Isradipine enhancement of virtual reality cue exposure for smoking cessation: Rationale and
study protocol for a double-blind randomized controlled trial

Santiago Papini^{a,b}, Cara C. Young^c, Catherine S. Gebhardt^{a,b}, Alex Perrone^{a,b}, Hitoshi
Morikawa^{d,e}, Michael W. Otto^f, John D. Roache^g, Jasper A. J. Smits^{a,b}

^aDepartment of Psychology, ^bInstitute for Mental Health Research, ^cSchool of Nursing, ^dInstitute
for Neuroscience, ^eDepartment of Neuroscience, The University of Texas at Austin, Austin, TX,
United States.

^fDepartment of Psychological and Brain Sciences, Boston University, Boston, MA, United States

^gDepartment of Psychiatry, University of Texas Health Science Center at San Antonio, San
Antonio, TX, USA

Correspondence concerning this article should be addressed to Santiago Papini, Department of
Psychology, University of Texas at Austin, 305 E. 23rd Street, Austin, TX, 78712.

Telephone: 512-475-8095; Email: spapini@utexas.edu

ISRADIPINE FOR SMOKING CUE EXPOSURE

Abstract

Cigarette smoking remains a leading cause of preventable death in the United States, contributing to over 480,000 deaths each year. Although significant strides have been made in the development of effective smoking cessation treatments, most established interventions are associated with high relapse rates. One avenue for increasing the effectiveness of smoking cessation interventions is to design focused, efficient, and rigorous experiments testing engagement of well-defined mechanistic targets. Toward this aim, the current protocol will apply a pharmacologic augmentation strategy informed by basic research in animal models of addiction. Our goal is to evaluate the enhancing effect of isradipine, an FDA-approved calcium channel blocker, on the extinction of craving—a key mechanism of drug relapse after periods of abstinence. To activate craving robustly in human participants, we will use multimodal smoking cues including novel 360° video environments developed for this project and delivered through consumer virtual reality headsets. Adult smokers will take either isradipine or placebo and complete the cue exposure protocol in a double-blind randomized control trial. In order to test the hypothesis that isradipine will enhance retention of craving extinction, participants will repeat cue exposure in a medication-free state 24 h later. The study will be implemented in a primary care setting where adult smokers receive healthcare, and smoking behavior will be tracked throughout the trial with ecological momentary assessment.

Keywords: nicotine; craving; virtual reality cue exposure; smoking relapse; immersive video environment; extinction enhancer

ISRADIPINE FOR SMOKING CUE EXPOSURE

1. Introduction

Cigarette smoking contributes to over 480,000 deaths each year in the United States, or about 1 of every 5 deaths [1]. Moreover, an estimated 8.6 million individuals live with chronic diseases caused by tobacco use including lung cancer, heart disease, and COPD [2,3]. Consequently, at least 6-9% of total US personal health expenditures, or approximately \$170 billion in direct medical costs, as well as \$156 billion in lost productivity, can be attributed to smoking-related conditions [4,5]. Significant strides have been made in the development of effective smoking cessation treatments, yet most established interventions are associated with relatively low long-term abstinence rates (15-35%) [6]. A promising avenue for increasing the effectiveness of existing smoking-cessation interventions is to target phase-specific challenges, such as preventing relapse after a successful period of abstinence. Toward this aim, the current protocol is designed to test an intervention targeting self-reported craving, which plays a key role in relapse [7].

Pavlovian learning mechanisms play a key role in craving and provide a systematic framework for testing the efficacy of interventions targeting craving. Addictive drugs have profound effects on reward learning in the brain, where overstimulation of dopaminergic neurons engages mechanisms of synaptic plasticity that establish functional connections between cues that are proximal to drug use and the satisfaction of craving [8]. Even in the absence of the addictive drug, exposure to cues is sufficient to trigger dopamine release, which plays a role in motivation, thus promoting drug-seeking behavior [9]. These mechanisms are highly conserved across species and play a central role in cigarette addiction where strong associations are formed between smoking and a variety of sensory cues, including proximal (e.g., cigarettes, lighters, ashtrays), contextual (e.g., social and physical environments in which smoking commonly

ISRADIPINE FOR SMOKING CUE EXPOSURE

occurs), or interoceptive (e.g., negative mood state) [10–12]. Among smokers who quit, strong cravings can be triggered by drug-associated cues even after periods of abstinence and beyond the withdrawal phase [13–17]. Thus, targeting these associations is key to the long-term impact on craving-induced relapse.

The current research protocol builds upon recent work that tested pharmacologic augmentative strategies in rats using conditioned place preference (CPP), a Pavlovian learning model of cue-induced drug relapse. In a series of experiments, calcium-channel blockage with isradipine was identified as a key mechanism of action to enhance and prolong extinction of CPP [11]. Although several preclinical studies with human subjects have examined off-label use of isradipine to target a variety of effects associated with acute and chronic stimulant use, none have administered isradipine *in combination* with a cue exposure protocol [18–23]. As an extension of CPP findings in animals, we will test whether isradipine, an FDA-approved calcium-channel blocker used to treat hypertension, can facilitate the effects of cue exposure on craving in cigarette smokers.

2. Methods

The study is funded by the National Institute on Drug Abuse (NIDA; 1R21DA049539-01) and is registered on clinicaltrials.gov (NCT03083353). Prior to acquisition of grant funding, an earlier version of the protocol was initiated under this trial registration but paused due to low recruitment ($N = 7$). The registration has been updated to reflect the procedures described below, which have been approved by the Institutional Review Board of the University of Texas at Austin. A Data Safety and Monitoring Board will oversee the study throughout the recruitment phase.

2.1. Primary outcome hypothesis

ISRADIPINE FOR SMOKING CUE EXPOSURE

The current research protocol is designed to test the hypothesis that isradipine (ISR), compared to placebo (PBO), administered in conjunction with cue exposure will enhance long-term extinction of self-reported craving to smoking cues, assessed in a subsequent medication-free cue exposure session (Figure 1). We selected self-reported craving as our primary outcome for several reasons. Whereas a variety of indirect measures of craving have been proposed for humans, including behavioral indicators (e.g., rate and latency of consumption, inter-puff-interval), psychophysiological measures (e.g., startle eye-blink, skin conductance response, and heart rate) and cognitive measures (e.g., attentional and cognitive biases to drug cues), the advantages of these measures over self-report for clinical applications remains unclear [24]. Meta-analysis of cue reactivity research shows robust increases in self-reported craving compared to physiological indices, including heart rate, skin conductance, and skin temperature [25]. Although functional MRI is a powerful tool for understanding the neural mechanisms of human addiction [26–28], it remains cost prohibitive as a routine clinical assessment tool. Importantly, treatment research employing prospective analyses [7] and ecological momentary assessment [29] have demonstrated that self-reported craving post-cessation and through the abstinence phase is a robust predictor of relapse, indicating the value of a simple and direct measure of craving as a potential mechanistic target.

2.2. Overview of design

Figure 1 illustrates participant study flow. Participants will be prescreened by internet and phone for basic inclusion and exclusion criteria prior to a final in-person medical evaluation. Eligible participants will initiate an abstinence challenge 24 h prior to the first cue exposure (verified by expired carbon monoxide levels $\leq 4\text{ppm}$). Isradipine (ISR) or placebo (PBO) will be administered in a double-blind randomization stratified by sex and baseline craving rating (block

ISRADIPINE FOR SMOKING CUE EXPOSURE

size of 4) collected prior to the administration of the study pill [30]. Stratification by sex is based on findings that men and women differ in their sensitivity to smoking cues [31] and their response to smoking cessation [32–34]. Stratification by baseline craving rating is to ensure that treatment effects are not due to differing craving levels between groups before the study pill is administered. For the purposes of stratification, four levels of baseline craving will be coded on the 0-100 scale: 0-25, 26-50, 51-75, and 76-100. Cue exposure session 1 will begin 90 m after administration when isradipine peaks in the brain [35] . Participants will return 24 h later to repeat the procedure in a medication-free state. This second cue exposure session will be used to test whether the isradipine group exhibits enhanced long-term extinction. During the period between the initiation of the abstinence challenge and completion of the study, ecological momentary assessment (EMA) of self-reported craving, exposure to smoking cues, and smoking behavior will be collected via smartphone application.

Figure 1. Participant study flow.

2.3. Participants

Participants will be recruited and enrolled applying the following criteria:

Inclusion Criteria. (1) 18-65 years old; (2) Willing and able to provide informed consent, attend all study visits, and comply with the protocol; (3) Daily smoker for at least one year; and (4) Currently smoke an average of at least 5 cigarettes per day.

Exclusion Criteria. (1) Current diagnosis of a psychotic, eating, developmental or bipolar disorder, or significant suicide risk; (2) Current treatment for smoking cessation or use of other nicotine products, including e-cigarettes; (3) Exclusion criteria related to isradipine

ISRADIPINE FOR SMOKING CUE EXPOSURE

administration: (a) known allergy or sensitivity to isradipine, (b) hypertension, (c) congestive heart failure, (d) any type of liver disease, (e) current pregnancy, (f) women of childbearing potential who are not using medically accepted forms of contraception, (g) current use of Rifampin, which decreases the availability of calcium channel blockers, or of Tagamet, which can increase hypotensive effects and inhibit hepatic metabolism of isradipine, (h) any other significant medical condition that increases risk, as determined by the study physician; (4) Significant vision problems that would prevent engagement with the 360° video environment; and (5) Past six month substance use disorder, other than nicotine use disorder, assessed by structured interview.

2.4. Recruitment and participant compensation

Individuals interested in participating in the study will be directed via various recruitment strategies to an internet prescreen. Recruitment sources include: 1) posting newspaper and Craigslist advertisements; 2) utilizing fliers in community-based organizations, bulletin boards, stores, and handing them out at events and various other sites; 3) utilizing social media sites (e.g., Facebook, Twitter, LinkedIn) to post status updates with links to our online prescreen; 4) utilizing ResearchMatch; and 5) seeking organizations (e.g. Live Tobacco Free Austin).

Eligible participants will be paid \$150 for completion of the study. Payment will be made as follows: \$10 for completing the medical screen, up to \$60 for ecological momentary assessment (up to \$30 each for Day 1 and Day 2 at \$2 per response, 15 times per day), \$30 for completing the first cue exposure session, and \$50 for completing the second cue exposure session. This payment is not contingent upon smoking status at the time of the final visit. Compensation is based on the time commitment required for each component of the study.

2.5. Screening procedures and measures

ISRADIPINE FOR SMOKING CUE EXPOSURE

An overview of assessments through the course of the study is provided in the table below, followed by a procedural description of each study phase.

Table 1. Assessment schedule.

Measure	Internet Prescreen	Phone Screen	Medical Visit	24 h EMA	1st Cue Exposure	24 h EMA	2nd Cue Exposure
Fagerström Test for Nicotine Dependence	×						
Medical, psychiatric, and substance use rule-outs	×	×					
Demographics	×				×		
Smoking history	×	×			×		
Columbia Suicide Severity Rating Scale		×					
Smoking Cue Appeal Survey					×		×
Medical evaluation			×				
Carbon monoxide			×		×		×
Alcohol breathalyzer			×		×		×
Vital signs			×		×		×
Smoking cues, craving, and cigarette use				×		×	
Self-reported craving to in-lab smoking cues					×		×
Minnesota Withdrawal Scale					×		×

Note. EMA = Ecological Momentary Assessment.

ISRADIPINE FOR SMOKING CUE EXPOSURE

2.5.1. Internet prescreen

Individuals interested in participating in the study will be directed via various recruitment strategies to an internet prescreen using REDCap, an online data collection platform that meets HIPAA compliance standards. The first page of the prescreen survey will include the informed consent document (ICD) for the prescreen survey. Participants who consent to the prescreen will complete the following measures:

Demographics. Participants will provide their age, sex assigned at birth, and (if they are eligible) name and contact information.

Medical and psychiatric status. Participants will answer questions addressing current diagnosis of a psychotic, eating, developmental or bipolar disorder, as an initial assessment of psychiatric exclusion criteria, and medical status questions assessing basic exclusion criteria associated with isradipine administration.

Fagerström Test for Nicotine Dependence (FTND) [36]. The FTND is a 6-item scale designed to assess severity of nicotine dependence.

Smoking history. Inclusion/exclusion criteria related with smoking behavior will be assessed by participant report of smoking frequency and quantity, and use of other nicotine or smoking cessation products.

Participants who pass the initial internet prescreen will be called for a phone screen.

Ineligible participants will be provided with a list of referrals.

2.5.2 Phone screen

Participants who pass the internet prescreen will be contacted by a research assistant for a scripted phone screen. Responses for the phone screen are stored in REDCap. The phone screen will assess the following:

ISRADIPINE FOR SMOKING CUE EXPOSURE

Mini International Neuropsychiatric Interview (MINI) [37]. Substance use disorders will be ruled out with the MINI 7.0.2, a short structured clinical interview that assesses DSM-5 criteria [38].

The MINI will be administered by trained research personnel with a B.S. or B.A. in psychology and will be supervised by the PIs.

Medical and psychiatric history. Current medication use, recent hospitalizations, and history of high or low blood pressure will be collected to assess basic exclusion criteria related to isradipine administration, and vision problems will be assessed for exclusion criteria related to virtual reality (VR).

Columbia Suicide Severity Rating Scale (CSSR) [39]. Suicidality exclusion criteria will be assessed with the CSSRS, a structured questionnaire used for suicide assessment in clinical practice.

Individuals who pass the phone screen and are willing to adhere to the 48 hour smoking abstinence will be scheduled for an in-person medical screening. Referrals will be provided to individuals who are not interested in participating or ineligible.

2.5.3. Medical screening.

Medical screening will be conducted or supervised by the study physician. Participants will review the informed consent document before the appointment. Upon arrival, a study coordinator will be available to answer questions the participant may have about the study. The following medical criteria must be met: vital signs within normal limits (i.e., temperature < 100.4, blood pressure >90/60 and <140/90, pulse rate >60 and <100, respiratory rate < 20), no significant cardiovascular or respiratory problems, no history or current diagnosis of diabetes, cancer, autoimmune disorder, cirrhosis or any liver disease, hepatitis, COPD, asthma, GERD,

ISRADIPINE FOR SMOKING CUE EXPOSURE

hypertension, hyperlipidemia, and (female only) the participant is not pregnant, not breastfeeding and, if recently or currently sexually active, is on contraception.

2.6. Abstinence challenge

Participants will be required to abstain from smoking beginning 24 h prior to the first cue exposure session. Our group has applied this challenge in past studies in order to increase ecological validity of early stage trials, which are designed to inform relapse prevention strategies that would be employed *after* successful smoking cessation [40]. After completion of the first cue exposure session, participants will be asked to remain abstinent for the 24 h prior to the second cue exposure session. However, participants who fail to remain abstinent between the first and second cue exposure session will not be excluded from the study so that all data of randomized participants can be collected and reported.

2.7. Intervention

2.7.1. Randomization and pill administration

Eligible participants will return to the clinic for the first cue exposure session. Isradipine (ISR) or placebo (PBO) will be administered in a double-blind randomization stratified by sex and baseline craving rating collected prior to the administration of the study pill. Stratification by sex is based on findings that men and women differ in their sensitivity to smoking cues [31] and their response to smoking cessation [32–34]. Stratification by baseline craving rating is to ensure that treatment effects are not due to differing baseline craving levels between groups before the study pill is administered. For the purposes of stratification, four levels of baseline craving will be coded on the 0-100 scale: 0-25, 26-50, 51-75, and 76-100. The randomization list was computer generated using R 3.6.1 [30] using the package *blockrand* [41] with a 1:1 treatment to control allocation stratified by sex (male or female) and the baseline craving (four levels described

ISRADIPINE FOR SMOKING CUE EXPOSURE

above) using a block size of four. The randomization list will be uploaded to REDCap prior to enrollment, after which point the list is inaccessible by research staff, and randomization will proceed by the stratified sampling functionality using the variables stored in REDCap for each participant as they are enrolled. Both participants and study personnel will be blind to study condition, and study medication will be stored in a bottle labeled either “A” or “B” by the pharmacy (MedSavers, Austin, TX) in order to blind the medication administration. If deemed medically necessary or to meet reporting requirements, only the MPIs (Young and Smits) will be able to break the blind by contacting the pharmacy.

Prior to randomization the following data will be collected:

Abstinence verification. Abstinence status will be verified by a Vitalograph Breathco Carbon Monoxide monitor (≤ 4 ppm) [42]. Participants that do not meet this criterion will not be randomized but will be allowed to reschedule once. Participants who fail this criterion a second time will not be randomized to the study.

Vital signs. Temperature (Temp), pulse (P), and blood pressure (BP) will be obtained. Vital signs outside normal limits will be handled thusly, (a) BP < 90/60 or >140/90, BP will be reassessed in 5 minutes. If BP is still outside limits participants will reschedule their research session for 1-week. If upon return BP is < 90/60 or >140/90 participants will be excluded from the study; (b) P < 60 or >100, recheck in 5 minutes. If P is still outside limits, participant will reschedule their research session for 1-week. If upon return P is < 60 or >100 participant will be excluded from the study; (c) Temp > 100.4, participants will reschedule their research session for 1-week. If upon return Temp is > 100.4 participants will be excluded from the study.

Alcohol screening. Participants will be asked to breathe into an AlcoBreath tube in order to assess for the presence of alcohol. Although there are no absolute contraindications to co-

ISRADIPINE FOR SMOKING CUE EXPOSURE

administration of isradipine with alcohol, both substances are metabolized through the liver.

Participants are advised to refrain from alcohol for at least 24 hours prior to administration of isradipine and 24 hours after administration of isradipine.

Baseline Craving. Baseline craving will be assessed with a Likert scale (see Fig. 3C). There are no inclusion/exclusion criteria related to baseline craving; however, randomization will be stratified by sex and the baseline craving collected prior to the administration of study pill.

Minnesota Withdrawal Scale [45]. Withdrawal severity will be assessed with the Minnesota Withdrawal Scale, a reliable and sensitive 10-item scale. This will also be collected during the second cue exposure session. Although there are no inclusion/exclusion criteria related to withdrawal, this information will be reported to characterize the sample during the intervention phase.

Participants who meet the abstinence and medical criteria above will be randomized to receive isradipine (ISR) or placebo (PBO). Study capsules will be prepared containing: (a) 15 mg immediate release isradipine or (b) pill placebo consisting of Avicel microcrystalline cellulose powder (non-digestible pass-through). Isradipine and placebo capsules will be identical in appearance to maintain the double-blind. The dosage of 15 mg is based on prior human addiction studies with isradipine [18–23]. Individual doses will be dispensed to participants by blinded personnel 75 m prior to the first cue exposure session and patients will be asked to remain in the clinic until session time.

Once participants have taken the study pill and entered the waiting period, several measures will be collected to further describe the randomized sample:

Demographic Questionnaire. Participants will provide their self-identified gender, race, ethnicity, and educational level.

ISRADIPINE FOR SMOKING CUE EXPOSURE

Smoking history. Smoking history and pattern will be assessed with the SHQ, a 30-item measure that includes smoking rate, age of onset of initiation, and years of being a regular smoker [41,42].

Smoking Cue Appeal Survey (SCAS) [40]. The SCAS measures cue appeal to sensory smoking cues and has demonstrated associations to smoking status and craving. This will also be collected during the second cue exposure session.

2.7.1. Cue exposure protocol and rationale

Clinical trials that apply cue exposure for smoking relapse prevention have yielded inconsistent findings, suggesting a need for improved procedures [43,44]. Many studies limit extinction training to select substance-use cues (e.g., the sight and smell of cigarettes), which do not capture the variety of environmental and social cues that form part of a smoker's rich conditioning history [44–46]. The increased availability of VR technology helps address this limitation by providing an immersive and standardized context that can be systematically applied to activate and extinguish cigarette cravings [47]. The use of VR is supported by recent reviews and meta-analysis of computer-generated smoking environments which found robust craving effects in cue-reactivity research [47–49]. However, there are several limitations of traditional, computer-generated VR environments, including the time and technical expertise required to produce them, and the video game quality of the graphics, which have not yet achieved an optimal level of realism.

Recent advances in consumer-level 360° video cameras have made it possible to film high-definition scenes that can be delivered through VR headsets. The current protocol incorporates multimodal drug cues, including the innovative use of 360° video environments to deliver immersive and realistic proximal, contextual, and complex cues through affordable and

ISRADIPINE FOR SMOKING CUE EXPOSURE

disseminable consumer VR headsets [50]. To our knowledge, our study is the first to apply 360° video environments for cue exposure, which were produced in house using the Samsung Gear 360 camera (Model #: SM-C200, \$159.00), which films 360° Ultra High Definition video to create immersive VR from real environments and people (as opposed to computer-generated environments). Participants with corrective lenses (i.e., glasses) are able to easily and comfortably wear VR headsets.

Prior to grant funding, data were collected for 7 participants completing an earlier version of the two-day cue exposure protocol, including study pill administration. In preparation for the current study, we conducted two additional pilots with 13 additional participants who completed a single cue exposure session after 24 h abstinence challenge without study pill administration. We evaluated and modified our cue exposure protocol based on data from these pilot studies. Specifically, in the first pilot participants alternated between VR and handling cigarette packs, in the second pilot participants maintained the VR headset on for all 10 trials and concurrently handled cigarette packs, and in the third pilot participants could alternate between several scenes while handling cigarette packs. Figure 2 shows peak craving data from our pilot phases, during which our 360° environments were tested. Results from Pilot 1 suggested that the incorporation of VR with traditional approaches (e.g., handling cigarette packs) was tolerable and effective in activating robust cravings. Additionally, there were no reports of side effects on the day of study pill administration, and day two data (examined without knowledge of group assignment) showed a wide range of craving activation ($M = 47.17$, $SD = 34.49$, range: 17 - 100, $N = 6$) on the first trial of the second cue exposure session. In Pilot 2 we sought to simplify the procedure by conducting the entire exposure session with the VR headset on. Results from Pilot 2 suggested that participants were able to wear the headset continuously while handling the

ISRADIPINE FOR SMOKING CUE EXPOSURE

cigarette pack without reporting dizziness or discomfort, and that the simplified procedure activated robust cravings. In Pilot 3 we sought to evaluate the differential impact of scenes on participants. Results from Pilot 3 suggested that craving may be more consistently activated across participants when they select a scene that is closest to their craving-eliciting environments, but that alternating between scenes within participants resulted in poorer extinction of craving.

Based on these pilot studies, the current research protocol will implement the following cue exposure procedure: (1) Participants will receive visual and written descriptions of the three available scenes and instructed to select the scene that is most likely to activate strong cravings or urges to smoke. The scene that is selected will be used throughout the entire procedure in order to avoid the poor extinction observed in Pilot 3, which allowed participants to change scenes between trials; (2) Participants will be instructed to handle the pack throughout the exposure in a way that is most likely to activate strong cravings or urges to smoke. Prior to initializing the VR, participants will practice handling the cigarette pack for 1 m and ; (3) Participants will put on the VR headset and begin the cue exposure session.

Figure 2. Mean craving ratings $\pm$ 1 SE from the pilot phase. In Pilot 1 ($N = 7$) participants first watched a 3 m scene displayed through a Galaxy 8 phone (Model #: SM-G950W, \$606.25) +

ISRADIPINE FOR SMOKING CUE EXPOSURE

Samsung Gear VR Headset (Model #: SM-R324, \$102.57) and then handled a pack of cigarettes for 1 m. In Pilot 2 ($N = 8$) participants handled cigarettes while viewing 10 trials of the same scene delivered through the Oculus Go VR headset (Model #: MH-A32, \$199.00). In Pilot 3 ($N = 5$), several scenes were used, which resulted in weaker extinction of craving.

2.8. Assessment of outcomes

2.8.1. Primary outcome

Self-reported craving will be collected after each cue exposure trial (10 per session). Participants will be asked to state the *highest* level of craving experienced using a Likert scale (range: 0-100) displayed in the VR environment. After the first trial, participants will identify the moment in the scene when their craving was the highest. For subsequent trials, participants will be reminded to focus (as opposed to avoid) the most activating part of the scene and report their craving.

Figure 3. Sample scenes depicting smoking cues (A & B) and self-reported craving scale (C).

2.8.2. Additional data collected

From the 24 h prior to the first cue exposure session to the end of the study, participants will complete EMA of craving, exposure to smoking cues, and cigarette use once per hour up to 15 times per day within a time window chosen by the participant on a smartphone application we developed for this project using the HIPAA-compliant Qualtrics platform. The EMA serves as a reminder of the abstinence challenge and will be reported to provide a description of participant smoking behavior across the study phase. In the 24 h period after the first cue exposure phase, during which participants who fail to remain abstinent will not be excluded from participating in the second cue exposure session. However, given the potential impact of relapse on the primary outcome of this study (e.g., individuals who resume smoking are likely to report lower craving

ISRADIPINE FOR SMOKING CUE EXPOSURE

during the second cue exposure session), these data will be examined to ensure proper interpretation of primary outcome results (see 3. Data analysis and power).

What was the highest craving you experienced in the last hour?

NONE MODERATE STRONG
0 10 20 30 40 50 60 70 80 90 100

Was it activated by a smoking cue?

YES
NO

Did you smoke since the last log?

YES
NO

Figure 4. Craving application for ecological momentary assessment.

3. Data analysis and power

The effects of Group (ISR vs. PBO), Trial (1-10), and Group $\times$ Trial on self-reported craving during the second cue exposure session will be examined in a mixed model with random subject effects to account for the within-subject correlation between trials. Figure 5 shows simulations of linear models with enhanced extinction outcomes in the isradipine group. However, to avoid applying potentially invalid assumptions about the shape of craving curves on session 2, we will fit several models to the complete dataset prior to breaking the blind (e.g., linear, quadratic, exponential, non-parametric, etc.). Once the best fitting model is selected, the effect of isradipine on craving will be tested by the Group $\times$ Trial interaction or main effect of Group (depending on the model selected). Significant effects of isradipine that demonstrate either a lower initial

ISRADIPINE FOR SMOKING CUE EXPOSURE

craving or faster rate of extinction on the second cue exposure session will be interpreted as evidence of target engagement and provide the evidence necessary to guide next-stage research.

The analytic plan for the primary outcome depends on several assumptions that will be checked prior to breaking the blind using dummy coded group labels (e.g., A vs. B). Although isradipine administration has demonstrated acute effects on cocaine-seeking behavior in rats after prolonged abstinence [51], an acute effect was not observed in the extinction of conditioned place preference in rats [11]. Given our experiment is modeled after the latter preclinical research, we are not predicting an acute effect of isradipine on session 1 craving. To check this assumption, the same analytical strategy described for session 2 will be applied to session 1. If these analyses indicate that groups significantly differ in the level of craving activation or craving extinction, then the analytic plan for the primary outcome will be adjusted to account for this unanticipated difference. Additionally, we will examine cigarette use in the 24 h between session 1 and 2 and adjust the analytic strategy to account for group differences in abstinence, which may impact craving levels and the interpretation of primary outcome results.

Recruitment target has been set at $N = 102$ (51 per group). Figure 5 illustrates results from power simulations conducted in the open source R statistical software [30] using the *simr* package [52]. These simulations assumed linear mixed models would best fit the data, and applied intercept, slope, random intercept effects, and residual variance estimates from the second pilot study, which followed a procedure that most closely matched the final protocol. Across the three simulations, which capture different ways in which long-term extinction can be enhanced, the power to detect a medium effect was $> 90\%$ for our target sample size and remained $> 85\%$ for group sample sizes above 40. Therefore, our target sample size assures that even with a 20% dropout rate our study has at least 85% power to detect medium effect sizes.

ISRADIPINE FOR SMOKING CUE EXPOSURE

Full code for the power simulations, including all outputs and package versions is available in the Open Science Foundation (OSF) site for this project (DOI 10.17605/OSF.IO/PK9YF).

Figure 5. Potential long-term extinction effects of isradipine on the second cue exposure session. Model 1 simulated a main effect of isradipine (A), model 2 simulated an interaction effect with group difference on the early trials (B), and model 3 simulated an interaction effect with group difference at the latter trials (C). Power simulations for the respective models showed > 90% power to detect medium sized effects with the target sample size (50 per group).

4. Discussion

Cigarette tobacco use is a leading cause of death that constitutes a major public health problem with significant personal and societal costs. The current research protocol applies the experimental therapeutics approach to measure target engagement in a pharmacologic augmentation strategy informed by basic research in animal models of addiction. The cue exposure protocol developed for this trial incorporates multimodal drug cues, including the innovative use 360° video environments to deliver immersive and realistic proximal, contextual, and complex cues through affordable and disseminable consumer VR headsets. To our knowledge, our study will be the first to apply 360° video environments, which are produced in-

ISRADIPINE FOR SMOKING CUE EXPOSURE

house and are often rated as more realistic than computer-generated environments. The proposed study will evaluate the enhancing effect of isradipine, a calcium channel blocker, on the extinction of craving—a pathophysiologically relevant mechanism of drug relapse after periods of abstinence. Findings will be used to guide next-stage research designed to target key clinical outcomes including smoking cessation and prolonged abstinence.

ISRADIPINE FOR SMOKING CUE EXPOSURE

Funding

This project was supported by NIH/NIDA 1R21DA049539-01 (MPI Young & Smits, Co-I Papini). The National Institutes of Health had no role in the writing of the report or in the decision to submit the manuscript for publication.

ISRADIPINE FOR SMOKING CUE EXPOSURE

Declaration of Conflicting Interests

A. Perrone, C. Gebhardt, J. Roache, and C. Young report no conflict of interests with their funding. S. Papini receives support from the National Institutes of Health and the Donald D. Harrington Foundation. H. Morikawa receives support from the National Institutes of Health. M. Otto receives support from the National Institutes of Health and compensation as a speaker and Chair of the Scientific Advisory Board for Big Health. J. Smits receives support from the National Institutes of Health, compensation for his work as a consultant to Big Health, as editor for Elsevier and the American Psychological Association, and royalties from various book publishers. The authors declared that these funding organizations had no influence on the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

References

- [1] National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health, The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General, Centers for Disease Control and Prevention (US), Atlanta (GA), 2014. <http://www.ncbi.nlm.nih.gov/books/NBK179276/> (accessed December 4, 2019).
- [2] G. Danaei, E.L. Ding, D. Mozaffarian, B. Taylor, J. Rehm, C.J. Murray, M. Ezzati, The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors, *PLoS Medicine*. 6 (2009) e1000058.
- [3] N.B. Johnson, L.D. Hayes, K. Brown, E.C. Hoo, K.A. Ethier, CDC national health report : Leading causes of morbidity and mortality and associated behavioral risk and protective factors — United States, 2005–2013, (2014). <https://stacks.cdc.gov/view/cdc/25809>.
- [4] K.E. Warner, T.A. Hodgson, C.E. Carroll, Medical costs of smoking in the United States: estimates, their validity, and their implications, *Tobacco Control*. 8 (1999) 290–300.
- [5] X. Xu, E.E. Bishop, S.M. Kennedy, S.A. Simpson, T.F. Pechacek, Annual healthcare spending attributable to cigarette smoking: an update, *American Journal of Preventive Medicine*. 48 (2015) 326–333.
- [6] C. Heaton, M.C. Fiore, Treating tobacco use and dependence: 2008 update US Public Health Service Clinical Practice Guideline executive summary, *Respiratory Care*. 53 (2008) 1217–1222.
- [7] J.D. Killen, S.P. Fortmann, Craving is associated with smoking relapse: findings from three prospective studies., *Experimental and Clinical Psychopharmacology*. 5 (1997) 137.
- [8] N.D. Volkow, R.D. Baler, Addiction science: uncovering neurobiological complexity, *Neuropharmacology*. 76 (2014) 235–249.
- [9] S.E. Hyman, R.C. Malenka, E.J. Nestler, Neural mechanisms of addiction: the role of reward-related learning and memory, *Annu. Rev. Neurosci.* 29 (2006) 565–598.
- [10] C.A. Conklin, N. Robin, K.A. Perkins, R.P. Salkeld, F.J. McClernon, Proximal versus distal cues to smoke: the effects of environments on smokers' cue-reactivity., *Experimental and Clinical Psychopharmacology*. 16 (2008) 207.
- [11] M. Degoulet, C.E. Stelly, K.-C. Ahn, H. Morikawa, L-type Ca²⁺ channel blockade with antihypertensive medication disrupts VTA synaptic plasticity and drug-associated contextual memory, *Molecular Psychiatry*. 21 (2016) 394.
- [12] A.B. Lazev, T.A. Herzog, T.H. Brandon, Classical conditioning of environmental cues to cigarette smoking., *Experimental and Clinical Psychopharmacology*. 7 (1999) 56.
- [13] K.S. Bagot, S.J. Heishman, E.T. Moolchan, Tobacco craving predicts lapse to smoking among adolescent smokers in cessation treatment, *Nicotine & Tobacco Research*. 9 (2007) 647–652.
- [14] B.L. Carter, S.T. Tiffany, Meta-analysis of cue-reactivity in addiction research, *Addiction*. 94 (1999) 327–340.
- [15] A.C. Janes, D.A. Pizzagalli, S. Richardt, B. deB Frederick, S. Chuzyi, G. Pachas, M.A. Culhane, A.J. Holmes, M. Fava, A.E. Evins, Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence, *Biological Psychiatry*. 67 (2010) 722–729.
- [16] J.D. Killen, S.P. Fortmann, Craving is associated with smoking relapse: findings from three prospective studies., *Experimental and Clinical Psychopharmacology*. 5 (1997) 137.

- [17] M.M. Owens, J. MacKillop, J.C. Gray, S.R. Beach, M.D. Stein, R.S. Niaura, L.H. Sweet, Neural correlates of tobacco cue reactivity predict duration to lapse and continuous abstinence in smoking cessation treatment, *Addiction Biology*. 23 (2018) 1189–1199.
- [18] B.A. Johnson, N. Ait-Daoud, L.T. Wells, Effects of isradipine, a dihydropyridine-class calcium channel antagonist, on D-methamphetamine-induced cognitive and physiological changes in humans, *Neuropsychopharmacology*. 22 (2000) 504–512.
- [19] B.A. Johnson, J.D. Roache, N. Ait-Daoud, L.T. Wells, J.B. Mauldin, Effects of isradipine on cocaine-induced subjective mood, *Journal of Clinical Psychopharmacology*. 24 (2004) 180–191.
- [20] B.A. Johnson, J.D. Roache, P.S. Bordnick, N. Ait-Daoud, Isradipine, a dihydropyridine-class calcium channel antagonist, attenuates some of d-methamphetamine's positive subjective effects: a preliminary study, *Psychopharmacology*. 144 (1999) 295–300.
- [21] B.A. Johnson, J.D. Roache, N. Ait-Daoud, C.L. Wallace, L.T. Wells, Y. Wang, M.A. Dawes, Effects of isradipine on cocaine-induced changes in cognitive performance in recently abstinent cocaine-dependent individuals, *International Journal of Neuropsychopharmacology*. 8 (2005) 549–556.
- [22] B.A. Johnson, L.T. Wells, J.D. Roache, C. Wallace, N. Ait-Daoud, Y. Wang, Isradipine decreases the hemodynamic response of cocaine and methamphetamine: results from two human laboratory studies, *American Journal of Hypertension*. 18 (2005) 813–822.
- [23] J.D. Roache, B.A. Johnson, N. Ait-Daoud, J.B. Mauldin, J.E. Thornton, L.T. Wells, W.L. Murff, Effects of repeated-dose isradipine on the abuse liability of cocaine., *Experimental and Clinical Psychopharmacology*. 13 (2005) 319.
- [24] H. Rosenberg, Clinical and laboratory assessment of the subjective experience of drug craving, *Clinical Psychology Review*. 29 (2009) 519–534.
<https://doi.org/10.1016/j.cpr.2009.06.002>.
- [25] B.L. Carter, S.T. Tiffany, Meta-analysis of cue-reactivity in addiction research, *Addiction*. 94 (1999) 327–340.
- [26] B.J. Everitt, T.W. Robbins, Neural systems of reinforcement for drug addiction: from actions to habits to compulsion, *Nature Neuroscience*. 8 (2005) 1481.
- [27] S.E. Hyman, R.C. Malenka, E.J. Nestler, Neural mechanisms of addiction: the role of reward-related learning and memory, *Annu. Rev. Neurosci.* 29 (2006) 565–598.
- [28] P.W. Kalivas, N.D. Volkow, The Neural Basis of Addiction: A Pathology of Motivation and Choice, *AJP*. 162 (2005) 1403–1413. <https://doi.org/10.1176/appi.ajp.162.8.1403>.
- [29] T.M. Moore, A. Seavey, K. Ritter, J.K. McNulty, K.C. Gordon, G.L. Stuart, Ecological momentary assessment of the effects of craving and affect on risk for relapse during substance abuse treatment, *Psychology of Addictive Behaviors*. 28 (2014) 619–624.
<https://doi.org/10.1037/a0034127>.
- [30] R Core Team, R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2017. <https://www.R-project.org/>.
- [31] K.A. Perkins, Sex differences in nicotine reinforcement and reward: influences on the persistence of tobacco smoking, in: *The Motivational Impact of Nicotine and Its Role in Tobacco Use*, Springer, 2008: pp. 143–169.
- [32] L.W. Hawk Jr, R.L. Ashare, S.F. Lohnes, N.J. Schlienz, J.D. Rhodes, S.T. Tiffany, J.C. Gass, K.M. Cummings, M.C. Mahoney, The effects of extended pre-quit varenicline treatment on smoking behavior and short-term abstinence: a randomized clinical trial, *Clinical Pharmacology & Therapeutics*. 91 (2012) 172–180.

- [33] D. Scharf, S. Shiffman, Are there gender differences in smoking cessation, with and without bupropion? Pooled-and meta-analyses of clinical trials of Bupropion SR, *Addiction*. 99 (2004) 1462–1469.
- [34] D.W. Wetter, S.L. Kenford, S.S. Smith, M.C. Fiore, D.E. Jorenby, T.B. Baker, Gender differences in smoking cessation., *Journal of Consulting and Clinical Psychology*. 67 (1999) 555.
- [35] Isradipine - FDA prescribing information, side effects and uses, *Drugs.Com*. (n.d.). <https://www.drugs.com/pro/isradipine.html> (accessed January 27, 2020).
- [36] T.F. Heatherton, L.T. Kozlowski, R.C. Frecker, K.-O. Fagerström, The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire, *British Journal of Addiction*. 86 (1991) 1119–1127.
- [37] D.V. Sheehan, Y. Lecrubier, K.H. Sheehan, P. Amorim, J. Janavs, E. Weiller, T. Hergueta, R. Baker, G.C. Dunbar, The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10., *The Journal of Clinical Psychiatry*. (1998).
- [38] A.P. Association, *Diagnostic and statistical manual of mental disorders (DSM-5®)*, American Psychiatric Pub, 2013.
- [39] K. Posner, G.K. Brown, B. Stanley, D.A. Brent, K.V. Yershova, M.A. Oquendo, G.W. Currier, G.A. Melvin, L. Greenhill, S. Shen, J.J. Mann, The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults, *AJP*. 168 (2011) 1266–1277. <https://doi.org/10.1176/appi.ajp.2011.10111704>.
- [40] M.J. Zvolensky, M.T. Feldner, E.W. Leen-Feldner, L.E. Gibson, K. Abrams, K. Gregor, Acute nicotine withdrawal symptoms and anxious responding to bodily sensations: A test of incremental predictive validity among young adult regular smokers, *Behaviour Research and Therapy*. 43 (2005) 1683–1700. <https://doi.org/10.1016/j.brat.2004.10.010>.
- [41] G. Snow, blockrand: randomization for block random clinical trials. R package version 1.3, 2013.
- [42] K.A. Perkins, J.L. Karelitz, N.C. Jao, Optimal Carbon Monoxide Criteria to Confirm 24-hr Smoking Abstinence, *Nicotine Tob Res*. 15 (2013) 978–982. <https://doi.org/10.1093/ntr/nts205>.
- [43] C.A. Conklin, S.T. Tiffany, Applying extinction research and theory to cue-exposure addiction treatments, *Addiction*. 97 (2002) 155–167.
- [44] S.G. Ferguson, S. Shiffman, The relevance and treatment of cue-induced cravings in tobacco dependence, *Journal of Substance Abuse Treatment*. 36 (2009) 235–243.
- [45] S. Shiffman, M. Hickcox, J.A. Paty, M. Gnys, T. Richards, J.D. Kassel, Individual differences in the context of smoking lapse episodes, *Addictive Behaviors*. 22 (1997) 797–811.
- [46] S. Shiffman, J.A. Paty, M. Gnys, J.A. Kassel, M. Hickcox, First lapses to smoking: within-subjects analysis of real-time reports., *Journal of Consulting and Clinical Psychology*. 64 (1996) 366.
- [47] I. Pericot-Valverde, L.J. Germeroth, S.T. Tiffany, The use of virtual reality in the production of cue-specific craving for cigarettes: a meta-analysis, *Nicotine & Tobacco Research*. 18 (2015) 538–546.
- [48] A. Hone-Blanchet, T. Wensing, S. Fecteau, The use of virtual reality in craving assessment and cue-exposure therapy in substance use disorders, *Frontiers in Human Neuroscience*. 8

- (2014) 844.
- [49] I. Pericot-Valverde, R. Secades-Villa, J. Gutiérrez-Maldonado, O. García-Rodríguez, Effects of systematic cue exposure through virtual reality on cigarette craving, *Nicotine & Tobacco Research*. 16 (2014) 1470–1477.
- [50] M.C. Mishkind, A.M. Norr, A.C. Katz, G.M. Reger, Review of virtual reality treatment in psychiatry: evidence versus current diffusion and use, *Current Psychiatry Reports*. 19 (2017) 80.
- [51] N.A. Addy, E.J. Nunes, S.M. Hughley, K.M. Small, S.J. Baracz, J.L. Haight, A.M. Rajadhyaksha, The L-type calcium channel blocker, isradipine, attenuates cue-induced cocaine-seeking by enhancing dopaminergic activity in the ventral tegmental area to nucleus accumbens pathway, *Neuropsychopharmacology*. 43 (2018) 2361–2372. <https://doi.org/10.1038/s41386-018-0080-2>.
- [52] P. Green, C.J. MacLeod, SIMR: an R package for power analysis of generalized linear mixed models by simulation, *Methods in Ecology and Evolution*. 7 (2016) 493–498. <https://doi.org/10.1111/2041-210X.12504>.