and circuit-level changes in the mesocorticolimbic (e.g., hippocampus, amygdala, nucleus accumbens) and prefrontal brain structures.[4,5] Associations between stimuli and nicotine are strengthened with each puff of a cigarette.[4] Ultimately, sensory smoking cues trigger positive expectancies of smoking and contribute to their high addictive potential.[6] In other words, the salience of these smoking cues becomes heightened. This is why non-nicotine factors significantly contribute to cigarette dependence.[6,7] Animal research has shown that nicotine-associated cues can impede cessation even with pharmacological treatment.[8] Using fMRI, blood-oxygen-level-dependent (BOLD) reactivity to nicotine-associated smoking stimuli has been linked to less control over cravings[9], reductions in withdrawal symptoms[10], and increased ad lib smoking during laboratory tasks.[11] We currently have a limited understanding of how the salience of smoking cues, measured via cue-reactivity, is affected by tobacco products varying in nicotine content the use of cessation aids.

While the salience of smoking cues increase for dependent smokers, the salience of non-smoking incentives, such as money, food, and socioemotional stimuli, is diminished.[12] This is evident by smokers' attenuated neural reactivity to the anticipation and receipt of monetary and food rewards during laboratory tasks compared to non-smokers.[13-15] In addition, smokers show executive dysfunction in sustained attention, working memory, and inhibitory control processes during acute abstinence that are integral to maintaining goal-directed behavior during withdrawal.[16-20] Executive control brain circuitry primarily includes the lateral and medial prefrontal cortex, anterior cingulate (ACC), superior and inferior parietal cortices, and in some cases subcortical structures.[21] There is considerable overlap and communication between the circuitry involved in executive control and incentive salience valuation.[22-24] Impairments in inhibitory control and working memory have been associated with relapse during quit attempts[25,26] and nicotine replacement therapy alleviates executive dysfunctions during withdrawal.[27] We are just beginning to understand how the circuitry underlying incentive salience and executive control work together to influence smoking dependence and treatment outcomes.[13,28,29]

We currently know little about how neural activity and connectivity of the incentive salience and executive control circuitry change during cessation treatment. Given the advancements in pharmacotherapy and non-invasive brain stimulation techniques,[30,31] gaining a nuanced understanding of how brain circuitry adapts during rehabilitation could identify neural targets for treatment. Verenicline and bupropion treatment are associated with reductions in neural activity throughout prefrontal brain circuitry during executive control and cue-reactivity tasks, respectively.[32,33] However, given the reductions in dependence for the control groups, these neural changes were likely due to the effects of the medication, not changes in dependence.[32,33] Very low nicotine content (VLNC) cigarettes have been used as an extinction-based cessation treatment to reduce the rewarding effects of cigarettes by significantly reducing nicotine delivery during smoking.[6,34] Smokers rate de-nicotinized cigarettes as satisfying and trials of VLNC cigarettes result in decreases in the number of cigarettes smoked per day and self-reported dependence.[35] VLNC cigarettes provide a unique opportunity to assess changes in neural circuitry while smokers extinguish the association between nicotine and smoking stimuli and become less dependent on smoking without the confounding effects of nicotine replacement therapy or pharmacotherapy.

The current study will examine functional neuroadaptations in incentive salience and executive control circuitry while smokers switch to VLNC cigarettes over 6-weeks. Identifying brain circuitry that is

modified at various stages of recovery can lead to the development of targeted neuropharmacological cessation aids and brain stimulation techniques. The findings of the proposed study will characterize changes associated with the extinction of conditioned cues and reductions in dependence without the confounding effects of pharmacological aids. By measuring neural processes and connectivity among circuitry mid-intervention, the results of the proposed study will pinpoint aspects of neural circuitry that are sensitive to (or reflective of) early intervention effects.

2.2 Previous Data

The Penn State Center for NMR Research (CNMRR) has pioneered the study of human olfaction, including circuitry involved in the detection and perception of odor[36] and links to motivation, learning, and reward.[37,38] Dr. Yang's mentee, Dr. Cortese, conducted preliminary work showing that the scent of fresh tobacco induced higher subjective craving and skin conductance compared to a no-odor control condition.[39] Using fMRI, pairing smoking odor and visual cues significantly enhanced cue-reactivity throughout frontal and temporal cortices, which was linked to control over craving.[9] The proposed study will extend Dr. Cortese's preliminary work by examining how smoke flavor (i.e., odor and taste) is modified by intervention and associated with dependence and cessation outcomes.

In preliminary work conducted by the Penn State Tobacco Center of Regulatory Science (TCORS) we found that resting state functional connectivity decreased in key regions involved in executive control (frontal pole), reward valuation (anterior cingulate) and craving (insula and thalamus) after nicotine administration with an e-cig.[40] Weaker coupling between reward and executive control networks was associated with less craving after use.[40] This cross-sectional pilot study demonstrated that flavored electronic cigarettes altered brain connectivity among brain regions involved in the development of smoking dependence. The current study extends this work to determine if flavor, without nicotine, is a central feature of the development of smoking dependence.

A 0.4 mg cigarette will be used in the current study to maximize efficacy for reducing smoking dependence and rates of compliance and retention, while minimizing the chance of compensatory smoking. In a large clinical trial, reduced nicotine content (RNC) cigarettes of 0.4 mg were associated with the largest reductions in the number of cigarettes smoked per day, urinary nicotine, and subjective ratings of withdrawal and dependence compared to all other nicotine contents.[35] A separate study found that cigarettes at 0.3 mg increased compensatory smoking over 0.5 mg cigarettes.[41] Preliminary results from the Penn State RNC trial with low socioeconomic status (SES) smokers shows that ratings of cigarette satisfaction only dropped 38% over the 7-month trial despite the 97% reductions in nicotine content, which likely contributes to their high rates of compliance and retention. In addition, preliminary fMRI research has shown that RNC cigarettes (2.4 mg) paired with a 21 mg nicotine patch was related to reductions in BOLD activation to smoking-related cues and increased activation to neutral cues in the amygdala after only 2 weeks.[34] Reduced activation in the thalamus over the course of intervention was predictive of improved cessation outcomes in a post-treatment quit attempt.[34]

2.3 Study Rationale

Tobacco use is the leading cause of preventable death in the U.S.[3] Smoking dependence is in part maintained by three interrelated cognitive processes; 1) enhanced incentive salience of smoking stimuli[42,43], 2) diminished incentive salience of non-smoking rewards,[14,44,45] and 3) impairments in executive control[25]. These interrelated processes lead to poorly controlled motivational drives to smoke and contribute to smoking maintenance and relapse during quit attempts.[46,47]

The incentive salience, or motivational value, of conditioned smoking stimuli becomes enhanced for regular smokers.[48] This is evident in the subjective and physiological reactivity smokers show in response to smoking-related cues.[49] In the laboratory, visual, tactile, and auditory smoking stimuli can elicit strong cigarette craving, shorter latency to smoking, and more frequent, higher volume cigarette puffs.[50] Flavor, a combination of odor and taste, is one smoking stimuli that has interested tobacco companies for its potential to increase dependence on cigarettes.[51,52] Despite evidence supporting the role of flavor in addiction and the rising popularity of new flavored tobacco products, we currently know little about the neurobiological impact of flavor on the development and maintenance of smoking dependence. This

is a research priority for NIH's Tobacco Regulatory Science Research Program due to its potential to inform tobacco policy.[53]

Alternatively, the salience of non-smoking incentives, such as money, food, and socioemotional stimuli, is diminished among smokers.[12] This is evident by smokers' attenuated neural reactivity to the anticipation and receipt of monetary and food rewards during laboratory tasks compared to non-smokers.[13-15] Attenuation of reward reactivity, most notable in the striatum during states of acute smoking abstinence, has been associated with relapse during cessation attempts.[14,15,54]

In addition to changes in incentive salience, there is growing evidence that smoking dependence is characterized by weakened executive control, in which "top-down" systems fail to inhibit the "bottom-up" incentive salience processes that drive smoking motivation.[17,55] Smokers show executive dysfunction in sustained attention, working memory, and inhibitory control processes during acute abstinence that are integral to maintaining goal-directed behavior during withdrawal.[16-20]

We currently know little about how neural activity and connectivity of the incentive salience and executive control circuitry change during recovery. Given the advancements in pharmacotherapy and non-invasive brain stimulation techniques,[30,31] gaining a nuanced understanding of how brain circuitry adapts during rehabilitation could identify neural targets for treatment. VLNC cigarettes have been used as an extinction-based cessation treatment to reduce the rewarding effects of cigarettes by significantly reducing nicotine delivery during smoking.[6,34] Over the course of a VLNC extinction trial with nicotine replacement therapy, smokers' reactivity in the amygdala to smoking over neutral visual cues decreased.[34] Participants who successfully abstained in a quit attempt following the extinction trial had reduced cue reactivity in the thalamus and ventral striatum compared to participants who relapsed.[34]

The central hypothesis underlying this award is that brain circuitry associated with incentive salience valuation and executive control can be altered by treatment interventions and, consequently, serve as potential neuromarkers of dependence reduction and cessation treatment outcomes. In a double-blind, randomized controlled trial, dependent smokers will be randomized to a 6-week VLNC cigarette intervention (N=50) or a 6-week normal nicotine content cigarette control condition (NNC; N=25). Participants will undergo fMRI scans at baseline, and 6-weeks to investigate the treatment-related modulation of brain circuitry involved in incentive salience valuation and executive control. Imaging tasks will assess the incentive salience of smoking cues and non-smoking rewards and executive function to identify changes in functional activity within, and effective connectivity between, known salience and executive control brain circuitry. A novel fMRI task using specialized odor presentation equipment and fMRI sequences will assess neural cue reactivity to smoke odors.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. 21-60 years old
2. Smoke ≥5 cigarettes per day
3. >1 year of daily smoking
4. No quit attempt in prior month and not planning to quit smoking within next 3 months
5. Able to understand and consent to study procedures
6. Educational attainment < college degree or annual household income < $50,000
7. Plan to live in local area next 3 months
8. Women not pregnant or nursing and not planning to become pregnant in the next 3 months
9. Able to read and write in English
10. Access to computer with internet service that allows for Zoom

3.2 Exclusion Criteria

1. Use of non-cigarette tobacco products in the past 7 days
2. Use of illicit substances more than once a week in the past 3 months (excluding marijuana)
3. Current alcohol abuse impairing participation

4. MRI safety contraindications (e.g., metal implants, claustrophobia)
5. Unstable or significant medical conditions (e.g., COPD, coronary heart disease)
6. Major neurological conditions or brain trauma
7. Major surgeries planned in next 3 months
8. Use of smoking cessation medication in prior month (e.g., varenicline, patch)
9. Uncontrolled serious mental illness, suicidality, or inpatient psychiatric hospitalization in the past 6 months
10. Unwillingness to provide urine samples
11. Unwilling to smoke study assigned cigarettes for the remainder of the trial
12. Plans to move or take extended travel out of the area in the next 3 months
13. Any other condition or situation that would, in the investigator's opinion, make it unlikely that the participant could comply with the study protocol
14. Self-reported color blindness
15. Left-handedness
16. Smell dysfunction as determined via standardized assessment

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

- Excessive visit cancellations or no-shows.
- Inability to attend the study visit within the allowed visit window.
- Inability or unwillingness to smoke study cigarettes.
- Lost contact.
- Pregnancy (confirmed by urinary pregnancy test at each MRI visit).
- Suicide attempts
- Cardiovascular (CVD) event: including MI (heart attack), PTCA (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease, arrhythmias and new valvular disease (e.g., mitral or aortic regurgitation).
- DVT/PE (deep vein thrombosis/pulmonary embolism)
- Participants may choose to remove themselves from the study by informing the research team at any point during the study.
- Significant baseline smoking rate increase at 3-week check-in or post-scan visit. Either one, or both criteria combined:
    - The average CPD increases by more than 100% from the average CPD on the baseline cigarette log.
- Worsening substance use in which the participant is behaving inappropriately at visits or demonstrates an inability to continue with the study.
- Any hospitalization in which participation in the study could be detrimental to the recovery process. (e.g., recovery from a major surgery, etc.)
- Any situation where participant is not able to smoke research cigarettes for a period of more than 3 days
- Participant doesn't comply with the protocol, behaves in an inappropriate or threatening manner, admits to lying about eligibility criteria, or is participating in other smoking research studies that could affect the primary outcome measures.

3.3.2 Follow-up for withdrawn subjects

Participants who report an inability to smoke research study cigarettes will be asked to complete a final MRI scan visit before being withdrawn from the study.

4.0 Recruitment Methods

4.1 Identification of subjects

All recruitment for this study will be routed through IRB Protocol #2213 which will also serve as the initial recruitment point of contact.

4.2 Recruitment process

Interested volunteers will complete a brief phone screen to determine preliminary eligibility and to learn more about the study. Interested and eligible participants will be scheduled for an in-person screening visit. Subjects that were unable to be contacted via phone will be sent an email asking them to reach out to the study team if they are interested.

4.3 Recruitment materials

The study will be described to interested volunteers over the phone using the phone screening script.

4.4 Eligibility/screening of subjects

Study staff will collect preliminary eligibility information over the phone. A full script and screening questions for this study are in the "Consent Forms and Recruitment Materials" section of the IRB application.

After a participant has met preliminary eligibility criteria over the phone, they will be scheduled to complete a final screening over the phone or ZOOM to determine study eligibility. See "7.0 Study Design and Procedures" and "Supporting Documents" for details on the screening assessment tools.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Screening portion: Subjects will have the screening portion of the study explained to them in detail over a phone call. They will have the opportunity to ask any questions and then will be asked to give their verbal consent to take part in the screening portion.

Randomization/MRI portion: During the phone screen, participants will have the study explained to them in detail, and be mailed a long form consent form to look over before their first MRI visit. They will have the opportunity to ask questions at both visits and then will be asked to sign their consent form at the MRI visit.

5.1.1.2 Coercion or Undue Influence during Consent

Once potential study volunteers are identified they will be given information about the study and offered the opportunity to participate. The researchers obtaining consent will be instructed to clearly indicate that the participant's enrolling in the trial is purely voluntary and the researchers will not offer comments about whether they believe the participant should enroll in the study or not. Given the number of contacts and visits involved in the study protocol, the compensation provided to the participant is modest.

5.1.2 Waiver or alteration of the informed consent requirement

N/A

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

The consent process will be documented in writing as follows::

- The current IRB approved long form written consent form will be used.
- The subject will sign the consent form during their MRI visit after both screenings have taken place.
- • A copy of the consent form will be provided to the subject/representative. Whenever possible the consent form will be provided to the subject in advance of the consent discussion.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

Volunteers who are interested in the study will be asked to provide verbal consent to allow the researcher to screen them for the study during a phone and a remote screening contact. First, volunteers will provide informed verbal consent prior to completing a brief phone screen to determine preliminary eligibility. Second, volunteers who meet preliminary eligibility, will complete a more in-depth screening assessment via ZOOM to determine final study eligibility. Volunteers will be emailed an electronic copy and mailed a paper copy of the Summary Explanation of Research prior to the final phone screen. Participants will be asked if their screening information can be retained so that the study team will know reasons that participants are not eligible for the study. The screening takes place prior to the randomization portion of the study and involves low risk procedures.

In addition, participants who are not eligible for the study, or those who begin the screening procedures but are not interested in completing it after learning more about the study, will be asked if they would be interested in being contacted for future studies being conducted by our research team. They will be informed that by providing their name and phone number, they will be consenting to allow the study team to contact them in the future.

5.3 Consent – Other Considerations

N/A

5.3.1 Non-English Speaking Subjects

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent

5.3.2.2 Adults Unable To Consent

5.3.2.3 Assent of Adults Unable to Consent

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

5.3.3.2 Assent of subjects who are not yet adults

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☐ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☒ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

All identifiers stored electronically will be permanently deleted, including the keys linking participant ID numbers to their identifying information and paper consent forms will be shredded before disposal according to federal regulations and institutional policies.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Information must be obtained from the subject during recruitment to determine/confirm eligibility. The screening visits will collect PHI to confirm eligibility (date of birth) and to allow for scheduling/reminders of future visits which requires us to have complete contact information.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Determining/Confirming eligibility prior to obtaining consent will ensure only eligible subjects are enrolled in the study. Several factors make the collection of written informed consent prior to the randomization visit impractical, including; time constraints with the use of the MRI facility,the requirement that subjects record their daily cigarette usage between screening determination and the randomization visit, the need to prepare product for dispensation

between eligibility determination and the randomization visit, and the risk of unnecessary burden on volunteers.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

This is a two-arm, randomized, double-blind parallel group trial. Smokers will be randomly assigned to smoke very low nicotine content (VLNC) (n=50) or normal nicotine content (NNC) (n=25) SPECTRUM cigarettes for 6 weeks. Participants and study staff will be blind to the experimental cigarette allocation until the study is complete. The groups will be stratified by gender.

7.2 Study Procedures

7.2.1 Final remote screen (Week 0)

A Penn State Health Zoom meeting link will be emailed to participant for the previously scheduled time.

A standardized smell test (this standardized test includes a No. 2 pencil and a pamphlet that the participant will complete on the Zoom meeting to allow the study team member to oversee the completion; the test will be scored over the Zoom session), paper cigarette logs, folder, written consent form, summary explanation of research, welcome letter and visit reminder card will be mailed to the participant to arrive before scheduled Zoom meeting. If there is a delay in the mail, the Zoom screening visit will be rescheduled.

The following information will be collected to determine eligibility and collect baseline information:

1. REDCap Survey Questionnaires:
    1. Compliance questionnaire
    2. Tobacco use history
    3. Demographics
    4. Legal history
    5. Audit C
    6. Butt-out
    7. Environmental Smoke Questionnaire
    8. Social support
    9. Smoking Motivation (WISDM-Brief)
    10. Craving questionnaire
2. Interview

1. Visit screener
2. Medical history and medications
3. NIDA Substance use quick screen
4. Cigarette details
5. Concomitant medications

3. Biomarkers
    1. Smell function will be assessed with the B-SIT Test. Gender-normed standard scores will be used to determine if participants have normal smell function for eligibility.
4. Participants will complete computerized decision-making tasks to gain familiarity prior to the MRI scan. The tasks include a stroop interference task, monetary temporal discounting task, and a Smoking Go/NoGo task. Participants will be shown a powerpoint that explains the screens/images they will see while in the MRI during an odor-cue reactivity task All tasks will be completed in approximately 15 minutes.
5. At the end of the visit, participants will be asked to keep a log of the cigarettes they smoke each day until their next visit. Participants will receive a daily REDCap survey link via text message using the Twilio service. The survey will ask participants to record the frequency and type of tobacco and alcohol used that day. Participants will be instructed on how to complete the survey and will be provided with a paper log to tally their cigarette use throughout the day. Participants who are unable or unwilling to receive study text messages will track their cigarette use on the paper log only. The REDCap or paper daily cigarette log surveys are not mandatory for participation.

Time commitment: 1.5 hour

Participants will be asked to refrain from smoking for 14 hours prior to MRI Visit 1. A Zoom call (**Remote Visit 1**) and In-person visit (**MRI Visit 1**) will be scheduled.

7.2.2 MRI visit 1

Participants will complete the following procedures in person after refraining from smoking for 14 hours prior to the visit.

Participants will sign their long form written consent at this visit prior to any further study procedures.

1. REDCap Survey Questionnaire
    a. Nicotine Withdrawal (MNWS)
    b. Smoking Urges (QSU)
    c. Craving questionnaire
2. Interview
    a. Penn State CNMRR MRI Safety
    b. Scent Ratings post MRI Scan

3. Biomarkers
    a. Urine collection for cotinine analysis and pregnancy determination: Obtain urine and process pregnancy test for women of child bearing age (have had a period in the past 12 months) who have not had a hysterectomy.
    b. Saliva collection for potential cotinine analysis, micro RNA (miRNA) biomarker analysis and use in future research.
    c. Exhaled carbon monoxide will be measured using a hand-held monitor.

4. A member of the study team will first review the MRI safety sheet and determine that it is safe for the participant to be scanned. If safe, participants will complete a one-hour MRI scan that will include the following tasks.

The risks and discomforts associated with this project are the same as that associated with standard clinical MRI and EEG studies, which are minimal. Risk exists from radio frequency heating of the head, but is safe at the specific absorption rate (SAR) limits prescribed by the FDA. The SAR of radiofrequency field exposure is monitored throughout the study and maintained below the limits established by the FDA.

The second risk is the potential danger of the magnetic field, which can produce injury if ferromagnetic devices are accidentally brought into proximity of the magnet. All patients and staff are screened for magnetic objects, and access to the magnet area is restricted. Discomforts may be caused by claustrophobic environment in the MRI scanner to some subjects as well as from the loud tapping noises made during the scan process.

a. High resolution anatomical scan (~10 minutes)
b. Monetary temporal discounting task (~15 mins).

Participants will be asked to choose 96 times via button box between two options with specified dollar amounts and time delays to receipt of the money.

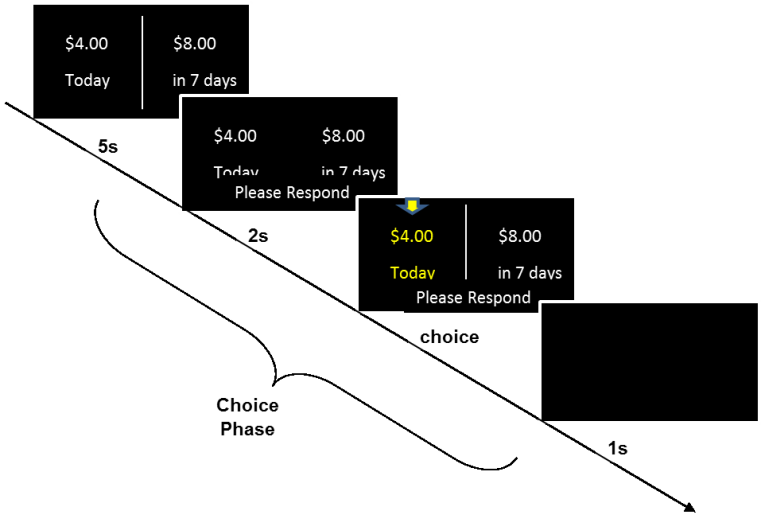
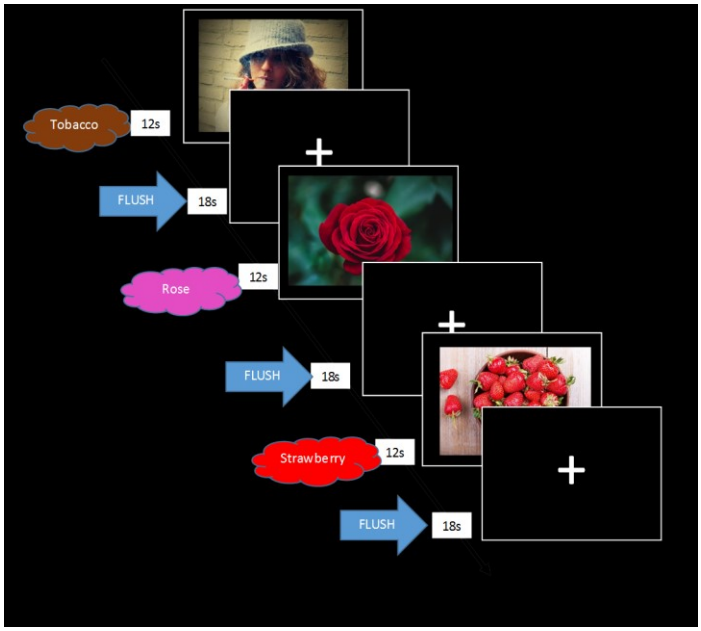


Figure 1. Illustration of monetary temporal discounting task

c. Tobacco odor cue-reactivity task (~15 minutes)

An odor cue-reactivity task will be used to compare neural reactivity to tobacco, strawberry vanilla, and neutral odors. Two runs of alternating blocks of tobacco smoke odor, strawberry vanilla odor, and neutral odor (propylene glycol) will be delivered for 15 presentations. The odor will be presented for 6 seconds followed by 22 to 38 seconds of no odor (fresh air). A standardized MRI-compatible olfactometer at the Penn State CNMRR will be used to deliver odors inside the scanner at the opening of the participant's nose through plastic Teflon tubing. Participants will wear a respiration belt that will monitor the natural pace of their breathing to deliver the odor prior to inhalation. The odors will be presented in randomized order.



d. Smoking Go/NoGo task (~25 mins)

Using a button box inside the scanner, participants will press a button (Go) as quickly as possible or inhibit their button press (NoGo) when presented with smoking and non-smoking pictures bordered in blue or yellow. Participants will respond to 768 pictures total in pseudorandomized order.

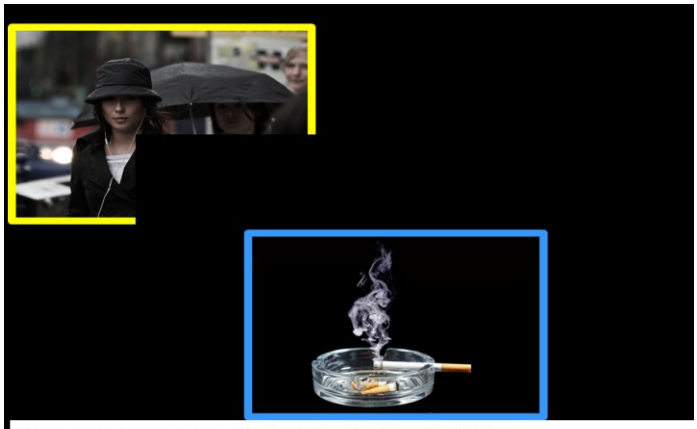


Figure 3. Illustration of smoking Go/No Go task.

5. Prior to the visit, an unblinded member of the study team will randomize the participant to either the VLNC or NNC cigarette group based on a pre-determined block randomization list. The unblinded study member will identify the cigarette packs with the assigned nicotine content by NRC code and prepare them for redistribution by re-labeling each pack with the participant ID number and a label indicating these are research cigarettes The unblinded study member will keep records of the RTI log numbers of the packs dispensed to each participant at each visit. At the end of MRI Visit 1 participants will be given an ample 6-week supply of their assigned cigarette (125% of baseline cigarettes per day) and instructed to only smoke study cigarettes until their next scheduled appointment. Participants may contact the study team to receive more study cigarettes if they run out prior to their next visit unless this is more than a 100% increase from their baseline CPD. Participants will be instructed to continue completing the daily REDCap cigarette log surveys that they receive via text message and will also be given paper cigarette logs to track use throughout the day.

Time commitment: 2 hours

7.2.3 Remote visit 1 (scheduled for +1 to +3 day(s) of in person MRI visit)

Participants will complete the following procedures over Zoom

1. REDCap Survey Questionnaire
    a. Depression (CESD)
    b. COPD (CCQ)
    c. Psychological Distress (Kessler K6)
    d. Nicotine Dependence
    e. Anxiety (ASQ)
    f. Sleep Disturbance
    g. Cigarette Liking
    h. Stages of Change
    i. Perceived Stress
2. Interview
    a. Concomitant medications
    b. Adverse event trigger questions
3. Out of scanner tasks
    a. Participants will complete a monetary temporal discounting task. During this computerized task, participants will choose between two options with specified dollar amounts and time delays to receipt of money (see MRI task image below).
    b. Participants will complete a computerized stroop interference task where they will view color words printed in the same color (i.e., blue, red, yellow, green), color words printed in an incongruent color (e.g., "blue" printed in red), and color neutral words printed in color (e.g., "hat" printed in red). Participants will be asked choose what color each word is printed in by pressing a button labeled to indicate each color.

7.2.4 Phone call 1

Participants will be contacted in the 2nd week of the randomization phase to check-in regarding their next scheduled appointment and their success with cigarette tracking and study cigarette compliance.

Time commitment: 15 minutes

7.2.5 Remote visit 2 (Week 3 ± 5 days)

Participants will complete a Zoom call three weeks into the randomization phase. During this visit participants will complete the following activities:

1. Review cigarette tracking logs with study staff.
2. Concomitant medication
3. Adverse event trigger questions
4. Discuss and problem-solve barriers to adherence
5. Computerized REDCap Survey Questionnaires (see Remote Visit 1 and MRI Visit 1)
6. Complete computerized out-of-scanner tasks.

Time commitment: 1 hours

Participants will be asked to refrain from smoking for 14 hours prior to MRI visit 2. The MRI visit 2 and Remote visit 3 will be scheduled.

7.2.6 Phone call 2

Participants will be contacted in the 4th week of the randomization phase to check-in regarding their next scheduled appointment and their success with cigarette tracking and study cigarette compliance.

Time commitment: 15 minutes

7.2.7 Remote visit 3 (scheduled for -1 to +1 day of in person MRI visit)

Participants will complete the following procedures over a Zoom call

1. Concomitant medications
2. Adverse event trigger questions
3. Perceived health risk rating
4. Computerized REDCap Survey Questionnaires (see Remote Visit 1)
5. Review cigarette tracking logs.
6. Complete computerized out-of-scanner tasks
7. Complete quit choice survey and counseling. Participants will be reminded that they will receive a text message survey in 12 weeks asking for information on quit attempts.

7.2.8 MRI visit 2 (Week 6 ± 5 days)

Participants will return to the CNMRR Center for their final MRI scan after refraining from smoking for 14 hours prior to the visit.

For the final study visit, participants will complete the following activities:

1. Return all (empty and full) cigarettes packs
2. Penn State CNMRR MRI safety and Scent Ratings (post MRI)
3. Urine collection for cotinine analysis and pregnancy determination: Obtain urine and process pregnancy test for women of child bearing age (have had a period in the past 12 months) who have not had a hysterectomy
4. Saliva collection for potential cotinine analysis, micro RNA (miRNA) biomarker analysis, and use in future research.
5. Exhaled carbon monoxide will be measured using a hand-held monitor.
6. Computerized REDCap Survey Questionnaires (nicotine withdrawal, smoking urges, craving)
7. The MRI technologist will first review the MRI safety sheet and determine that it is safe for the participant to be scanned. If safe, participants will complete a one-hour MRI scan.

Time commitment: 2 hours

7.2.7 Text message with quit attempt survey (Week 18 ± 5 days)

Participants will receive a text message with a REDCap survey link inquiring about current smoking status and past 12-week quit attempts. Participants will be sent a second text message if they do not complete the survey within 72 hours of the first message. The study coordinator will call participants who are unwilling or unable to receive text messages to complete the survey.

7.3 Duration of Participation

Participants who complete all study visits in the ideal time frame will be in the study for 18 weeks. The majority of participants are expected to complete the study in 7 to 18 weeks.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Participants will be provided with research cigarettes that have a similar nicotine content to current commercially available cigarettes (11.6mg) or a very low nicotine content (0.29mg). Participants will have a 0.67 probability of being assigned to the very low nicotine content research cigarette and a 0.33 probability of being assigned to the usual nicotine content cigarette. The cigarettes will be managed by an unblinded study member.

7.4.2 Treatment Regimen

Participant will be asked to smoke their assigned study research cigarettes (11.6 mg or 0.29 mg nicotine content) for 6 weeks.

7.4.3 Method for Assigning Subject to Treatment Groups

Participants will be randomized to one of two experimental conditions based on a blocked randomization sequence stratified by gender. A 2:1 randomization strategy will be used, resulting in 0.67 probability of being assigned to the very low nicotine cigarette, and a 0.33 probability of being assigned to the usual nicotine cigarette. The randomization key will be stored in REDCap and will be accessible only to unblinded study members and the faculty project mentor. The principal investigator will not have access to the code to ensure blinding.

7.4.4 Subject Compliance Monitoring

Participants will track the number of cigarettes they smoke each day in the REDCap surveys sent to them via text message and using a paper tally tracking log. Participants will be given detailed instructions on how to complete the logs and they will be reminded at each study contact to only use the research cigarettes they have been given. Questions will be asked at each contact to review their log and verify how many cigarettes they are smoking each day. Participants will also be asked to self-report their other tobacco use including products such as cigars, pipes, chew, snus, dip, hookah, electronic cigarettes and dissolvable tobacco. Exhaled carbon monoxide measurements, urine, and saliva will be taken at each contact to verify smoking intensity and cotinine levels.

7.4.5 Blinding of the Test Article

Cigarette cartons will arrive to the PI's laboratory with a packaging slip that provides information about the cartons in the shipment which includes the NRC code nicotine content, RTI log carton bar code number and a batch/lot number. Each carton is labeled with the RTI Log number. The RTI Log number and corresponding NRC code will be carefully recorded by the unblinded study member in the REDCap randomization database. Individual packs do not contain any identifiable information; however with each shipment a set of labels indicating the RTI log numbers are also included. At the time of dispensing, the unblinded study team member will remove the RTI log number from the carton. If less than a full carton is dispensed to a participant, the remaining packs in the carton will be labeled with the RTI log number labels. At the time each pack is dispensed, the RTI log number label will be removed and maintained by the unblinded study team member as confirmation that the correct product was dispensed to the subject at the visit.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

Experimental cigarettes will be provided free of charge to the investigators via the NIDA Drug Supply Program (see Notice: NOT-DA-13-002). Cartons (10 packs/carton) with packs of 20 cigarettes/pack will be received from the Research Triangle Institute in North Carolina.

7.4.6.2 Storage

At Penn State Hershey, cigarettes will be stored in locked, -20 freezers that are maintained by the PI's Department. Standard laboratory protocols for freezer temperature control monitoring and recording will be followed. Prior to cigarette assignment, the cigarettes may be stored unfrozen for a period of time up to 3 weeks.

7.4.6.3 Preparation and Dispensing

Assignment: When a new participant is randomized, they will receive the packs labeled with their study ID number indicating that these are research cigarettes.

Preparation: Once the cigarettes are received, they will be blinded by the unblinded study member. At the time of dispensation, the unblinded study member will prepare a bag of cigarette packs labeled with the participant ID number and indicating that they are research cigarettes. The RTI log number labels will be removed from the packs/cartons at the time of preparation for dispensing.

Where: All receiving, sorting, blinding of the initial study product will be done by an unblinded member of the study team in a designated space for this study at Penn State Hershey. Dispensing of product to study participants will occur at the Center for NMR Research where participants will complete their MRI visits.

Dispensing: Cigarette packs containing 20 cigarettes will be prepared by the unblinded study member prior to a participant's in person visit. All packs will be given to participants in the original packaging. Each individual pack of cigarettes will have a label with the participant ID number and a list of possible nicotine doses the cigarettes may contain. The coordinator will give the cigarettes to the participant at their second visit. The number of packs dispensed will be determined by the self-reported number of cigarettes per day they smoke determined by the baseline week cigarette log. Participants will be provided with 125% of the cigarettes necessary for each week of usual smoking. Participants will be able to smoke as many or as few cigarettes as they choose and will be required to return all packs (empty and full) at the next visit.

7.4.6.4 Return or Destruction of the Test Article

The unblinded study member will track all receipt, dispensing, and blinding of cigarettes for the duration of the project. The study coordinator will track all dispensing of blinded cigarettes for the duration of the project. The unblinded study member will have access to receipt and dispensation logs to create reconciliation reports on an ongoing basis. Participants will be instructed to bring all research cigarette packs to the next visit, regardless of whether they are empty, unopened or partially used. The number of unused packs will be recorded and returned to the study participants at the end of the visit. We will not ship experimental cigarettes back to the NIDA Drug Supply Program. Empty packs dispensed to and returned by study participants will be destroyed once the usage information has been documented.

7.4.6.5 Prior and Concomitant Therapy

Concomitant medication use will be collected regularly throughout the trial to serve as covariates during analysis and to monitor participant health conditions. Participants taking varenicline, bupropion or nortriptyline as a smoking

cessation medication in the prior month will be excluded from the study. Participants taking bupropion or nortriptyline for depression management and who expect to continue use of the medication throughout the trial will be eligible to participate. Additionally, participants who are prescribed bupropion or nortriptyline for depression management at any point during the study will be eligible to continue with the study. Medications related to certain medical conditions that are exclusions to the study, such as COPD and current heart conditions, will serve to alert the study staff of the presence of these conditions during screening. Once the participant is entered into the randomized double blind phase of the study, there are no medications that will interfere with the participant's ability to participate.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

We expect to enroll approximately 90 participants in order to retain 75 study completers.

8.2 Sample size determination

Dependent smokers of low SES (n=75) will be recruited for the current study through the TCORS study call center (protocol #2213). Two-thirds of the sample (n=50) will be randomized to the VLNC group to maximize power for the within-subjects repeated measures analyses while still allowing for an analysis of between-subjects effects. There is not currently an accepted method for determining sample size a priori for repeated measures fMRI designs. With repeated measures behavioral data, to detect a medium effect size (f=0.25) with 80% power and a Type I error rate of .05, a sample size of 28 is required to detect within-subjects effects, 86 for between-subject effects, and 28 for within x between interactions. The estimate for detecting such effects with fMRI is likely somewhat higher; however, my mentors have found within-subject effects with similar tasks that will be used for this project with comparable sample sizes; smoking cue reactivity (n=22)[61] card-guessing task (n=44)[5], and the n-back task (n=33)[62]. Thus, we estimate that the current design will have adequate power to detect small to medium within-subjects effects and medium to large between-subjects effects. The design will serve as pilot data to determine sample size for future studies. TCORS found retention rates of 85% for their 18-week trial and a prior 6-week VLNC intervention found retention rates at 92%.[49] Retention for the proposed study will likely be higher given frequent contact with participants (3-week visit and two phone-check-ins); however, with a conservative estimate of 80% retention and adequate compliance, the final sample size (n=60) would still be adequately powered. We will recruit until we have 75 study completers. It is likely that participants that complete informed consent at the remote screening will be ineligible. Therefore, we expect around 90 participants to complete informed consent and 75 to complete the entire study.

8.3 Statistical methods

Data Analysis. Images will be preprocessed using FSL, including registration to high resolution anatomical images and standard space, brain extraction, slice timing correction, spatial and temporal smoothing, intensity normalization, physiological noise correction, and motion correction for 6 motion parameters and artifacts identified via ICA-AROMA.[63] For task-based images, contrasts of the relevant conditions will be determined during first level analyses as described above and averaged across multiple runs for each participant.

Aim 1: Examine the longitudinal effect of VLNC cigarettes on changes in task-related functional neural activation within brain circuitry associated with incentive salience valuation and executive function. Treatment-related within-subject and between-subject changes in BOLD activation during all fMRI tasks will be assessed in linear mixed-effects models using FSL software. Whole-brain analyses and ROI analyses based on pre-determined salience and executive control circuitry will be conducted. Paired t-tests will identify anatomical regions showing statistically significant differences from baseline to 6-week scans across groups.

Aim 2: Assess the longitudinal effect of VLNC cigarettes on changes in effective (directional) connectivity between incentive salience and executive control brain circuitry. Dynamic causal modeling (DCM) using SPM12 software will measure effective connectivity between ROIs in the incentive salience and executive control networks.[64] Specifically, DCM identifies models with task-specific increases in the dependence of the BOLD activity timecourses between a priori selected nodes and estimates directionality. We expect that the use of the VLNC cigarettes will strengthen the influence of the executive control over incentive salience circuitry during the smoking Go/NoGo and temporal discounting tasks. ROIs will be selected a priori for these analyses. Given the novelty of the odor cue reactivity task, active brain circuitry identified in Aim 1 will be included as nodes in the DCM model to test the hypothesis that non-smoking reward circuitry will exert an increasing influence over smoking salience circuitry. Connectivity estimates from the models will be included in a mixed-effects ANOVA to determine between-subjects and within-subject effects across the trial.

Aim 3: Establish measurable and objective neural outcomes of successful reductions in smoking dependence. FSL's Randomise one-sample t-test will be conducted on change scores to determine if changes in BOLD activity are associated with reductions in subjective markers of dependence (FTND, HONC, MNWS, QSU), cigarettes smoked per day, and quit intention and success. Changes in connectivity estimates will be correlated with changes in subjective and behavioral outcomes.

9.0 Confidentiality, Privacy and Data Management

9.1 Confidentiality

See the Research Data Plan Review Form

9.1.1 Identifiers associated with data and/or specimens

9.1.1.1 Use of Codes, Master List

9.1.2 Storage of Data and/or Specimens

9.1.3 Access to Data and/or Specimens

9.1.4 Transferring Data and/or Specimens

9.2 Subject Privacy

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

The study coordinator will be responsible for the daily oversight of subject safety. Research staff will assess for adverse events at each study visit and will make appropriate referrals to medical providers. Dr. Hobkirk, will meet regularly with the study staff to review participant's progress and their experiences with the tobacco products, including any adverse events. Entrance criteria will be reviewed following screening. Medical history will be reviewed by Dr. Hobkirk for any contraindications for the treatment products and smoking behavior will be checked at each visit.

10.2 Data that are reviewed

Data that will be reviewed include:

- Accrual and retention
- Adverse events and serious adverse events
- Protocol deviations/violations
- Misconduct

- Conflict of interest
- Participants' ability to achieve study requirements
- Changes in cigarette consumption from baseline

10.3 Method of collection of safety information

All data, including safety data, will be coded directly into REDCap case report forms during study visits, over the phone or via online REDCap survey. Participant adverse events and serious adverse events will be assessed at each in-person study visit but can be reported at any time during the study.

10.4 Frequency of data collection

Safety data including adverse events and serious adverse events will be collected at each in-person visit. Cigarettes smoked per day will be collected regularly at in person visits.

10.5 Individuals reviewing the data

The study coordinator will be responsible for the daily oversight of subject safety. Dr. Hobkirk, will meet regularly with the study staff to review participants' progress and their experiences with the tobacco products, including any adverse events.

10.6 Frequency of review of cumulative data

Safety data will be reviewed cumulatively every six months by the principal investigator.

10.7 Statistical tests

Statistical methods will be used to analyze the safety data to determine whether harms are occurring. Paired sample t-test (or nonparametric Wilcoxon Rank-Sum test) will be used to examine the changes in cigarette consumption from the baseline. In addition, the point estimates and 95% confidence intervals for the accrual and retention-dropout rate, completion rate, and the proportions of adverse events and serious adverse events will be generated. The data will not be reviewed across treatment groups to maintain blinding; however, if the principal investigator perceives a need to assess safety based on an unblinded analysis, she can request this information and it will be provided.

10.8 Suspension of research

Due to the low risk of the intervention, it is unlikely that there will be a need to suspend the research. However, should the principal investigator identify any issues after reviewing the data, stopping rules for the trial will be developed and followed.

11.0 Risks

Potential risks for subjects are minimal. The cigarettes which will be administered to subjects have been previously tested and found to be of no greater risk than cigarettes the participants are already using. Only regular smokers who are not planning to quit will be recruited to the study. All participants will be free to reduce or quit smoking throughout the study, and smoking cessation counseling will be given to all participants at the end of the study. Subjects will be under supervision throughout their participation in the study and adverse symptoms will be recorded at each visit and monitored by the Principal investigator. The major side effects associated with RNC cigarettes are similar to usual brand cigarettes.

Additional potential risks include:

- Magnetic resonance imaging: MRI does not involve radiation and there are no known long-term risks of MRI. Participants will be assessed for MRI safety at the screening visit and again at each scan visit before entering the scanner. We will be assessing for potential MRI hazards like metal fragments in the body or metal implanted devices that could shift during scanning. Participants will be instructed to remove all metal from their body and clothing before entering the scanning room. The major discomforts of fMRI scanning include lying still in a supine position for a sustained period of time and hearing loud tapping sounds during image acquisition. Participants may be uncomfortable inside the MRI scanner, especially if they do not like to be in closed spaces

("claustrophobia"). In between tasks, participants will be able to talk with the MRI staff through a speaker system. At any time, the participant can choose to stop the scan by squeezing a button.

- The scans done during this study are NOT designed to detect or evaluate any medical condition. They are intended solely for research purposes. The investigators for this project are not trained to perform medical diagnosis, and the scans to be performed in the study are not optimized to find abnormalities. On occasion, a member of the research team may notice a finding on a scan that seems abnormal. When a finding is noticed, one of the investigators may consult a physician specialist, such as a radiologist or neurologist, as to whether the finding merits further investigation. If the specialist recommends further follow-up, the investigator or another member of the research team will contact the participant within **48 hours** of the recommendation and suggest that the participant contact his or her private medical provider for follow-up. To facilitate follow-up care, the participant may be given a copy of the images upon written request. Being told about a finding may cause the participant anxiety as well as suggest the need for additional tests and financial costs. Medical insurance may be affected whether or not the finding is ultimately proved to be of clinical significance. Costs for clinical follow-up will not be covered in the cost of research. Participants will be told that their decision as to whether to proceed with further examination or treatment is their own.
- Increased compensatory smoking: Compensatory smoking may lead to increased levels of toxicant exposure. In prior studies, compensatory smoking was minimal and higher levels of toxicant exposure were generally not observed. Cigarette consumption will be monitored throughout the 6-week randomization phase. Safety rules are in place to identify and remove participants who increase their smoking rate significantly.
- Nicotine withdrawal symptoms: Decreased nicotine cigarettes and abstaining from nicotine may result in nicotine withdrawal symptoms (e.g. irritability, anxiety, restlessness, depressed mood, increased appetite, fatigue, insomnia/sleep problems, impatience, headache, difficulty concentrating, frustration, anger, craving for sweets, constipation, coughing, dizziness, nausea and sore throat).
- New pregnancy or intention to become pregnant: Smoking is known to be harmful to the developing human fetus, either from cigarettes or at the recommended therapeutic dose of nicotine replacement therapy. Although there are no known risks of MRI during pregnancy to the woman or fetus, future unknown medical problems could occur. For these reasons women of child-bearing potential must not be trying to become pregnant during the study. Pregnancy status will be confirmed with a urinary pregnancy test at the screening visit and each scan visits.
- Loss of confidentiality: There is a risk of loss of confidentiality if information is obtained by someone other than the investigators. Precautions will be taken to prevent this including direct coding of data in REDCap.
- Randomization in clinical trials: Participants will be assigned to a treatment program by chance. The treatment they receive may prove to be less effective or to have more side effects than the other research treatment(s) or other available treatments.
- Questionnaires: It is possible that some of the questions in the screening assessment interview or questionnaires may make participants uncomfortable. They will be instructed that they are free to skip any questions that make them uncomfortable.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

There are minimal benefits to study participants other than the (uncertain) possibility that participation in the study may reduce their nicotine dependence. Those who complete the study will be offered smoking cessation counseling.

12.2 Potential Benefits to Others

The main benefit to society and others from the study is a greater scientific understanding of the effect of switching to reduced nicotine content cigarettes on neuroadaptations in brain circuitry. This neurobiological process may be a target for future cessation treatment and can inform our basic understanding of addiction.

13.0 Sharing Results with Subjects

This study is not designed to diagnose any disease or condition. However, if during the course of conducting clinical procedures (e.g., MRI), a participant is found to have a result outside of clinical norms, the result will be discussed with the participant at the visit where the result is identified (MRI) or via phone after the visit. The participant will be given a letter indicating what procedure was done and will direct them to contact a medical provider for further evaluation. If a woman tests positive for pregnancy, the results will be shared with the participant and they will be advised to follow up with their doctor for prenatal medical care. They will not be allowed to participate in the study. Abnormal medical results, adverse changes in mental health status, increased toxicant exposure (CO and cigarette consumption) and other outcomes of the study will be treated as Adverse Events. They will be discussed with the participant, documented and the results will be reviewed by the study PI.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

All payments for time compensation, and study completion bonus will be added to their gift cards as they are earned. In total subject will earn up to $370 for participation in the study.

Bonus description: Participants can receive a $75 bonus for returning used and unused cigarette packs, completing all cigarette logs and attending all study visits.

Visit compensation:
Final remote screen: $30
MRI visit 1: $85
Remote visit 1: No compensation
Phone call 1: $15
Remote visit 2: $65
Phone call 2: $15
Remote visit 3: No compensation
MRI visit 2: $85 + $75 completion bonus
12-week Follow-up Text Survey: No compensation

15.0 Economic Burden to Subjects

15.1 Costs

There are no costs that subjects will be responsible for related to the research.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

All in-person participant visits will take place in the Center for NMR Research. Urine and saliva specimens will be stored, processed and analyzed in the Biomarkers and Analytical Chemistry Core (BACC) laboratory on the 3rd floor of the Cancer Institute or sent to another Biosafety approved HMC laboratory if the BACC does not have capacity. These laboratories will not charge participants or insurance organizations for analysis procedures.

16.2 Feasibility of recruiting the required number of subjects

The smoking prevalence in South Central Pennsylvania is 19% of the adult population and approximately 40% of these smokers have no current plan to reduce or quit smoking. Penn State has been conducting clinical trials of new tobacco products for four years and has amassed a database of thousands of smokers interested in research participation (Study# 0002213). With the use of this database we expect to recruit 90 subjects over four years.

16.3 PI Time devoted to conducting the research

Dr. Hobkirk has 75% protected time for research through a NIDA K23 Award, of which this is the primary project. The majority of her time is devoted to research, including this project. The rest of the research team will also have appropriate percent times covered by this grant or Departmental funds.

16.4 Availability of medical or psychological resources

All of our participants will be seen by appropriately trained research staff. Any serious AEs or concerning test results will be passed on to participants along with a letter to their doctor as requested. We do not anticipate any urgent psychological distress requiring psychological care; however, Dr. Hobkirk is a licensed clinical psychologist and will evaluate patients and refer to appropriate emergency mental health resources as necessary. Any urgent health problem will require accompanying the participant to the ER.

16.5 Process for informing Study Team

At least monthly team meetings will be conducted where study procedures, questions and issues will be discussed and resolved. In addition regular project meetings will be held to discuss study progress with the research staff.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Per federal regulations, an Investigational Tobacco Product (ITP) application was submitted and approved by the FDA. A Certificate of Confidentiality is issued automatically for this NIH-funded project.

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☒ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Clinical Research Center (CRC) Advisory Committee– All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☐ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

N/A

18.1 Communication Plans

18.2 Data Submission and Security Plan

18.3 Subject Enrollment

18.4 Reporting of Adverse Events and New Information

18.5 Audit and Monitoring Plans

19.0 Adverse Event Reporting

19.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening

suspected adverse reaction	adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

19.2 Recording of Adverse Events

Research subjects will be routinely questioned about adverse events at in person study visits.
All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study cigarettes will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:
1) The test finding is accompanied by clinical symptoms
2) The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
Note: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
3) The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
4) The test finding is considered an adverse event by the investigator.

19.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study cigarettes for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study cigarettes", this determination and the rationale for the determination will be documented in the respective subject's case history.

19.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

19.4.1 Written IND/IDE Safety Reports

N/A

19.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

N/A

19.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.6 Unblinding Procedures

If an adverse event requires the subject to be unblinded, the unblinded study personnel (cigarette administrator) will be able to provide that information as needed. Otherwise, participants will not be unblinded to their cigarette allocation. The principal investigator will begin by reviewing the protocol and establishing guidelines for data and safety monitoring including any additional procedures for unblinding of participants.

19.7 Stopping Rules

The principal investigator will also develop trial stopping rules to help define the point at which the risks to subjects of continuing the study outweigh the likely benefits. A brief report will be generated and provided to the Penn State IRB.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Study Monitoring Plan

20.1.1 Quality Assurance and Quality Control

Data will be collected from participants and coded directly by either using the REDCap survey tool (participant entered data) or through REDCap data entry forms (researcher entered data). The codes that link the name of the participant and the study ID will be kept confidential in REDCap. Any paper forms (consent) will be securely transported to the PI's data entry center. Any additional data that is generated will be stored electronically on the Department server in password protected files.

Study data will be managed using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes The Pennsylvania State University and was initiated at Vanderbilt University. The database is hosted at the Penn State Hershey Medical Center and College of

Medicine data center, which will be used as a central location for data processing and management. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team. This iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap is HIPAA compliant. Data are stored on a secure server; data in REDCap are encrypted; access to the database requires authentication (a unique username and password); data are accessed based on the individual's role on the project; every interaction with the data is logged, creating an audit trail. Random data entry checks will be implemented regularly to identify problems with data entry. Data quality tools included in REDCap will be utilized to identify incorrect data types, out of range data and outliers. In addition, electronic edit checks, and random internal quality and assurance checking will be performed manually. Data quality will be monitored by random inspection of the completed electronic forms by one of the research assistants or principal investigator and any problems detected will be discussed with the PI. If necessary, re-training of researchers will be conducted. The responsibility for data quality and study conduct lies with the PI. Site visits will be conducted by the Penn State research team to ensure that procedures are being executed in compliance with the protocol, and IRB policies.

20.1.2 Safety Monitoring

The principal investigator will monitor the safety of study participants. The Principal Investigator will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, and sponsor of all applicable AEs as appropriate. We will consult licensed medical professional at the Penn State College of Medicine and the project faculty mentors as needed. The research coordinator will ensure that AEs are correctly entered into REDCap and complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, and FDA of all Unanticipated Problems/SAE's.

21.0 Future Undetermined Research: Data and Specimen Banking

21.1 Data and/or specimens being stored

Saliva collection specimens will be stored with an ID code and date of collection attached. Storage and processing will be tracked in REDCap.

21.2 Location of storage

Specimens will be stored in a locked freezer room in the research laboratory of Drs. Muscat and Richie on the 3rd floor of the Cancer Institute, the Department of Psychiatry on the 5th floor of the College of Medicine, or in the Department of Pediatrics on the 7th floor of the College of Medicine.

21.3 Duration of storage

Specimens will be stored indefinitely with code number attached. Data will be stored indefinitely with identifiers attached in REDCap.

21.4 Access to data and/or specimens

The lab managers, technicians, study coordinators and PI will have access to the freezer rooms where the specimens will be stored. The researchers will have access to the stored data in REDCap although role specific rights will be granted to forms (i.e., researchers who see participants will not have access to data that may allow them to become unblinded to a participant's treatment allocation).

21.5 Procedures to release data or specimens

Investigators interested in obtaining samples from this project for ancillary studies will first be required to submit a detailed written proposal to the principal investigator. The investigator will then need to obtain all other regulatory approvals (IRB, departmental scientific committees, etc.) prior to samples being released to the investigator.

21.6 Process for returning results

Investigators will be required to provide a written report on their study results to the principal investigator. Individual participants will not be provided with the results of the analyses of their samples.

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