TARGETING REWARD DYSFUNCTION AS A MECHANISM TO IMPROVE SMOKING CESSATION

NCT02927847

PI: Maggie M. Sweitzer, Ph.D.

PURPOSE

The goal of this project is to evaluate the effects of a novel, integrated intervention combining pre-quit use of very low nicotine content cigarettes (VLNC's) with behavioral activation therapy (BA) on neural response to smoking and non-smoking rewards and smoking cessation outcomes. It is hoped that the results of this study will provide insight into mechanisms contributing to smoking relapse and preliminary data to estimate effect sizes for powering future larger scale clinical trials.

BACKGROUND & SIGNIFICANCE

Tobacco smoking remains a leading cause of death and disability in the developed world. Many who wish to quit smoking are unable to do so. Although substantial advances have been made to identify neurobehavioral mechanisms underlying nicotine dependence, there is a great need to translate these findings into targeted, efficacious interventions, and to understand the mechanisms by which successful interventions exert their effects.

Theoretical models and a growing empirical literature suggest that addictive disorders, including tobacco dependence, are characterized by mesolimbic hypersensitivity to smoking reward and related cues and hyposensitivity to nonsmoking rewards, particularly during withdrawal that occurs during the early stages of a quit attempt. Evidence suggests that this dysregulated reward processing may contribute to relapse and thus presents a promising target for intervention. **The overarching goal of this research is to develop and evaluate a novel intervention that directly targets this reward processing imbalance by both a) decreasing smoking reinforcement through pretreatment with very low nicotine cigarettes (VLNC's) and b) increasing reinforcement from other non-drug rewards through behavioral activation (BA).**

Smokers who are interested in quitting will be randomly assigned to one of two treatment conditions. In the BA +VLNC condition (*n* = 24) smokers will switch to VLNCs while wearing either a 21mg/d or 14 mg/d nicotine patch for 4 weeks prior to their quit date, depending on their initial smoking rate. They will also participate in weekly BA treatment sessions. Smokers in the VLNC Only group (*n* = 24) will undergo the same pharmacological pretreatment but will not participate in BA. Following the quit date, both groups will undergo standard nicotine replacement therapy. At baseline and pre-quit, BOLD response to smoking and non-smoking rewards will be measured using fMRI after 24 hr abstinence. Latency to relapse will serve as a continuous clinical outcome measure. A schematic of overall study design is illustrated in Figure 1 below. Prior to initiating data collection, we will collect pilot data (n=7) to determine feasibility and acceptability of the proposed intervention.

The proposed research study has the following aims: 1) To examine the effects of BA + VLNC compared with VLNC Only on brain and subjective sensitivity to smoking and monetary rewards; 2) To gather preliminary data on the effects of combined BA + VLNC compared with VLNC only on smoking cessation outcomes; and 3) To examine mediating and moderating effects of pre-and post-treatment brain function on smoking outcomes.

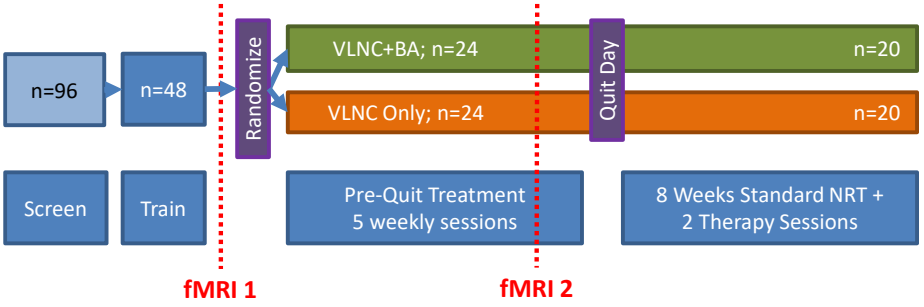
The proposed research will have significant scientific impact by increasing our understanding of the role of reward dysregulation as a mechanism of nicotine dependence. Clinical research and practice will also be impacted by determining the efficacy of novel, integrated treatment designed to target reward dysregulation as

a mechanism to improve smoking cessation outcomes. Results of this study can be used to improve cessation treatments for those attempting to quit smoking.

DESIGN AND PROCEDURES

An overview of the study design is presented in Figure 1 below. We propose to obtain consent from up to 150 participants in order to identify 55 who meet all inclusion and exclusion criteria and enroll in the study. At the beginning of the study, 7 of these subjects attempted to complete all phases of the study but did not undergo fMRI scanning, in order to assess feasibility and acceptability of the treatment protocol prior to beginning full recruitment. Following pilot testing, 48 individuals will be enrolled in the full study with the aim of obtaining complete, useable datasets from 40 participants. 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.

Figure 1. Overview of study design and anticipated sample size for full study



Screening session. During screening, all aspects of the study will be described to subjects and informed consent will be acquired. Breath and urine samples will be collected in order to verify smoking status and breath alcohol level (BAL); and measures of smoking history, nicotine dependence, and mood will be collected (see Table 1 below for key measures acquired at each visit). Vitals such as heart rate, blood pressure and weight/height will also be measured. Urine samples will be obtained in order to screen for illicit drug use and to assess pregnancy status. Females who test positive for pregnancy will be excluded from the study and will be given options for smoking cessation programs. Use of illegal drugs will be exclusionary. Marijuana use will not be exclusionary, but participants must agree to not use marijuana for 24 hours prior to sessions and may not mix their marijuana with tobacco (i.e., blunts). Participants will also be interviewed regarding their smoking behavior, and will be asked to identify pleasant activities that do or do not include smoking.

Participants must record a breath alcohol level of 0.0 at screening. Volunteers who test positive for alcohol, or who indicate that they have smoked marijuana in the past 24 hours, will not be permitted to continue with the screening and will be asked to reschedule. If the screening visit is rescheduled due to intoxication, participants will be asked to repeat the informed consent process. Volunteers testing positive for alcohol on more than one occasion will be excluded from the experiment.

If a participant has a BAL above the legal limit at the screening or any subsequent visit, study staff will ask the participant if they drove to the lab. If the participant indicates that they did drive, study staff will provide a safe mode of transportation home (e.g. taxi, uber) at no cost to the participant.

Patients will be asked about medical history and complete the Brief Medical History Questionnaire and BIAC Screening Form. We will give subjects the option to view the mock scanner if they have any worries about it. If they do not wish to complete the fMRI portion of the study, they will be dismissed with payment.Participants will also complete a brief measure of cognitive functioning and a computerized psychiatric screening measure and follow-up interviewing to assess current and past psychiatric disorders. Indications of severe psychiatric mental health problems (e.g., active psychosis or mania) or suicidality will trigger medical review by the study physician and emergency referral to psychiatric services if necessary. Subjects who meet all entry criteria listed below will be provided with the option to continue with the training session.

Inclusion criteria:

1) generally healthy;
2) between the ages of 18 and 55;
3) intact intellectual functioning (K-BIT2 ≥ 80)
5) smoking of at least 5 cig/day of a brand delivering ≥ 0.5 mg nicotine (FTC method) for past 6 months
6) daily smoking ≥ 2 years lifetime;
7) an afternoon expired CO concentration of at least 9 ppm (to confirm inhalation) or morning urinary cotinine indicating tobacco use (NicAlert > 3);
8) interested in quitting smoking within the timeframe of the experiment.

Exclusion criteria:

1) no desire to quit smoking;
2) inability to attend all required experimental sessions;
3) report of significant health problems including but not restricted to chronic hypertension, emphysema, seizure disorder, history of significant heart problems;
4) use of psychoactive medications;
5) current participation in psychotherapy;
6) current unstable psychiatric illness as assessed by the SCID;
7) suicidal ideation with plan or intent; potential subjects who endorse items 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) and/or 5 (Active Suicidal Ideation with Specific Plan and Intent) on the Columbia Suicide Severity Rating Scale will be excluded from study participation, and referred to appropriate psychiatric treatment;
8) use of other tobacco products or e-cigarettes on > 9 out of the past 30 days;
9) use of Spectrum cigarettes or low nicotine content cigarettes in past year
10) quit attempt in past 30 days resulting in greater than 3 days abstinence
11) primary use of roll-your-own cigarettes
12) current alcohol or drug abuse;
13) use of illegal drugs as measured by urine drug screen;
14) current use of nicotine replacement therapy or other smoking cessation treatment;
15) presence of conditions contraindicated for nicotine replacement therapy (e.g., skin allergies)
16) (for full study only) left-handed as measured by a three-item scale used in our laboratory;
17) (for full study only) presence of conditions that would make MRI unsafe (e.g., pacemaker);
18) (for full study only) brain abnormality (including but not limited to stroke, brain tumor, and seizure disorder);
19) (for full study only) claustrophobia
20) (for full study only) history of fainting

21) (for full study) No tattoos or permanent make-up above the neck
22) (for full study) Tissue expanders (plastic surgery)
23) breath alcohol level > 0.0 (participants failing for BAL will be allowed to rescreen once)
24) systolic blood pressure > 160 or diastolic blood pressure > 100 (participants failing for blood pressure will be allowed to rescreen once)
25) resting heart rate > 100 (participants failing for heart rate will be allowed to rescreen once)
26) expired CO concentration of > 80 ppm
27) household member enrolled in study concurrently
28) unstable living condition that would compromise compliance to study procedures
29) pregnant, trying to become pregnant, or breastfeeding
30) Glaucoma or color blindness or other uncorrected vision problem
31) Weighing over 300 pounds

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. A second urine pregnancy test will be conducted at fMRI session 1 (or treatment session 1 for pilot subjects), which takes place before any study product is provided.

Participants will be asked to indicate in the consent form whether they would like to be contacted about future studies while the present study is ongoing. 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.

Participants who complete the screening visit (described above) and meet all study requirements will then complete a training session, 2 fMRI sessions, 8 treatment sessions, and 2 follow-up visits. Pilot subjects will not complete the fMRI sessions. In addition, pilot subjects will complete an additional 1 hour interview to assess their satisfaction and feedback regarding the treatment protocol. This session will take place at the conclusion of the final treatment session.

Table 1. Core Measures Table

Timeframe	**Baseline**			**Weeks 1 to 4**				**Week 5**			**Wk 6**	**Wk 7**	**Wk 8**	**Wk 11**	**Wk 15**
Visit Type	**Screen**	**Train**	**fMRI**	**Treatment Sessions**				**fMRI**	**Treatment Session**		**Treatment Sessions**			**Follow-up Sessions**	
Session Number			**1**	**1**	**2**	**3**	**4**	**1**	**5**		**6**	**7**	**8**	**2**	**3**
Informed Consent	X														
Demographics	X														
Urine Drug Screen	X														
Nicalert (cotinine)	X														
Expired CO	X		X	X		X		X	X		X		X	X	X
Breath Alcohol Level	X		X	X		X		X	X		X		X	X	X
Vital Signs	X		X	X		X		X	X		X		X	X	X

Pregnancy Test	X		X					X							
Medical & Smoking Hx	X														
SCID & Diagnostic Inter	X														
Mood/Anxiety scales	X		X	X		X		X	X		X		X	X	X
Nicotine dependence	X		X	X		X		X	X						
K-BIT2	X														
Smoking cessation Q's		X													
Quit Self-Efficacy		X							X						
Trait anhedonia		X													
Reward scales		X	X	X		X		X	X		X		X	X	X
Craving & Withdrawal			X	X		X		X	X		X		X	X	X
Timeline follow back			X	X		X		X	X		X		X	X	X
Caff-ETOH			X					X							
Guessing Task (fMRI)			X					X							
Cigarette Purchase Task			X					X							
EEfRT Task			X					X							
Randomization			X												
Cigarette Eval Scale			X					X							
Provide study cigs				X		X									
Provide patches		X		X		X			X		X		X	X	
Patch adherence log				X		X			X		X		X	X	X
Study cigarette log				X		X			X						
Health change form			X	X		X		X	X		X		X		
Adverse Events Form			X	X		X		X	X		X		X	X	X

*Screening and training visits may occur on the same day. However, the training visit must occur within 30 days of the baseline visit. Quit initiation occurs on treatment session 5.

Training Session. Participants will complete the training session on a separate day from the screening session. Participants will be required to complete both the training session and the first fMRI 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 rescreened.

During the training session a breath CO and BAL sample 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. Participants will also complete several brief questionnaires regarding their mood, attitudes toward smoking cessation, and behavior, including measures of rewarding activities. Participants will have the opportunity to experience the mock MRI scanner and will be trained on the rewarded guessing task and behavioral incentive delay task. Participants will then be scheduled for their first fMRI session.

fMRI Sessions. Participants will complete two fMRI scanning sessions in which they will complete 1) a five minute resting state BOLD scan, 2) 2 8-minute runs of the rewarded guessing task, 3) 2 8-minute runs of the behavioral incentive delay task, and 4) a high-resolution anatomical scan. Participants will be scanned at baseline (fMRI 1) and after the fourth week of the pretreatment period (fMRI 2). Participants will be asked to abstain from smoking for 24 hours prior to their fMRI scans but will be provided with a 21 mg/d or 14 mg/d transdermal nicotine patch to wear during this time. Abstinence will be verified by self-report and a CO < 8 or a 50% reduction from their baseline CO level. Participants who do not meet abstinence criteria will have the opportunity to reschedule.

During the first hour of each scanning session, the following measures will be collected: breath CO and breath alcohol level; measures of self-reported recent smoking and other tobacco use; measures of recent caffeine and alcohol use; measures of smoking withdrawal, nicotine dependence, and mood; and a measure of recent rewarding experiences. Participants will also complete a hypothetical cigarette purchase task on the computer in order to assess relative reinforcing value of smoking. During this task, participants will be asked about their willingness to purchase cigarettes available at different hypothetical prices. Participants will then complete the Effort Expenditure for Rewards Task (EEfRT or “effort”), an objective measure of motivation and anhedonia. This task is a computerized button-pressing game in which the participant chooses between an easy or hard task on each trial in order to earn variable amounts of reward. The hard task requires participants to make 100 button presses with the non-dominant pinkie finger within 21 seconds. The easy task requires participants to make 30 button presses with the dominant index finger within 7 seconds.

Participants will then be escorted to the fMRI suite. Once inside, they will complete additional questionnaires regarding their current mood, craving, and withdrawal symptoms. Expired CO will again be measured and recorded. The participant will be given specific instructions regarding data collection procedures and be placed in the scanner. Following positioning and shimming, an anatomical series will be acquired, followed by the resting state scan. BOLD signal will then be acquired during the rewarded guessing task and behavioral incentive delay task.

The rewarded guessing task has been previously used in our lab to measure mesolimbic reactivity to smoking and monetary rewards. Participants will be instructed that they are playing a game in which they can earn money and puffs from a usual brand cigarette by guessing whether an unknown number with a value from 1-9 is higher than or lower than 5. Each trial begins with a 4-s decision period, in which participants make a guess via button press. During a 6-s anticipation period, participants view an image indicating the reward available on that trial (50¢, puff, or neutral). During the outcome period, participants see the “actual” number on the screen followed by an upward-facing green arrow for win or a yellow circle for non-win (i.e., incorrect response) outcomes. Trials are presented in predetermined pseudorandom order. The task will be divided into two 24-trial runs (each 8 min). To increase the salience of rewards, participants will remain in the lab for 60 min after the

scan; they will be given the rewards earned (money and puffs), but otherwise not allowed to smoke. Participants will not be required to smoke earned puffs.

The behavioral incentive delay (BID) task was previously developed and validated by Dr. Stacey Daughters, modified from the monetary incentive delay task. Participants will complete 40 trials, lasting approximately 13 seconds each. Each trial begins with a 2-s cue indicating whether it is a “reward” trial (grey triangle) or a “neutral trial” (blue circle). Participants are then shown a fixation cross during a brief delay (anticipation period), followed by a target symbol in which they must press the space bar as quickly as possible. Required response time will be titrated to achieve approximately 67% accuracy for each participant. On-time responses will result in presentation of a 3-second photo depicting people engaged in enjoyable activities (reward trials) or household objects (neutral trials). Delayed responses will be followed by feedback with no picture presentation. Participants will complete 2 runs of the task lasting approximately 8 minutes each.

Following the final functional series, the participant will be removed from the scanner. After being removed from the scanner, participants will complete post-session withdrawal and mood questionnaires and provide a post-session breath CO sample. Participants will then be escorted to a laboratory testing room and provided with rewards earned during the scanner task ($6 and 12 puffs of a cigarette). Smoking behavior (latency to first puff and number of puffs taken) will be observed and recorded. Participants will then complete a measure of subjective reactions to smoking their earned puffs (Cigarette Evaluation Scale; CES), and an additional measure of recent pleasant events (Pleasant Events Schedule, administered following fMRI 2).

Regardless of when they choose to smoke, participants will remain in the lab for the expected 1 hour waiting period.

At the end of the 1 hour waiting period, participants will be provided with additional information about subsequent visits:

- At the end of fMRI 1, participants will be given information regarding upcoming sessions. Participants will also set a quit date and schedule remaining treatment and fMRI sessions. fMRI 2 must occur a minimum of 2 days prior to the designated quit date.
- At the end of fMRI•2, participants will be reminded of their previously agreed upon quit date and the time of their next scheduled session.

Breath alcohol levels will also be assessed prior to each scanning session with a handheld breathalyzer (Alco-Sensor IV; Intoximeters) and participants must record a BAL of 0.0. Volunteers who test positive for alcohol will be excluded from participation that day. Volunteers testing positive for alcohol on more than one occasion will be excluded from the experiment. Females of child bearing potential will undergo a urine pregnancy test immediately before each fMRI scanning session.

Group Assignment/Treatment Sessions. Following fMRI 1, participants will attend 8 60-minute weekly treatment sessions. Four of these will take place before the quit date, one will occur on the quit date, and 3 will take place after quitting smoking. Half of the sample (n=24) will be randomly assigned to the BA + VLNC condition, which will include behavioral activation treatment as the primary therapy component. The other half (n=24) will be assigned to the VLNC Only group, which will include health education, supportive counseling and relaxation sessions matched for contact time instead of behavioral activation. Participants in both groups will undergo identical study procedures; only the content of the therapy sessions will differ. Participants will not be told of their treatment group assignment, and all therapists will provide treatment to participants in both

groups. Smokers in both groups will switch to VLNCs while wearing either a 21 mg/d or 14 mg/d nicotine patch for 4 weeks prior to their quit date. Both treatment groups will include content related to tips and strategies for quitting smoking.

Very Low Nicotine Content (VLNC) cigarettes. In both conditions, participants will smoke VLNC cigarettes for one month prior to the quit date. VLNCs will be NRC-102 (non-menthol) and NRC-103 (menthol) SPECTRUM research cigarettes obtained from the NIDA Drug Supply Program with the following specifications: .03 $\pm$ .01 mg nicotine yield and 9 $\pm$ 1.5 mg tar. The effects of these cigarettes are currently under investigation in our lab (U54DA031659) and have similar specifications as Quest 3 cigarettes (<.05 mg nicotine; 9 mg tar) used in prior studies (R01DA025876) in our lab. As in these studies, participants will be instructed to smoke the same number of VLNCs as they smoked of their usual brand and will be given a comparable supply.

Nicotine patches. Transdermal nicotine skin patches (Nicoderm CQ Rugby®, Leader, or equivalent purchased from the Duke Pharmacy) will be used to administer nicotine prior to and after quitting. In both groups, participants will start either wearing a 21 mg/d or 14 mg/d patch during the one month they smoke VLNCs depending on whether they smoke more or less than 10 cigarettes per day. If participants smoke 10 or more cigarettes per day, they will undergo a standard regimen of nicotine replacement following the quit day: four weeks of 21 mg/d, two weeks of 14 mg/d and two weeks of 7 mg/d. If they smoke less than 10 cigarettes per day, participants will wear six weeks of 14 mg/d and two weeks of 7 mg/d. Participants will be instructed to wear one patch per day but to remove it before bed. Nicotine replacement packaging will include specific instructions for patch use and contact information including the 24 hr pager number (staffed by the study physician). Symptoms associated with nicotine toxicity include, lightheadedness, dizziness, nausea, and vomiting. Symptoms considered moderate to severe in nature, will be evaluated by the study medical staff by telephone or in person, depending upon the level of severity. Upon evaluation, the subject will then be given the choice of continuing in the study at a reduced dose or discontinuing patch use. Dose reduction will consist of lowering the dose from 21 mg/d to 14 mg/d to 7 mg/d, to no treatment. This will be done under the guidance of the study physician and will be logged. Dose lowering has not been necessary in our previous fMRI studies using these patches. The data from participants for whom dose lowering occurs, will not be used in final analyses. However, these subjects will be allowed to continue with treatment.

In addition to the above, at each laboratory visit, participants will rate nicotine patch side effects using a 23-item self-report questionnaire to measure psychological (e.g. Do you feel jittery?) and physical (e.g. Do you feel nauseated?) symptoms. Items will be rated on a 7-point Likert scale (1=not at all to 7=extremely). This questionnaire has been validated in numerous clinical trials in the Duke CNSCR (PI: Rose). This questionnaire will be completed at the beginning of each visit and reviewed immediately by staff in order to identify possible adverse reactions. Data from this questionnaire will be monitored and tabulated but not statistically analyzed.

Treatment Sessions. Sessions will occur on a weekly basis and last one hour. The treatment component will consist of Behavioral Activation (BA) or Control sessions, depending on group assignment. An overview of the content of treatment sessions for each condition is provided below. Therapy session content will be pilot-tested prior to beginning full recruitment. In addition to group-specific content, content for both groups will include brief discussion (~10 min/session) of standard smoking cessation strategies consistent with clinical guidelines.

Behavioral Activation. Smokers randomized to the BA+VLNC condition will attend 8 1-hr individual sessions (4 pre-quit, 1 quit-day, and 3 post-quit) addressing the following topics: 1) Treatment overview, rationale, and monitoring of daily activities, with brief activity scheduling; 2) Identification of values, goals and activities within

key life areas and brief activity scheduling; 3) Prioritization of life areas and setting weekly activity goals; 4) Monitoring progress toward daily goals and contracts for continued success; 5) Continued monitoring, social support contracts, and ongoing weekly goals; 6-8) Review and maintenance of skills, continued monitoring and goal setting. Treatment manuals will be modeled after the BA Treatment for Smoking (BATS) and Life Enhancement Therapy for Substance Abuse (LETS ACT) protocols developed by Dr. Daughters. Sessions 1 through 5 are designed to cover core content aimed at increasing participants' engagement in valued life activities. Sessions 6 through 8 are added as maintenance sessions to reinforce learned strategies and provide additional support once abstinence is initiated.

Control Sessions. Smokers assigned to VLNC Only will attend an equal number of 1-hr sessions to control for overall contact time. Content will include health education (e.g., dietary guidelines), supportive counseling and relaxation. Supportive counseling will include empathy and supportive listening for concerns raised by the participant, but will minimize giving advice. Relaxation has been used in previous research as a control condition and is neither harmful nor effective for smoking cessation. The control condition content will similarly be modeled after Dr. Daughters' control treatment manual and government Dietary Guidelines for 2015 - 2020.

Therapeutic content for BA was be pilot-tested among 7 smokers (without fMRI) to determine feasibility and acceptability. Objective outcome measures and qualitative feedback will be elicited to determine if changes to the treatment protocol are needed prior to beginning full study recruitment. An interview to elicit qualitative feedback will be conducted following treatment sessions 7 and 8.

Treatment sessions will be conducted by the PI or other post-doctoral or graduate-level clinical psychology students and will be audiotaped to allow for supervision and assessment of treatment fidelity. Student therapists will be added as key personnel to the IRB protocol prior to initiating any study-related activities. Student therapists will complete a 1 day training provided by the PI, which will include content overview and role plays. Therapists will then be observed conducting mock therapy sessions prior to initiating treatment. The PI will provide ongoing (weekly) supervision of graduate students, under overall supervision of Dr. Daughters. A randomly selected subset of audiotapes (20%) from both BA and control treatment sessions will be monitored by Dr. Daughters or another rater not otherwise associated with treatment delivery, using a checklist adapted from her existing measures to assess therapist adherence to, and competence with, the protocol and discriminability of the two treatments. Feedback and further training will be provided as necessary to address deviations from the protocol.

Assessment Sessions. A total of 7 30-min laboratory assessment sessions will be conducted during the course of the study. Five of these will coincide with treatment sessions occurring at weeks 1, 3, 5, 6, and 8. Additionally, two follow-up sessions will occur at weeks 11 and 16. Each assessment session will consist of: obtaining vital signs (e.g., blood pressure, heart rate, weight), breath CO and breath alcohol level; completion of self-report measures (e.g. withdrawal, mood, involvement in rewarding activities); and review of study and non-study cigarette use and patch use over the previous two weeks. Current medications, changes in health status, and side effects will also be reviewed. Dependent measures will be collected by the research assistant, who will remain blind to treatment condition. Depending on session, participants will be provided with study cigarettes and nicotine patches and instructions for use. During post-quit and follow-up assessment sessions, in the case that a participant has relapsed since their last point of contact, a timeline follow-back procedure will be conducted in order to establish date of relapse. In addition, participants will be asked for qualitative feedback about their experience with the study and the treatment protocol.

Follow-up Phone Calls. Participants will be contacted by phone 6 and 12 months after completing the study to complete a brief interview about current smoking status and nicotine dependence.

DATA ANALYSIS

The primary dependent measures will be percent signal change in *a priori* brain regions of interest for anticipation of smoking and monetary rewards relative to neutral trials; and smoking cessation outcomes (i.e. latency to lapse and relapse). Latency to lapse will be defined as the first cigarette following quitting smoking and relapse will be defined as 7 consecutive days of smoking. Secondary data are self-reported craving, mood, anxiety, smoking and nonsmoking reward sensitivity, withdrawal, nicotine dependence, and breath CO levels.

To assess **Aim 1** hypotheses on the effects of treatment on BOLD response to smoking and monetary rewards, a voxel-wise 2 (Group) x 2 (Scan) x 2 (Reward Type) mixed model ANOVA will be conducted in FSL within a mask of regions of interest (ROIs) of mPFC, ventral striatum, and dorsal striatum. To test the **Aim 2** hypothesis that the BA+VLNC group will achieve longer continuous abstinence than VLNC only, survival analysis using Cox regression will be conducted to compare group differences in days to relapse. To assess mediating and moderating effects of brain activation on treatment outcomes in **Aim 3**, multiple linear regression will be conducted using mean percent signal change extracted from anatomical ROIs described above. We hypothesize that pre- to post-treatment increases in activation to monetary reward will mediate the effect of BA+VLNC treatment on cessation outcomes. We further hypothesize that effects of treatment on cessation outcomes will be stronger for those exhibiting greater pre-treatment deficits in monetary reward anticipation.

RISK/BENEFIT ASSESSMENT

Women of childbearing potential:
Pregnant or nursing women will be excluded from the study. Female participants will undergo a urine pregnancy test at screening administered by a trained study staff member. The pregnancy test kits to be used are approved by the Department of OBGYN. Subjects must also agree to use contraception during the course of the trial. They will be encouraged in the consent form to notify study staff if they believe a change in their pregnancy status has occurred during the trial. A second urine pregnancy test will be conducted prior to dispensing study medications.

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.

Nicotine Patch:
Insomnia or 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.

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

MRI

MRI provides clinically relevant anatomic and functional information non-invasively and with minimal risk, if the well-known contraindications (such as pacemakers) and potential hazards (such as attraction of metallic objects) are avoided. To minimize discomfort associated with confinement the small space within the MRI machine or loud noises during scanning, participants will be provided with a training session in which they will be introduced to all aspects of the scanning procedure using a mock scanner in our laboratory. Participants will be reminded of their option to withdraw from the study at any time.

Management of side effects:

Reports of side effects will be obtained by study technicians and communicated to the principle investigator, who will determine the most appropriate course of action, which may include options for termination of study participation. Participants will be reminded of their option to withdraw from the study at any time.

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, generalized anxiety disorder, bipolar disorder, and eating disorders. Any changes in nicotine or cigarette consumption could adversely affect psychiatric conditions. Mood and anxiety will be monitored at each visit over the course of the study. Reports of worsening psychiatric symptoms will be communicated to the principle investigator, who will determine the most appropriate course of action, which

may include options for termination of study participation and referral to more intensive psychiatric treatment.

Suicidality:
Screening sessions will include assessment of suicidality. If participants endorse suicidal ideation or intent during the interview, or by answering the BDI-II suicidality item at 2 ("I would like to kill myself") or 3 ("I would kill myself if I had the chance") during subsequent visits, the participant will be asked to wait in order to speak with a senior staff member. The senior staff member will follow up with the suicidal ideation and intent items of the Columbia-Suicide Severity Rating Scale. Participants indicating "yes" on items 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) and/or 5 (Active Suicidal Ideation with Specific Plan and Intent) will receive further follow-up. Screening participants will be given the choice of following up with an established treatment provider (e.g., paging their psychologist or psychiatrist; following the safety plan established with their provider) or if they do not have a current provider, presenting to the nearest emergency department for further care. If participants are unwilling to contact a treatment provider or to voluntarily present to the ED, the senior staff member will ask them to remain at their current location, and will call EMS. EMS will be provided with the interviewee's name and current location, as well as their stated suicidal intent. A staff member will offer to stay on the phone with the interviewee until EMS arrives, and suicide prevention steps will be documented in the research record. As noted above, suicidality will continue to be monitored throughout the duration of the study, and appropriate steps will be taken if an increase in suicidality is indicated.

Treatment Referral:
The initial in-person evaluation will include assessment of psychiatric disorders. Participants with unstable psychiatric disorders will be excluded from the study and referred for appropriate treatment. Individuals with psychiatric symptoms that do not interfere with study participation (e.g., mild depression or anxiety) will be allowed to participate provided that a) symptoms are contributing to no more than mild to moderate impairment; b) symptoms have been stable with no psychiatric treatment for the past 3 months; and c) participant is deemed to be at minimal risk for self-harm based on suicide screening measures. Although behavioral activation has empirical support as a treatment for depression, only 50% of participants will be randomized to that condition, and no pharmacotherapy will be administered as part of the trial. As such, participants will be fully informed that participation in the study is intended to help them quit smoking, but is not intended as a primary treatment for depression or other psychiatric disorders. Participants who are experiencing more than mild to moderate impairment, or who are primarily seeking treatment for psychiatric conditions will be excluded from the study and referred for appropriate treatment. In addition, information regarding smoking cessation treatment resources and appropriate referrals will be provided to all participants who consent but do not pass screening for whatever reason.

As noted above, worsening psychiatric symptoms among participants who have passed screening may also result in referral to more intensive psychiatric treatment, as needed. In this case, participants will be provided with referral information and encouraged to seek treatment without the disincentive of being withdrawn from the study if they do so, provided that continued study participation does not pose any additional risk.

Confidentiality:
All research material gathered on participants is confidential and will be appropriately protected. No identifying subject information will be revealed without the agreement of the participants.

PARTICIPANT RECRUITMENT AND COMPENSATION

We will advertise in local newspapers, the radio, flyers on bulletin boards and on the internet (trianglesmokingstudies.com and craigslist). When we receive calls from potential subjects we will return their call and ask information including name, address, age, and smoking, mental, and medical health history. They will be given a brief description of our studies and will be asked questions to determine interest and eligibility. If they do qualify we will schedule a screening session where we will follow all IRB protocols of informed consent.

We propose to obtain consent from a total of 150 smokers in order to have 40 complete usable data sets for the full study. We enrolled 7 smokers as pilot subjects to attempt all aspects of the study except fMRI scanning to determine feasibility and acceptability of the treatment protocol prior to beginning full recruitment. As with previous studies, we will make every effort to maximize participant retention via a thorough informed consent process, careful screening, and other practices (e.g., contacting participants with a reminder phone call the night before experimental sessions).

Participants will receive no compensation for the phone screening. They will receive $40 for the initial evaluation visit, provided they pass the drug screen, CO, and breath alcohol tests. Participants enrolled in the study will receive $10 for completing the training session, $20 for each of the first 5 assessment sessions, $25 for each of the 2 follow-up assessment visits, and $125 for each fMRI session ($430 total). Participants will not be compensated for attendance at individual treatment sessions, but will be reimbursed for parking or transportation as needed. In addition, participants can earn a completion bonus of $50 for completing all of the first four weekly pre-quit treatment sessions. Participants can also earn an additional $50 on-time bonus for completing fMRI2 on time as scheduled and meeting abstinence criteria. As such, total compensation for completing all aspects of the study is $550. Participants can also earn $12 during the rewarded guessing task completed in the fMRI sessions, and an additional bonus (up to $10) during the EEfRT task completed at each fMRI session. Participants that decide to withdraw from the study before fulfilling all of the requested tasks will be given compensation for each session completed.

SERIOUS ADVERSE EVENT REPORTING PLAN

The Principal Investigator will report all serious adverse events and unanticipated problems relating to the study in an expedited manner to the Duke University Health System (DUHS) Institutional Review Board (IRB) office and all applicable regulatory authorities in accordance with the Center’s standard operating procedures.

COSTS TO PARTICIPANTS

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 SAFETY AND MONITORING PLAN

Data collected for this study are gathered via paper-and-pencil measures, computer-based measures, audio recordings, and brain imaging techniques. Data gathered is either automatically downloaded to an excel sheet (computer measures) or other electronic data file (brain imaging), or entered by hand (paper and pencil measures). All source documents will be stored in participant binders. All paperwork and electronic files will be checked by the research scientist for completeness on a daily basis. 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. The Subject Identifier will be a numeric code that will include information about study number and subject ID number. Study consent forms and any PHI will be stored in a locked file cabinet in a separate location from study data. The link between the participant's names and codes will be stored on a password protected spreadsheet on a secure server. Audio recordings of treatment sessions will be collected on a password-protected Duke iPad and will be immediately transferred to a secure server after the conclusion of the session. All information collected as part of this study will be accessible only to study staff. Internal audits to ensure quality assurance occur at the beginning of the study, mid-way through and at the end of enrollment.

AE's will be collected at each assessment visit. Participants will also be instructed to contact study personnel at any time should they experience physical discomfort. A 24 hr pager number will be provided for this purpose. Should a possible AE be reported during non-business hours, the study physician will assess the situation with the participant and make the determination regarding whether immediate care is necessary. The participant will be instructed to visit the lab the next day and further collection of information regarding a possible AE will take place at that time.

DATA STORAGE AND CONFIDENTIALITY

Participants will be informed, in their consent forms, of the data storage and confidentiality safeguards, which are practiced according to current HIPAA regulations. MRI scanning session data is stored on a secure server and then transferred to DVD for final storage. All PHI is removed from the scanning data before it is posted on the secure server and is coded with a unique id. 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. Stacey Daughters at UNC-Chapel Hill will be a collaborator for the study, and is listed as outside key personnel. Given her role in supervising and evaluating treatment fidelity for the behavioral activation and control treatments, she will require access to audio recorded treatment sessions, which includes PHI. When needed, audiofiles will be shared using the secure, password-protected Duke Box sensitive folder. This folder has been configured to protect PHI and prevent anonymous sharing of data. In addition, password protection will require multifactor authentication. Dr. Sweitzer will maintain responsibility for removing files from the Duke Box sensitive folder as soon as they are no longer need (e.g., when supervision or evaluation of treatment compliance for that session is complete).