Approach Bias Retraining to Augment Smoking Cessation

NCT03325777

Last Revised: 4/8/21

PUBLIC HEALTH NARRATIVE

Smoking remains a significant public health problem and there is a need for more effective interventions. Theory and initial empirical findings justify testing whether a simple computerized intervention targeting the approach action tendency – or approach bias – toward stimuli related to cigarette smoking can augment smoking cessation. The goal of the current research is to evaluate the potential efficacy of an intervention that integrates this computerized intervention with standard smoking cessation care.

ABSTRACT

Cigarette smoking remains a leading cause of preventable death[1], contributing to over 480,000 deaths each year[2]. Although efficacious, standard care for smoking cessation is associated with high non-response rates, suggesting there is a need to develop augmentation strategies[3]. Theory and empirical findings suggest that targeting automated, impulsive, implicit processes may hold promise[4–9]. Specifically, retraining approach bias, or the approach action tendency toward stimuli related to the substance of interest has been effective in alcohol use disorders (i.e., reduction in relapse rates by 10%-13%)[10–13]. We recently extended this work to smoking by demonstrating that approach bias retraining reduced approach bias and the reduction in approach bias was associated with the number of days quit in the week following a self-guided quit attempt[14].

The goal of this application is to pilot test an intervention that integrates approach bias retraining with standard care for smoking cessation. The integrated intervention involves seven weekly 60-minute sessions. Each session involves 15 minutes of computerized approach bias retraining followed by 45 minutes of individual CBT. The target quit week is set at week 5, at which time nicotine replacement therapy is prescribed. Adult smokers (N=100) will be recruited and randomly assigned to (1) the integrated intervention or (2) a control intervention that combines standard smoking cessation care as described above with a computerized intervention that does not target approach bias. Abstinence will be assessed during the intervention (weeks 0-7), at posttreatment (week 8), and at 1-month (week 9), 2-month (week 13) and 3-month (week 17) follow-up (i.e., post-quit). Measures of putative mediators will be assessed during the intervention (weeks 0-7).

The proposed study represents a crucial and important stage in translating basic research to strategies for treating nicotine dependence. The investigation addresses an important public health issue by testing an integrated intervention - informed by basic research - that may lead to a more effective treatment for at-risk smokers while simulatenously isolating explanatory mechanisms. The expected findings should: (1) guide advances in the theoretical conceptualization of the mechanisms involved smoking; and (2) provide initial effect size data for the integrated smoking cessation intervention, and thus provide the necessary data for a large-scale follow-up trial.

SPECIFIC AIMS

Overview

This R34 application proposes to test whether a computerized intervention can augment smoking cessation by reducing approach bias. It was guided by the following observations and research findings:

- Contributing to over 480,000 deaths each year[2], cigarette smoking remains a leading cause of preventable death[1].
- Associated with relatively low abstinence rates (15-35%), established standard care interventions fall short, justifying the development of augmentation strategies[3].
- Dual process models of addiction underscore the potential of augmenting standard care for smoking cessation with interventions designed to target automated, impulsive, implicit processes[4–9].
- Approach bias – or the approach action tendency toward stimuli related to the substance of interest – has emerged as a viable target for augmentation strategies:
  - Approach bias is evident in problem users of alcohol[7,9,10,15] and cannabis[16] as well as smokers[17–19].
  - Approach bias retraining has been effective in alcohol use disorders, yielding significant reductions in approach bias and associated relapse rates[10–13].
  - In a pilot study involving adult smokers motivated to quit, we demonstrated that (1) approach bias retraining reduced approach bias (i.e., target engagement) and (2) the reduction in approach bias was associated with the number of days quit in the week following a self-guided quit attempt[14].

This application builds directly on this research and corresponding pilot work by evaluating a smoking cessation intervention that integrates standard care (ST; cognitive behavioral treatment [CBT] plus nicotine replacement therapy [NRT]) with approach bias retraining (ABR). Specifically, the integrated intervention involves seven weekly 60-minute sessions. Each session involves 15 minutes of computerized approach bias retraining followed by 45 minutes of individual CBT. The target quit week is set at week 5, at which time NRT is prescribed. In order to obtain initial effect size data for a larger R01 follow-up study, we will randomly assign 100 adult smokers to either: (1) ST+ABR or (2) standard care plus a computerized training that assesses but does not retrain approach bias (ST+CTRL). Abstinence will be assessed during the intervention (weeks 0-7), at posttreatment (week 8), and at 1-month (week 9), 2-month (week 13) and 3-month (week 17) follow-up (i.e., post-quit). Measures of putative mediators will be assessed during the intervention (weeks 0-7).

Specific Aim 1: Smoking Cessation

1. To compare, in a randomized clinical trial, the effects of ST+ABR vs. ST+CTRL on the following smoking cessation outcomes:
   A. Short- and long-term point prevalence abstinence (PPA) and prolonged abstinence (PA). We expect that PPA and PA will be higher, both in the short term and long term, for those in the ST+ABR condition than for those in the ST+CTRL condition. Similarly, we expect the rate of decline in abstinence over time to be smaller in ST+ABR condition than for those in the ST+CTRL condition.
   B. Time to first smoking lapse and time to smoking relapse. We expect mean time to first lapse and to relapse to be greater for those in the ST+ABR condition than for those in the ST+CTRL condition.

Specific Aim 2: Mechanisms of Action

2. To examine potential mechanisms of action:
   A. To test the putative mechanism of action. We expect that a reduction in approach bias mediates the effects of the intervention on abstinence.
   B. To explore the role of reduced craving as a mechanism underlying the approach bias-abstinence relation. We expect that reduced craving mediates the relation between reduced approach bias and abstinence.
   C. To explore possible moderators. We will test whether the efficacy and mechanisms vary as a function of nicotine dependence and sex, respectively.

RESEARCH STRATEGY

A. SIGNIFICANCE

A1. Public Health Significance of Developing Smoking Cessation Interventions

Cigarette smoking remains leading cause of preventable death in the United States (U.S.), contributing to over 480,000 deaths each year[2], or about 1 of every 5 deaths[2]. Though approximately 70% of current adult smokers are motivated to quit[20], and significant strides have been made in the development of effective smoking cessation treatments, most established interventions are associated with relatively low long-term abstinence rates (15-35%)[3]. Accordingly, the most recent guidelines for clinical practice on treating tobacco use and dependence indicate there a need for innovative, potent strategies for smoking cessation[3].

A2. An Experimental Therapeutics Approach to Developing Interventions

Informed by theory and basic research findings, a number of studies from our group and others has (1) helped identify a viable target for interventions that aim to aid smoking cessation; and (2) provided promising pilot data for an intervention that can engage this target.

A2a. Dual Process Models of Addiction Identify Implicit Processes as a Target

According to dual process models, addiction is thought to arise from an imbalance between two distinct, yet interacting, systems: the impulsive and reflective systems[4–9]. The impulsive system relies on associative memory and often operates unconsciously. This system can be difficult to control. Conversely, the reflective system is limited in capacity and relies on symbolic processing and often incorporates flexible learning[7]. Wiers and colleagues[21] have used a “horse and rider” metaphor to describe the interaction between these two systems, such that the horse (i.e., the impulsive tendencies) can be controlled by the rider (i.e., the reflective processes) should the rider acquire the necessary skills and strength. This metaphor underscores the rationale for using interventions like cognitive-behavioral treatment (CBT), which targets reflective systems, but also the potential importance of prescribing interventions that target the automated, impulsive, implicit processes. Specifically, interventions that engage or target implicit processes, especially when combined with interventions like CBT, have the potential to enhance long-term quit success[7,22].

A2b. Tobacco-Related Approach Bias as Specific Target for Intervention

Consistent with incentive-sensitization-theory[23], dual process models of addiction posit that repeated drug use sensitizes the automated impulsive, implicit processes[7]. Specifically, because drug-related cues become a signal of reward over time, heavy users and addicted individuals develop an approach action tendency – or approach bias – toward stimuli related to the substance of interest[7,9]. Among different assessment strategies, the Approach-Avoidance Task (AAT)[24] has emerged as a suitable tool for assessing approach bias[25,26]. This 15-minute computerized task instructs participants to use a joystick to either pull toward themselves or push away from themselves images presented on the screen that vary in content (i.e., substance-related, neutral, positive) and format (e.g., right- or left-tilted). Specifically, using indirect task instructions (i.e., responding to the format instead of content), participants are told that all pictures will be slightly tilted to the left or right, and that they are to pull right-tilted pictures and push left-tilted pictures. Importantly, pulling the joystick increases the size of the image, while pushing the joystick decreases the size of the image, thus causing visual approach and avoidance effects, respectively. The AAT involves multiple trials (i.e., presentation of images) and records reaction times (RT) for each trial. The RTs for each trial are then used to compute an index of approach bias – i.e., the relative tendency to pull rather than to push in response to the presentation of substance-related images[16,27]. Using the AAT, researchers have shown that approach bias is evident in problem users of alcohol[7,9,10,15] and cannabis[16] as well as smokers[17–19], although there are studies that have not observed the relation between substance use problems and approach bias[27].

Manipulating approach bias – or training persons with substance use problems to push away substance-related images – has shown promise for enhancing outcomes of substance use treatments[7,10–13]. Approach bias retraining involves repeated administrations (sessions) of a modified AAT, which involves changing the contingencies of the AAT assessment task ensuring that participants learn to engage in avoidance (pushing the joystick) when presented with substance-use related pictures. In the treatment of alcohol use disorder, an initial study involving 214 inpatients receiving CBT showed that, compared to those who received no training or 4 sessions of a control intervention (i.e., repeated AAT assessment tasks involving equal number of avoidance and approach movements to alcoholic and non-alcoholic drinks), participants assigned to receive 4 sessions of

approach bias retraining evidenced significantly lower relapse rates at 1-year follow-up[10]. Importantly, this finding was replicated and extended in a larger sample (N=509), indicating approximately a 10% reduced relapse rate in training vs control and evidence of reductions in approach bias mediating the clinical effect[11].

Building upon this research, we recently completed an initial pilot study[14] involving adult smokers motivated to make a quit attempt (N=52) and tested (1) whether 4 sessions of approach bias retraining would reduce approach bias (i.e., target engagement) and (2) whether target engagement would be associated with the numbers of days quit in the week following an unaided and self-guided quit attempt (i.e., initial estimate of efficacy[28]). Data supported both hypotheses and provided evidence for a small, albeit statistically non-significant, effect of training on days quit in the week following the quit attempt[14]. Together, these promising findings support next-stage research aimed at evaluating approach bias retraining to aid smoking cessation.

A3. Next Step in Treatment Development: Testing the Combination of Approach Bias Retraining and Standard Smoking Cessation Treatment

According to dual process models[4–9], an intervention that includes approach bias retraining may be most effective if it also targets reflective processes. Hence, the research involving samples with alcohol use disorder reviewed above conceptualized and tested approach bias retraining as an intervention to augment standard interventions provided in the inpatient setting (CBT)[10–12]. Inpatients in these studies underwent interventions to achieve abstinence and then subsequently started approach bias retraining aimed at reducing the chance of relapse[10–12]. As we aimed to isolate the effects of the intervention on approach bias in our pilot study with smokers[14], we (1) provided no additional intervention to approach bias retraining and (2) delivered all 4 approach retraining sessions prior to a self-guided quit attempt. Accordingly, theory and empirical findings justify testing whether approach bias retraining can augment standard smoking cessation treatment when training commences prior to the quit attempt and is extended through the initial weeks following the quit attempt.

A4. Mechanisms of Action and Moderators of Approach Bias Retraining

Mechanistic research is critical for optimizing interventions[29]. Hence, although the primary aim of this application is to examine whether approach bias retraining can aid smoking cessation, we will test (1) whether the effect of training on abstinence is in fact accounted for by a reduction in approach bias (i.e., target engagement). Consistent with incentive-sensitization-theory[23], initial research in smokers shows that approach bias covaries with self-reported craving[19,30] and research in alcohol use disorders shows that approach bias retraining reduces craving[10,11,31]. Because reduced craving has been shown to mediate other treatments for smoking cessation[32,33], we will test (2) whether reduced craving mediates the relation between reduced approach bias and abstinence. Recognizing that the efficacy of interventions and their mechanisms may vary depending on individual difference variables[29], we will also explore (3) the potential moderator effects of nicotine dependence, which has been related to approach bias[30,34] and smoking cessation outcomes[35], respectively, as well as sex, consistent with priorities of the NIH (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html).

A5. Need for the Proposed Pilot Trial (R34)

Consistent with the R34 mechanism, the application proposes a pilot randomized double-blind controlled trial to evaluate the novel integrated intervention for smokers. Indeed, at this time there is no data available to estimate the degree of benefit of approach bias retraining may offer to improve cessation outcomes. As detailed below, the proposed pilot study is designed to gather this information that will be sufficient to properly inform the design of a full-scale clinical trial.

Although collecting the essential data on efficacy and mechanisms of action using a tightly controlled study design with high internal validity are the aims of this application (i.e., Stage I[36]), we plan to complement this research with efforts aimed at developing an iteration of the integrated intervention that is easily transportable. Specifically, we will collaborate with local colleagues (see http://sagalab.utexas.edu) to develop a version of approach bias retraining that can be completed outside the clinic and thus has the potential to be integrated with other real-world interventions (e.g., Quitline). Accordingly, if the R34 research provides data consistent with hypotheses (e.g., meaningful effect sizes), we will develop a scalable and transportable iteration of the integrated intervention and a follow-up R01 application to test its efficacy (i.e., Stage II[36]).

B. INNOVATION

This application has a number of innovative features, including the following:

- The proposed research translates basic research findings emphasizing the role of automated implicit biases in the maintenance of substance use disorders into a targeted intervention.
- This application proposes the next step in an experimental therapeutics approach which has shown evidence for approach bias retraining to reduce approach bias (target engagement) and reductions in approach bias resulting in improved outcomes (efficacy).
- This application proposes the first examination of approach bias retraining to augment smoking cessation in adult smokers motivated to quit smoking.
- This application involves the testing of a computerized intervention for smoking cessation.
- This application proposes to test the efficacy of an intervention that has the potential to be easily disseminated and reach a large group of smokers.

C. APPROACH

C1. Research Team

Our team consists of experienced clinical trial investigators, including Drs. Jasper Smits, Richard Brown, Christopher Beevers (University of Texas at Austin), Dr. Mike Rinck (Radboud University) and Dr. David Rosenfield (Southern Methodist University). We have a history of productive collaboration. Each of investigators bring to this application complementary expertise. Dr. Smits brings expertise in the development and evaluation of integrative interventions for smoking and will oversee the training and supervision of the study therapist. Dr. Brown brings expertise in the development and evaluation of innovative smoking cessation interventions and will aid in the implementation of the treatment and assessment protocols. Dr. Beevers is an experienced researcher in cognitive bias modification and will oversee the quality assurance of the protocol for implementing the computerized intervention. Dr. Rinck brings expertise in the assessment and modification of approach bias and will be responsible for programming the assessment and intervention protocols and aid in the implementation of these procedures. Dr. Rosenfield is a biostatistician who will be responsible for randomization and statistical analysis.

Figure 1. Effect of ABR on Approach Bias

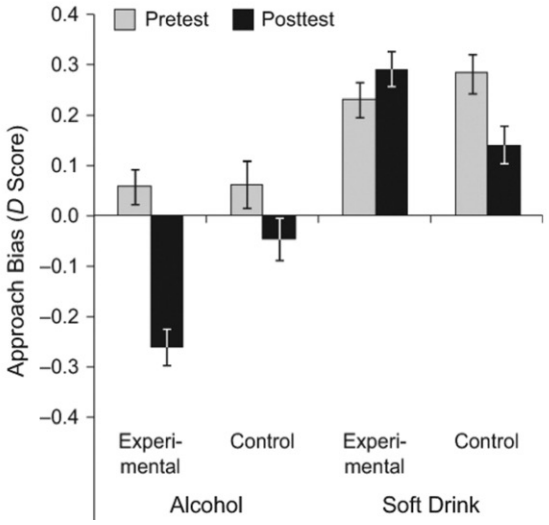
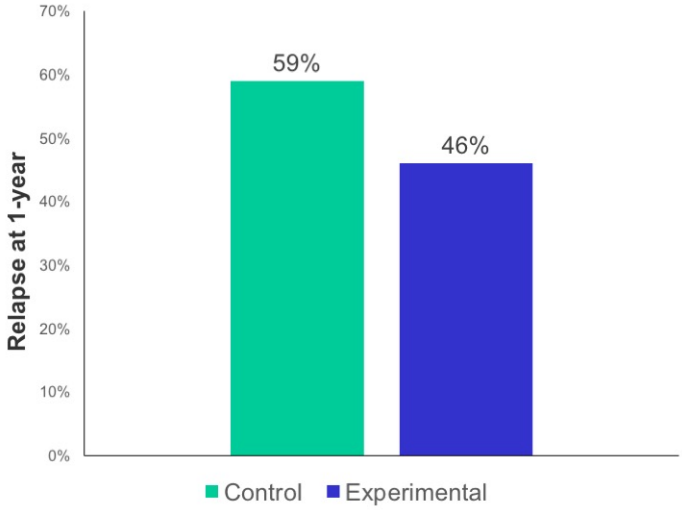


Figure 2. Effect of ABR on Alcohol Relapse



C2. Preliminary Studies

We will review here findings of key studies that have guided the the current investigation.

- Retraining automatic action tendencies changes alcoholic patients' approach bias for alcohol and improves treatment outcome[10]. This study tested the effects of a ABR that targeted an approach bias for alcohol in 214 alcoholic inpatients. Patients were assigned to one of two experimental conditions, in which they were explicitly or implicitly trained to make avoidance movements (pushing a joystick) in response to alcohol pictures, or to one of two control

conditions, in which they received no training or sham training. Four brief sessions of ABR preceded regular inpatient treatment. In the experimental conditions only, patients' approach bias changed into an avoidance bias for alcohol (see Figure 1). Patients in the experimental conditions showed better treatment outcomes a year later (see Figure 2). These findings indicate that a short intervention can change alcoholics' automatic approach bias for alcohol and may improve treatment outcome.

- Approach bias modification in alcohol dependence: Do clinical effects replicate[11]? This study aimed to replicate and extend the previous study. Alcohol-dependent patients (N=509) received inpatient CBT and were randomly assigned to ABR or no training. The group receiving ABR developed alcohol-avoidance behavior and reported significantly lower relapse rates at one-year follow-up (see Figure 3). Change in alcohol-approach bias mediated this effect. These findings indicate that ABR can be employed to enhance CBT by modifying approach bias.
- Reducing approach bias to achieve smoking cessation: a pilot randomized placebo-controlled trial[14]. This study aimed to provide a preliminary test of the efficacy of a brief cognitive bias modification program for reducing approach bias in adult smokers motivated to quit. Participants were 52 smokers who were randomly assigned to four sessions of ABR (experimental) or CTRL training (control). Participants were asked to make a self-guided quit attempt upon completion of the final training session. Approach bias was assessed at baseline and at the end of each session, and days abstinent was assessed 1-week following the quit attempt. Individuals assigned to the experimental evidenced significantly greater reductions in approach bias relative to those in the control condition ($p<.001$; see Figure 4). Baseline approach bias did not moderate the between-group effect ($ps>.41$); however, higher levels of approach bias at baseline were associated with greater approach bias reduction over time ($p<.001$). Consistent with prediction, the reduction in approach bias during the intervention period was significantly related to the number of days abstinent following the quit attempt ($p=.033$; see Figure 5). These findings extend recent work in alcohol use disorders by showing that approach bias reduction, in this case for smoking-related stimuli, may also facilitate smoking cessation.

Figure 3. Effect of ABR on Alcohol Relapse (Replication)

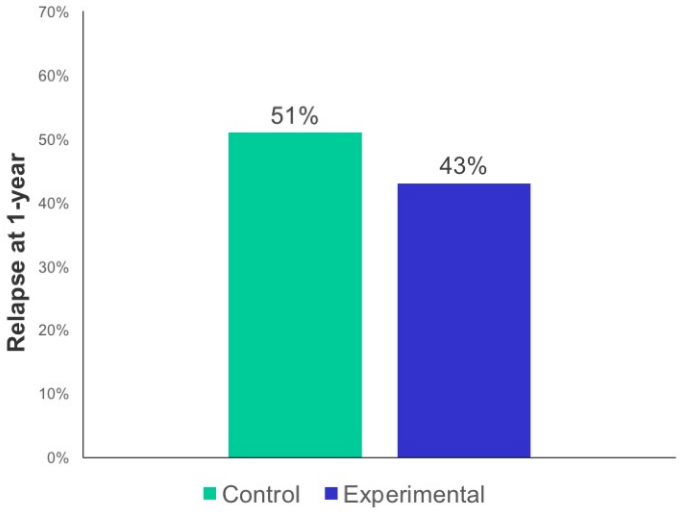


Figure 4. Effect of ABR on Approach Bias (Smoking)

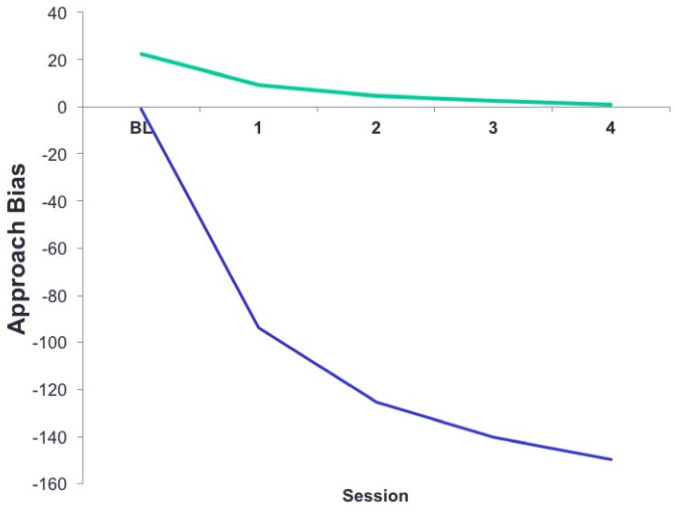
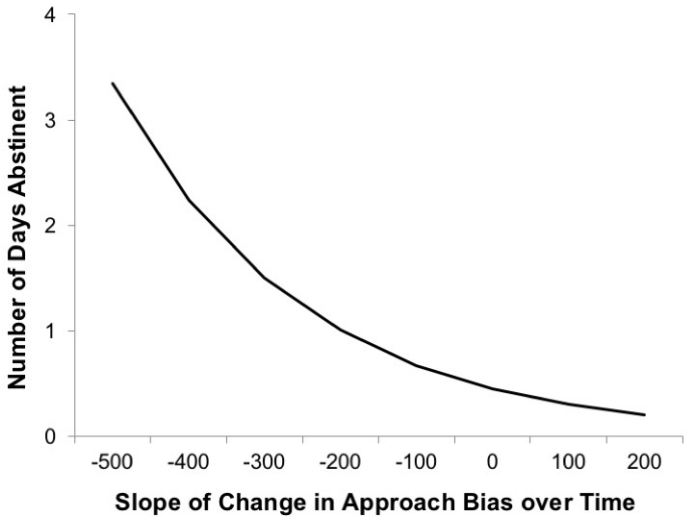


Figure 5. Approach Bias Reduction and Abstinence (Smoking)



C2. Study Overview and Experimental Design

The primary aim of the proposed study is to obtain estimates of the efficacy of a smoking cessation intervention that integrates standard care (ST; cognitive behavioral treatment [CBT] plus nicotine replacement therapy [NRT]) with approach bias retraining (ABR). The secondary aim is to perform an initial examination of the putative mechanisms underlying the hypothesized augmentation effect of ABR. The integrated intervention comprises seven weekly 60-minute sessions, of which the first 15 minutes involve computerized approach bias retraining followed by 45 minutes of individual CBT. The target quit week is set at week 5, at which time NRT is prescribed. In order to achieve the study aims, we will randomly assign, in a double-blind fashion, 100 adult smokers to either: (1) ST+ABR or (2) standard care plus a computerized training that assesses but does not retrain approach bias (ST+CTRL). Abstinence will be assessed during the intervention (weeks 0-7), at posttreatment (week 8), and at 1-month (week 9), 2-month (week 13) and 3-month (week 17) follow-up (i.e., post-quit; see Figure 6). Measures of putative mediators will be assessed during the intervention (weeks 0-7; see see Figure 6).

C2a. Design Considerations

Rationale for the Dose. Initial research on dose-response effects for ABR in alcohol use disorder indicates that, on avarage, persons may need at least 6 sessions to achieve a strong effect on approach bias[12]. Although our pilot data with smokers showed promise for prescribing 4 sessions of approach bias retraining *prior* to a quit attempt[14], research in alcohol use disorders points the efficacy of prescribing approach bias retraining at a time of abstinence[7,10–13]. Accordingly, matching our pilot work in smokers[14], we decided to retain the prescription of 4 sessions of approach bias retraining pre-quit (sessions 1-4), and following the research in alcohol use disorder[7,10–13], we decided to extend the training by 3 sessions post-quit (sessions 5-7).

Rationale for Using NRT in the Treatment Protocol. Because clinical guidelines recommend that all smokers attempting to quit receive pharmacotherapy, we believe it is important to include pharmacotherapy (NRT) as part of our smoking cessation treatment. We chose to provide the patch for 8 weeks because longer than 8 weeks does not appear to improve treatment efficacy[3]. We chose the Nicoderm CQ®, 24-hour transdermal nicotine patches (TNP) as part of the study because of the extensive empirical literature supporting its effectiveness and safety, its ease of use, and its relatively benign side effect profile that have led to its approval as an over-the-counter medication[37].

Rationale for Using a 3-month Follow-Up. We considered using a longer follow-up period (e.g., 6- and 12-month), but 3-month follow-up seems reasonable given the well-accepted finding that most relapses have occurred by 3 months, with only minor changes occurring thereafter[38–40]. Using the shorter-term follow-up is also reasonable given the shorter funding period for the R34 mechanism.

C3. Study Participants

We plan to recruit 100 male and female participants between the ages of 18 and 65. Inclusion criteria are: (1) daily smoker for at least one year, smoking an average of at least 10 cigarettes per day, and motivated to quit smoking (> 5 on a 10-point scale). Exclusion criteria are (1) use of other tobacco products (including e-cigarettes); (2) psychiatric conditions that are contraindications to the use of any treatment option in the protocol (e.g., currently suicidal or high suicide risk, current or past psychotic disorders of any type, bipolar disorder, schizophrenia or schizoaffective disorder, anorexia, bulimia, alcohol or substance disorder within the last 6 months); (3) current use of any pharmacotherapy or psychotherapy for smoking cessation not provided by the researchers during the quit attempt; and (4) insufficient command of the English language.

C3b. Recruitment and Timeline

We have a history of successful recruitment for NIH-funded trials of smoking cessation interventions and will use the approach that has been effective in these studies. Specifically, we will advertise through numerous community organizations that promote quit smoking initiatives and also use social media and Internet outlets to advertise our study. The greater Austin, TX area has a population of 1.9 million. The enrollment period will be 127 weeks (of 156 weeks), allowing sufficient time for start-up activities (12 weeks) and participants to complete the study protocol (17 weeks) and complete data analysis (starting at week 139). Accordingly, we need to enroll 0.8 patients every week or 4 patients every 5 weeks. Currently, we screen, on average, 22.45 individuals weekly (or 112 every five weeks) for ongoing smoking cessation studies. Given the required conversion rate is 4% (4 of 112), we deem this targeted enrollment feasible.

C3c. Screening Procedures

An initial web screen will be performed with all potential participants to determine initial eligibility (e.g., smoking history, motivation to quit). A UT staff member will contact potential participants who appear eligible following screen to provide more details about the study and, if the participant provides informed consent, the staff member will conduct the Mini International Neuropsychiatric Interview (MINI)[41,42] to assess psychiatric exclusion criteria. Participants who are eligible and remain interested will be enrolled.

C4. Procedures

C4a. Randomization and Baseline Visit

Eligible participants will be randomized to study condition prior to the baseline visit. The project biostatistician, Dr. David Rosenfield, will oversee the randomization. He will use variable-sized permuted block-randomization (block sizes will vary from 4 to 12). Prior to data analyses, Dr. Rosenfield will check the balance of randomization and control for any factors that are imbalanced. The baseline visit serves to obtain initial assessments on the outcome and mechanisms variables.

C4b. Interventions

Participants will receive a standard, individual smoking cessation treatment based on the most recent clinical practice guideline from the U.S. Department of Health and Human Services, Treating Tobacco Use and Dependence[3]. Consistent with the manualized procedures we have employed in past and ongoing NIDA-funded investigations[43–46], the standard intervention (ST) involves a combination of CBT plus NRT.

CBT. As outlined in the therapist manual, CBT will involve 40-minute weekly sessions over a 7-week period. During session 1, therapists will congratulate participants for deciding to quit smoking, review the positive health consequences of quitting, and express their willingness to help the participant succeed. Participants' past quit attempts will be reviewed to identify what strategies contributed to success and what factors hindered their previous attempts and a target quit date will be set for week 5. Lastly, participants will initiate self-monitoring or track each cigarette they smoke through Quit date and note situational cues for smoking (e.g. times of the day, activities while smoking). During sessions 2-4, therapists will assist participants in anticipating situations in their lives that will likely place them at risk for relapse and prepare them for the possibility of lapsing and given strategies for coping with the potential negative emotional reactions to lapsing. Therapists will also help participants develop coping strategies. For each high-risk situation identified, therapists will assist participants to develop behavioral and cognitive strategies for coping with high-risk situations. Participants also will receive training in deep breathing relaxation. In addition, therapists will advise all participants to avoid or reduce drinking and advise all participants to tell their friends and family about their quit date and will discuss ways to increase social support during the quit attempt. Lastly, therapists will instruct participants in the proper use of the nicotine patch (e.g., placement of patch, use one a day, importance of not smoking while using the patch) and help them prepare for the quit day (e.g., removing all tobacco products from their environment). On the day of the quit attempt (session 5), therapists will provide individual support for participants during this early period of abstinence. This contact will provide the opportunity for more tailored and elaborate discussions of quitting experiences and coping strategies for anticipated high-risk situations. Therapists will also reinforce success and provide support and encouragement for participants who slip and smoke and ask participants to anticipate potential challenges to remaining abstinent from smoking and discuss strategies for coping with those situations. In addition, during this session, therapists will ask participants to discuss social supports for nonsmoking, help to develop strategies for maximizing social support systems and develop participants' skills in requesting behavioral changes from others. Sessions 6-7 focus on relapse prevention. Therapists will continue with relapse prevention tactics, including provision of social support, avoiding high-risk situations, using social support from friends/co-workers, and maintaining non-smoking lifestyle changes.

NRT. All participants will receive Nicoderm CQ®, 24-hour transdermal nicotine patches and will be educated about the use of the patch at the session immediately prior to quit date. They will be instructed to apply one patch daily, beginning on quit date (week 5). Participants will use the full strength 21-mg patch for 6 weeks and then be instructed to taper to the 14-mg patch for the next 1 week, and then to the 7-mg patch for the remaining 1 week. Participants who continue to smoke or lapse after quit day will not be instructed to discontinue the patch until their smoking level reaches 4 cigarettes/day for 4 days[3]. Smokers who lapse will be

encouraged to set a new quit date and continue their cessation attempt. At each visit, participants will be administered a side effect and symptom profile.

ABR. Participants assigned to the ST+ABR condition will be told that seven weekly computerized training sessions of 15 minutes in length complement the behavioral counseling by weakening automatic cigarette-approach and strengthening automatic cigarette-avoidance[14]. Using indirect task instructions, participants will be instructed to pull or push the joystick depending on the tilt of the picture (i.e., right-tilted vs. left-tilted). Each training session will consist of 192 training trials, consisting of 96 positive pictures with the to-be-pulled tilt and 96 smoking images with the to-be-pushed tilt. Accordingly, in these trials participants will always avoid smoking-related images and always approach positive images. Each training session also includes an additional 12 "training-incompatible" smoking-related images distributed evenly across the second half of the training trials, where smoking images are tilted so they have to be pulled and positive images are tilted so they have to be pushed. We use these incompatible smoking-related trials to calculate an approach bias score for each ABR training session, allowing us to measure the change in approach bias over time (see C5c and C8).

It is important to note that without these incompatible trials, it would be impossible to measure approach bias because there would be no comparison trials (i.e., trials where participants “pull” smoking images). However, if there are too many incompatible trials (or a separate assessment of approach bias with many incompatible trials), there is the potential for the incompatible trials to interfere with (or even reverse) the effects of training. Hence, this approach allows us to retrain approach biases AND simultaneously measure change in approach bias over the course of training[11,14], thus aiding us in achieving aim 2a of this proposal (see C5c and C8).

CTRL. In order to create comparable expectancy effects and enhance experimental control, we will also provide participants assigned to the ST+CTRL training condition with a highly plausible rationale for augmenting standard smoking cessation care with computerized training. Similar to our pilot study examining ABR for smoking cessation[14] and our other past work examining ABR for preventing relapse in alcohol use disorder[10,11], we will tell participants assigned to ST+CTRL that the computerized training weakens the automatic tendency to approach cigarettes by improving control over this automatic tendency (e.g., learning to ignore urge to approach and respond only to task instructions) and that following the training, they will be easily able to approach or avoid regardless of image content. They also will be instructed to pull or push the joystick depending on the tilt of the picture (i.e., pull right-tilted vs. push left-tilted). However, instead of avoiding all smoking-related pictures, participants in the ST+CTRL condition will pull and push all pictures equally often. This yields 96 training-compatible trials (48x push smoking, 48x pull positive) and 96 incompatible trials (48x pull smoking, 48x push positive). We will use the 48 smoking-related trials from the last half of training to calculate an approach bias score for each CTRL training session, allowing us to measure whether the approach bias changes over time in this condition (see C5c and C8).

C5. Assessment

We describe here the instruments we propose to employ for achieving the aims (see Figure 6). In an effort to increase retention and adherence to the assessment schedule, we will collect all assessment data using REDCap. REDCap is a secure, web-based application, which provides an intuitive user interface that streamlines project development and improves data entry through real-time validation rules (with automated data type and range checks). REDCap also provides easy data manipulation (with audit trails for reporting, monitoring, and querying patient records) and an automated export mechanism to common statistical packages. In-person assessments (i.e., biochemical verification of abstinence) will be conducted at UT.

C5a. Screening

As in past and ongoing work[43–46], the initial online screening will include assessment of demographics, smoking history and motivation to quit. Demographic information will be obtained using a standard form we use in ongoing studies. Smoking history will be assessed using a standard survey we have used in previous studies[43,47] and includes but is not limited to: rate, brand, nicotine content, previous quit attempts and duration, and age of onset. Nicotine dependence will be assessed using the Fagerström Test for Nicotine Dependence (FTND)[48], which has strong psychometric properties[48]. This measure will be employed for the moderator analysis. Motivation to quit will be assessed on a 0-10 Likert scale[47]. Finally, the Mini International Neuropsychiatric Interview (MINI), which is a structured screening interview for assessing psychiatric disorders, will be administered via telephone by UT staff to assess for psychiatric exclusion criteria.

C5b. Efficacy

As in past an ongoing work[43–46], self-reported smoking status will be assessed during the intervention (weeks 0-7), at posttreatment (week 8), and at 1-month (week 9), 2-month (week 13) and 3-month (week 17) follow-up (i.e., post-quit; see Figure 6). Self-reported abstinence will be verified by expired carbon monoxide (CO). Abstinence at the 2-month (week 13) and 3-month (week 17) follow-up will additionally be verified with saliva cotinine. We will use the timeline follow-back (TLFB) procedure at all assessments to assess cigarette consumption at each day following the previous assessment, which has demonstrated good reliability and validity[49]. Self-reported abstinence will be overridden by a positive carbon monoxide (≥4ppm)[50] or saliva cotinine verification (>10 ng/mL)[51]. If neither CO nor cotinine levels are available to verify abstinence at an assessment, abstinence will be considered missing data[52]. We will employ 7-day point prevalence abstinence (PPA) and prolonged abstinence (PA)as the primary outcomes. PPA will be defined as no smoking, not even a puff, in the 7 days prior to any assessment. Failure to maintain PA at any assessment will be defined by smoking on 7 consecutive days or smoking at least once each week over 2 consecutive weeks[40].

Figure 6. Assessment Schedule

	Protocol Weeks						
	-3,-2,-1	0	1-4	5	6	8	9-17
	End Points						
	Pre-Screen	Baseline	Pre-Quit	Quit Week	1-Week Follow-up	Posttreatment	1-, 2-, and 3-Month Follow-up
Screening							
Demographics	X						
Smoking history	X						
Motivation to quit	X						
Nicotine dependence (FTND)	X						
Psychiatric diagnosis and suicide (MINI)	X						
AIM 1: Efficacy							
Self-reported smoking (TLFB)		X	X	X	X	X	X
Carbon monoxide		X	X	X	X	X	X
Saliva cotinine							X[1]
AIM 2: Mechanisms of Action							
Craving (QSU-B)		X	X	X	X		
Approach Bias (AAT; session data)		X	X	X			

[1] Only assessed at 2- and 3-month follow-up

C5c. Mechanisms of Action

We will use the Questionnaire of Smoking Urges-Brief (QSU-B[53]), which is a psychometrically sound measure of craving. We will administer the AAT[14,18,22] in order to assess approach bias at baseline. The ATT instructs participants to pull a joystick upon seeing an image tilted to the right and to push the joystick upon seeing a left-tilt image, while ignoring the image content (i.e., indirect instructions). By pulling the joystick (approach), the picture grows in size; by pushing the joystick away (avoidance), the picture shrinks. The AAT includes 96 trials in which each of 24 smoking-related pictures (e.g., woman lighting a cigarette) and each of 24 positive images (e.g., group of friends exercising) will be pulled and pushed. An approach bias score for smoking-related pictures will be computed for each participant by subtracting the average time it takes to pull smoking-related images from the average time it takes to push away these images. Thus, a positive value indicates an approach tendency toward smoking stimuli, whereas a negative value is indicative of avoidance of smoking images. As discussed in section C4a, the ABR also involves 12 incompatible smoking-related trials in the last half of each training session, allowing us to compute the approach bias at the end of each of the seven training sessions in ABR[11,14]. Specifically, the approach bias score will be computed by subtracting the average time it takes to pull smoking-related images (the 12 incompatible trials in the second half of each session) from the average time it takes to push smoking-related images (48 trials). Similarly, we will compute an approach bias score for the end of each of seven CTRL training sessions by subtracting the average time it takes to pull smoking-related images (the 24 incompatible trials in the second half of each session) from the average time it takes to push smoking-related images (the 24 compatible trials in the second half of each session)[11,14]. Finally, we will explore scoring algorithms for the AAT and session data that standardize the bias scores by dividing an individual's difference in response times by a personalized standard deviation of these response latencies. A similar scoring approach has been used successfully for a related task, the Implicit Association Test (IAT[54]).

C6. Training and Quality Assurance/Quality Control

C6a. Checks of Integrity of Screening Procedures

We will use the same procedures as in ongoing and previous studies[43–46]. Personnel involved in screening will be certified in diagnostic interviewing. Certification will involve attending a workshop provided by Dr. Smits and successful screening of 5 potential participants under supervision of certified personnel.

C6b. Checks of Integrity of Treatment Procedures

Drs. Smits will provide in-person training and supervision to Mrs. Dutcher, who will deliver the CBT sessions. Adherence scores will be used as part of supervision, which will occur on a monthly basis.

Approach bias retraining latencies will be checked for treatment integrity. Training trials with errors (i.e., participants pushed when they should have pulled and vice versa) and unusual response latencies (i.e., very long (> 2000ms) or very fast (< 200ms) trials) will be dropped. Training integrity for a given session will be considered unacceptable when 20% or more of the trials are dropped. Based on our past experience, we expect high levels of training integrity[10–12,14].

C7. Participant Adherence and Incentives for Participation

We will utilize a number of strategies in efforts to promote adherence and retention. Prior to randomization, participants will have completed an extensive screening process. Participants will also be provided a behavioral expectations document informing them of the requirements of their assigned group.

Mrs. Dutcher, supervised by Drs. Smits, will manage retention of the participants. She will be able to meet with participants on 6-7 days of the week for their sessions. If a participant misses a session, she will call to check in, encourage attendance, and help problem solve if a barrier to participation is present. Mrs. Dutcher will also monitor adherence to the assessment schedule. She will place reminder calls/emails to participants three days prior to each scheduled follow-up session. Participant self-reported abstinence will be verified for each of these major end point assessments

Finally, we will provide $250 per individual (i.e., $50 for completing each major outcome assessment; weeks 0, 6, 9, 13, and 17) as an incentive for participation in the study. We think this amount is appropriate given the amount of time required for completing the assessments.

C8. Data Analysis

Per study protocol (i.e., pre-registered hypotheses and analyses as published in Smits et al., 2019), multivariate generalized linear mixed modeling (GLMM) using a binomial distribution and a logistic linking function was employed to analyze change in biochemically-verified PPA and PA over time. We used multivariate GLMM (with PA and PPA as the multiple dependent variables [DVs]) because multivariate mixed models have greater power than univariate mixed models (Hox et al., 2017) and because assessments at each time point are included as long as at least one of the DVs is available at that time point. Hereafter, we use the general term “abstinence” to refer to the multivariate outcome of PPA and PA.

As in previous smoking research (O’Cleirigh et al., 2018; Smits et al., 2021), we used a piecewise growth curve model to model abstinence over the 18-week study period. This model comprised the pre-quit treatment phase (weeks 1–6), a discontinuity (jump) in abstinence during the quit attempt (between weeks 6–7), and the post-quit follow-up phase (weeks 7–18). The GLMM included a diagonal matrix for the covariance of the errors of the repeated measures and associated random effects. Treatment group was included as a moderator of the discontinuity (jump) in abstinence and the slope of change in abstinence during the post-quit follow-up phase. As per our registered analysis plan (Smits et al., 2019), to minimize Type II error and to provide more stable (replicable) and parsimonious models that fit the data, we recomputed the final multivariate GLMM model after removing non-significant interaction terms (sensitivity analyses showed that results did not change if we did not remove these non-significant interactions).

To examine our pre-registered analysis for whether the intervention was effective in changing avoidance tendencies, we used intent-to-treat multilevel modeling (MLM) to analyze the growth curve of avoidance tendency scores over the 7 weeks of ABR. Since the change over time in avoidance tendency scores may not be linear, we examined linear, quadratic, and logarithmic models for the change over time and selected the model that best fit the data (lowest Akaike Information Criterion [AIC] and lowest Bayesian Information Criterion [BIC]) since failing to do so can lead to incorrect results. In exploratory analyses, we examined whether the initial avoidance tendency score moderated the intervention efficacy.

As per our pre-registered analysis plan (Smits et al., 2019), we examined the equivalence of the treatment groups on demographic and key psychological variables prior to treatment; variables on which the groups differed were included as covariates in the final analyses if they were significantly related to outcome. The only variable that differed between groups was the initial avoidance tendency score ($t(94) = 2.88$, $p = 0.005$), which was added as a covariate in all analyses. A priori power analysis indicated greater than 0.80 power to detect a significant condition effect if the abstinence rate in ST+ABR
was 42 % or greater (effect size $\omega = .238$) with a sample size of 100 (see Smits et al., 2019 for more details).

PROTECTION OF HUMAN SUBJECTS

Risks to Subjects

Human Subjects Involvement and Characteristics

We plan to enroll 100 participants total. The participant population will be comprised of both males and females of mixed ethnic and socioeconomic backgrounds. All participants meeting entrance criteria will be offered the opportunity to participate. Participants will not be excluded on the basis of gender or race. Inclusion and exclusion criteria are presented in the Figure 7.

Figure 7. Study Entry Criteria

Inclusion Criteria	
18 to 65 years old	
Informed consent	The capability and willingness to give written informed consent, to understand inclusion and exclusion criteria, and to accept the randomized group assignment are required.
Daily smoker	Smoking status will be assessed via self-report at screening. Only participants who currently smoke ≥10 cigarettes per day can be eligible.
Motivated to quit	Reporting motivation to quit smoking (>5 on a 0-10 scale).
Exclusion Criteria	
Use of other tobacco products	Use of tobacco products, including e-cigarettes, will be assessed during screening.
Psychiatric disorders	Currently suicidal or high suicide risk, current or past psychotic disorders of any type, bipolar disorder (I, II, or NOS), schizophrenia or schizoaffective disorder, anorexia, bulimia, alcohol or substance dependence within the last 6 months, patients with comorbid psychiatric conditions that are relative or absolute contraindications to the use of any treatment option in the protocol. These will be assessed by the MINI.
Current treatment	Current use of any pharmacotherapy or psychotherapy for smoking cessation not provided by the researchers during the quit attempt. Current use of psychotropic medication. Here, although subjects will be excluded at intake for use of psychotropic medications and asked not to initiate pharmacotherapy during the study period, we believe it would be unethical to prevent them from starting these medications once the study has begun. Thus, we will assess for the initiation of psychotropic medications throughout treatment and utilize this information when analyzing the study results. Concurrent psychotherapy initiated within three months of baseline, or ongoing psychotherapy of any duration directed specifically toward the treatment of anxiety or mood disorder other than general supportive therapy initiated at least 3 months prior to the study.
Other exclusions	Insufficient command of the English language (i.e., they cannot carry on a conversation with an interviewer in the English language or read associated text).

Sources of Research Material

Research material will consist of patient treatment history, symptom and functioning assessments, records of treatment sessions and demographic information collected during the study for research purposes. All research materials are similar to what is commonly collected in routine clinical practice. The specific patient assessment and self-report questionnaires that will be utilized in this study are as follows: Mini International Neuropsychiatric Interview (MINI), The Fagerström Test for Nicotine Dependence (FTND), Smoking History Questionnaire, Saliva cotinine, Carbon monoxide analysis of breath samples, Smoking Urges-Brief (QSU-B) and the Approach-Avoidance Task (AAT).

Potential Risks

Human subject risk related to the assessment and intervention procedures are small. Potential risks include nicotine patch side effects. More common side effects include local skin irritation at the site of the patch, nausea if the dose is too large or if the patient continues to smoke at a high level while using the patch, and disturbed and vivid dreams. Less common are allergic skin reactions. Other potential risks include withdrawal symptoms after quitting as well as breach of confidentiality. Below, we detail how we will guard against each of these potential risks. No known risks are associated with the other interventions.

Protection of Human Subjects from Research Risk

Recruitment and Informed Consent

Subjects will be recruited from the community and from physician referrals. Any subjects meeting the entrance inclusion criteria will be provided the opportunity to participate in this study. Research associates obtaining consent will explain the study procedures and answer any questions the potential participant might

have. Informed consent will be obtained from all participants prior to undergoing any screening procedures. The Institutional Review Board for The University of Texas at Austin (UT) consists of an independent body of reviewers. Research associates will receive training regarding procedures required to obtain informed consent, and training is completed yearly in order to continually reinforce such procedures.

Adequacy of Protection Against Risks

We developed and followed strict safety guidelines during previous and pilot studies that will be applicable to the proposed study. The YMCA has safety procedures in place that include established emergency procedures for physical injury and CPR training of all supervising staff. We also have detailed safety procedures for dealing with adverse mental health events. The PIs are available for intervention as needed and back-up plans are established including involvement of the study physicians and referral to a hospital emergency department. These safety procedures have been effective in dealing with adverse physical and mental health events in previous and ongoing studies. Upon study completion, all participants will be referred to follow-up care if needed.

To minimize skin reactions due to nicotine patch, smokers will be instructed to move the site of patch placement each day and not repeat site use for at least one week. Smokers who smoke 4 cigs/day for 4 days will be asked to discontinue the patch until they are able to cut down or quit smoking again. The initial 21 mg/day dose may be adjusted downward to 14 mg or 7 mg if there is significant nausea or other adverse reactions. Smokers will be instructed to remove the patch before bed if it significantly interferes with sleep. The patch will be discontinued entirely if severe skin reactions develop.

In regard to withdrawal symptoms, there is a strong likelihood that most study participants will experience some nicotine withdrawal symptoms, including anxiety, restlessness, anger, irritability, sadness, problems concentrating, appetite change and weight gain, insomnia, and decreased heart rate. Because all participants will use the nicotine patch, this should diminish the overall severity of withdrawal discomfort, although the patch will not necessarily eliminate withdrawal discomfort entirely. Moreover, withdrawal symptoms are usually short-lived, with most symptoms abating within 1-2 weeks. Importantly, Mrs Dutcher is trained and experienced in addressing these issues as they emerge. Using the study instruments and clinical interviews, staff members will determine whether treatment or additional treatment for a specific psychological problem is needed and work with the participant and Dr. Smits to refer them to appropriate service centers.

To deal with the potential risk of loss of privacy (judged to be minimal), we will maintain confidentiality by numerically coding all data, by disguising identifying information, and by keeping all data in locked file drawers. Participant information will be accessible only to research staff. Identifying information will not be reported.

Potential Benefits of Proposed Research to the Subjects and Others

Participants will have opportunity for direct benefit in the care and treatment for smoking. The population of anxiety vulnerable adult smokers in general has a great opportunity for benefit since the results of the study may be valuable in the treatment of smoking.

Importance of Knowledge to be Gained

If we find that exercise augments standard care for smoking cessation, then, smokers could elect this augmentation strategy to improve their quality of life. Further, the proposed study (i.e., design, assessment schedule, and analyses) offer the potential to improve the understanding of the mechanisms that underlie these effects. Additionally, although there are some risks associated with use of the nicotine patch, these are judged to be minor. Moreover, nicotine patches have been in wide-spread clinical use for several years, have been judged to be generally safe and efficacious, and are now widely available without prescription. The anticipated benefits of the study are twofold: the results will be used to advance understanding of the factors related to smoking after attempts at smoking cessation, and significant knowledge about the combined effects of ABR and standard care. All participants should benefit from the smoking cessation treatment provided as part of the study. The results of the study will have implications for matching treatments to specific characteristics of smokers.

Data Monitoring, Management Procedures, and Attrition Safeguards

General Approach and Meeting Schedule

The organizational system for the study is based upon the past successful projects. Here, it is worth noting that these have resulted in numerous published studies. The general format for the project uses an

organizational system, as explicated below. First, we will have regular weekly team meetings (60 minutes in duration) to discuss project activities (e.g., data collection, budget, recruitment, treatment problems, data management and analysis, integrity of assessment and intervention procedures) activities. These team meetings will be coordinated by Dr. Smits. Second, Dr. Smits will also have a regular weekly phone meeting with the co-investigators to address problems. Third, Dr. Smits will hold weekly supervision meetings with the Mrs. Dutcher (separately) to problem-solve issues around implementation and will be available for additional meetings as need.

Data Management Organizational Structure

Our general policy for data management is that research assistants copy all data files and these files are reviewed by Dr. Smits on a monthly basis. The research assistants routinely evaluate the data and discuss any problems and questions with the study staff and Dr. Smits at the regular weekly team meetings. Accuracy of data entry will be ensured by a standard double-entry procedure. Data management formal reports on record status across the three following domains will be employed: entered, verified, and edited. These reports of data records will be evaluated 1 time a month during the final team meeting of the month. To help ensure data protection, backup copies, automatically generated by our computer systems, will be available.

Study data (e.g., measurements and questionnaires) will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure, web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). REDCap also provides a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. The system was developed by a multi-institutional consortium which includes University of Texas at Austin and was initiated at Vanderbilt University. The database is hosted at the Population Research Center, which will be used as a central location for data processing and management. The PRC server has been cleared for Category-I data collection by UT's Information Security Office. Network transmissions (data entry, survey submission, web browsing, etc.) in REDCap are protected via Secure Sockets Layer (SSL) encryption. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the PRC. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap provides a secure, web-based application that is flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules at the time of entry.

Paper data will be kept stored under lock and key for use in further ratings and maintained until three years after the publication of study results, at which time they will be shredded or deleted. All data and samples are considered confidential (i.e., data can potentially be linked to participants), in that they will be labeled by a participant ID. However, the participant IDs will only be linked to patient specific information (e.g., name, phone number, demographic information, etc.) in a password protected Excel document accessible only by research staff (i.e., the PI and co-PIs). This document is necessary to retain contact information for participants and link all study materials. Upon completion of the project, the Excel document will be deleted from UT servers.

The data and samples will not be shared by other researchers for research purposes not detailed in this study. Confidentiality is assured by a number of factors. Most importantly, participants will be identified on REDCap only by participant number, visit number, and date of visit, assuring confidentiality of the anonymized data on the web. By recording the study data in this manner, the information can be considered 'de-identified,' and therefore, compliant with the Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule") of the Health Insurance Portability Act of 1996 ("HIPAA"). Additional measures to ensure the confidentially of study data include the following: a dedicated personal computer will permit the electronic authentication/signature of all information and data collected during the study. When data are submitted, the user id, password, date, time, and IP address of the computer are logged. As a result, the number of locations from which the database can be accessed will be limited, effectively restricting access to individual computers. Access to the dedicated personal computer will be restricted to participants, investigators and staff involved in the study. Each user of the system will be assigned a unique user-id. Each user-id will be associated with a subset of participants. Thus, project staff will only be able to access the records of participants for whom they are responsible and for those individuals registered in the study (to allow for cross coverage of participants when necessary). Data will be accessed by participant number, visit number, and specified form of interest.

Participants will have access only to the current visit, and only to the subset of forms that they will be filling out. As a result, participants will require the assistance of project staff member to access other aspects of their record.

Attrition Safeguards/Protection of Loss of Data

A notable methodological consideration pertaining to the proposed research is protection against attrition. Attrition can have a negative impact on the outcome of this study in at least two key ways: (1) reduced sample size would decrease statistical power and thereby increase the probability of Type II error; and (2) follow-up samples may be non-representative of the original samples due to loss of subjects, and hence, adversely impact external validity. Our research groups have conducted numerous prospective studies, including clinical intervention work. In our previous work we have learned that individuals with substance use histories are best retained in studies when financial remuneration is offered, there is familiarity with study personnel with this population (e.g., ability to effectively establish rapport), and team-based persistence in conducting follow-up assessments. We have outlined our incentive-based approach in the proposal.

DATA AND SAFETY MONITORING PLAN

The data and safety monitoring plan was developed in consultation with Dr. Smits and other research team personnel. The PI, Dr. Smits, will take ultimate responsibility for data safety monitoring in the study. As discussed, potential risks include nicotine patch side effects, withdrawal symptoms after quitting, and breach of confidentiality.

Breach of confidentiality is highly unlikely because all data will be identified only by numeric code and are stored in locked file cabinets/online secure server. A master list of names and numbers will be kept in a separate location and is used to facilitate the collection of follow-up data. Only senior project staff will have access to the master list linking names and code numbers. Clinically important assessment data (e.g., medical history) will be made available to clinical staff to more effectively coordinate services. All staff will be fully trained in relevant ethical principles and procedures, particularly around confidentiality. All assessment and treatment procedures will be closely supervised by the project's professional staff. All audiotapes will be erased upon completion of data analysis. As with any type of medication, there is the risk for unexpected side effects from the patch. Side effects will be monitored by study staff at each contact and select clinical staff will be available at all times by pager. Participants will be given contact information and instructed to notify study staff immediately if they experience any adverse side effects. We also will monitor participants closely by direct observation and through participant's subjective reports of discomfort.

Functions of the Data and Safety Monitoring Board (DSMB)

A Data and Safety Monitoring Board (DSMB) will be created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support those purposes, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality.

As in any clinical trial, it is not possible to anticipate all possible adverse events. We do extensive training with our staff on ascertaining, monitoring, and documenting adverse events. The study investigators have extensive experience in clinical trials organization and management, including data safety monitoring for single site and multi-site trials. We have established procedures for rendering first aid and life threatening emergencies. All staff involved in the conduct of supervised exercise sessions will be CPR certified. All investigators and study staff will be trained in monitoring and documenting adverse events. Furthermore, they will be trained in proper first aid procedures.

Membership of the DSMB

The data and safety monitoring board will consist of four members (not part of the investigative team) with expertise in a variety of disciplines including mental health, physical activity, statistics, clinical trials conduct, and medicine.

Functional Organization of the DSMB

One individual will serve as Chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communication pertaining to review of serious adverse events (SAEs) will occur within a week of receiving any new SAE report. Reporting and communication about other matters will occur on a regular basis for the duration of the study.

Monitoring of Safety Data by the DSMB

Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.

Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but other data that may reflect differences in safety between treatment groups. This includes treatment retention rates, and reasons for drop-out.

Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. For purposes of this study, all SAEs will be required to be reported to the DSMB, regardless of any judgment of their relatedness to the study treatment. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, the subject's medical history and current conditions, and all relevant laboratory data. Notification by e-mail, and FAX transmittal of all related study forms shall be made to the DSMB within 2 days of the occurrence of any SAE. Information will be reviewed and a determination made of whether there was any possible relevance to the study. Additional reporting to the IRBs will be done within 24 hours of the SAE; reporting to NIH will be made according to the NIH regulations governing SAE reporting.

Non-Serious Adverse Events – At periodic intervals, the DSMB will be provided with summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.

Other Safety-Related Reports – Throughout the course of the study, the DSMB will receive summary reports of treatment retention and reasons for drop-out.

Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated. Stopping rules for the trial could include stopping because of a significant number of injuries or illnesses that could be attributed to participation in exercise, inability to recruit and measure the required number of participants to conduct the primary outcomes analyses, and poor intervention quality and delivery.

Monitoring of Data Quality by the DSMB

At least on a quarterly basis during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and intervention as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize participants and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Annual DSMB Report

Annually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings, as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the local IRBs along with the annual renewal report.

Policies and Procedures for Adverse Event Reporting

The PI will inform the IRB of any SAE within 24 hours and will also inform the DSMB.

INCLUSION OF WOMEN & MINORITIES

Fifty percent of participants will be female, allowing us to achieve aim 2c of the proposal. We will make a concerted effort to promote awareness of our research project among women to ensure adequate representation in our sample. These efforts will include a) involving female research staff in patient recruitment; and b) advertisements in local media outlets popular with women. Recruitment materials will be tailored to low-literacy populations. Given the ethnic and racial compositions of the greater Austin area (approximately 35.1% Hispanic/Latino, 48.7% non-Hispanic; 68% White, 8.1% Black, .1% Asian/Pacific Islander, .9% American Indian; 2007 estimates), an ethnically and racially diverse sample is expected. If eligible, participants will be enrolled without regard to ethnic background. To increase minority participation, we will utilize a multimedia campaign with the following strategies: public service announcements on local radio stations, announcements in church bulletins, information booths at community functions, community presentations, promotional mailings, and placement of informational materials in retail outlets and organizations known to serve minorities. In addition, we will work with health clinics to target minorities. We expect that the ethnic/minority composition of the sample obtained by our recruitment efforts will approximate that of the communities in Austin.

INCLUSION OF CHILDREN

Children under the age of 18 will not be included in the proposed research study for several reasons. First, in order to include these children, the assessment protocols being tested would require significant modification to take into account their differing cognitive and psychosocial development. Making these modifications would result in a fundamentally different set of tasks and would essentially necessitate the conduct of two different studies. We do not consider this feasible, short of submitting two different grant applications. Second, the FDA has not approved the use of nicotine replacement therapy in children under the age of 18, so we would not be able to provide the full treatment to those individuals, making the use of the protocol less than ideal and no longer state-of-the-art. Third, modal quit behavior for smoking occurs in adulthood, making this developmental time period particularly well suited to a test of mediating processes during a smoking cessation intervention[65]. Overall, we adopted a balanced approach to admitting a young to older age adult sample (ages 18-65). In addition to not overly restricting the number of eligible subjects, this age range allows us to capture participants and meaningfully evaluate processes related to the maintenance of smoking.

FACILITIES & OTHER RESOURCES

Data collection will occur in the Anxiety & Health Behaviors Laboratory (Dr. Smits) at the University of Texas at Austin. Overall, the scientific environment at the University of Texas is excellent. The Department of Psychology has a long history of productivity and international visibility. Since its creation in 1927, the department has attracted stellar researchers and instructors, including several members of the prestigious National Academy of Sciences, presidents of the American Psychological Association, American Psychological Society, and dozens of more specialized academic organizations. Our new building, a $52 million investment, boasts state-of-the-art laboratories and equipment. In the most recent rankings, U.S. News & World Report listed the Department's graduate program at 14th in the nation (clinical psychology was ranked 8th); a strong affirmation of the quality of our faculty, facilities, and education overall.

General Resources, Department of Psychology at University of Texas at Austin

The Psychology Department has its own clinic with a full-time clinic director and administrative assistant. The physical space includes four individual treatment rooms, 1 group therapy room, and four individual assessment rooms. The clinic is available for project-related referrals. The Department of Psychology also makes available significant computer resources to grant funded projects, including workstations, servers, secure networks, and technical personnel. The Department's connection to the Internet is via multiple redundant Gigbit optical fiber links, and all network traffic passes through a protective firewall. All out-world access to Fileservers holding research data require secure encrypted VPN connections, and all workstations and servers require passwords for access. The Department has well over 800 computer workstations, and about 24 web/file/streaming-video servers hosting nearly 10 Terabytes of data. The Departmental technical support staff consists of 7 full-time technicians including web, audio-video, database, security, and computer publications specialists.

Institute for Mental Health Research (IMHR)

The IMHR is an organized research unit with the College of Liberal Arts that reports to the Dean of the College of Liberal Arts. All faculty have appointments in academic departments but research effort occurs within the IMHR. In January 2015, the IMHR moved into research space located in College of Liberal Arts (CLA) Building. This space was selected because it is centrally located on campus, accessible and identifiable to research participants who are unfamiliar with campus, and there is substantial room for expansion. The IMHR initially includes approximately 8,000 square feet of dedicated office and research space that will contain research labs tailored to the needs of each investigator, a participant waiting room, a conference room, three therapy/assessment rooms, a computer lab for data processing and analysis, a biospecimen collection and storage room (with centrifuge and freezers), office space for faculty, staff, post-doctoral fellows, and graduate students, a break room, and a mailroom.

CLA is very close to the heart of campus (where many undergraduate classes are held) and a 10-minute walk to the Department of Psychology. This space will allow IMHR faculty members to work in state-of-the-art facilities designed to foster collaboration and innovation while simultaneously allowing IMHR faculty to access collaborators and resources from around the campus community.

Anxiety & Health Behaviors Laboratory

The Anxiety & Health Behaviors Laboratory is located within the Institute for Mental Health Research (see below) and is also affiliated with the Department of Psychology at the University of Texas at Austin. The laboratory is directed by Dr. Jasper Smits, professor and licensed psychologist. Other personnel include Dr. Mark Powers, licensed psychologist and Dr. Carlos Tirado, a board-certified psychiatrist. The laboratory is further staffed by two research staff members, and 5 doctoral students, who are trained and certified in the conduct of diagnostic evaluations as well as the delivery of behavioral interventions for anxiety and smoking cessation.

The Anxiety & Health Behaviors Laboratory consists of two adjacent research suites and a research office. The testing suite contains three individual testing rooms and an office for the laboratory manager. This testing suite, which will be used for ABR and CTRL training, is sound attenuated with multiple layers of soundproof gypsum board specifically designed for this purpose, and houses the human psychophysiology of emotion equipment (see below). The exercise suite consists of a room that houses the exercise equipment (see below) and a locker room with shower. The research office contains filing cabinets and equipment (e.g., two iMac

desktop computers, phones, etc.) required for staff to support research efforts (e.g., screening, scheduling, data entry/analysis). All rooms are networked and equipped with state-of-the-art computers. All staff, including Dr. Smits, has offices located nearby in the IMHR, allowing for close contact between research staff and key personnel on this project.

Human Psychophysiology of Emotion Equipment

Dr. Smits's Laboratory is equipped with a psychophysiological suite that allows assessment of psychophysiological responses associated with symptoms of mood, anxiety, and substance use disorders using state-of-the-art technology. The lab has an acoustic startle system coupled to the BIOPAC MP150 Psychophysiological Recording Apparatus that allows us to measure acoustic startle (electromyogram, EMG), and skin conductance (GSR). The Human Psychophysiology of Emotion set up contains three iMac desktop computers and Dell PC all for the purposes of stimulus presentation (SuperLab 4.0, Cedrus Corporation, San Pedro, CA), data collection (AcqKnowledge 4.0), and psychophysiological data analysis (Mindware, Mindware Technologies, Gahanna, OH).

Exercise Equipment

Dr. Smits's Laboratory is equipped with a Cybex 770 AT total body arc trainer and The Cybex 770T treadmill. The exercise machines face two individual TV screens and are connected to polar heart rate monitors. The exercise suite also is equipped with an AED and telephone.

RedCap

Study data will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure, web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). REDCap also provides a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. The system was developed by a multi-institutional consortium that includes University of Texas at Austin and was initiated at Vanderbilt University. The database is hosted at the University of Texas. The REDcap server has been cleared for Category-I data by UT's Information Security Office. Network transmissions (data entry, survey submission, web browsing, etc.) in REDCap are protected via Secure Sockets Layer (SSL) encryption. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the PRC. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap provides a secure, web-based application that is flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules at the time of entry. The REDCap Consortium is composed of 681 active institutional partners in 58 countries. The consortium supports a secure web application (REDCap) designed exclusively to support data capture for research studies.

DATA SHARING PLAN

We will provide de-identified data from this project to interested individuals one year following achievement of the aims of the project (i.e., publication of main outcome paper). These data will be provided in digital format (i.e., disk), with clear labels for all variables. Data will be released directly by Dr. Smits's team to investigators providing evidence of their institution's IRB approval for planned analyses of the data Dr. Smits's team will be available to address queries.

BIBLIOGRAPHY

1. Johnson NB, Hayes LD, Brown K, Hoo EC, Ethier KA. CDC National Health Report: Leading Causes of Morbidity and Mortality and Associated Behavioral Risk and Protective Factors-United States, 2005-2013. Morb Mortal Wkly Rep Surveill Summ Wash DC 2002. 2014 Oct 31;63:3–27. PMID: 25356673

2. U.S. Department of Health and Human Services. The health consequences of smoking—50 years of progress. A report of the surgeon general. Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014 Jan.

3. Fiore M, Jaen CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, Dorfman SF, Froelicher ES, Goldstein MG, Healton CG, others. Treating tobacco use and dependence: 2008 update. 2008 [cited 2015 Jun 4]; Available from: http://www.rfpdb.com/process/download/name/Request-for-Proposal-Department-of-Public-Health_Public-Health-Initiatives-Branch-Telephone-QUITLINE-Services.pdf

4. Deutsch R, Strack F. TARGET ARTICLE: Duality Models in Social Psychology: From Dual Processes to Interacting Systems. Psychol Inq [Internet]. 2006 Jul 1 [cited 2016 Sep 20];17(3):166–172. Available from: http://dx.doi.org/10.1207/s15327965pli1703_2

5. Wiers RW, Bartholow BD, van den Wildenberg E, Thush C, Engels RCME, Sher KJ, Grenard J, Ames SL, Stacy AW. Automatic and controlled processes and the development of addictive behaviors in adolescents: A review and a model. Pharmacol Biochem Behav [Internet]. 2007 Feb [cited 2016 Sep 20];86(2):263–283. Available from: http://www.sciencedirect.com/science/article/pii/S0091305706003236

6. Gladwin TE, Figner B, Crone EA, Wiers RW. Addiction, adolescence, and the integration of control and motivation. Dev Cogn Neurosci [Internet]. 2011 Oct [cited 2016 Sep 20];1(4):364–376. Available from: http://www.sciencedirect.com/science/article/pii/S187892931100065X

7. Wiers RW, Gladwin TE, Hofmann W, Salemink E, Ridderinkhof KR. Cognitive Bias Modification and Cognitive Control Training in Addiction and Related Psychopathology Mechanisms, Clinical Perspectives, and Ways Forward. Clin Psychol Sci [Internet]. 2013 Jan 9 [cited 2016 Sep 20];2167702612466547. Available from: http://cpx.sagepub.com/content/early/2013/01/08/2167702612466547

8. Stacy AW, Wiers RW. Implicit cognition and addiction: a tool for explaining paradoxical behavior. Annu Rev Clin Psychol. 2010;6:551–575. PMCID: PMC3423976

9. Wiers RW, Rinck M, Kordts R, Houben K, Strack F. Retraining automatic action-tendencies to approach alcohol in hazardous drinkers. Addict Abingdon Engl. 2010 Feb;105(2):279–287. PMID: 20078486

10. Wiers RW, Eberl C, Rinck M, Becker ES, Lindenmeyer J. Retraining automatic action tendencies changes alcoholic patients' approach bias for alcohol and improves treatment outcome. Psychol Sci. 2011 Apr;22(4):490–497. PMID: 21389338

11. Eberl C, Wiers RW, Pawelczack S, Rinck M, Becker ES, Lindenmeyer J. Approach bias modification in alcohol dependence: Do clinical effects replicate and for whom does it work best? Dev Cogn Neurosci [Internet]. 2013 Apr [cited 2016 Sep 26];4:38–51. Available from: http://www.sciencedirect.com/science/article/pii/S1878929312000850

12. Eberl C, Wiers RW, Pawelczack S, Rinck M, Becker ES, Lindenmeyer J. Implementation of Approach Bias Re-Training in Alcoholism—How Many Sessions are Needed? Alcohol Clin Exp Res [Internet]. 2014 Feb 1 [cited 2016 Sep 27];38(2):587–594. Available from: http://onlinelibrary.wiley.com/doi/10.1111/acer.12281/abstract

13. Kakoschke N, Kemps E, Tiggemann M. Approach bias modification training and consumption: A review of the literature. Addict Behav [Internet]. 2017 Jan [cited 2016 Sep 27];64:21–28. Available from: http://www.sciencedirect.com/science/article/pii/S0306460316302787

14. Baird SO, Rinck M, Rosenfield D, Davis ML, Fisher J, Becker ES, Powers MB, Smits JAJ. Reducing Approach Bias to Achieve Smoking Cessation: A Pilot Randomized Placebo-Controlled Trial. Under review;

15. Field M, Kiernan A, Eastwood B, Child R. Rapid approach responses to alcohol cues in heavy drinkers. J Behav Ther Exp Psychiatry. 2008 Sep;39(3):209–218. PMID: 17640615

16. Cousijn J, Goudriaan AE, Wiers RW. Reaching out towards cannabis: approach-bias in heavy cannabis users predicts changes in cannabis use. Addict Abingdon Engl. 2011 Sep;106(9):1667–1674. PMCID: PMC3178782

17. Larsen H, Kong G, Becker D, Cousijn J, Boendermaker W, Cavallo D, Krishnan-Sarin S, Wiers R. Implicit motivational processes underlying smoking in american and dutch adolescents. Front Psychiatry. 2014;5:51. PMCID: PMC4032927

18. Machulska A, Zlomuzica A, Adolph D, Rinck M, Margraf J. “A cigarette a day keeps the goodies away”: smokers show automatic approach tendencies for smoking--but not for food-related stimuli. PloS One. 2015;10(2):e0116464. PMCID: PMC4333198

19. Wiers CE, Kühn S, Javadi AH, Korucuoglu O, Wiers RW, Walter H, Gallinat J, Bermpohl F. Automatic approach bias towards smoking cues is present in smokers but not in ex-smokers. Psychopharmacology (Berl) [Internet]. 2013 Apr 19 [cited 2016 Sep 27];229(1):187–197. Available from: http://link.springer.com/article/10.1007/s00213-013-3098-5

20. Centers for Disease Control and Prevention (CDC). Quitting smoking among adults--United States, 2001-2010. Morb Mortal Wkly Rep. 2011 Nov 11;60(44):1513–1519. PMID: 22071589

21. Friese M, Hofmann W, Wiers RW. On taming horses and strengthening riders: Recent developments in research on interventions to improve self-control in health behaviors. Self Identity [Internet]. 2011 Jul 1 [cited 2016 Sep 20];10(3):336–351. Available from: http://dx.doi.org/10.1080/15298868.2010.536417

22. Machulska A, Zlomuzica A, Rinck M, Assion H-J, Margraf J. Approach bias modification in inpatient psychiatric smokers. J Psychiatr Res. 2016 May;76:44–51. PMID: 26874269

23. Robinson TE, Berridge KC. Addiction. Annu Rev Psychol [Internet]. 2003 Feb 1 [cited 2016 Sep 20];54(1):25–53. Available from: http://www.annualreviews.org/doi/10.1146/annurev.psych.54.101601.145237

24. Rinck M, Becker ES. Approach and avoidance in fear of spiders. J Behav Ther Exp Psychiatry. 2007 Jun;38(2):105–120. PMID: 17126289

25. Kersbergen I, Woud ML, Field M. The validity of different measures of automatic alcohol action tendencies. Psychol Addict Behav J Soc Psychol Addict Behav. 2015 Mar;29(1):225–230. PMID: 25134039

26. Watson P, De Wit S, Hommel B, Wiers RW. Motivational mechanisms and outcome expectancies underlying the approach bias toward addictive substances. Cognition [Internet]. 2012 [cited 2016 Sep 27];3:440. Available from: http://journal.frontiersin.org/article/10.3389/fpsyg.2012.00440/full

27. Woud ML, Maas J, Wiers RW, Becker ES, Rinck M. Assessment of Tobacco-Related Approach and Attentional Biases in Smokers, Cravers, Ex-Smokers, and Non-Smokers. Front Psychol. 2016;7:172. PMCID: PMC4767899

28. Perkins KA. Improving efficiency of initial tests for efficacy in smoking cessation drug discovery. Expert Opin Drug Discov. 2014 Nov;9(11):1259–1264. PMID: 25138487

29. Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. Arch Gen Psychiatry. 2002 Oct;59(10):877–883. PMID: 12365874

30. Department of Developmental Psychology, University of Amsterdam, The Netherlands, Watson, de Wit, Cousijn, Hommel, Wiers. Motivational Mechanisms Underlying the Approach Bias to Cigarettes. J Exp Psychopathol [Internet]. 2013 Jul 21 [cited 2016 Sep 27];4(3):250–262. Available from: http://jep.textrum.com/index.php?art_id=132

31. Wiers CE, Stelzel C, Gladwin TE, Park SQ, Pawelczack S, Gawron CK, Stuke H, Heinz A, Wiers RW, Rinck M, Lindenmeyer J, Walter H, Bermpohl F. Effects of Cognitive Bias Modification Training on Neural Alcohol Cue Reactivity in Alcohol Dependence. Am J Psychiatry [Internet]. 2014 Dec 19 [cited 2016 Sep 27];172(4):335–343. Available from: http://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2014.13111495

32. Piper ME, Federmen EB, McCarthy DE, Bolt DM, Smith SS, Fiore MC, Baker TB. Using mediational models to explore the nature of tobacco motivation and tobacco treatment effects. J Abnorm Psychol. 2008 Feb;117(1):94–105. PMID: 18266488

33. McCarthy DE, Piasecki TM, Lawrence DL, Jorenby DE, Shiffman S, Baker TB. Psychological mediators of bupropion sustained-release treatment for smoking cessation. Addict Abingdon Engl. 2008 Sep;103(9):1521–1533. PMCID: PMC2879164

34. Mogg K, Field M, Bradley BP. Attentional and approach biases for smoking cues in smokers: an investigation of competing theoretical views of addiction. Psychopharmacology (Berl). 2005 Jul;180(2):333–341. PMID: 15696322

35. Baker TB, Piper ME, McCarthy DE, Bolt DM, Smith SS, Kim S-Y, Colby S, Conti D, Giovino GA, Hatsukami D, Hyland A, Krishnan-Sarin S, Niaura R, Perkins KA, Toll BA. Time to First Cigarette in the Morning as an Index of Ability to Quit Smoking: Implications for Nicotine Dependence. Nicotine Tob Res [Internet]. 2007 Dec 1 [cited 2016 Sep 27];9(Suppl 4):S555–S570. Available from: http://ntr.oxfordjournals.org/content/9/Suppl_4/S555 PMID: 18067032

36. Rounsaville BJ, Carroll KM, Onken LS. A Stage Model of Behavioral Therapies Research: Getting Started and Moving on From Stage I. Clin Psychol Sci Pract [Internet]. 2001 Jun 1 [cited 2016 Aug 23];8(2):133–142. Available from: http://onlinelibrary.wiley.com/doi/10.1093/clipsy.8.2.133/abstract

37. Fiore MC, Smith SS, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation. A meta-analysis. JAMA. 1994;271:1940–1947.

38. Hughes JR, Callas PW. Errors in Interpreting Abstinence Curves in Studies of Smoking Cessation. Nicotine Tob Res [Internet]. 2006 Feb 1 [cited 2016 Sep 19];8(1):7–12. Available from: http://ntr.oxfordjournals.org/content/8/1/7 PMID: 16497595

39. Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. Addict Abingdon Engl. 2004 Jan;99(1):29–38. PMID: 14678060

40. Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: issues and recommendations. Nicotine Tob Res Off J Soc Res Nicotine Tob. 2003 Feb;5(1):13–25. PMID: 12745503

41. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a

structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33-57. PMID: 9881538

42. Lecrubier Y, Sheehan D, Weiller E, Amorim P, Bonora I, Harnett Sheehan K, Janavs J, Dunbar G. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. Eur Psychiatry [Internet]. 1997 [cited 2015 Apr 29];12(5):224–231. Available from: http://www.sciencedirect.com/science/article/pii/S0924933897832968

43. Smits JAJ, Zvolenksy MJ, Davis ML, Rosenfield D, Marcus BH, Church TS, Powers MB, Frierson GM, Otto MW, Hopkins LB, Baird SO. The efficacy of vigorous-intensity exercise as an aid to smoking cessation in adults with high anxiety sensitivity: A randomized controlled trial. Psychosom Med. 2016;78(3):354–364.

44. Powers MB, Kauffman BY, Kleinsasser AL, Lee-Furman E, Smits JAJ, Zvolensky MJ, Rosenfield D. Efficacy of smoking cessation therapy alone or integrated with prolonged exposure therapy for smokers with PTSD: Study protocol for a randomized controlled trial. Contemp Clin Trials. 2016 Sep;50:213–221. PMID: 27568069

45. Smits JAJ, Kauffman BY, Lee-Furman E, Zvolensky MJ, Otto MW, Piper ME, Powers MB, Rosenfield D. Enhancing panic and smoking reduction treatment with d-cycloserine: Study protocol for a randomized controlled trial. Contemp Clin Trials. 2016 May;48:46–51. PMCID: PMC4885779

46. Smits JAJ, Zvolensky MJ, Rosenfield D, Marcus BH, Church TS, Frierson GM, Powers MB, Otto MW, Davis ML, DeBoer LB, Briceno NF. The efficacy of vigorous-intensity exercise as an aid to smoking cessation in adults with elevated anxiety sensitivity: study protocol for a randomized controlled trial. Trials [Internet]. 2012 Jan [cited 2014 Dec 22];13(1):207–221. Available from: http://ezproxy.lib.utexas.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=85625307&site=ehost-live

47. Zvolensky MJ, Baker KM, Leen-Feldner E, Bonn-Miller MO, Feldner MT, Brown RA. Anxiety sensitivity: association with intensity of retrospectively-rated smoking-related withdrawal symptoms and motivation to quit. Cogn Behav Ther. 2004;33:114–125.

48. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict. 1991 Sep;86(9):1119–1127. PMID: 1932883

49. Brown RA, Burgess ES, Sales SD, Whiteley JA, Matthew D, Miller IW. Reliability and validity of a smoking timeline follow-back interview. Psychol Addict Behav. 1998;12(2):101–112.

50. Perkins KA, Karelitz JL, Jao NC. Optimal Carbon Monoxide Criteria to Confirm 24-hr Smoking Abstinence. Nicotine Tob Res [Internet]. 2013 May [cited 2016 Jan 21];15(5):978–982. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3733388/ PMCID: PMC3733388

51. SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. Nicotine Tob Res Off J Soc Res Nicotine Tob. 2002 May;4(2):149–159. PMID: 12028847

52. Blankers M, Smit ES, Pol P van der, Vries H de, Hoving C, Laar M van. The Missing=Smoking Assumption: A Fallacy in Internet-Based Smoking Cessation Trials? Nicotine Tob Res. 2015 Mar 5;ntv055. PMID: 25744969

53. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine Tob Res Off J Soc Res Nicotine Tob. 2001 Feb;3(1):7–16. PMID: 11260806

54. Greenwald AG, Nosek BA, Banaji MR. Understanding and using the implicit association test: I. An improved scoring algorithm. J Pers Soc Psychol. 2003 Aug;85(2):197–216. PMID: 12916565

55. Kraemer HC, Mintz J, Noda A, Tinklenberg J, Yesavage JA. Caution regarding the use of pilot studies to guide power calculations for study proposals. Arch Gen Psychiatry. 2006 May;63(5):484–489. PMID: 16651505

56. Hall SM, Delucchi KL, Velicer WF, Kahler CW, Ranger-Moore J, Hedeker D. Statistical analysis of randomized trials in tobacco treatment: longitudinal designs with dichotomous outcome. Nicotine Tob Res. 2001;3:193–202.

57. Hox JJ, Moerbeek M, Schoot R van de. Multilevel Analysis: Techniques and Applications, Second Edition. Routledge; 2010.

58. Baldwin SA, Imel ZE, Braithwaite SR, Atkins DC. Analyzing multiple outcomes in clinical research using multivariate multilevel models. J Consult Clin Psychol. 2014;82(5):920–930.

59. Cohen J. Applied Multiple Regression/correlation Analysis for the Behavioral Sciences. Taylor & Francis; 1983.

60. Olatunji BO, Rosenfield D, Tart CD, Cottraux J, Powers MB, Smits JAJ. Behavioral versus cognitive treatment of obsessive-compulsive disorder: an examination of outcome and mediators of change. J Consult Clin Psychol. 2013 Jun;81(3):415–428. PMID: 23421734

61. Curran PJ, Bauer DJ. The Disaggregation of Within-Person and Between-Person Effects in Longitudinal Models of Change. Annu Rev Psychol [Internet]. 2011 [cited 2015 Jun 2];62:583–619. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3059070/ PMCID: PMC3059070

62. Hamaker EL, Kuiper RM, Grasman RPPP. A critique of the cross-lagged panel model. Psychol Methods. 2015 Mar;20(1):102–116. PMID: 25822208

63. Wang LP, Maxwell SE. On disaggregating between-person and within-person effects with longitudinal data using multilevel models. Psychol Methods. 2015 Mar;20(1):63–83. PMID: 25822206

64. Tofighi D, MacKinnon DP. RMediation: An R package for mediation analysis confidence intervals. Behav Res Methods [Internet]. 2011 Apr 13 [cited 2016 May 18];43(3):692–700. Available from: http://link.springer.com/article/10.3758/s13428-011-0076-x

65. Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC. Addiction motivation reformulated: an affective processing model of negative reinforcement. Psychol Rev. 2004 Jan;111(1):33–51. PMID: 14756584