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Smartphone-Delivered Attentional Bias Modification Training for Quitting Smokers

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A. SPECIFIC AIMS

More than 70% of smokers who receive first-line therapies relapse within 6 months [1]. Thus, alternative and complementary smoking-cessation therapies are needed. Given its success in treating anxiety and alcohol disorders [2,3], *Attentional bias modification (ABM)*, a computer-delivered intervention, has been proposed to treat nicotine dependence. ABM reduces the attentional bias (AB) towards smoking cues that develops over time as a result of conditioning processes through which smoking cues become strongly motivationally salient [4]. AB to smoking cues becomes part of the cycle maintaining nicotine dependence, a cycle in which smoking cues "grab" attention, triggering craving to smoke, which in turn leads to increases in AB to smoking cues and further craving, until relief is sought from this escalating cycle by smoking [5,6]. ABM with smokers has been attempted, but with limited success [7,8]. We have identified three weaknesses with the smoking ABM approaches to date: (1) Existing smoking ABM studies have relied on only a single laboratory training session, falling short of a realistic and generalizable assessment of the technique's potential to influence neurobiological mechanisms associated with AB and smoking behavior; (2) No published smoking ABM study has evaluated the generalizability of ABM to AB experienced in multiple environments, to AB across multiple modalities, and to alter AB in the long-term; (3) No previous study has examined the potential additive benefits of ABM on first-line smoking cessation therapy.

The *objective* of this grant-funded proposal (R01CA184781) is to determine the feasibility of smartphone-delivered, in-home ABM to reduce AB to smoking cues and to reduce smoking behavior in the short- and long-term. Participants will be 250 treatment-seeking smokers, who will receive 8 weeks of nicotine replacement therapy (NRT) after completing either ABM (AB away from smoking cues and toward neutral cues) or sham training. Smokers will attend 3 sessions. The 1st lab session will establish each smoker's baseline smoking behavior and AB towards smoking picture and word cues by assessing reaction time (RT) and event-related potential (ERP) electroencephalography to modified dot-probe (MDP) and Stroop color-word naming tasks. After the 1st lab session, participants will complete 13 days of daily in-home training (ABM or sham), assessments to track changes in AB, and ratings of smoking behavior and craving, that will be administered through provided smartphones, with compliance and ABM accuracy rewarded monetarily. The 2nd lab session will occur immediately after the 2 weeks of in-home training and will involve the same assessments as the 1st session, to gauge the short-term impact of ABM on AB and smoking behavior. All participants will then receive counseling and the first half of an 8-week supply of NRT to quit smoking. The 3rd lab session, which will occur after NRT, will evaluate the longer-term impact of training on smoking behavior and AB. We propose the following *specific aims* and *hypotheses* that will address PQA3 of this RFA:

Aim 1: Identify the impact of in-home ABM on AB. We hypothesize that 2-wk in-home ABM, compared to sham training, will decrease AB towards smoking cues and increase AB towards neutral cues, as measured by RT to the MDP and Stroop tasks. We hypothesize that the changes in AB will generalize to novel and cross-modal stimuli. We hypothesize that short-term changes in AB will also be present at 8 weeks following the completion of training.

Aim 2: Identify the impact of in-home ABM on smoking behavior. We hypothesize that 2-wk in-home ABM, compared to sham training, will result in fewer cigarettes (including little cigars) smoked per day, lower expired carbon monoxide, lower urine cotinine values, decreased craving to smoke, and lower nicotine dependence after 8 weeks of NRT.

Exploratory Aims: We will also examine the impact of ABM training type on the ERP components assessed during the MDP and Stroop task after 8 weeks of NRT. We will also examine the impact of ABM training type on urine anabasine (a measure of smoking exposure), the reinforcement effects of cigarettes, smoking withdrawal symptoms, mood states, symptoms of anhedonia, distress tolerance, anxiety sensitivity, impulsivity, and smoking cessation rates.

The ***significance*** of this project is a new non-pharmacological intervention that normalizes AB and reduces smoking behavior in treatment-seeking smokers that can be used as an adjunct to first-line cessation therapies. The ***innovations*** of this project are as follows: 1) We will be the first to administer multiple-session in-home ABM training using smartphones which offers the potential of maximizing ABM's effects to smokers' naturalistic environments; 2) We will be the first to evaluate the impact of ABM in conjunction with a first-line smoking cessation therapy (NRT); 3) We will be the first study to directly assess the generalizability of ABM on AB measured using multiple modalities, including central nervous system indicators of changes using ERP methodology, which its high temporal resolution is ideal for examining early attentional processes that RT cannot duplicate; and 4) By using multiple sessions, we will be able to assess trajectories of change in AB over time, allowing us to determine, in an exploratory analysis, the optimum number of ABM training sessions. We anticipate that our study will have a ***positive impact*** on reducing smoking-related cancers by developing an innovative low-cost non-pharmacological smoking cessation intervention that can be used as an adjunct to first-line cessation therapies.

B. SIGNIFICANCE AND INNOVATION

Significance

Smoking accounts for 12% of global adult mortality. If current smoking patterns continue, by 2020 tobacco will kill about 10 million people every year [9]. One crucial step to changing this trend is to increase the long-term success of smoking cessation interventions. More than 94% of those making an unaided cessation attempt relapse within one year [10]. Even 70% of smokers who receive first-line smoking cessation therapies relapse by 6 months post-quit [1]. The high risk of relapse has been attributed to the ability of addictive drugs like nicotine to hijack the neural mechanisms that evolved to shape behaviors related to the pursuit of rewards and the cues that predict them [4,11]. Most contemporary theories of drug dependence postulate that chronic drug-users develop AB to stimuli previously associated with drug use, making the drug cues more salient than other stimuli, including intrinsically pleasant stimuli [4,6,12,13]. Evidence largely supports this postulation, as chronic users of drugs [14–16] and tobacco [17] exhibit AB to drug-related cues that is absent in nonusers. Brain imaging studies from our lab and that of others have shown that, in smokers, cigarette-related cues automatically attract attentional resources and are processed as motivationally relevant stimuli [18–23]. Additionally, decreased AB to drug-related cues has been associated with better treatment outcomes [24–28]. The theoretical and empirical support for the association between AB, substance use, and treatment outcome has led many to pursue research into directly altering AB using ABM, a computer-delivered intervention designed to reduce AB toward drug-related cues. ABM, performed over multiple sessions, has been shown to reduce AB to alcohol-related cues and to reduce long-term alcohol consumption in problem drinkers [29] and in the alcohol dependent [2,3]. The two published studies that assessed the impact of ABM on smokers found no impact of training on smoking behavior and craving, but both relied on a single training session in a laboratory [7,8], which has not been found to be effective in alcohol studies [30–32].

ABM is a promising treatment for smoking, but it has not been effectively evaluated. To advance our understanding of ABM's potential, our proposed study will provide a rigorous assessment of ABM as a complementary smoking cessation intervention. Our proposal is significant because it offers the potential of a non-pharmacological intervention that could be used in conjunction with first-line therapies to reduce relapse rates among smokers. With this study, we will be able to evaluate whether multiple in-home ABM sessions, delivered over a smartphone, are efficacious at producing generalizable reductions in both AB towards smoking stimuli and smoking behavior. Given that current first-line therapies for smoking cessation result in relapse in the majority of quit attempters a few months after quitting, alternative and complementary smoking-cessation therapies are needed. An effective but low-cost intervention like ABM offers the potential to decrease relapse rates by focusing directly on a neurobiological

process that may place smokers at greater risk for relapse as they encounter smoking cues in the natural environment.

Innovation

This study's innovative approach will significantly advance our understanding of ABM as an intervention for smoking reduction. First, we will be the first to administer multiple-session in-home ABM training using smartphones. Previously published addiction studies restricted ABM training to the laboratory, often to a single training session. This may have prevented the therapeutic effects of ABM from generalizing to drug cues encountered in smokers' naturalistic environments, leading to equivocal results. Furthermore, use of smartphones will allow us to collect detailed information about the environment in which training is completed, to both ensure compliance with the ABM treatment protocol and to identify environmental factors that potentially influence the efficacy of ABM. Second, we will be the first to evaluate the impact of ABM in conjunction with a first-line smoking cessation therapy, NRT. No previous smoking cessation study has examined the potential additive benefits of ABM on first-line smoking cessation therapy. Third, we will be the first to directly assess the effect of ABM on AB measured using multiple modalities, including central nervous system indicators through our use of ERP methodology, the "gold standard" for examining early attentional processes due to its high temporal resolution. Finally, by using multiple sessions, we will be able to assess, in exploratory analyses, trajectories of change in AB over time to determine the optimum number of ABM training sessions. With these innovations, we feel that our study will be a more thorough and comprehensive evaluation of ABM's ability to modify AB and smoking behavior compared to previous studies. We anticipate that our ABM procedures will prove to be efficacious in reducing AB and smoking-related behaviors, which will lead to future studies where we evaluate it as a novel treatment approach for smoking cessation.

C. APPROACH

Justification & Feasibility

AB is a core concept of substance dependence models. Exposure to drug-related cues has been found to elicit alterations in physiology, self-reported mood and craving, and drug-seeking behavior, collectively called cue reactivity [33]. A key supposition of cue reactivity is that a chronic drug-user's attention is drawn to stimuli previously associated with drug use, making the drug cues more salient than other stimuli, in a phenomenon called attentional bias (AB). Many theories have postulated that the increased AB to drug cues is a key feature of drug dependence. In the incentive-sensitization model, the motivational (“wanting”) system becomes sensitized by drug use, causing the user to assign too much salience to drugs, drug cues, and the act of drug taking [4,34]. Other theories suggest that AB acts as a mediator between the perception of drug cues and the act of drug-seeking in response to those cues [6,13]. The Impaired Response Inhibition and Salience Attribution (I-RISA) model, informed by human neuroimaging studies, also postulates the centrality of heightened AB to drug cues in maintaining drug dependence [12].

AB is associated with substance dependence and treatment outcome. This theoretical link between AB and substance dependence has largely been supported by the literature with several drugs of abuse using cognitive tasks such as the Stroop color-word naming task, dual-task procedures, and the implicit association Test (IAT). Waters and Sayette [17] reviewed the literature on smoking and AB and found that smokers demonstrate significant AB towards smoking cues, and much more than nonsmokers. Similar relationships between AB and drug cues have been found for alcohol abusers [15], heroin addicts [14,16], and social alcohol and marijuana users [35], compared with respective drug nonusers. Thus, chronic, and in some cases social, users of drugs of abuse exhibit AB to drug-related cues that is not shown by nonusers. This suggests that AB may act as a gauge of motivation to use drugs [36,37].

AB to drug cues has also been associated with treatment outcome. Among the substance dependent, AB has been associated with treatment compliance [38] and treatment outcome [24–28]. AB, in the form of a smoking Stroop task given on the first day of quitting, was found in one study to be a better predictor of smoking cessation outcome than traditional measures of dependence [28]. Pre-treatment AB to a heroin Stroop task was found to predict 3-months post-treatment relapse status in heroin users attending an inpatient treatment center [27]. In a sample of alcoholics undergoing in-patient treatment, patients who later relapsed after discharge were found to produce increased AB on an alcohol Stroop task given during day 1 and week 4 of treatment, while non-relapsers and controls showed a decrease in AB during that time period [25].

ABM reduces AB to drug-related cues. The theoretical and empirical support for the association between AB and substance use has led many to pursue research into directly altering AB using ABM. ABM for substance abuse developed out of interventions designed to reduce AB in individuals with anxiety, given that a hallmark of anxiety disorders is an AB towards threat-related stimuli [39–41]. The majority of ABM interventions involve a modified visual probe task [42]. The classic visual probe task, used to ***assess*** AB, is a measure of visual attention where a pair of photographs, one bias-related (i.e., drug-related) and one neutral, are briefly presented simultaneously on a screen. After both pictures are removed from the screen, a small visual probe is presented in the former location of one of the pictures, with participants instructed to respond to the probe as quickly as possible with a button press. Each picture is probed an equal number of times. Drug dependent participants consistently respond faster to probes occurring in the place of drug-related pictures compared to neutral pictures, including smokers [43], heavy drinkers [44], and the opiate dependent [16], suggesting that drug-related stimuli capture attention in those with drug problems. In the ***modified*** visual probe task, ***used to deliver ABM interventions***, the majority or all of the probes replace neutral pictures. This task trains participants to attend to neutral pictures and away from drug-related pictures.

To date, the majority of ABM has focused on individuals with alcohol problems. ABM has been found to reduce AB in heavy drinkers [30–32]. However, these single-session ABM interventions were not effective in generalizing reductions in AB to stimuli beyond those that were used in training or in reducing alcohol use and craving [30,32]. Stimulus generalization is important because it potentially signifies the extent to which a person's AB is reduced to stimuli in the broader environment. The key to increasing stimulus generalization appears to be multiple ABM sessions, which have been found to result in stimulus generalization of this AB reduction in heavy drinkers [29] and the alcohol dependent [2,3]. Similar stimulus generalizations following multiple training sessions have been found with anxiety ABM [39,41]. Thus, ABM can reduce AB towards drug-related cues in heavy drinkers and the alcohol dependent, though multiple training sessions are likely required for stimulus generalization.

Multiple-sessions of ABM reduce alcohol use. Most [30–32] (but not all [45]) single-trial ABM studies with alcohol dependent individuals did not report reductions in use or craving. However, studies that used multiple training sessions have been consistently successful. In the initial study that included multiple training sessions, social and heavy drinkers from the community received multiple ABM sessions, but no control group was included. Compared to baseline, ABM reduced AB to alcohol-related cues and reduced alcohol consumption at the 3-month follow-up [29]. In two randomized clinical trials, alcohol-dependent inpatients who received multiple brief ABM sessions showed reductions in AB to alcohol-related stimuli, increased stimulus generalization of the AB reduction, and better treatment outcomes out to 3 months [2] and 1 year later [3] compared to inpatients who received sham training. It should be noted that none of the three studies used more than five brief (15 to 30 min) ABM sessions, and that each used a different ABM task, yet all were able to reduce drinking for at least 3 months after training. The improvements shown by those in the ABM group were clinically significant; in one study [2], alcoholics in the ABM group were discharged 1 month earlier than those in the control group (Cohen's d=2.16), and those who relapsed took 1.5 months longer to do so.

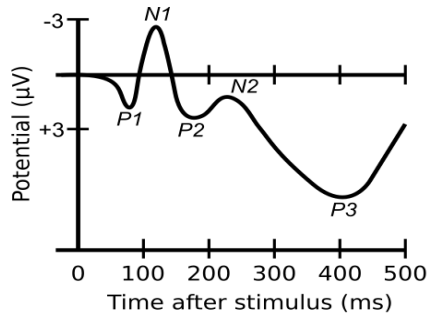
ABM studies of smoking dependence have been limited. Three published studies have evaluated the impact of ABM on smoking, but all have been limited by reliance upon a single session of ABM training [7,8,46]. The first study to do so, Attwood et al. [7], manipulated AB to smoking cues using a modified visual probe task in which smokers were trained to either attend to (i.e., the target probes followed smoking cues) or avoid (i.e., the target probes followed neutral cues) smoking cues. As expected, those trained to avoid smoking cues had less AB than those trained to attend to such cues, but only men reported greater craving in that condition. Unfortunately, this initial study suffers from several flaws similar to those that plagued the early alcohol ABM studies, including having no control group, a single training session, no measure of the impact of ABM on stimulus generalization, and no accounting for levels of nicotine dependence. The second study to investigate the impact of ABM on smoking sought to address some of the deficiencies of the Attwood et al. [7] study by including a no-ABM control group and by measuring stimulus generalization [8]. As hypothesized, AB was found to be larger among smokers trained to attend to smoking cues compared to those trained to avoid smoking cues and those in the control group. However, ABM had no impact on craving, in-lab smoking behavior, or stimulus generalization, either to new stimuli or to a different task. The authors concluded that their overall lack of findings was due to relying upon a single session of ABM, and recommended that multiple sessions over an extended period of time be evaluated. The final study was largely a replication of Attwood et al. [7], and failed to find an impact of a single session of ABM training on AB or craving [46].

Multiple in-home ABM sessions have the potential for greater generalization of training. Research from the training literature has found that the degree of training generalization depends on the extent to which the training environment matches the evaluation environment, known as context-dependency effects [47]. Thus, to decrease AB to smoking cues frequently encountered in a smoker's daily life, training should ideally be in the smoker's naturalistic environment. *Unfortunately, all of the published ABM studies involving drug dependence have restricted ABM training to the laboratory environment, which has little relation to the environment where smokers typically smoke, possibly minimizing the generalization of the ABM effect on AB.* The one study to evaluate multiple in-home ABM sessions found that such training did generalize to AB measured in a laboratory environment. This anxiety study, involving incoming foreign university students, evaluated the impact of a 2-week in-home ABM training regimen on state anxiety measured the day of arrival at the university [48]. The ABM used a MDP task to reduce AB to threat words. Compared to a no training control group, the ABM group demonstrated reduced AB to threat words presented in-home. More importantly, the ABM group demonstrated reduced state anxiety upon initial arrival at the university, and reduced trait anxiety, compared to the control group. The authors concluded that multiple ABM training sessions in the participants' home environments generalized to reduced trait anxiety and to state anxiety in response to real-world stressors.

One unpublished study has demonstrated the feasibility of administering an in-home ABM intervention in smokers that alters AB to smoking cues [49]. In this preliminary study, smokers not interested in quitting (n=60) were randomly assigned to complete 3 ABM or 3 sham training sessions per day and 1 AB assessment per day for a week. The training and assessment was a MDP task administered through a personal data assistant (PDA) hand-held computer. The participants completed 71% of the training sessions, with no differences in completion rates by intervention group. There was a significant group by time interaction, such that smokers in the ABM training group demonstrated reduced AB to smoking cues over time compared to those in the sham training group. However, neither smoking behavior, long-term changes in AB, stimulus generalization of ABM effects to other AB modalities, nor ERP measures of AB were assessed in this study, all of which we intend to evaluate with this proposed grant project.

ERP measure changes in AB. ERPs provide a multidimensional measure of the components of attention processing. ERPs are EEG signals that are time-locked to the onset of

Figure 1. The temporal location of the P1 ERP component.



a stimulus or response, and then averaged over many trials to provide waveforms whose time course has been associated with stages in the attention spectrum, from sensory to evaluative processes [50]. While both RT and ERPs are sensitive to AB, ERPs' temporal resolution provides an advantage for examining early attentional processes that RT cannot duplicate. One ERP component in particular, the P1, has been helpful in studying AB (**Figure 1**). The P1 component is thought to be influenced by location of the stimulus with respect to the subject's spatial attention [51]. The generators of the P1 are primarily located in the occipital areas of the brain, peaking within 90 to 160 ms from visual stimulus onset [52]. Several studies demonstrate the sensitivity of the P1 to detect AB. A study of AB in non-anxious participants using the MDP task to present fearful and neutral faces found that probes replacing fearful faces produced significantly larger occipital P1 than probes that replaced neutral faces [53]. A similar study of high and low anxious participants, using threatening and neutral pictures, found that P1 to probes were larger to the threatening compared to the neutral pictures only for high anxious individuals [54]. These studies suggest that unpleasant or threatening stimuli are subject to an AB, particularly for anxious individuals. However, another study suggests that normal participants can have AB to pleasant as well as unpleasant stimuli [55], as the P1 to pleasant (baby faces) and unpleasant (anger faces) stimuli were both larger when compared to neutral faces. These studies suggest that P1 reflects a general attentional mechanism that is sensitive to individual differences in AB, making it an ideal procedure for evaluating the impact of ABM on AB on the nicotine dependent.

Preliminary Studies

Multiple-sessions seem to maximize the ABM training effect among heavy drinkers and the alcohol dependent, but no published study has evaluated intensive training in smokers. In-home ABM training may increase the generalization of its effect on AB and smoking behavior. In this section, we review our studies of AB in smokers and our efforts to develop computerized smoking interventions for use outside of the laboratory. Our research group has extensive experience studying attentional and motivational aspects of nicotine dependence. With our preliminary studies, we wish to show that we have experience (a) developing and administering mobile interventions and assessments for use outside of the laboratory; (b) evaluating AB in smokers using RT tasks, (c) assessing in-home AB in smokers trying to quit; and (d) using ERPs as a reliable measure of AB in smokers.

We have expertise in the development and use of mobile interventions and assessments. These efforts include a recently completed NCI-funded R01 (R01CA97893 – co-PI: Vidrine) by co-investigator Damon Vidrine, Dr.P.H., which consisted of a 2-group RCT comparing a mobile phone-delivered intervention (CPI) to a usual care (UC) control group. The study sample consisted of 474 ethnically diverse, underserved persons living with HIV/AIDS. Feasibility of the CPI was demonstrated by high retention and intervention delivery rates (each approximately 80%) [56]. Importantly, the overall treatment effect (through 12-month follow-up) was significant (*OR*=2.46, 95% *CI*: 1.03, 5.94) [57]. In a subsequent study (R01CA132636 – PI: Vidrine) targeting smokers with HIV, Dr. Vidrine used cell phones to administer weekly assessments over a 3-month period to smokers with newly diagnosed HIV/AIDS. Approximately 400 participants were enrolled in this prospective study, and compliance with the cell phone-administered assessments was over 80%. Dr. Vidrine is also currently PI of an ongoing NCI supported R01 (R01CA141628) that utilizes an interactive text messaging smoking cessation intervention. This study required the development of a novel delivery system (produced in collaboration with MD Anderson's Duncan Family Institute e-Health Technology Program, headed by co-I Alexander Prokhorov), which provides individually tailored smoking cessation

content to low SES smokers from the greater Houston area. Finally, Dr. Vidrine has developed a smartphone application that enables real time data transfer to secure servers, complex rule building, and real time notifications (text or email).

We have experience evaluating AB in smokers using RT tasks. For example, in one study we examined whether AB to smoking words, as measured by the smoking Stroop task, was associated with the motivational salience of smoking pictures, as measured by peripheral physiology [58]. Scores for the smoking Stroop and for the peripheral physiology, including zygomaticus major ("smile muscle") electromyography (EMG), corrugator supercilii ("frown muscle") EMG, heart rate (HR) and skin conductance (SC), were created by taking a difference score for each measure by subtracting the responses to the neutral from the smoking stimuli. Smokers who had slower RTs to smoking words produced larger zygomaticus major EMG to smoking cues than those with faster RTs. However, scores on the smoking Stroop were unrelated to the corrugator supercilii EMG, HR, or SC responses to smoking stimuli. These results suggest that AB to smoking cues is more strongly associated with appetitive motivational measures (i.e., zygomaticus major activity) than with measures of avoidance (i.e., corrugator supercilii activity) or measures of physiological arousal (i.e., HR, SC). This is consistent with theories that smoking cues are associated with conditioned responses that capture attention, and are consistent with other work from our lab [59,60].

We have experience assessing in-home AB in smokers trying to quit. As part of an Ecological Momentary Assessment (EMA) study, we had 119 community smokers carry around a personal data assistant (PDA) during the first week following their scheduled quit attempts [61]. As part of multiple planned and random assessments per day, participants recorded their craving to smoke and completed a modified Stroop task, a measure of AB to smoking words. Overall, the smokers produced a significant smoking Stroop effect, (17.9 ms, *SD*=46.6; *t*[118]=4.19, *p*<.0001, Cohen's *d* = 0.38), indicating AB to smoking words, and the smoking Stroop effect was positively correlated with craving ratings, *r*(117)=.28, *p*<.01. These results demonstrate that reliable and significant AB can be captured on a hand-held device in a participant's day-to-day environment, and that this AB is associated with self-reported craving.

We have used ERPs, including the P1, as a reliable measure of AB in smokers. We evaluated ERP differences among picture categories using randomization tests on time regions of interest identified by temporal principal component analysis [23]. We found that both emotional and cigarette-related pictures prompted significantly more positivity than did neutral pictures over central, parietal, and frontal sites in the 452-508 ms time window. During the 212-316 ms time window, both pleasant and cigarette-related pictures prompted less positivity than neutral images did. However, only cigarette-related pictures, and not the emotional pictures (pleasant and unpleasant), significantly enhanced the amplitude of the P1 component (136-144 ms) relative to neutral conditions. These results demonstrate that, for smokers, cigarette-related cues uniquely capture attentional resources very early during visual processing and engage brain circuits normally involved in the processing of intrinsically motivationally relevant stimuli.

Figure 2: Study event diagram, relative to the baseline laboratory session.

Lab Session	Day	Study Event
1	1	Baseline Lab Session, 1-day pre-training
	2 … 14	Daily In-Home ABM training and AB assessment … Daily In-Home ABM training and AB assessment
2	15	Follow-up Lab Session; Given NRT
	16	Begin NRT; Quit Smoking
	29	Taking NRT; Phone counseling
	43	Taking NRT; Phone counseling
	57	Taking NRT; Phone counseling
3	72	Stop NRT; Follow-up Lab Session

D. RESEARCH DESIGN AND METHOD

Study overview. Participants will be 250 community smokers, currently interested in quitting smoking, who will be randomly assigned (stratified by gender) to receive either ABM or sham training. Smokers in both groups will attend three laboratory sessions (Figure 2). The first lab session will establish each smoker's baseline smoking behavior and AB towards smoking picture and word cues by assessing reaction time (RT) and event-related potential (ERP) electroencephalography to modified dot-probe (MDP),Stroop color-word naming tasks and a passive picture viewing task. After the first lab session, participants will complete 13 days of daily in-home training (ABM or sham) and AB assessments that will be administered through a provided smartphone, with compliance and accuracy rewarded monetarily. The second lab session will occur the day after the final day of in-home training and will involve the same assessments as the first session, to gauge the short-term impact of ABM on AB and smoking behavior. At the end of the second lab session, participants will have a 30-minute counseling session with a smoking cessation counselor and be given the first half of an 8-week supply of NRT. The participants will be instructed to quit the next day, and will have 3 biweekly phone counseling sessions while on NRT. After participants complete one biweekly phone counseling session, they will be mailed the remainder of their 8-week supply of NRT. Participants will be given a window of seven days after the scheduled date of their second lab session to complete the session. The final lab session, which will occur 8 weeks after the second session, will measure the longer-term impact of training on smoking behavior and AB. Participants will be given a window of fourteen days after the scheduled date of their final lab session to complete the session. Out of window visits will be noted in the progress notes but will not be considered a protocol deviation. Visit 3 has a window with an ending period of whenever final abstinence data is collected or the trial ends, whichever is sooner. A study staff member will make attempts to contact participants who miss Visit 3 until the end of the study or until the participant requests no further efforts be made to contact them. For those who miss Visit 3, a study staff member will call them to invite them to come in as originally planned so that abstinence (e.g., TLFB assessment since last contact, CO, urine cotinine, and anabasine), and lab data can be collected. If participants are unable to attend Visit 3, staff will ask participants to complete TLFB over the telephone to record CPD since last visit. Staff also will offer to send participants' questionnaires via email. If smoking abstinence is reported, staff will invite participants to come in or will offer to send them a NicAlert or comparable urine cotinine test to biochemically verify abstinence. Participants will be asked to send a picture of the cotinine test to research staff via text message, email, or postal mail.

Participants

We will recruit 250 adult smokers (125 women), who are interested in quitting smoking in the next 30 days, from the Houston metropolitan area. Participants will provide informed consent to a protocol that will be approved by the University of Texas MD Anderson Cancer Center's Institutional Review Board. The participant will be presented with an optional procedure regarding their electronic communication preference in regards to receiving communication via unsecured (e.g., text messaging, unencrypted email) or secured methods (e.g., in person consultation, encrypted email, telephone calls). Inclusion criteria includes being between the ages of 18 and 65, smoking an average of 5 or more cigarettes or little cigars per day (CPD) for 30 days prior to phone screen, producing an expired carbon monoxide (CO) level greater than or equal to 6 ppm or NicAlert urine cotinine greater than 2 at the first laboratory session, having a working telephone, seeking smoking cessation treatment, possessing fluency in spoken and written English and sign the picture consent form. Individuals will be excluded if they are taking psychotropic, anticonvulsive, or narcotic medication, unwilling to alter or remove hairstyle, hair extensions, or wig during clinic visits, meet criteria for a current Major Depressive episode or suicidality, have a history of neurological illness or closed head injury, reports diagnosis of seizure disorder, report uncorrected vision problems, are involved in current smoking cessation activity, test positive on a urine drug screen for drugs of abuse/potential abuse, are pregnant or

breastfeeding, share the same address as a currently enrolled participant, unwilling to take nicotine replacement therapy as prescribed, or are considered by the investigator to be an unsuitable or unstable candidate (e.g., due to cognitive impairment). To facilitate compliance, participants may earn up to $500 for attending all 3 laboratory sessions, completing 13 in-home sessions, performing perfectly on all the ABM training and AB assessments and completing all 3 telephone counseling calls. This breaks down to $60 per laboratory session ($42 for attending + $8 AB assessment performance bonus + $10 for completing Qualtrics questionnaires prior to the visit), $15 per in-home smartphone session ($11 for the ABM training and $4 for the AB assessment) and $25 for each telephone counseling calls. Participants will be compensated for completed smartphone sessions at Visit 3 to ensure accuracy of the data and earnings. If participants complete all visits and in-home smartphone sessions, a $50 bonus will be provided at Visit 3. A smartphone return incentive of $30 will be provided to participants who return their study smartphone to project staff in good working order. Participants who complete Visit 3 (i.e., TLFB and questionnaires) via telephone call will be provided $20 in addition to $25 for each completed telephone counseling call. A cotinine incentive of $5 will be provided to participants who report abstinence and return a picture of their NicAlert or comparable urine cotinine test to project staff. Participants will also be reimbursed for parking or metro tickets during the 3 laboratory sessions. See Appendix CC for the compensation schedule.

Procedures

Phone screen: Initial eligibility. All participants will be screened by phone to determine initial eligibility. The CO criterion and mental health screen will be assessed at the baseline session. All participants who are initially eligible will be informed that they may be sent an email with a questionnaire consent statement, and, should they consent, they will be automatically connected to questionnaires hosted on MD Anderson's Qualtrics platform, prior to their scheduled baseline laboratory session. Participants will receive a phone call, email, and/or text message before their laboratory sessions to remind them of the appointment.

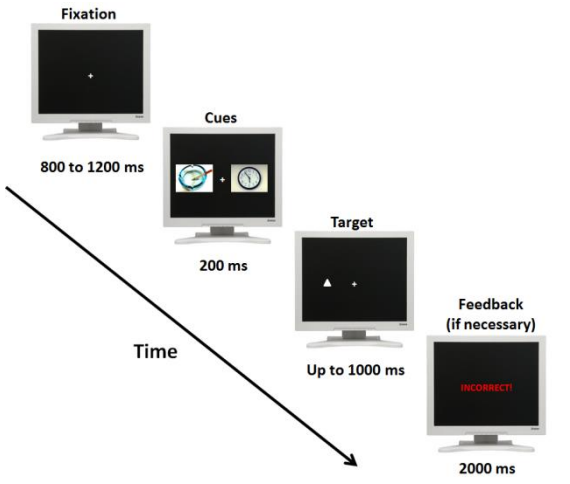
Baseline laboratory session: Final eligibility. Participants will be instructed to smoke ad lib prior to their baseline lab session. At the baseline, which will occur within 30 days of the telephone screen, participants will have their smoking status assessed, as a final determinant of eligibility, using expired CO or the NicAlert strip.To determine eligibility with the Major Depression and suicidality criteria, participants will complete the Patient Health Questionnaire-9 (PHQ-9), a reliable and valid self-administered diagnostic instrument that assesses depression severity and risk for suicide [62,63]. Additionally, the subject will be assessed for interest in providing a genetic sample according to procedures described in our IRB-approved genetic banking protocol (Protocol # Lab 09-0099). Any individual who is deemed ineligible for study participation due to the PHQ-9 will be assessed by a master's level counselor and will be given referral recommendations for local psychiatric resources (see "Project SmartMod Mental Health Procedures" in the Appendix, for details). Urine will be collected and tested to evaluate eligibility on the drug use and pregnancy criteria, and participants will be considered ineligible if they are pregnant or have a positive toxicology screen for any of the following drugs: cocaine, opiates, methadone, benzodiazepines, barbiturates, amphetamines, methamphetamines, PCP, or THC. Final eligibility will be determined by the PI, Jason Robinson, a licensed and credentialed psychologist, and his designated study staff members.

Laboratory sessions: Smoking behavior assessment. Prior to each of the 3 lab sessions, participants may be sent a link to complete the visit questionnaires via email. At each of the 3 lab sessions, participants will provide an expired CO sample, a urine sample to measure cotinine (a tobacco metabolite that measures nicotine exposure) and anabasine (a tobacco metabolite that will allow us to distinguish NRT use from smoking [64]), and complete TLFB [65] to record CPD for the prior seven days at visit 1 and CPD since last visit for visits 2, 3 and each of the telephone counseling sessions. Next, if not previously completed, participants will complete a computerized battery of questionnaires related to smoking behavior. Nicotine

dependence will be assessed by the Fagerström Test for Nicotine Dependence (FTND) [66]. We have chosen to measure these indices of smoking behavior because we believe that they will be responsive to ABM. AB has been positively associated with both dependence severity [67–69] and craving [70–72]. Reinforcement effects of cigarettes will be assessed by the modified Cigarette Evaluation Questionnaire (mCEQ) [73] and withdrawal symptoms will be assessed using the Wisconsin Smoking Withdrawal Scale (WSWS) [74]. Mood state will be assessed at each visit using the Positive and Negative Affect Scale (PANAS) [75], which has been shown to be predictive of smoking behavior [76]. During the first lab visit participants will complete several additional questionnaires. The Specific Loss of Interest Scale (SLIPS) [77] will be used to measure anhedonia and the SUPPS-P [78,79] and a computerized Delay-Discounting Task (DDT) [80] will be used to measure trait impulsivity. The DDT, a measure of impulsivity that gauges preference for smaller, more immediate rewards over larger, more delayed rewards, will be used to identify whether in-home ABM training reduces impulsivity, a possible treatment mechanism not measureable with our EEG-derived measure of attentional bias.

The Cigarette Purchase Task (CPT) [81,82] will be used to measure the behavioral-maintaining properties of nicotine, called relative reinforcing efficacy (RRE), which is a temporally stable measure of motivation for drug use [83]. We will use it to compare with our EEG-derived measured of motivational salience. The Distress Tolerance Scale (DTS) [84] and the Anxiety Sensitivity Index (ASI) [85] will be used to assess participants' tolerance to stressors, which has been associated with relapse behaviors [86]. Finally, the Chapman Handedness questionnaire [87] will be administered in order to account for potential differences in hemispheric function between left- and right-handed individuals [88]. At the final lab session, participant will complete a Post-Lab Questionnaire to assess participant attention and attitudes toward the lab and smartphone tasks. The laboratory smoking behavior assessments will take about 30-45min to complete and are included in the Appendix. Upon completion, a computer questionnaire acknowledgment form will then be signed by the patient that allows them to acknowledge the questionnaires they just completed.

Figure 3. The MDP laboratory task



Laboratory sessions: AB assessment using the MDP task. After completing the smoking behavior assessments, participants will complete an MDP task designed to evaluate AB to smoking compared with neutral pictures. First, they will be fitted with an EEG sensor net (see below), which will take approximately 20 min. The participants will then receive instructions about the laboratory AB assessment task and will be notified of the monetary rewards associated with completing each trial accurately and quickly. The participants will complete 8 practice trials involving pictures of abstract art before starting the test trials. Each practice and test trial will begin with a fixation cross at the center of the screen, functioning as an inter-trial interval (ITI) that will vary randomly from 800 to 1200 ms (**Figure 3**). Participants will be instructed to keep their eyes focused on the fixation cross at all times. After the ITI, two pictures, of smoking and neutral content, will be displayed simultaneously on either side of the fixation cross for 200 ms. The 200 ms stimulus presentation time was chosen because it, unlike the 500 ms presentation used in several other studies, reflects AB in orientation to [89], and not disengagement from [90], substance-related stimuli. The pictures or words then disappear and a probe randomly

occurs in place of one them until a button is pressed, or until 1000 ms has passed. Participants will be instructed to press a button corresponding to the side of the screen (left or right) where the probe appears. Incorrect responses, or responses that occur outside of 20-1000 ms interval after probe onset, will result in the word "incorrect" appearing on screen in red for 2000 ms. The laboratory AB assessment will consist of 16 picture pairs repeated 10 times over four blocks, for a total of 160 trials. Every picture pair will be probed, with random probes following each picture or word an equal number of times, and each picture or word randomly located on the left and right of the screen equally often. After each block of 40 trials, participants will receive feedback on their performance, including accuracy and mean RT, and be instructed to relax for 20 s before the start of the next block. An on-screen tally of money earned and lost will also appear as part of this feedback, with participants gaining $0.025 for each correct response within the response window ($4 maximum). An AB score will be calculated by taking the mean RT difference between the CIG and NEU targets on trials with correct responses within the response window [7,91]. As part of the exploratory data analyses, participants' eye movements will also be tracked using the Tobii TX-300 eye tracking system developed by Tobii Technology, Inc. during a paired picture-viewing task. Eye movement data will be used to supplement RT data collected during the MDP, because recent studies of attention-bias for both alcohol [92] and tobacco [93] use disorders have called into question the reliability of reaction time as the primary outcome measure of AB. Laboratory sessions, including smoking behavior and ERP assessments, will be conducted by a laboratory technician and overseen by PI Jason Robinson, and co-I Jeffrey Engelmann, experts in using electrophysiology to study attentional and affective processes. The laboratory AB assessment will last approximately 10 min. Prior to beginning the first MDP task, the Self-Assessment Manikin (SAM) will be administered to allow participants to rate the images used in the experiment on the dimensions of affective valence and arousal [94].

Laboratory sessions: AB assessment using the modified Stroop task. In order to determine generalizability of ABM training across stimulus modalities, participants will complete a modified Stroop task designed to evaluate AB to smoking words [28]. The modified Stroop task is predictive of relapse in nicotine-, alcohol-, and heroin-dependent individuals [25,27,28]. Participants will be told that a series of words will appear on the screen in different colors, that they should press a button on the response box corresponding to the color of the text used to present the word, and that they should respond as quickly and accurately as possible. The monetary rewards associated with quick and accurate performance will also be explained. Participants can earn $0.025 for each correct response, within the response window, in the neutral and smoking blocks ($4 maximum). The Stroop task will consist of three blocks, with a 5-s rest period between blocks: (a) practice (40 trials), (b) neutral words (80 trials), and (c) smoking words (80 trials). The neutral block will be presented before the smoking block to avoid carryover effects [28]. Each trial will begin with a fixation cross at the center of the screen for 500 ms, functioning as the ITI. After the ITI, the fixation cross will disappear and a word will be presented in its place using one of four text colors: red, green, blue, or yellow. The word will remain on the screen until the participant responds, for a maximum of 3 s. During the practice block, if the participant makes an error, or does not respond within 3s, a notification will be rapidly flashed on the screen for 200 ms. The practice stimuli will be 10 repeated letter strings (e.g., HHHHHH, XXX). The neutral stimuli will be 20 neutral words (e.g., ARRIVAL, CLOCK). The smoking stimuli will be 20 smoking-related words (e.g., SMOKE, PUFF). Each word will be presented four times per block, once in each color. The words will be delivered in a random order with the following restrictions: Each word will appear once in each sub-block of 20 consecutive trials (10 trials for the practice block), and the same color will not appear on two consecutive trials. An AB score will be calculated by taking the mean RT difference between the smoking and neutral words on trials with correct responses within the response window. The Stroop task will take approximately 7 min to complete.

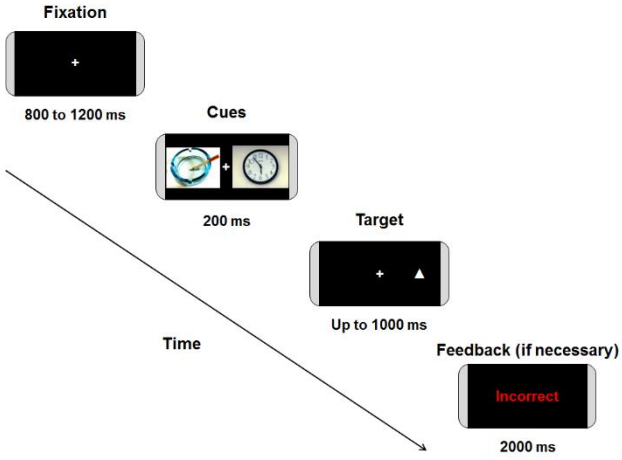
Laboratory sessions: EEG assessment of reward sensitivity. The picture-viewing task and ERP assessment will take place at visit 1. It will consist of EEG recorded during

passive viewing of neutral, emotional (pleasant and unpleasant), and cigarette-related pictures (**Figure 5**). Pictures will be selected from the International Affective Picture System (IAPS) [95] and from cigarette-related picture collections previously used in our [96] and other [97] laboratories. The picture set will include 4 picture categories, pleasant (PLE), unpleasant (UNP), neutral (NEU), and cigarette-related (CIG), with 30 pictures each (total: 120 pictures per set). During the picture presentation, pictures will be shown in pseudo-random sequences with no more than two pictures of the same category presented consecutively. Each picture will be shown for 4 seconds and will be followed by a random intertrial interval of 3-5 s, during which a black fixation cross will be presented on a gray background. The entire picture presentation will last approximately 20 min (the pictures will be shown twice during the session, for a total of 240 pictures). Each session will be divided into 8 equivalent blocks lasting 3.8 min each and separated by a 30-s interval, during which the participant will have the opportunity to relax. Stimuli will be presented using E-prime software (v1.4; Psychology Tools Inc., Pittsburgh, PA) on a video screen placed approximately ~65 cm from the participant's eyes. The pictures will subtend approximately a 24° horizontal viewing angle. For each session for each participant, we will calculate the average ERPs at each scalp site for each picture category and, in line with previously published data [98–101], we will compute the amplitude of the LPP ERP between 400 and 700 ms over central and parietal sites. The LPP ERP means will be used to estimate reward sensitivity to drug-related and emotional cues. We will use this measure of reward sensitivity in exploratory analyses to determine its impact on ABM.

Laboratory sessions: Software development. Presentation of the laboratory MDP and Stroop task stimuli, ERP event synchronization, and RT timing will be controlled using E-prime software (PST Inc., Pittsburg, PA), stimulus presentation software with which we have over 10 years of experience developing programs for the assessment of AB [58,102] and electrophysiological response [59,101,103]. The neutral pictures will be selected from the International Affective Picture System [95] and the cigarette-related picture from collections previously used in our [96] and other [97] laboratories. The smoking and neutral pictures used in the MDP task will be matched on brightness, luminosity, color distribution, perceptual complexity, and object size and location to reduce potential confounding from factors known to influence early attention allocation [104]. The smoking and control words for the Stroop task will be selected from those used in previous research [28,105,106]. The words will be matched on length, number of syllables, frequency of occurrence in the English language, and semantic relatedness, which are all dimensions that can bias attention and response [107]. E-Prime programming and scoring will be done by co-I Jeffrey Engelmann, an expert in programming E-Prime.

Laboratory sessions: ERP data collection and reduction. The AB assessments completed at the 3 laboratory sessions will involve an ERP measure of attentional processing. The number of ABM trials to be assessed (n=320) was chosen to have an adequate signal-to-noise ratio for measuring the P1 component [50]. EEG will be recorded with a 129-channel net and amplified with an AC-coupled high-input impedance (200 MΩ) amplifier (Geodesic EEG System 250; Electrical Geodesics, Inc., Eugene, OR) referenced to Cz. The sampling rate will be 250 Hz, and data will be filtered online with a 0.1-Hz high-pass filter. After data collection, we will apply a 100-Hz low-pass filter, and interpolate channels contaminated by artifacts for more than 50% of the recording. Eyeblinks will be corrected by using a spatial filtering method [108]. After eyeblink correction, the EEG data will be transformed to the average reference and segmented into 700-ms segments starting 100 ms before onset of the picture or word pair. Baseline will be defined as the 100-ms interval preceding the picture or word pair. Segments with more than 10% of the sensors contaminated will be rejected; otherwise, the contaminated channels will be interpolated. For each session for each participant, we will calculate the average ERPs at each scalp site for each category (smoking, pleasant, neutral) and we will compute the amplitude of the P1 component between 100 and 150 ms over occipital sites [109].

Figure 4. The MDP smartphone task.



The P1 means will be used to estimate AB to smoking vs. neutral and pleasant cues. The steps outlined above for the EEG\ERP data reduction and the statistical analyses will be performed using software (i.e., BESA, MEGIS Software GmbH, Gräfelfing, Germany; Brain Vision Analyzer, Brain Products GmbH, Munich, Germany; SAS 9.2, SAS Institute Inc., Carey, NC) that we have used in previous studies [23,110]. ERP post-processing will be overseen by co-I Jeffrey Engelmann, an expert in EEG and ERP scoring and analysis.

In-Home Smartphone: ABM training and AB assessment. At the end of the Laboratory Session 1, the participants will be trained in the use of the smartphone. They will be told that the in-home smartphone ABM training will help them prepare to quit, and that their quit dates will be scheduled for the day after Laboratory Session 2. The participants will be instructed that they can, but are not required to, reduce or eliminate their smoking before their quit date. During the in-home ABM training sessions, participants will complete daily 30-minute training (ABM or sham) and AB assessment sessions on their provided smartphone for 13 days. The 13-day training period was selected because two weeks of in-home training reduced AB in an anxiety study [48]. Participants will be trained on the ABM tasks at the end of the baseline session. The participants will be instructed to complete the task in a quiet, well-lit location in their homes, free from distraction and interruption, at approximately the same time each day. Compliance and accuracy on the training and assessment tasks will be tracked by the program and rewarded by on-screen tallies of money earned at the end of each ABM block. Participants who fail to complete a training and assessment session, or who do so poorly (25% or more incorrect), will receive a message (SMS text or phone call, depending on participant preference) reminding them to complete the training and/or assessment tasks accurately the next day. If a participant fails to complete the task for 2 or more consecutive days, or has 25% or more errors during a training session, a staff member will call him or her to troubleshoot any impediments and encourage training participation.

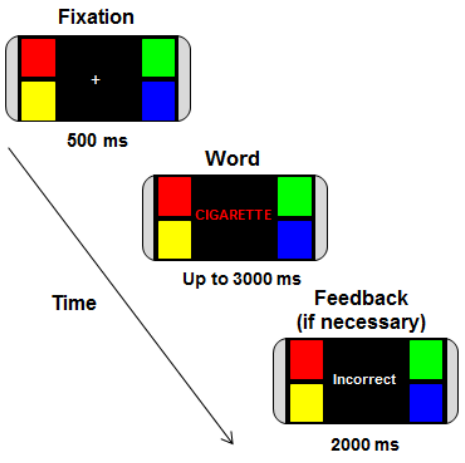
The smartphone-delivered ABM and sham training (**Figure 4**) will both involve the same MDP task timing, scoring, and monetary reinforcement schedule as the laboratory AB assessment, with several exceptions. First, the ratio of probes following each picture type will differ by ABM group. In the ABM group, 100% of the probes will replace neutral pictures, to reduce participants' AB to smoking cues, while in the sham group, probes will follow each of the 2 picture types an equal number of times, to avoid influencing AB. Second, the training groups will both involve more blocks of trials than the AB assessment, consistent with other ABM studies [2]. The ABM training session will consist of 22 picture pairs repeated 20 times over 8 blocks, for a total of 440 trials, 55 per block. Third, the task will be presented over the smartphone, with no EEG collected. Each picture will be 5 cm wide by 5 cm high, and the response will be considered correct if the participant taps within this region on the side of the screen where the probe is presented. The maximum performance bonus for the MDP task for each session is $11 ($0.025 per trial). The in-home ABM training will last for approximately 20 min.

In-Home Smartphone: AB assessment using the Stroop. After completing the last block of ABM or sham training, participants will immediately and seamlessly transition to the in-home AB assessment component. The in-home AB assessment will use the Stroop task. The in-home Stroop task will be identical to the laboratory task, except that it will be given over the smartphone. Thus, the 4 response buttons will be presented on the touch screen, 2 each to the left and right of the word (**Figure 5**). The placement of the buttons on the left and right side of the screen will allow for participants to respond quickly with their thumbs. The color assigned to each of the four buttons will be randomly varied from day to day. The word will be presented in the center of the screen, approximately 4 cm wide and 2 cm high. Each button will be 3 cm wide by 3 cm high. The in-home AB assessment will take approximately 7 min to complete. The maximum performance bonus for the Stroop task for each session is $4 ($0.025 per trial).

In-Home Smartphone: Assessments of Smoking and Craving. At the start of the ABM training, the smartphone will be used to assess daily cigarette consumption and cigarette craving. Participants will be asked to provide the number of cigarettes smoked so far on the day of the assessment, the time that they smoked their most recent cigarette, and a rating of their current "urge" to smoke on a scale from 0 (no urge) to 9 (maximum urge). This single-item measure of craving has been previously used in ecological momentary assessment studies and has been shown to be both reliable and valid (e.g., predictive of subsequent smoking) [111,112]. Additionally, participants will also be asked to provide the amount of caffeine and alcohol that has been consumed each day. Importantly, this assessment will only take about 1 minute to complete, which will minimize burden and allow the participants to immediately proceed to the ABM training.

In-Home Smartphone: Assessment of Training Environment. We will use the smartphone to assess characteristics of the training environment. This will allow us to explore possible relationships between environmental distractions and performance, and also serve as a measure of compliance regarding the instruction to complete the task in a quiet, well-lit location. Throughout the ABM training and assessment period, the smartphone will sample the ambient lighting, background noise levels in dB (no sounds or video will be recorded), and motion (using an accelerometer reading) every 30 s. If the tri-axial accelerometer detects excessive motion, the task will automatically pause at the end of the next block and a message will be displayed reminding the participant to hold the phone still when completing the task. When the motion subsides, the task will resume and the block during which excessive motion was detected will be repeated.

Figure 5. The Stroop smartphone task.



In-Home Smartphone: Software development. The smartphone software will be developed by MD Anderson's e-Health Technology program, which is overseen by Alexander Prokhorov, a co-I on this proposal. The e-Health programmers have extensive experience developing smartphone-based interventions and assessments for grant-supported projects. The e-Health programmers will design and implement the smartphone software, the SQL Server database to store data collected by the smartphone, and the web-based application to allow research staff to oversee in-home smartphone compliance. Damon Vidrine, a co-I on this proposal with extensive experience using smartphones, will also provide oversight and input into the development of this software and procedures. Additionally, e-Health will provide research staff training on these applications, maintain and manage the software and hardware,

and ensure that the project complies with MD Anderson information security (and HIPAA) requirements. The 25 smartphones and cellular data plans will be provided by T-Mobile, with whom the e-Health Technology programmers have experience working with on smartphone applications. Participants will be temporarily given a touch-screen smart phone (Samsung Galaxy Avant or compatible device) for use during the 13-day in-home training and assessment phase of the study. The large (6.9 x 12.7 cm), full-color, high-resolution (1920 × 1080; 441 pixels per inch) display is ideal for presenting stimuli and measuring user responses.

Smoking cessation: NRT and counseling. Smokers entering this study will be told that formal smoking cessation treatment will begin the day following Laboratory Session 2. At the end Laboratory Session 2, following the questionnaires and AB assessment, a master's level counselor will meet with the participant. The counselor will provide the participant with the first 4 weeks of an 8-week supply of NRT (NicoDerm CQ; GlaxoSmithKline, Research Triangle Park, NC), instruct the participant on the use of NRT, provide a smoking cessation treatment manual based on PHS guidelines (see the Appendix), and prepare the participant to quit smoking during a 30-minute counseling session. The participant will be educated and provided literature on the use and risks of nicotine patch use, and will be asked to begin using NRT and quit smoking the following day. Participants who complete at least one counseling call in this study will receive 8 weeks of NRT, consisting of 4 weeks of 21-mg patches, 2 weeks of 14-mg patches, and 2 weeks of 7-mg patches. The NRT treatment duration was chosen because meta-analysis suggests that there is little benefit of using NRT beyond 8 weeks [113]. During the 8 weeks of NRT use, participants will receive three biweekly 15-min counseling calls from the counselor (study days 29, 43, & 57; see **Figure 2**, above). Participants will be given a window of three days before and/or after the scheduled date of their phone counseling sessions to complete the session. During these phone sessions, the counselor will assess participants for medication changes, and patch and tobacco usage. At least two call attempts will be made during the course of the day however before the call will be considered missed. Missed phone sessions will be recorded in the study database but will not be logged as protocol deviations because they are expected in smoking cessation trials. After the last day of NRT use (study day 72), participants will return for their final laboratory session. Adverse events will be assessed throughout the study, and participants may choose to reduce or stop the NRT dosage in the unlikely event of dangerous or distressing adverse events. Our procedures for dispensing NRT, evaluating study compliance, and assessing adverse events follow standard FDA and clinical practice guidelines [114] and are well established in our research programs (e.g., [115,116]). Occasionally, research subjects may fail to utilize the NRT patch as instructed. In such cases, subjects will be instructed to mark the patch as missed in their smoking diaries and return the missed patch to the study team. Returned medications patches will be logged, stored in a locked file cabinet maintained by the study team, and will be destroyed per institutional guidelines. Missed patches and missed returns will not be logged as protocol deviations because they are expected in smoking cessation trials. In our previous trials about 75% of all participants take at least 80% of their intended patch use. Only adverse events related to use of the nicotine patch will be reported. The NRT and counseling component will be overseen by co-I Paul M. Cinciripini, who has over 25 years of experience designing and conducting smoking cessation trials.

Statistical Approach & Expected Outcomes

Aim 1. Identify the impact of in-home ABM on AB. We will evaluate this aim using 2 (group: ABM vs. sham) X 3 (session: baseline, 1-day post-training, and 8-weeks post-training) linear mixed model using RT difference scores (neutral-cigarette) as the dependent measures and subject as the random effect. We will conduct separate analyses on the dependent measures (within-modality: MDP RT difference scores; between-modality: Stroop RT difference scores) collected at baseline, 1-day post-training, and 8-weeks post-training. We predict that post-training AB scores, calculated from RT, will decrease from baseline for those in the ABM training, but not in the sham training condition, indicating a reduction in AB to smoking cues.

Aim 2. Identify the impact of in-home ABM on smoking behavior. We will evaluate this aim using two types of models. For the continuous (i.e., normally distributed) measures of smoking behavior, we will conduct mixed between-within repeated measures ANOVA using the same predictors and covariates as are described in Aim 1. Separate analyses will be run for each of the continuous dependent measures, including mean CPD over the past 7 days, expired CO, cotinine, FTND, and WSWS Craving. We expect that ABM training, compared to sham training, will decrease measures of smoking exposure (CPD, expired CO, cotinine), levels of dependence (FTND), and levels of craving (WSWS Craving) at the 1-day and 8-weeks post-training sessions. For the categorical variable of 8-weeks post-NRT abstinence, we will conduct a chi-square test of independence on the 2 (abstinent vs. nonabstinent) x 2 (ABM vs. sham training) table. We expect that ABM training, compared to sham training, will result in a higher rate of abstinence.

Exploratory analyses. We will examine the Aim 1 and 2 models covarying the total number of completed ABM or sham training sessions, the number of in-home training sessions completed, in-home training sessions accuracy rates, baseline FTCD, sex at birth, and CPD at each session. We will conduct the following exploratory analyses using multilevel modeling: (1) We will examine the impact of ABM on AB, CPD, and craving assessments collected by smartphone to determine whether the optimal length of training is less than 13 days; (2) We will examine whether individual differences, measured at baseline, predict response to the ABM training on our measures of AB and smoking behavior. These individual differences will include baseline levels of nicotine dependence (i.e., FTND, mCEQ, CPT, and WSWS), mood (i.e., PANAS), anhedonia (i.e., SLIPS), impulsivity (i.e., DDT, SUPPS-P), tolerance to stressors (i.e., DTS and ASI), reward sensitivity (i.e., Passive Picture Viewing), smoking exposure (i.e., CPD and expired CO), gender, handedness (i.e. Chapman Handedness questionnaire), and AB to smoking cues; (3) We will examine whether participants' contingency awareness of the ABM task influenced ABM's effectiveness, because one ABM study with smokers found that only those participants who were aware of the relationship between the probe and stimulus type were responsive to ABM [7]; (4) We will use data about the training environment collected using the smartphone (e.g., location, dB levels, ambient lighting) to examine whether these environmental characteristics influenced ABM's effectiveness; (5) We will use the EEG data collected using our 129-channel sensor net to perform event-related potential (ERP) analyes (including the P1 component), along with source localization analysis to attempt to identify areas in brain that are responsive to ABM. We will preliminarily target occipital regions that have been found to activate in the presence of motivationally salient visual cues [91,124]. (6) We will examine the effects of AB on eye-tracking metrics (e.g., fixation, gaze duration) and compare the reliability of eye tracking with traditional reaction time metrics of AB.

Power analysis. To demonstrate that this proposal has adequate sample size to detect meaningful amplitude changes in the continuous measures taken at the post-training laboratory sessions (Specific Aims 1 & 2), we conducted a power analysis using the G*Power program (v3.1.2; Heinrich Heine University, Düsseldorf, Germany). We calculated power to ensure that we could detect a significant 2-way (ABM intervention by time) ANOVA interaction for any of our continuous measures, as assessed at the baseline, 1-day post-training, and 8-weeks post-training sessions. If we assume a conservative Bonferroni-corrected Type I error rate of α=0.01, 250 participants, moderately correlated within-subject observations (r=0.5), and a conservative nonsphericity correction (ε=0.75) we have 80% power to detect differences corresponding to a Cohen's f of 0.11 or larger for the 2-way interaction. Even if we were to experience an unlikely 30% attrition rate, we would have power to detect a Cohen's f of 0.13 or larger. According to Cohen [117], a Cohen's f of 0.10, 0.25, and 0.40 correspond to a small, medium, and large effect size, respectively, meaning that we have the power to detect a small effect size or greater on our continuous measures. To demonstrate that we would have adequate power to detect likely AB differences for Aim 1, we searched the literature for studies with a similar design to ours. Given that no previous study has evaluated the impact of multi-session ABM on AB in

smokers, we decided to estimate a likely effect size from the one alcohol study that used the MDP task for both multi-session ABM and the AB assessments [2]. We estimated a Cohen's *f* value for this study by taking the square root of the *F* ratio multiplied by the ratio of the degrees of freedom [117]. From this formula, we estimated a Cohen's *f* of 0.64, based on the reported *F* value for the significant ABM training group (ABM, sham) main effect, $F(1,23)=9.4$, $p<.01$. This Cohen's *f* value corresponds to a large effect size and is well within the range for which we have sufficient power to detect. We recognize that this alcohol study does not provide an ideal comparison for the effects sizes we will likely obtain, but it does suggest that ABM produces large effects on AB, effects which should be well within the power requirements of our study to detect.

To demonstrate that this proposal has adequate sample size to detect likely changes in abstinence after 8 weeks of NRT (Aim 2), we conducted a power analysis using G*Power to calculate effect size *w*, the square root of the standardized chi-square statistic [117]. Given a total sample size of 250 (missing participants will be assumed to be smoking), 1 degree of freedom, and a Type I error rate of $\alpha = 0.05$, we have 80% power to detect differences corresponding to an effect size *w* of 0.177 or larger, which means that we will have enough power to detect a difference in abstinence rates of 12.6% or higher between training groups. To estimate likely abstinence rates, we turned to the ABM and alcohol literature, because there are no published ABM and smoking studies that report abstinence outcome. In a study comparing ABM to sham treatment in 214 alcoholics, Wiers and colleagues [3] reported that 54% of those in the ABM group, and 41% in the control group, were abstinent at 1-year follow-up, a difference of 13%. Given that between-group substance-dependence treatment differences are often greatest at the end of treatment, and narrow by 1-year follow-up, we believe that we will have adequate power to detect likely differences in abstinence rates.

Potential Problems & Alternative Strategies

Participant recruitment. We expect to have no difficulty recruiting the needed number of participants. In the past 5 years, for example, our team has recruited more than 800 community volunteers for our various smoking research studies. We have had considerable success enrolling participants into studies involving RT and EEG/ERP recordings and our procedures allow us to collect highly reliable data.

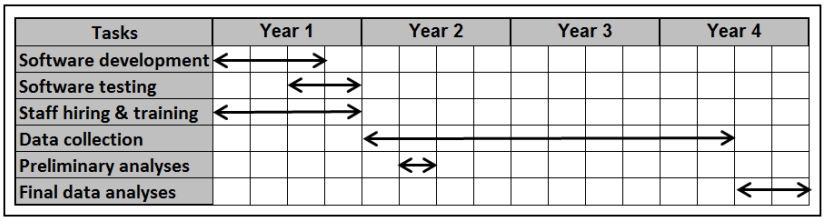
In-home task compliance and accuracy. We expect high compliance and accuracy rates with the in-home ABM training and AB assessments. We were able to obtain compliance rates of 80% in a study in which we administered smoking cessation interventions and assessments with mobile phones to underserved persons living with HIV/AIDS, a high rate considering that many of them were homeless [56]. The only previous study to involve in-home ABM training, which was daily for 2 weeks, did not report a compliance rate, but did report an accuracy rate of 96% on the at-home ABM and AB MDP tasks [48]. Our ABM and AB tasks will have features designed to improve compliance and accuracy, including feedback after each block, and monetary incentives for task completion and accuracy. We will also have contingency procedures for contacting participants who do not comply with the in-home tasks, including email/texting and staff phone calls, if necessary. Compliance and accuracy rates will also be included in the statistical models used to evaluate our study aims.

AB assessment. The MDP and Stroop tasks that we are using to assess AB has been found to reliably detect AB across a variety of populations, including the healthy, the anxious, and the substance dependent. It has been found to be sensitive to multi-session ABM conducted with problem drinkers [29] and with the alcohol dependent [2,3]. Thus, we expect our AB tasks to be similarly reliable and sensitive to our ABM training. In terms of our exploratory ERP measure, the P1 ERP has been found to be a reliable indicator of AB in most [53,55,91] (but not all [118]) prior studies that evaluated P1 to a MDP task with motivationally relevant stimuli. However, if the P1 ERP is unable to distinguish AB, we would examine other ERP components, including the P2, N2, and the P3, all of which have been associated with later

stages of AB [118]. The P2 has been associated with attentional disengagement [119], the N2 with attentional control and inhibition [120], and the P3 with orienting of attention [121].

ABM is distinct from previous interventions to reduce cue reactivity. ABM is distinct from extinction-based treatments. ABM does not target the reinforcement contingencies associated with drug-related stimuli, but instead seeks to reduce the salience of these stimuli that trigger craving and drug-seeking behavior. While AB is a consequence of classical conditioning [4], once established in the dependent user, it helps to maintain dependence by creating a reciprocal cycle in which craving increases AB to drug-related stimuli, and attention to drug-related stimuli increases craving [6]. If AB to drug-related stimuli can be reduced, then craving and drug-seeking behavior should also be reduced. ABM is also distinct from attempts to cognitively reframe responses to drug-related stimuli. Cognitive-behavioral interventions have combined exposure with meta-cognitive skills instruction to help smokers become less responsive to drug-related cues [122,123]. In contrast, the targets of ABM are early attentional processes that are considered to be less susceptible to conscious cognitive intervention due to functioning below awareness on the level of corticostriatal circuitry [6].

Figure 6. Project Timetable.



Timetable

This project will take 4 years to complete (**Figure 6**). The first year will be spent developing and testing the smartphone software and database needed for administering the in-home ABM training intervention and AB assessment, developing the laboratory AB assessment that is integrated with EEG recording, developing the patient screening, tracking, and questionnaire database, and hiring and training the staff. We expect to commence subject recruitment at the start of the 2nd year, with the intent of accruing 8 participants per month. After accruing the initial 8 participants, we will conduct preliminary analyses to verify that our laboratory and smartphone procedures are working as intended. We will dedicate the last 6 months to the final data analyses and the preparation of scientific papers.

Future Directions

At the conclusion of this project, we hope to have identified a new nonpharmacological intervention that reduces AB and promotes smoking cessation in quitting smokers. These data will improve our understanding of how ABM affects brain mechanisms and smoking behavior in quitting smokers and offer a new treatment intervention to assist in smoking cessation efforts. Long-term smoking cessation relapse rates continue to be high, and novel interventions are needed. This study represents an important next step for us, and leverages our expertise in the neuroscience of addiction and in the development of novel treatments of smoking dependence. We anticipate that the findings from this project will result in future projects designed to (1) identify who is likely to benefit most from ABM training; (2) identify other first-line smoking cessation therapies that are likely to benefit from the inclusion of adjunct ABM training; (3) evaluate whether ABM training by itself is a viable smoking cessation therapy, and what training duration is optimal. In summary, we believe that our study will significantly advance smoking cessation efforts by identifying an innovative low-cost intervention for future smoking cessation clinical trials and by advancing our understanding of the relationship between AB and smoking.

E. PROTECTION OF HUMAN SUBJECTS

Human Subjects Involvement, Characteristics and Design. Participants recruited for this study (n=250) will be current smokers from the Houston metropolitan community. Inclusion and exclusion criteria are presented in **Table 1**. All smokers meeting these qualifications will be accepted into the study.

Sources of Materials. Participants will be providing physiological data in the form of expired CO, urine metabolites and EEG/ERP imaging. Questionnaire data will be obtained that assess smoking history, health history, psychiatric history. Cognitive data will be collected in the form of the visual dot probe and Stroop task. All data will be collected specifically for research purposes and will be coded to maintain confidentiality.

Potential Risks. Nausea, vomiting, weakness, dizziness, and rapid heartbeat occur rarely and are most often caused by continuing to smoke while using the patch. If these reactions occur, and the participant is currently smoking and using the patch (i.e., the participant has lapsed but still is wearing the patch), participants will be counseled to reestablish a target quit day and gradually reduce their smoking rate. Participants will not be instructed to discontinue their patches if they have lapsed unless a serious adverse event has occurred, because research indicates that: 1) continuing patch use even when a lapse to smoking has occurred can increase the probability that recovery to abstinence will occur [125]; 2) high doses of nicotine, including 63-mg doses, do not lead to serious adverse events even with concurrent smoking [126]; and 3) patch use prior to a designated target quit day and with concurrent smoking does not lead to serious adverse events and can increase the chances for successful cessation [127]. Such findings have led to a general reconceptualization of the issue of concurrent tobacco and nicotine patch use in which smokers are now advised to continue nicotine patch use even if they have lapsed following a target quit day [128]. Some individuals who use the patch experience minor skin irritation, such as redness, rash, or minor swelling, and insomnia and dream abnormalities. Insomnia and dream abnormalities can be resolved by removing the patch during the night while sleeping. All of these reactions cease once the patch is removed. The EEG assessment carries the minor risk of skin irritation from the electrolytic solution, although this reaction is rare and easily treated. It is unlikely that completing the questionnaires, the attentional bias assessment, or the attentional bias modification task would lead to any potential risks for participants. In the event that an individual's response to a questionnaire indicates that there may be a mental health concern, staff will contact a mental health assessor and follow established procedures for handling mental health emergenices.

Table 1. Inclusion/Exclusion Criteria.

Inclusion Criteria
-Age: 18-65 year old.
-Smoking: an average of 5 or more cigarettes or little cigars per day prior to phone screen.
-Expired carbon monoxide (CO): ≥ 6 ppm or NicAlert >2.
-Having a working telephone.
-Seeking smoking cessation treatment.
-Fluency in spoken and written English.
-Must sign the picture consent form.

Exclusion Criteria
-Taking psychotropic, anticonvulsive, or narcotic medication.
-Unwilling to alter or remove hairstyle, hair extensions, or wig during the clinic visits to allow for correct EEG sensor placement.
-Meet criteria for a current major depressive episode or suicidality.
-Has a history of neurological illness or closed head injury
-Reports diagnosis of seizure disorder.
-Uncorrected vision problems.
-Involved in current smoking cessation activity.
-Testing positive on a urine drug screen for drugs of abuse/potential abuse.
-Women who are pregnant or breastfeeding.
-Shares the same address as a currently enrolled participant.
-Unwilling to use NRT.
-Considered by the investigator to be an unsuitable or unstable candidate (e.g., due to cognitive impairment).

2. Adequacy of Protection Against Risks

Recruitment and Informed Consent. Participants will be recruited from the Houston community by using one or more of the following means: mail, public service announcements, media interviews, MD Anderson Internet, newspaper advertisements, MD Anderson Conquest Magazine, and advertisements and mailers from the MD Anderson community liaison and outreach offices sent to all affiliated providers on the mailing list. The Tobacco Research and Treatment Program's web screener database for tobacco users, outlined in IRB-approved PA18-0423, also may be used as a recruitment source for this study. This database houses data collected from an internet-based screening questionnaire (See Appendix ZZ) to recruit tobacco users from the Houston area, as well as across Texas more broadly, who may be interested in participating in tobacco use and cessation studies at MD Anderson Cancer Center. PA18-0423 allows the sharing of data with IRB-approved MD Anderson protocols. Verbal consent will be obtained and documented before the telephone screening, and written consent will be obtained at onset of the orientation interview, where the participant will sign both the Informed Consent Document and the Picture Consent Form (See Appendix). Participants will be provided with a detailed description of the study, information about risks, and their right to withdraw from the study.

Protection Against Risks.

NRT is an FDA approved medication for smoking cessation. We will use an 8 week course of NRT as described in our methods. Moreover, we will also provide smoking cessation counseling consistent with the Clinical Practice Guidelines for Smoking Cessation.

The typical side effects of the nicotine patch are not usually serious in nature. Adverse effects will be assessed at each of the post-baseline laboratory and counseling sessions. In the event of a SAE being reported, a member of the medical team will be consulted. The SAE will be documented and reported according to institutional guidelines. The Tobacco Research & Treatment Program (TRTP) has trained medical personnel on staff that will be available to assist the PI and other personnel in managing medically related study issues.

Confidentiality will be protected by identifying subjects only by numbers in all data files. Identification numbers will only be connected to individual participant names in a separate file that will be accessible only by the PI and his staff. All study data files will be server-maintained with limited access by using passwords and logins restricted to study staff. All information will be reported in aggregate form, and individual participants will not be identified in any public reports or documents. We expect these procedures to be highly effective for protecting participant confidentiality.

3. Potential Benefits of the Proposed Research to Participants and Others

A primary benefit to participants in the proposed study is smoking cessation. All participants will receive empirically validated treatments for smoking cessation, concurrent NRT and smoking cessation counseling. We anticipate that many of them will continue to be non-smokers after the completion of the study. Smoking cessation is important in cancer prevention, cardiovascular events and emphysema rate reduction therefore reducing medical costs, and increasing well-being for both the participants and society in general. Smoking cessation is cost effective and results in a substantial reduction in healthcare costs for both the individual and society.

4. Importance of the Knowledge to Be Gained

At the conclusion of this project, we anticipate that our study will have a positive impact on smoking cessation treatment by identifying an innovative low-cost non-pharmacological intervention that alters AB and smoking behavior and that could be used as an adjunct with current first-line cessation therapies. Given the high relapse rates of smokers who receive first-

line therapies, greater than 70% by 6 months post-quit [1], alternative and complementary smoking-cessation therapies are needed that focus on reducing the salience of smoking cues that activate neurobiological signals associated with smoking behavior. An effective but low-cost intervention like ABM offers the potential to decrease relapse rates by focusing directly on a neurobiological process that may place smokers at greater risk for relapse as they encounter smoking cues in the natural environment. The significant potential benefits that would accrue with increased effectiveness in smoking cessation will far outweigh the minor risks associated with the proposed research.

5. Data And Safety Monitoring Plan

The IRB of The University of Texas MD Anderson Cancer Center reviews and approves the Data and Safety Monitoring Plan for all clinical trials. This study will be monitored for safety by the PI and co-investigator or by the institutional Data Monitoring Committee (DMC) as determined by the IRB during their review of the protocol. Plans and procedures for maintaining data integrity, defining and reporting AEs/experiences, and IRB oversight and monitoring of this project (including monitoring of participant eligibility and accrual, AEs, and interim data analyses) are described below. The procedures for IRB monitoring are described in a separate section below, followed by sections defining and further describing procedures for reporting AEs and procedures for ensuring data quality and integrity. All data will be stored in the Tobacco Research and Treatment database (APPID-264846).

IRB Monitoring

During the protocol review-and-approval process, the IRB determines the level of safety monitoring required for each protocol. The minimum monitoring requirements for low-risk trials include investigator monitoring of participant safety, AE reporting in compliance with IRB, NIH, and FDA guidelines, and participation in the Continuing Review process with the IRB. All other trials may also be monitored by the DMC. Outcomes of IRB and DMC reviews are conveyed to the PI via the administrative support staff in the Office of Protocol Research (OPR).

Guidelines for Filing Reports of Adverse Events at MD Anderson Cancer Center

We anticipate that when an AE occurs, it will be associated with NRT application site reactions, the most frequent adverse events associated with NRT. The use of the electrolytic solution for EEG collection might cause temporary skin rash in sensitive participants. Soon after removal of the EEG net, the skin redness disappears and does not result in serious adverse health consequences.

Adverse Events Requiring Prompt Reporting

Internal Serious Adverse Events (SAE) that are unexpected (not listed in the Informed Consent Document) and are related (possible, probable and definite) must be reported to the IRB within 5 working days. Deaths that are related and occur within 30 days after completion of treatment must be submitted to the IRB within 24 hours. Adverse events not meeting these criteria will be reported to the IRB at Continuing Review according to IRB policy.

Serious Adverse Event

A Serious Adverse Event is an event that meets one of the following: results in death, is life-threatening, results in hospitalization, results in persistent or significant disability/incapacity, results in a congenital anomaly/birth defect, based upon appropriate medical judgment, or may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Data Quality and Integrity

Because of the ongoing monitoring of the project, study investigators and staff are responsible for ensuring that data quality assurance procedures are developed and maintained. Several procedures will be used to maintain the integrity of the data. All databases will be stored in a centralized location on one of the departmental servers, which is backed up daily, with access limited to specific users at the discretion of the PI. The PI will assure that audits of selected subsets of data are performed and that appropriate safeguards of participant privacy are maintained. Privacy safeguards will include appropriate password protection and physical security for all computer systems.

Additional quality assurance procedures include a data collection protocol documented in a protocol manual; a two-stage editing procedure for survey data collection consisting of the initial review of the data collection form by a project member immediately following data collection, and a second review by a project member who will record any significant deviations from the protocol; and regular meetings between the study statistician, the PI, data managers, and other project staff to review problems and solutions, and discuss concerns. Data entry systems, whether via a CATI, or QDS, system, scannable forms, or hand entry with verification, specifically provide field checks, range checks for continuous variables and valid value checks for categorical variables; checks for legitimate dates and times and logical consistency. During data collection, we will issue reports weekly, or even following any new data entry, depending on the needs of the project. Queries and reports will be provided to the PI. Preliminary review will be initiated shortly after data collection begins to allow monitoring of data quality.

F. INCLUSION OF WOMEN AND MINORITIES

Inclusion of Women

Women will comprise approximately 50% of the targeted sample. In our previous research, we encountered no difficulty in recruiting women participants.

Inclusion of Minorities

According to the U.S. Census Bureau (2010), the population of the Houston community from which the sample will be drawn (including Harris County) is estimated at 4,070,989 people. The ethnic distribution has been reported as 73% white (35% of whom are not of Hispanic origin), 19% African American, 6% Asian, and 40% Hispanic or Latino (of any race). We expect to recruit minority smokers in proportion to the population demographics and CDC 2009 smoking prevalence. We have had good success in recruiting from ethnic minority populations, especially African Americans, across all of our studies. Our success with Hispanic smokers has been more modest, although it must be noted that smoking rates are lower in the Hispanic and Latino community compared with rates in the non-Hispanic community.

If needed, we may also attract minority smokers to the proposed study by using direct public service advertisements targeted to minority smokers on Houston radio stations and newspapers supporting a large minority audience. Houston has two television stations and several radio stations and newspapers that serve the Hispanic community. The Office of Public Affairs at MD Anderson has also agreed to assist us by arranging for our participation in institution-wide cancer prevention outreach programs directed at the Hispanic community. Such events are sponsored several times a year in areas of the community with high concentrations of minority Houstonians. We will focus additional recruitment effort on these venues to increase our recruitment of Hispanic smokers. Such efforts will be in addition to the normal interviews, advertisements, and news releases conducted on our behalf by the Office of Public Affairs at MD Anderson.

G. INCLUSION OF CHILDREN

We will exclude smokers younger than 18 years of age. The characteristics of smokers previously recruited in similar experiments have been very consistent in our recruitment as well as in national samples. The average age of these smokers is older than 40 years; they consume about a pack of cigarettes or less per day, have made numerous quit attempts, and have smoked for more than 15 years. Significant differences between adults and adolescents are likely in several domains, including attentional and physiological response to nicotine and nicotine cues. Therefore, the study of the brain mechanisms associated with smoking behavior among adolescent smokers would require a separate focus on those factors that are relevant for this population.

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