Perelman School of Medicine
University of Pennsylvania

GeoScan and Remote Geo Smoking Study: Neural and Behavioral Correlates of Smokers' Exposure to Retail Environments

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Study Summary

Title	Remote Geo Smoking Study: Behavioral and Geospatial Correlates of Smokers' Exposure to Retail Environments
Short Title	Remote Geo
IRB Number	850796
Methodology	This study will utilize a randomized trial to examine the effects of point-of-sale tobacco marketing on smoking behaviors and brain activity. After a two week observational period, participants will be randomized to one of three behavioral intervention conditions for the duration of a four week intervention period.
Study Duration	Five years
Study Center(s)	Single-center
Objectives	● The primary objectives of this study are to understand the effects of point-of-sale tobacco marketing (POST-M) on smoking behavior and cravings in smokers. We will examine whether experimental group assignment affects cigarette cravings and cigarette consumption during the intervention period relative to the baseline period. ● For a subset of participants, we will examine brain responses during the smoking cue reactivity task.
Number of Subjects	343 [Actual]
Main Inclusion and Exclusion Criteria	Key Inclusion Criteria for remote participation: ● Be between the ages of 21-65 ● Smoke at least 5 cigarettes a day for the past 6 months ● Own an iPhone or Android smartphone that can be used on a daily basis ● Be residents of Pennsylvania, New Jersey, or Delaware ● Read and speak English fluently ● Fully vaccinated against COVID-19 Key Exclusion Criteria for remote participation: ● Current enrollment or plans to enroll in a smoking cessation program in the next 3 months ● Plan to use nicotine substitutes or smoking cessation treatments in the next 3 months ● Urine cotinine concentration below 200ng/mL ● Pregnancy ● Inability or refusal to complete study tasks The complete list of study inclusion and exclusion criteria, including exclusion criteria for the fMRI subset, is included within the Characteristics of the Study Population section of this protocol.

Intervention	Random assignment of retail environment (high POSTM; low POSTM, control [no store]) to visit 5 times per week during the 4-week intervention period.
Statistical Methodology	We will use linear regression and multilevel models (in R) to test our hypotheses, as well as tools from nipype, SPM, and fmriprep to process and model fMRI data.
Data and Safety Monitoring Plan	The principal investigator will monitor the safety, privacy, and data integrity during the course of the study. In addition, we will provide the required project reports to the sponsor.

● Background and Study Rationale

This document is a protocol for a human research study. This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations.

1 Introduction

Cigarette smoking is the leading cause of preventable death and illness in the United States and throughout the developed world. Recent work suggests detrimental links between exposure to point-of-sale tobacco marketing (POSTM), increases in cigarette cravings, and the failure to quit smoking. Understanding how individuals are influenced by and react to environmental cues when making health decisions is critical to cancer control efforts and policymaking. We propose to use an innovative set of methods to test whether repeated, real-world exposure to POSTM affects smoking behavior, and whether this is mediated by changes in craving and neural responses to POSTM. Our approach combines mobile-phone based geolocation tracking, ecological momentary assessment (EMA), and functional magnetic resonance imaging (fMRI). Research using geospatial location tracking and surveys suggests that high levels of POSTM exposure may increase craving; however, correlational studies preclude causal inferences about POSTM effects. Relatedly, laboratory studies have documented neural and behavioral reactivity to standardized visual smoking cues, such as photographs of cigarettes in an ashtray, but the brain's response to naturalistic POSTM exposure has not been explored. By adding the ecological validity of observational field methods to the mechanistic insight of neuroimaging, and causal inferences from an experimental pre-post design, we aim to significantly advance actionable insight about POSTM effects in cancer control.

1.1 Background and Relevant Literature

Summary:
The tobacco industry has come to rely increasingly on point-of-sale tobacco marketing (POST-M), with large displays near cash registers in retail outlets such as convenience stores and gas stations [1]. Recent work utilizing geospatial location tracking has found that smoking

lapses while smokers are trying to quit are more likely on days when smokers are exposed to POST-M, particularly when their general tobacco craving levels are otherwise low [2]. This suggests that POST-M exposure may increase craving, making abstinence more difficult. This finding converges with recent survey results demonstrating that during quit attempts, a significant percentage of smokers experience urges to purchase cigarettes when exposed to POST-M, and feel that the removal of POST-M would make quitting easier [3]. These reports indicating that incidental exposure to cigarette cues adversely affects smoking abstinence are supported by laboratory studies. A typical laboratory cue reactivity paradigm involves presenting participants with pictures or video of smoking cues, such as a hand holding a cigarette, followed by a measurement of participants' craving intensity. Smoking abstinence has been found to potentiate self-reported craving in response to cigarette cues [4-7,8], suggesting a mechanism for the finding that exposure to POST-M during a quit attempt leads to poorer outcomes. No studies, however, have experimentally manipulated exposure to POST-M cues in vivo. To this end, we will examine whether assigning smokers to a high or low level of POST-M exposure as part of their daily routine affects several smoking outcomes. A location tracking smartphone application (Google Maps) will be used to document participants' exposure to retail outlets and link each person to the retail environment. Measurements will assess longitudinal tobacco-use patterns and perceptions across the study period, as well as changes in cravings. If it is the case that low POST-M exposure reduces smoking, this emphasizes the importance of further regulation of retail advertising for tobacco.

In addition to the hypotheses and analysis plans described here, the study team has preregistered additional hypotheses and analysis plans which are not the focus of the clinical trial component of the study. These are available at https://osf.io/kyb64/registrations.

Background:

Tobacco dependence is a significant public health problem. Cigarette smoking is the leading cause of preventable death and illness in the United States and throughout the developed world[1]. Smoking increases the odds of developing the most frequently diagnosed cancers and other leading causes of death, accounting for 1 in 5 deaths in the US each year [2,3]. Due to restrictions in other communication outlets, the tobacco industry currently concentrates over 80% of its $8.1 billion annual marketing budget on retail environments, including **point-of-sale tobacco marketing (POSTM)**[4–8]. Tobacco advertising and products are placed prominently in "power walls" near or behind cash registers in retail outlets like convenience stores and gas stations[9,10,11], such that all customers are exposed to this marketing. This widespread and frequent exposure to POSTM in smokers and nonsmokers alike is of great interest in tobacco control and cancer prevention research worldwide, and has led to recent bans of POSTM in 42% of countries in Europe[12]. In this study, we aim to test whether repeated, real-world exposure to POSTM affects smoking behavior through heightened neural smoking cue reactivity and subjective craving. We will test both correlational (Aims 1-2) and causal (Aim 3) pathways. To this end, we propose an innovative combination of geolocation tracking as an ecologically valid, objective measure of real-world POSTM exposure[13,14]; ecological momentary assessment (EMA)[15] to assess real-time behavior and craving; and functional magnetic resonance imaging (fMRI) to assess neural responses to cigarette cues[16–18]. Understanding both the neural (laboratory-based) and behavioral (real-world) consequences of exposure to POSTM will clarify the mechanisms of POSTM impact, and ultimately aid in the design of more effective cancer prevention and tobacco regulatory policies.

How are smokers influenced by point-of-sale tobacco marketing (POSTM)? Past work suggests detrimental relationships between exposure to POSTM and other environmental smoking cues and smoking behavior in individuals (e.g.,[19,20]) and the larger population (e.g.,[21])

across countries, measures and study designs (for a review:[22]). Within current and recently quit smokers, field work consistently reports associations between POSTM exposure in naturalistic settings, and increased smoking cravings, purchase urges, and impulse purchases[23–28]. The density of POSTM in an individual's neighborhood, a proxy for exposure, also influences smoking behavior[29–33]; for example, longitudinal work finds that smokers are more likely to relapse during a quit attempt if they live near a POSTM store[34]. In a virtual store study, enclosing the POSTM display reduced smokers' purchase attempts and urges to smoke[35]. This body of research thus suggests that further regulation of POSTM would be beneficial from a cancer control perspective; however, causal evidence linking longitudinal, naturalistic exposure and smoking outcomes, as well as neural evidence supporting the mechanisms of cumulative and causal effects, would substantially bolster science-based policy making.

The significance of geolocation tracking and ecological momentary assessment. Geolocation tracking provides the unique ability to objectively and unobtrusively assess participants' exposure to POSTM outlets. The recent ubiquity of geolocation tracking built-in to smartphones provides the opportunity for incorporating this methodology into experimental designs with reduced participant burden. This is a significant improvement over prior POSTM exposure work, which is limited by reliance on self-reports of the timing and degree of POSTM exposure, or by the need to initiate or observe single, non-representative exposures. In PA, DE, and NJ, where data collection will take place, obtaining a local cigarette dealer license is mandatory for cigarette retailers[36] and listings of licensed outlets are publicly available and updated monthly[37]. Layering smokers' geolocation tracks onto maps of tobacco retail outlets allows objective quantification of an individual's exposure to POSTM in their natural environment. [38]. In parallel with geolocation tracking, we will sample participants' behaviors and craving throughout each day using EMA, to capture time-sensitive fluctuations in a representative manner[15]. EMA optimally complements the naturalistic geolocation tracking data by tagging participants' location history with reports indicating natural smoking behavior and craving on a moment-to-moment basis. Thus, this project will link individuals' smoking cravings and behavior to the POSTM environment in both time and location. Our team's expertise with mobile device-based EMA collection[41,42] makes us uniquely suited to conduct this multi-level integrative research.

Combining responses to tobacco-related cues in the real world and cue-reactivity in the neuroimaging laboratory will provide a mechanistic understanding of how POSTM influences smokers. The scientific premise for this study derives from theoretical models and empirical studies of addiction, which suggest that exposure to drug-cues, such as images of drug paraphernalia, enhances craving and consumption behavior in drug users, including smokers[43,44]. Laboratory work has shown increased neural activity in regions associated with drug cue-reactivity as well as increased ratings of subjective craving in smokers after exposure to smoking cues such as pictures of cigarettes[16,43]. Craving ratings scale positively with neural cue-reactivity[17,45,46], and both metrics predict smoking behaviors in a later ad-lib smoking session [18,47]. Thus, laboratory experiments implicate neural smoking cue reactivity and cigarette craving as mechanisms linking exposure to smoking cues and behavior. In contrast to many other addictive substances, advertising for cigarettes is professionally produced, legal, and prevalent in smokers' natural environments. Neural cue reactivity effects have been generalized from completely standardized cues to more naturalistic pictures of personal smoking environments, such that exposure to photographs of places where participants often smoke (e.g., one's home) evokes stronger neural and behavioral craving responses than exposure to generic environmental photographs (e.g., an unfamiliar bus stop)[18,48,49]; however, the generalizability of such effects to POSTM cues and complex retail environments has not been tested. We will test whether baseline exposure to photographs of POSTM elicits activation in the

same brain regions as standardized, proximal smoking cues. A recent meta-analysis shows that a specific set of neural regions consistently responds more strongly to standard smoking cues as compared to neutral images, including the extended visual system, precuneus, posterior cingulate gyrus, anterior cingulate gyrus, dorsal and medial prefrontal cortex, insula, and dorsal striatum[16].

Brain activity as a key, mechanistic indicator of message impact over time. Functional neuroimaging allows an unobtrusive examination of both conscious and unconscious processes induced by exposure to standard smoking cues[16] and mediated messages such as marketing materials[50–52]. Our team and others have developed multi-method approaches to test the generalizability and predictive validity of laboratory-based neural effects to real-world behaviors [51–69]. This work has shown that neural reactivity to persuasive messaging inside the fMRI scanner reliably predicts health behaviors, including reductions in smoking and sedentary behavior, above and beyond the predictive capacity of commonly used self-reports [51,59,60,64,65,70–75]. Further, findings obtained in small groups have been shown to be scalable, such that message-induced neural activity in small samples has been used to predict population-level message impact, including the generation of quitline calls [51] and sharing of health-related information [76,77]. In a past experimental health intervention, our team successfully used brain activity to predict experimental effects on subsequent behavior at timepoints up to a month later [62].

Causal manipulation of exposure to tobacco marketing. Most extant field work focused on POSTM, despite including large samples and naturalistic settings, has been correlational, with a few notable exceptions. For example, Shadel et al created an experimental convenience store, and found that removal of the POSTM power wall reduced susceptibility to future cigarette smoking in adolescents[78]. The current study proposes to significantly extend these findings by manipulating adult smokers' real-world, daily POSTM exposure over the course of one month, rather than assessing the impact of a single exposure in one experimental session. After an observation period of geolocation tracking and EMA, individuals will be randomly assigned to 1 of 3 groups. Two groups enter and make small, non-tobacco purchases at a store which displays POSTM (tobacco retailer condition) or a store that displays pro-cessation messaging (nontobacco retailer condition). Approaching the register for this purchase constitutes an exposure to POSTM (tobacco retailer condition) or pro-cessation marketing (nontobacco retailer condition). A third group receives no instruction to change their routine exposure to POSTM.

2 Study Objectives

2.1 Primary Objective

The primary objectives are to examine the relationships between smoking behavior, cigarette cravings, and exposure to point-of-sale tobacco marketing. We will examine whether experimental group assignment affects cigarette cravings and cigarette consumption during the intervention period relative to the baseline. For the subset of participants who undergo fMRI scanning, we will compare craving ratings and brain activity during different task conditions.

3 Investigational Plan

3.1 General Design

Study Type: Interventional
Primary Purpose: Other
Study Phase: N/A
Interventional Study Model: Parallel Assignment
Random assignment of retail environment (tobacco retailer, non-tobacco retailer, no store) to visit 5 times per week during the 4-week intervention period

Number of Arms: 3
Masking: Single (Investigator)
Investigator will not know the condition assignment of individual participants unless reassessment is triggered by the stopping rule.

Allocation: Randomized
Enrollment: 343 [Actual]

3.2 Allocation to Interventional Group

Participants who completed the required tasks during the baseline period were randomized within blocks [blocked by gender (male, female, other) and smoking level (high, low; high was 20 cigarettes or greater per day)]. At the beginning of data collection, condition assignment was fully random; blocked-randomization was implemented part-way through the study on 12/01/2022.

3.3 Study Measures

	SCREEN A	SCREEN B	INITIAL CALL	SURVEY 1	BASELINE	SURVEY 2	INTERVENTION	SURVEY 3	FMRI
Measures				Day 0	Day 1 – 15	Day 15	Day 15 – 45	Day 45	
File submissions									
Vaccination card (photo)		X							
Location tracking (timeline export)		X				X			
Urine cotinine test (photo)				X					X
Receipts (photos)							20X		
Screening and Covariates									

Eligibility screening	X	X							
Smoking behavior survey				X		X		X	1 item
Nicotine dependence survey (FTND)				X		X		X	X
Smoking habits survey				X				X	
Smoking cessation intentions survey				X				X	
Smoking info exposure questionnaire				X		X		X	
Smoking beliefs survey				X				X	
Smoking attitudes survey				X				X	
Social smoking norms survey				X				X	
Smoking motivation survey				X					
Tobacco policy support questionnaire				X				X	
Social interactions & smoking survey						X (weekly survey)	4X (weekly survey)		
Demographics survey				X					
Stressful Life Experiences Inventory						X			
Microaggressions survey				X		X (weekly survey)	4X (weekly survey)	X	
Purpose in life survey				X	1 item daily		1 item daily		
Smoker self-concept survey				X				X	

Perceived stress scale				X				X	
CES-D Depression scale				X				X	
Code switching survey				X				X	
Mindfulness (MAAS)									X
Impulsiveness (BIS-11)									X
Alcohol consumption									X
Outcomes									
Cigarette consumption-self-report				X		X		X	
EMA text surveys - smoking and craving					X		X		
Cue reactivity task						X		X	X

3.4 Study Endpoints

3.4.1 Primary Study Endpoint

The primary endpoints will be cigarette smoking and craving at the end of the intervention period, measured through EMA multiple times daily. The primary endpoints for the fMRI scan session will be measured through fMRI scanning (brain activity).

3.4.2 Secondary Study Endpoints

4 Study Population and Duration of Participation

The target population is current smokers, ages 21-65, who have smoked at least 5 cigarettes a day for the past 6 months, are smartphone users, and live in PA/NJ/DE.

4.1 Duration of Study Participation

The target behaviors (smoking frequency, cravings for cigarettes) will be assessed for an approximately 2 week baseline period and for an approximately 4 week intervention period. Thus, total study participation is expected to be approximately 6 weeks of active participation, with possible breaks in between the baseline and intervention periods. Total duration of

participation will thus be approximately 2 months, with some exceptions (such as pauses in active participation because of the University's special winter vacation, or as requested by participants due to external constraints). A subset of participants will be invited to complete an optional fMRI scan after their final online session; flexibility will be allowed in the timing of the scan session, which can be as long as 6 months after the final online session. This subset of participants will participate for a longer duration (total duration of participation can be up to 8 months [2 months of active participation, with a scan session up to 6 months later].

4.2 Total Number of Subjects and Sites

Our initial recruitment plan specified that "Recruitment will end when approximately 400 participants have been enrolled. It is expected that 400 enrolled participants will produce 180 evaluable subjects after attrition and data issues. Penn is the only site." See 6.1 for final plan, adjusting for COVID and other constraints.

4.3 Inclusion Criteria

- Be between the ages of 21-65
- Smoke at least 5 cigarettes a day for the past 6 months
- Own an iPhone or Android smartphone that can be used on a daily basis
- Be residents of Pennsylvania, New Jersey, or Delaware
- Read and speak English fluently
- Fully vaccinated against COVID-19

4.4 Exclusion Criteria

- Current enrollment or plans to enroll in a smoking cessation program in the next 3 months
- Plan to use nicotine substitutes or smoking cessation treatments in the next 3 months
- Pregnancy
- Refusal to install Google Maps or LifeData applications on mobile phone
- Inability or refusal to upload Google Timeline data after receiving instructions and guidance during or after the initial intake call
- During the first two weeks of the study, failure to complete the study tasks (response to at least 75% of the brief EMA survey questions)
- Urine cotinine testing at Session 1 indicates a non-smoker level of cotinine
- The phones of potential participants will be assessed by trained recruiters during a phone call used to invite eligible participants who completed Screen A to participate in the study. Specifically, recruiters will assess whether phones' functionality allows easy reception and sending of text messages, the use of the geolocation tracking and LifeData applications and whether phones have an adequate battery life to allow participants to fulfill study requirements.
- Inability to provide informed consent or complete any of the study tasks as determined by the Principal Investigator and/or Study Physician.
- Any physical or visual impairment that may prevent the individual from using a computer keyboard or completing any study tasks.

Additional criteria for fMRI component:

- Demonstrate urine cotinine concentration below 200 ng/mL at scanning session
- Currently or recently (within the last 5 years) receiving medical treatment for substance abuse (e.g., alcohol, opioids, cocaine, marijuana, or stimulants). Treatment of substance use disorders that occurred greater than 5 years prior to study participation is acceptable if participants are in stable condition

- Report consuming any of the following drugs within the past two weeks or indicate plans to do so within the coming 6 weeks during the screening call: Benzodiazepines, Amphetamines, Methamphetamines, Cocaine, MDMA, Methadone, Barbiturates, PCP, Heroin, Oxycodone, Opiates (e.g., morphine, heroin), Buprenorphine
- Test positive for any of the above drugs at the scan appointment
- Schizophrenia or psychosis, regardless of treatment status.
- History of stroke or other neurological disorder likely to affect cognition
- Psychiatric hospitalization within the past year
- Propensity to experience claustrophobia
- Ferromagnetic metal in the body, including anything that might set off a metal detector. Examples include bullet shrapnel, metal shavings (e.g., from welding without protection), or any implant that may be attracted to or damaged by magnets. Dental fillings are generally acceptable.
- Metal in the body of an unverifiable origin.
- Non-removable piercings.
- Non-removable retainers or other dental work not compatible with fMRI.
- Any orthopedic implant above the neck.
- Due to constraints of the fMRI scanner, participants whose weight exceeds 350 pounds also will be excluded. The size of the scanner will be discussed with all participants during the consent addendum procedure.
- Any medical condition or concomitant medication that could compromise participant safety or treatment, as determined by the Principal Investigator and/or Study Physician.
- Unable to schedule a scan within 6 months after completing the third Online Session

4.5 Subject Recruitment

Direct recruitment may occur through newsletters, fliers, online ads/posts (e.g., Craigslist, Facebook, Instagram), newspaper listings, and/or ads on TV (or streaming media services). Recruitment materials may be posted by the study team or by BuildClinical. We will also collaborate with another smoking research group at the University of Pennsylvania which has IRB approval for passing on contact information of interested participants to other research teams. Only participants who have indicated that they are interested in being contacted for future studies will be approached. Upon contact, it will be made clear to participants that there is a possibility for them to participate in the study and they will be provided with IRB-approved recruitment materials such as flyers, text, and/ or oral information about the study, depending on the mode of contact. All recruitment material will include links (e.g., URLs, QR codes) directing potential participants to the screening survey (Screen A). The study email address and/or phone number may be included, depending on the recruitment medium. Interested individuals will complete Screen A on their own device at a time that is convenient to them.

Vulnerable Populations:

Not applicable

5 Study Procedures

5.1 Screening

5.1.1 Screen A

Those who express interest in the study by reacting to the recruitment efforts will be directed towards an online screening survey (Screen A) where they answer questions relevant to their eligibility for the study and provide their contact information. Screen A will also include a question that asks about the participants' interest in receiving information on opportunities to participate in other remote and/or in-person studies.

- Screen A will be administered online via RedCap or BuildClinical and is estimated to take less than 5 minutes to complete.
- [Note: If one's screening survey responses indicate that they are not eligible to participate in this study, they will receive an email informing them of this.]
- [Note: If one's screening survey responses indicate that they are interested in, and potentially eligible for, the in-person version of this study (protocol 822815), they may be provided a link to that study's screening survey and will be filtered through the process outlined in the 822815 protocol. If they are then found to be ineligible for the in-person study, they may be redirected to this remote study.]

Survey respondents who are potentially eligible to participate in the remote study will be emailed and/or texted a link to Calendly (appointment booking system) to allow participants to sign up for a time for an initial phone call to find out more about the study.

5.1.2 Initial Call

During the initial call, participants will be informed about the study, including the risks and benefits of participation, and will be given the opportunity to ask questions. Eligibility criteria will be confirmed on this call as needed.

- The initial call will be conducted over the phone (Google Voice) and is expected to take approximately 30 minutes. The researcher conducting the call will enter participant responses into RedCap.

At the end of the initial call, potential participants who are still eligible and interested will be invited via email to complete Screen B at a time of their choosing within 1 month of the initial call.

5.1.3 Screen B

Screen B begins with a RedCap e-consent form for the screening survey, which will guide potential participants to provide their shipping address and submit a picture of their COVID-19 vaccination card. The instructions will then guide them through downloading and/or setting up Google Maps on their phone, then exporting and uploading their Google timeline (location history) data.

- Screen B will be administered online using RedCap and Qualtrics (with Penn Box as a back-up method for submitting location data, if needed). The screen is expected to take 5 - 15 minutes of active participation, which excludes the passive time (when participants are not asked to do anything) while Google is compiling the participants Timeline data for export.
- Potential participants who have difficulty with the Google Maps set-up or timeline export will be able to sign up for an additional phone/video call at a later time to receive help from a researcher.

Researchers will then confirm A) that potential participants live in the study area (PA, NJ, or DE) using the uploaded timeline data and shipping address and B) that the potential participant is fully vaccinated against COVID-19, both of which are required to be eligible to participate in this study.

- [Note: Those who are unable/unwilling to complete any component of Screen B, live outside of the specified study area, or are not fully vaccinated will be ineligible for this study and will not be given the opportunity to enroll. The team will inform them of their ineligibility, delete their geolocation data, and provide them with instructions for turning off Google Timeline and uninstalling Google Maps.]
- [Note: If potential or enrolled participants are no longer interested in enrolling in the study at any point during or after the Google Maps set up, they will be provided with instructions for turning off Google Timeline and uninstalling the app.]

5.1.4 Mailing Materials

Eligible individuals will then be mailed a box containing study materials, including items such as the urine cotinine test, KN95/KF94 or N95 masks, and a Greenphire Clincard. Upon receipt of the study materials, participants will be given instructions to enroll in the study and begin their participation by completing Session 1.

5.2 Study Observational Phase

5.2.1 Online Session 1 (S1)

In Session 1, participants will read through the consent form and provide electronic consent via RedCap to participate in the full study and provide information required for payment (legal name, date of birth, and Social Security number). Participants will then follow the survey instructions to: complete physiological measurements (urine cotinine) and self-report measures; receive instructions for the Baseline period EMA task and answer questions assessing their comprehension of the task; and install, set up, and practice using RealLife Exp (the EMA app) on their smartphone.

- Session 1 will be administered over RedCap and Qualtrics, and is expected to take 30-60 minutes.
- If a participant's urine cotinine test result is not above the threshold required for eligibility, the participant will be excluded from continuing in the study.

5.2.2 Observational Phase

The baseline period will begin after completion of Session 1, and will last for 14 days. During the baseline period, participants will complete EMA and location tracking.

- Participants will be excluded for non-compliance at the end of the baseline period if they have not responded to at least 75% of EMA prompts.
- Following the baseline period, participants will be assigned to an experimental condition.

5.3 Study Interventional Phase

5.3.1 Online Session 2

Participants will be invited to complete Session 2 online after completing the baseline observational period. They are encouraged to complete the session within 4 days and no longer than 1 week (with possibility for exceptions at experimenters discretion) after receiving the invitation. Participants complete self-report measures; an image rating task; geolocation data

export and upload; EMA setup and practice; and instructions and practice for the Intervention tasks.

- Session 2 will be administered over Qualtrics, and is expected to take 30-60 minutes.

5.3.2 Intervention Phase

The Intervention Period will begin after completion of Session 2. During the 4 week intervention period, all participants will complete EMA, location tracking, and weekly surveys. The specific study-related tasks participants are asked to carry out during the intervention period depends on which experimental group they have been randomized to. The two experimental groups (tobacco retailer and nontobacco retailer) will be asked to enter a specific store 5 times per week for 4 weeks. The control group will not be asked to enter a store.

5.3.3 Online Session 3

Following the Intervention Period, participants will be invited to complete Session 3 online, which they are encouraged to complete within 4 days and no longer than 1 week (with possibility for exceptions at experimenters' discretion) of receiving the invitation. Participants will complete surveys; an image rating task; and geolocation data export and upload. At the end of the session, participants will be instructed on how to uninstall study-related smartphone applications and turn off smartphone location tracking, as desired. If not interested in and/or potentially eligible for the scan session, participants will also be provided with a debriefing form, which includes details about the study procedure and research goals, and may request a phone call or video call to go over the content of the form. They will be provided with a Quit Resources document, which contains information about services that provide smoking cessation assistance. For participants interested in being screened for the scan, debriefing and provision of the quit resources document will occur after the scan or as soon as scan session ineligibility is determined.

5.3.4 Optional fMRI session

- fMRI Screening: Participants who complete Session 3 and are potentially eligible to participate in the optional, in-person fMRI session (as determined by self-report questions in previous screening surveys and online sessions) may be informed of the opportunity and invited to complete an additional, optional fMRI screening survey. The fMRI screen will contain questions relevant to their eligibility for the in-person component of the study.
- fMRI session: This is a 2 hour session. After confirming that the participant meets any COVID-19 screening requirements (e.g., symptom screen, temperature check), during the in-person session, researchers will review the consent addendum document with participants. After providing written informed consent, participants will complete any required forms (e.g., W-2, additional metal screen) and provide a urine sample to confirm eligibility. Eligible participants will receive safety and task-related instructions/training before completing the fMRI scan. During the 1-hour scan component of the session, participants will complete an image rating task. Depending on time of arrival, participants may be asked to complete a brief survey before and/or after the scan.

5.4 Unscheduled Visits

At the end of Screen B and at the end of each online session, participants will be invited to provide feedback on their experience in the study to that point, via an open answer text box. We may follow up with participants by email or phone to clarify feedback as needed.

5.5 Subject Withdrawal and Exclusion

Subjects may withdraw from the study at any time without penalty. Participation in the study may also be stopped at the discretion of the Investigator for lack of adherence to study instructions, or if the Investigator determines exclusion is best for subject safety or health. Specific exclusion criteria are detailed below.

ONLINE SESSION 1: If a participant's cotinine test result is not above the threshold required for eligibility, the participant will be excluded from continuing in the study. Participants who are found to be ineligible during Session 1 (e.g. due to the results of their cotinine tests) will be paid $75 on their Clincard for the tasks they completed but will be excluded from continuing their participation in this study.

BASELINE PERIOD: If participants are excluded (e.g., for responding to less than 75% of EMA) or withdraw during the baseline or intervention periods, they will be issued payment on their Clincard at the rate of $4 per day that they responded to at least 75% of EMA surveys.

INTERVENTION PERIOD: Participants in the experimental group who discontinue participation during the intervention period will also be paid according to the standard schedule for EMA compliance ($4/day at 75% or higher) and receipt submission ($5 per verified daily receipt). Participants who do not complete required study tasks during the intervention (e.g., submitting fewer than 20 store receipts, EMA compliance below 75%) will not receive the study completion bonus.

Withdrawn and excluded participants who complete an optional offboarding call will be compensated for their time at a rate of $15/hour.

FMRI SESSION: Participants who must be excluded or asked to reschedule by the experimenter after arriving for the in-person session will be paid $15 for their time via their ClinCard or petty cash.

In the event of lateness, technical issues, unexpected ineligibility for specific components of the protocol, or any reason that a participant is unable to complete a specific portion of the protocol, the study team may have them complete all other portions for which they are eligible to complete at the experimenters discretion and pay them the standard compensation rate.

5.5.1 Data Collection and Follow-up for Withdrawn Subjects

All withdrawn and excluded participants are sent instructions to turn off location tracking & delete the RealLife Exp app. They are also informed that they can contact us to schedule an optional offboarding call if they would like assistance with this process. This optional offboarding call will be compensated for their time at a rate of $15/hour. These participants will also be sent a link to submit geolocation data for a final time for an additional $5 payment (estimated 20 minutes at a rate of $15/hour).

5.6 Early Termination Visits

All withdrawn and excluded participants are sent instructions to turn off location tracking & delete the RealLife Exp app. They are also informed that they can contact us to schedule an optional offboarding call if they would like assistance with this process. This optional offboarding call will be

compensated for their time at a rate of $15/hour. These participants will also be sent a link to submit geolocation data for a final time for an additional $5 payment (estimated 20 minutes at a rate of $15/hour).

5.7 Safety Evaluation

We evaluated safety according to our original plan:

1. After collection of 60 participants (approximately 20 in each group) and 120 participants (approximately 40 in each group), we will use EMA data to identify:

a. The distribution (histogram) of each participant's daily cigarette consumption (cig/day) during the baseline period (*b0*)

i. Including each ppt's mean baseline consumption ($\underline{cigs/day_{b0}}$)& standard deviation (SD_{b0})

b. The distribution (histogram) of each participant's daily cigarette consumption (cig/day) during weeks 3 and 4 of the intervention period (*i3-4)*

i. Including each ppt's mean consumption ($\underline{cigs/day_{i3-4}}$) & standard deviation (SD_{i3-4}) for intervention weeks 3 and 4

2. Participants will be identified as "increased smokers" if their average daily cigarette consumption during the final 2 weeks of the intervention period is more the 3 standard deviations above their baseline mean

a. Increased smokers: $\underline{cigs/day_{i3-4}}$ > ($\underline{cigs/day_{i3-4}}$ + 3SD)

3. If the number of "increased smokers" in the Tobacco retailer condition is significantly ($p \leq .01$) greater than the number of "increased smokers" in the control condition, this will trigger the study team to reconvene for a reassessment with members of the study team, the Primary Investigator, the Co-Investigators who have expertise in tobacco research, and the external stakeholders. This may result in the termination of this arm of the study and reassignment of future participants to the other two groups. Additionally, as part of this review, we will reach out to the participants in all conditions who met the criteria for an "increased smoker" to offer additional counseling on smoking cessation resources. The group will further make a plan to mitigate future risks to participants.

6 Statistical Plan

6.1 Sample Size and Power Determination

Our initial target was to obtain 60 complete datasets (meaning that participants finished Online Session 3, two fMRI sessions [before and after the intervention period], and also completed all 20 store visits) per intervention condition (total N = 180). Due to pandemic-related resource constraints and time delays, we were unable to reach this goal. We collected the maximum number of participants possible with the resources available from our grant. Prior to looking at the data, we elected to randomize more individuals into the experimental conditions than to the control condition, since less than 50% of participants typically completed all 20 store visits and provided fully complete datasets. Before we conducted any hypothesis testing, we reassessed power in consultation with our study team's biostatistician to determine which original hypotheses would be adequately powered with the available data and planned analysis

methods. Using PANGEA, we estimated that with at least 40 complete datasets (participants who completed all 20 store visits) in each intervention condition, we could detect interaction effects (time * group) sized d = 0.1 with 95% power. We ultimately randomized 105 to the Non-tobacco retailer condition, 107 participants to the Tobacco retailer condition, and 70 participants to the Control condition resulting in 175 complete datasets. We scanned as many participants as we were able to obtain within constraints of the larger study. Power analysis suggests that with N=32 and at least 10 observations per condition in the fMRI dataset, per participant, we have >80% power to detect effects of *d* = .2 (i.e., a small effect size) within person.

6.2 Statistical Methods

Behavioral data (ecological momentary assessment, smoking behavior) as well as neural activity aggregates from regions of interest will be analyzed using the statistical software R. Data will be analyzed using multi-level regression and repeated measures ANOVA, or alternative appropriate statistics, given observed distributions.

fMRI data will be analyzed using Statistical Parametric Mapping (SPM; Wellcome Trust Centre for Neuroimaging) and NiPype. We will examine neural responses to tobacco marketing and to other smoking-related images, and how these responses relate to tobacco marketing exposure in the real-world, as well as group differences in these responses.
Prior to analysis, we will apply standard data screening/cleaning procedures to: (a) screen for data-entry errors, (b) check for outliers, (c) assess the extent and pattern of missing data, (d) create all summary scores needed for analysis, and (e) check that appropriate assumptions of normality are met. The assumptions underlying the application of all the statistical methods that are used will be examined, principally through the use of standardized residuals, influence diagnostics, and graphical displays. Neuroimaging analysis will be done in nipype and SPM12, beginning with slice-time correction, realignment, coregistration of functional and structural images, and normalization to the standard Montreal Neurological Institute (MNI) brain. This processing will include image quality assessment (QA) procedures that examine global and ROI based raw and processed temporal signal-to-noise ratio, absolute and relative motion, and visual inspection. Response amplitude (percent signal change) within each ROI will be extracted using SPM or nipype tools; primary tests of our aims will be performed in R, α=.05, two tailed. Whole-brain exploratory analyses will be performed in SPM12, thresholded to correspond to p<.05, FDR-corrected.

6.3 Control of Bias and Confounding

Participants who complete the required tasks during the baseline period (Period 1) will be randomized. All participants must be able to complete tasks in any condition to participate, and so all participants have an equal chance to be in any of the conditions. Conditions are coded with a numeric value so they can be analyzed by researchers blinded to the participants' specific group assignment.

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

6.3.2 Analysis of Primary Outcome of Interest

Daily cigarette and craving analyses

Hypothesis 1: Reported craving will be higher for those in the Tobacco retailer condition, relative to the Control and Nontobacco retailer conditions, during the intervention phase, but not the baseline phase. To test hypothesis 1, we will use a linear mixed effects model (in R). To examine associations between study phase and craving, we will create a binary Study Phase variable indicating whether an observation for a participant occurred during the baseline (0) versus intervention (1) phase. To examine associations between condition assignment and craving, we will create two dummy coded variables indicating the condition assignment for each participant. A Control condition variable indicates whether the condition assignment is the Control condition (1) or the other two conditions (i.e., Tobacco and nontobacco retailer) (0). A Nontobacco retailer condition variable indicates whether the condition is the Nontobacco retailer condition (1) or the other two conditions (i.e., Control and Tobacco retailer conditions) (0). Thus, the Tobacco retailer condition is indicated when both the Control condition and Nontobacco retailer condition variables are equal to 0. We will test the interactions between study phase and condition assignment.

At level 1, the formal model is constructed as:

$$Craving_{it} = \beta_{0i} + \beta_{1i} StudyPhase_{it} + e_{it}$$

where β_0 is the intercept, indicating the average level of craving for the prototypical participant in the sample; β_{1i} indicates the difference in the level of craving between the baseline phase and intervention phase; and e_{it} are residuals that are allowed to autocorrelate.

Person-specific intercepts and associations (from the Level 1 model) are specified (at Level 2) as:

$$\beta_{0i} = \gamma_{00} + \gamma_{01} ControlCondition_i + \gamma_{02} NontobaccoRetailerCondition_i + u_{0i}$$
$$\beta_{1i} = \gamma_{10} + \gamma_{11} ControlCondition_i + \gamma_{21} NontobaccoRetailerCondition_i + u_{1i}$$

where the γs are sample-level parameters and the *u*s are residual between-person differences that may be correlated with each other but are uncorrelated with e_{it}. Parameters γ_{11} and γ_{21} test the key hypotheses that craving will be higher for those in the Tobacco retailer condition, relative to the Control condition, during the intervention phase but not the baseline phase (γ_{11}) and that craving will be higher for those in the Tobacco retailer condition, relative to the Nontobacco retailer condition, during the intervention phase but not the baseline phase (γ_{21}).

Hypothesis 2: Reported cigarettes smoked will be higher for those in the Tobacco retailer condition, relative to the Control and Nontobacco retailer conditions, during the intervention phase, but not the baseline phase. To test hypothesis 2, we will use a linear mixed effects model (in R). To examine associations between study phase and cigarettes smoked, we will create a binary Study Phase variable indicating whether an observation for a participant occurred during the baseline (0) versus intervention (1) phase. To examine associations between condition assignment and cigarettes smoked, we will create two dummy coded variables indicating the condition assignment for each participant. A Control condition variable indicates whether the

condition assignment is the Control condition (1) or the other two conditions (i.e., Nontobacco retailer and Tobacco retailer conditions) (0). A Nontobacco retailer condition variable indicates whether the condition is the Nontobacco retailer condition (1) or the other two conditions (i.e., Control and Tobacco retailer conditions) (0). Thus, the Tobacco retailer condition is indicated when both the Control condition and Nontobacco retailer condition variables are equal to 0. We will test the interactions between the study phase and condition assignment.

At level 1, the formal model is constructed as:

$$Smoking_{it} = \beta_{0i} + \beta_{1i} StudyPhase_{it} + e_{it}$$

where β_0 is the intercept, indicating the average number of cigarettes smoked per day for the prototypical participant in the sample; β_{1i} indicates the difference in the level of craving between the baseline phase and intervention phase; and e_{it} are residuals that are allowed to autocorrelate.

Person-specific intercepts and associations (from the Level 1 model) are specified (at Level 2) as:

$$\beta_{0i} = \gamma_{00} + \gamma_{01} ControlCondition_i + \gamma_{02} NontobaccoRetailerCondition_i + u_{0i}$$
$$\beta_{1i} = \gamma_{10} + \gamma_{11} ControlCondition_i + \gamma_{21} NontobaccoRetailerCondition_i + u_{1i}$$

where the γs are sample-level parameters, and the *u*s are residual between-person differences that may be correlated with each other but are uncorrelated with e_{it}. Parameters γ_{11} and γ_{21} test the key hypotheses that the number of cigarettes smoked will be higher for those in the Tobacco retailer condition, relative to the Control condition, during the intervention phase but not the baseline phase (γ_{11}) and that the number of cigarettes smoked will be higher for those in the Tobacco retailer condition, relative to the Nontobacco retailer condition, during the intervention phase but not the baseline phase (γ_{21}).

<u>for fMRI-related analyses:</u>

Hypothesis 1: To test hypothesis 1 - that neural activity in smoking cue reactivity regions will be greater in response to standardized images of cigarette cues (standard smoking cues) than in response to standardized, approximately compositionally matched sets of images of non-cigarette cues (standard nonsmoking cues) - we will average neural activation across voxels in the aggregate craving ROI to assess differences in neural cue reactivity between standardized smoking cue blocks and standardized non-smoking cue blocks. Specifically, we will extract contrast estimates of each condition compared to rest, from the aggregate craving ROI. We will then use a linear mixed effects model (in R), to account for some participants having two sets of fMRI scans. To examine associations between neural activity in the cue reactivity ROI and the two task conditions (standard smoking and nonsmoking cues), we will create a binary TaskCondition variable indicating whether an observation occurred during the standard smoking cue blocks (1) vs standard non-smoking cue blocks (0). If we do not find a significant difference between these conditions in the ROIs defined in the pilot dataset using this approach, we will examine whole-brain effects using MarsBaR and will define cue reactivity ROIs for hypotheses 5 and 6 based on prior meta-analyses (e.g., Engelmann et al., 2012; Lin et al., 2020).

Lme (ROI ~ TaskCondition, random = ~ 1 | Participant / Session))
Where TaskCondition represents standard smoking cues vs standard nonsmoking cues.

Hypothesis 2: To test hypothesis 2 - that neural activity in smoking cue reactivity regions will be greater in response to viewing photos of the cash register area at a convenience store with tobacco marketing and products (tobacco retail images), than to photos of the cash register area at a pharmacy store without tobacco marketing and products (nontobacco retail images) - - we will use a parallel model to the model specified for Hypothesis 1, where for Hypothesis 2, the TaskCondition variable represents tobacco retail images vs nontobacco retail images.

6.3.3 Interim Analysis

At two time points during data collection, we will assess whether the study is producing unexpectedly positive or negative effects on participant outcomes. After collection of 60 participants (approximately 20 in each group) and 120 participants (approximately 40 in each group), we will test whether individuals in the Tobacco retailer condition have significantly changed the number of cigarettes that they smoke per day (as described in 5.7). If this group of participants changes their cigarette consumption by a clinically significant level, we will stop assigning participants to that group and assign all further participants equally to the other groups.

7 Safety and Adverse Events

7.1 Definitions

7.1.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events.

Incidental findings in the fMRI component of this study are considered to be adverse events if the finding:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- required intervention to prevent permanent impairment or damage
- a congenital anomaly or birth defect
- an important medical event

7.2 Recording of Adverse Events

Smoking behavior will be self-reported at each study session and multiple times daily during the baseline and intervention periods. This data will be used at set points as described in section 5.7. Experimenters will record medical or other life events that may be considered adverse events as reported by participants (e.g., hospitalization or injury in between study sessions). Information on all adverse events will be recorded in the source document immediately upon discovery, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal incidental findings results will be recorded in the source document.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious and related adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs during an in-person session and is considered to be possibly related to the study intervention or study participation will be recorded and reported.

7.3 Relationship of AE to Study

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology.

The PI will make this determination.

7.4 Reporting of Adverse Events and Unanticipated Problems

The Investigator will promptly notify the Penn IRB of all on-site unanticipated, Serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the HS-ERA and in accordance with the Penn IRB timeline of 10 working days. All instances of related SAEs will be reported to the appropriate IRB and the NCI Program Officer within 24-hours of discovery, whereas probably or definitely related SAEs will be reported to the appropriate IRBs within 10 days of occurrence using the on-line system.

7.4.1 Follow-up Report

If an AE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAEs that are probably or definitely related to the study are followed until either resolved or stable.

7.4.2 Investigator reporting: notifying the study sponsor

The procedures for adverse event reporting are consistent with NIH and UPenn-specific guidelines and are as follows:

1) Report all instances of related SAEs to the NCI Program Officer (in addition to the IRB, as mentioned above) within 24-hours of occurrence or discovery.2) Inform all members of the study team actively involved in data collection about any and all reports of adverse events; and
2) Notify the NCI Program Officer of any suspension/termination of IRB approval and any actions taken by the IRBs with regard to data safety monitoring within 5 days of IRB notification or approval.

7.4.3 Data and Safety Monitoring Plan

During the course of the study, data and safety monitoring were performed on an ongoing basis by the Principal Investigator, project staff and IRB at the University of Pennsylvania. The IRB reviewed the study, including any adverse events (AEs) and serious adverse events (SAEs). The Principal Investigator, Dr. Emily Falk, Ph.D., was responsible for overseeing and completing the monitoring process in collaboration with the Research Director, Dr. Nicole Cooper, Ph.D. Any deviations and potentially serious and related adverse events were reviewed by Dr. Falk and Dr. Cooper. The research staff members were responsible for collecting and recording all data, as well as maintaining subject privacy and data privacy. Any inconsistencies/deviations were documented.

Our original target was that enrollment would be complete when 180 subjects were consented and completed the study with usable data (see section 6.1 for an updated explanation of practical constraints that arose during final data collection). Individuals were screened prior to admission into the study and those at risk for adverse reactions were excluded. Participants enrolled were monitored closely for AEs.

The following monitoring activities were conducted by Dr. Falk and study staff according to standard operating procedures.

Protocol Monitoring: Protocol monitoring includes a survey of those activities that are associated with protocol adherence such as study visit deviation, and violation of inclusion/exclusion criteria. All accrued cases will be subjected to protocol monitoring throughout the duration of the study.

Data Auditing: Dr. Falk will review safety and efficacy. All accrued cases will be subjected to auditing throughout the duration of the study. A Study Binder Review will include the following essential documents: IRB Protocol, Consent Form and Amendment Approvals, IRB Closure Letter, Human Subjects Certifications, Protocol and Amendment Signature Pages, Curriculum Vitae, Financial Disclosure Questionnaires, and Monitoring Log. Additional monitoring may include: source documentation verification; adverse event documentation; and facility assessment. During the course of the study, safety and data quality monitoring will be performed on an ongoing basis by the Research Coordinators, Research Director, and Principal Investigator. The Research Coordinators will be responsible for collecting and recording all data.

- *Assessing Adverse Events:* Monitoring for adverse events will be conducted in real time by the study team under the supervision of Dr. Falk and Dr. Cooper. Based on previous experience, we do not expect there to be SAEs or persistent adverse events. However, it is possible that injuries will occur as a result of fMRI scanning, for example if participants do not fully disclose the presence of metal implants in their body. It is possible that our experimental manipulation will have unexpectedly large effects on participant outcomes. As described above, we will institute a stopping rule to protect against unexpected risk to participants. The PI and study team will follow all subjects who are discontinued due to a serious and related adverse event and will refer subjects to a physician (i.e., specialist) as clinically indicated. All AEs and SAEs will be documented on an Adverse Event Report Form. This information will, in turn, be reported immediately to all necessary regulatory committees.

  - Adverse Event Reporting: Any serious and related adverse event case will be reviewed by Dr. Falk. After removal of identification information, all serious adverse events will be reported to the University of Pennsylvania Institutional Review Board, the CTSRMC, and the funding agency. All adverse events will be recorded.

Incidental Findings: The fMRI scans conducted in this study are not indicated to be clinically diagnostic. However, if any incidental findings are noted by the study team or scanning technician, the subject will be advised to consult a neurologist.

Data Security: Using network firewall technologies, the database is designed to prevent the three major sources of data security problems: unauthorized internal access to data, external access to data, and malicious intent to destroy data and systems. Controlled user access will help ensure that only appropriate and authorized personnel are able to view, access, and modify study data.

Staff Training: Staff training will consist of an explanation and review of the protocol, and a training period, during which all sessions conducted by the staff member in training will be observed by a senior staff member. The duties of each staff person will be outlined and all applicable regulations will be reviewed. A manual of Standard Operating Procedures will be used for staff training. Senior personnel will supervise junior staff and provide re-training in the study protocol as needed.

- *Evidence of Training in Human Subject Research:* All research personnel associated with this study have completed (or successfully transferred credit for) the University of Pennsylvania's Collaborative Institutional Training Initiative (CITI program), or their respective university equivalent, or the NIH patient oriented research training program, as well as HIPAA Compliance Training.

8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

Wherever feasible, identifiers will be removed from study-related information. Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords. Precautions are in place to ensure the data is secure by using passwords and encryption. Participants and screened respondents names and contact information will be stored in order to permit the researchers to: (1) contact the subjects during the study; (2) re-contact the subjects after the study to clarify any information provided; and (3) re-contact the subjects to invite them to participate in future studies if they choose to be recontacted. Participants will be informed that this research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify the participant in any action or suit unless the participant approves. Authorities also cannot provide any information, documents, or samples from this study as evidence unless the participant has agreed. This

protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena. Participants will also be informed that no data will become part of a participant's permanent record outside of the Communication Neuroscience Lab, such as employment records or academic records. There are no repercussions of participation/non participation for Penn-affiliated staff or students. Participants will be given the opportunity to opt out of having their location history from before the study period used for research purposes, other than for the purpose of establishing study eligibility (see opt-out section of the screening B consent form).

8.2 Data Collection and Management

The team uses a variety of tools to protect participant data. We review these by platform and study component, below:

- GENERAL: All information collected through this study will be treated as strictly confidential. Identifying information will be removed from the data as much as possible and will be accessible only to study staff. Data that is de-identified will be coded using this study's dual ID system: Survey A automatically assigns a RedCap record ID number to each screen respondent who expresses interest in participating. This number is different from the study ID number, which is only assigned to enrolled participants (those who have signed the full electronic informed consent on RedCap that begins Session 1).
- GREENPHIRE: In order to pay participants through the Greenphire ClinCard system, we will be required to enter their information (required: name, date of birth, address, and Social Security Number; optional: email address and/or cell phone number for notifications). For more information on this system, please see https://www.finance.upenn.edu/wp-content/uploads/Greenphire-Clincard-Human-Subject-Payments.pdf.
- REDCAP: RedCap is an online database system and survey platform: https://ascRedCap.asc.upenn.edu/. Access to the RedCap database will only be provided to authorized study staff included in this IRB application. Screen A will collect identifiable information (names, phone numbers, and e-mail addresses) through a RedCap (or BuildClinical) survey. Information collected via BuildClinical will be transferred securely to RedCap. Eligible participants will be automatically identified through a built-in reporting feature on the RedCap database (i.e., there will be no need to download identifiable data from RedCap on a regular basis). RedCap will serve as the location for linking categories of subject identifiers and subject names. Electronic consents for Screen B, the main study (at the beginning of Online Session 1), and the optional fMRI Session (after completion of Online Session 3) will also be recorded and stored using RedCap. For participants who complete the optional fMRI session, results of the urine drug screen and drug use questions will be recorded in RedCap.
- BUILDCLINICAL: BuildClinical is a data-driven software platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. BuildClinical has worked with IRBs in the USA to ensure they adhere to all the appropriate guidelines and procedures. They utilize study-specific advertisements to engage participants on digital platforms such as Facebook, Google, WebMD, etc., and redirect them to a study-specific landing page should they click it. On the landing page, the person can complete an online pre-screen questionnaire that gets routed into BuildClinical's platform. BuildClinical's Secure Socket Layer (SSL) software, which encrypts all inputted information, keeps information private and HIPAA compliant. BuildClinicals backend servers are stored in the USA at some of the most secure data centers in the world.
- PARTICIPANT CONTACT. Participants will be provided with the phone number of the study Google Voice account and the study GMail address, both of which exist within the lab's

GSuite of Falklab.org. These accounts will be used for participant recruitment calls, scheduling, and other contact as needed. Account passwords are shared only with members of the study team.

- QUALTRICS: Only authorized study staff will be granted access to Qualtrics surveys. Survey data that are collected through Qualtrics will be coded with a study identifier. Qualtrics will contain a link between email addresses and study identifiers for creation of survey distribution links. Qualtrics surveys will not contain identifiable data, other than indirect identifiers that could be gleaned upon extensive analysis of the files [photographs and geolocation data] that participants may submit.
- LIFEDATA: LifeData is a third-party tool for collecting ecological momentary assessments (EMA) through their proprietary RealLife Exp smartphone application, (https://www.lifedatacorp.com/mobile-app/). developed by LifeData to request and store (1) responses to EMA and (2) pictures of store purchase receipts. The app does not require any identifiable information; all data collected and stored by LifeData will be coded with the study ID and a unique, LifeData-generated user number.
- GOOGLE MAPS: Geolocation data will be collected through the Google Maps app and Google Timeline, which is Google's location tracking service. These apps might already be active on some participants' phones as they come pre-installed on Android phones. If approved by the user, Google Maps automatically tracks geolocation. Google will be able to access and use the mobility data collected through these apps per their data agreement with the user. The data can be downloaded by the user in the form of a .json or .kml file which includes all location data collected by Google. Participants will have the option to upload their location data via Qualtrics survey or PennBox. This downloaded file will be what the participants submit as part of Screen B and Sessions 2 and 3. If the participant opts out of providing their location history from before the study period, other than for the purpose of establishing study eligibility (see opt-out section of the main study consent form), all data which was collected by Google outside of the timespan between Session 1 and Session 3 will not be included in data analysis, other than for the purpose of establishing study eligibility.
- fMRI DATA: Neuroimaging data are collected at scanners located on Penn's campus. Imaging data is standardly stored and archived on (1) a secured, password protected computer located at the scanner site, which is only accessible with specific access rights, and (2) on Flywheel, a cloud-based research platform, only accessible with specific access rights. Data for this study will additionally be stored on the ASC server (details below).
- ASC SERVER: The study team will store the submitted location data files and neuroimaging data, tagged with the participant's study ID, on a secure server that is maintained by the Annenberg School for Communication (ASC) and is accessible only to the study team (including approved collaborators at New York University, as detailed in the Data Disclosure section). As this server is our most secure platform for data storage, it may also serve as a back-up location for data that is collected by and/or stored on any of the platforms mentioned in this section.
- PENNBOX: PennBox (aka Penn+Box; http://box.upenn.edu/) is a cloud-based collaboration service for securely managing and sharing files and folders within the Penn community and externally. Files containing coded data, such as EMA data and survey responses, will be stored on PennBox in folders that are only shared with the individuals mentioned in the Study Personnel and Data Disclosure sections of this protocol. Any files on PennBox that contain identifiable data will be stored in a separate folder and will be password-protected for an additional level of security.
- STUDY LOGISTICS: We will keep track of participants' study progress through a spreadsheet logging study appointments and the completion of the various measures. This spreadsheet will be coded by study identifiers and study staff is trained to not include any personally identifiable information (e.g., names, emails, phone numbers) in this spreadsheet.

The spreadsheet will be stored using Google Drive, Qualtrics, RedCap, and/or Box in a manner such that it is only accessible to authorized study staff. The study's Google account will also be associated with a study calendar which will include information about study appointments. All appointments will be coded by study ID and will not include personally identifiable information. Only Communication Neuroscience Lab members and collaborators will have access to this calendar. We may use a booking system such as https://simplybook.me or calendly to allow participants to sign up for a time for their intake call. Participants will have the option to include their contact information in the reservation, but we will explicitly recommend that they not do so, as sharing contact information to a third-party platform can incur minimal additional risks to confidentiality, and if they choose to include their contact information, they accept that risk. In addition, some of the systems and services we use (such as BuildClinical and e-Ship) may send non-optional notification emails to staff Penn or GSuite email accounts that include participant contact information (such as name and address). Those notification emails will be deleted from all staff accounts immediately, but will be saved for documentation purposes on the study email account, which already contains participant information (for contact purposes).

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The study PI will be responsible for the ongoing quality and integrity of the research study, in collaboration with the Research Director.

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

10 Ethical Considerations

10.1 Risks

- There may be a risk of unintentional breach of confidentiality, but we will take all necessary steps to prevent this from happening. Internet data transfers between mobile device users and the study web-server will be based on a session ID unique to the user and the date and time of access. All information collected via the Internet will be kept secure in transit using the Secure Socket Layer (SSL) protocol, the same technology used to encrypt credit card numbers during transmission over the Internet. All data will be stored in a database subject to both physical and electronic protection.
- Past literature suggests that there may be negative consequences of increased exposure to POST-marketing, such as increased difficulty in quitting and increased craving during a quit attempt. However, our manipulation does not involve a quit attempt, and does not go beyond a level of POST-marketing exposure that participants may be expected to have in their normal daily lives. At most, participants are asked to enter a POST-marketing store, such as a common convenience store, once per day. Thus, the study design poses risk to participants on par with everyday life.
- For the duration of the COVID-19 pandemic, entry into retail stores as part of this study

may increase participants' risk of being exposed to and spreading SARS-COV-2, the virus that causes COVID-19 disease. To reduce transmission risks, the study team will send participants KN95/KF94 or N95 respirators (masks) in their box of study materials, which they will be strongly encouraged to wear during study-related store visits (in accordance with local guidelines) and in their daily life. Participants are also required to be vaccinated against COVID-19.

- For optional fMRI session component: Safety concerns in MR environment: The magnetic field of the MRI environment has the potential to cause burns or bodily injury if ferrous metal objects are implanted in the body or if personal articles containing ferrous material are brought into the MR environment. Because we are excluding subjects with contraindications for MR studies (e.g., metallic implants such as pacemakers, surgical aneurysm clips, or known metal fragments embedded in the body) using a standard screening form, the risk of damage due to implanted metal is low. Investigators and personnel of the MRI unit have extensive experience with standard safety precautions, including safety screening on paper and verbally by a trained technologist. These considerations minimize the risk of accident or injury in the MR environment. Psychological discomfort secondary to MRI acquisition may occur in some subjects due to claustrophobia. Claustrophobia is also part of the exclusion criteria, and participants are informed that they may stop the study at any time without consequences to them. Risk of discomfort due to fMRI scanner noise will be minimized by providing earplugs for participants. The level of noise is not great enough to pose a health risk, with or without earphones. There is a risk that the magnetic resonance image will reveal a minor or significant lesion in the brain, e.g. a tumor, previously unknown to the subject. Structural MRI scans will not be read by a radiologist, and subjects will be informed of this. No diagnostic or clinical information will be provided, and participants will be informed of this before consenting to participate. We exclude subjects with contraindications for MR studies (e.g., metallic implants such as pacemakers, surgical aneurysm clips, or known metal fragments embedded in the body) using a standard screening form. Investigators and personnel of the MRI unit have extensive experience with standard safety precautions, including safety screening on paper and verbally by a trained technologist. These considerations minimize the risk of accident or injury in the MR environment. Claustrophobia is also part of the exclusion criteria, and participants are informed that they may stop the study at any time without consequences to them. The risk of discomfort due to fMRI scanner noise will be minimized by providing earplugs for participants. Thus, the risk of discomfort will be minimized. Participants will be provided with a hand-squeezable pneumatic signaling device for communicating with investigators during scanning should they experience intolerable discomfort of any kind.

10.2 Benefits

There are no direct benefits to subjects as a result of participation in this study other than monetary and gift card compensation. Participants may benefit from heightened awareness of the way point-of-sale marketing affects their smoking behavior and decision-making about the use of tobacco products.

10.3 Risk Benefit Assessment

Given the minimal risk of the study and the great potential benefit for understanding the relationship between the brain and behavior, the potential benefits to society outweigh the risks.

10.4 Informed Consent Process / HIPAA Authorization

- SCREEN B CONSENT: Screen B will begin with a consent that explains the purpose and nature of this screening. (See ScreeningSurveyBConsent.docx) To continue into the screening survey, participants will have to indicate that they have read and understood this consent. This includes an optional section that gives participants the opportunity to opt out of having their location history from before the study period used for data analysis, meaning the study team would only use the data uploaded in this survey for the purpose of establishing study eligibility (not for any further analysis or publication). This section explicitly states that declining to consent to analysis of their full history does not preclude participation in the rest of the study. The Screen B consent also explains that individuals who are found to live outside of the specified study area or are not fully vaccinated will be informed that they are ineligible for this study, and that the study team will delete their geolocation data and provide them with optional instructions for turning off Google Timeline and uninstalling Google Maps.
- FULL STUDY CONSENT: If eligible following screens A and B, participants will be invited to consent electronically to the full study. Participants will read, and be sent a PDF version of, the informed consent form to be signed electronically (or not). Please see the attached file for the content of the consent form for the full study. Experimenters will talk through this consent form with participants during the intake call and will answer any questions. Consent will be deemed provided if after reading the consent document, the prospective participant electronically signs it using RedCaps HIPAA compliant system for e-signature.
- OPTIONAL fMRI SESSION CONSENT: After confirming that the participant meets any COVID-19 screening requirements (e.g., symptom screen, temperature check), at the in-person session, researchers will review the consent document with participants. Participants will provide informed consent via RedCap.

11 Study Finances

11.1 Funding Source

This study is financed by an R01 grant from the National Cancer Institute at the US National Institute of Health.

11.2 Conflict of Interest

The investigators declare no conflicts of interest.

11.3 Subject Stipends or Payments

Each participant can earn compensation of up to $500.00 through a Greenphire ClinCard by participating in this study and by fulfilling all the study requirements. Some participants may be eligible for an optional in-person fMRI scan session, with additional compensation of $95, paid through ClinCard. Please consult the compensation schedule (table) below for detailed descriptions of subject compensation.

Conditions 1 & 2 = Tobacco and Nontobacco retailer conditions
Condition 3 = Control

KEY:	All conditions	Cond. 1 & 2	Cond. 3		
Period of task	**Task completed**	**Payment Rate**	**Max possible**	**Max Total STORE**	**Max Total CONTROL**

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University of Pennsylvania

Online Session 1	Cumulative payment for Screens A & B, initial call, and Online Session 1		$95	**$95 at Online Session 1**	**$95 at Online Session 1**
Baseline (2 weeks)	EMA response	$28/week * 2 weeks for 75% compliance	$55	**$90 at Online Session 2**	**$75 at Online Session 2**
Online Session 2	Session 2		$20		
Intervention (4 weeks)	Store purchase funds (week 1)	$3/visit * 5 visits/week	$15		
	Store purchase funds (week 2)	$3/visit * 5 visits/week	$15	**$15 after Intervention Week 1**	**n/a**
	Store purchase funds (week 3)	$3/visit * 5 visits/week	$15	**$15 after Intervention Week 2**	**n/a**
	Store purchase funds (week 4)	$3/visit * 5 visits/week (cond. 1 or 2)	$15	**$15 after Intervention Week 3**	**n/a**
	EMA response	$28/week * 4 weeks for 75% compliance	$110	**$270 at Online Session 3**	**$330 at Online Session 3**
	Store receipt photographs	$5/receipt * 20 receipts (cond. 1 or 2)	$100		
	Weekly survey	$2.50 each for completion of 4 weekly surveys	$10		
Online Session 3	Session 3		$20		
	Study completion	$30 for cond. 1 or 2 $190 for cond. 3	$30 $190		

Maximum payment for completing all remote tasks		***$500***	***$500***	***$500***
OPTIONAL In-Person Session	*2-hour session (includes 1-hour fMRI scan)*	*$95*	***$95*** *at the optional In-Person Session*	***$95*** *at the optional In-Person Session*
Maximum total payment for all remote AND in-person tasks		***$595***	***$595***	***$595***

12 Publication Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial has been registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

Final research data, with all identity-related information deleted and in consultation with the relevant IRBs, will be made available to the scientific community for collaborative research with members of the study team, upon request, in spreadsheet format for all non-imaging data and in NIFTI format for fMRI data. These data will be shared upon request in consultation with relevant IRBs for further analysis once the study's primary results have been published. Qualified investigators who wish to access the study materials will be able to complete a form on the main project website, which describes the proposed study and delineates the data specifics of data use. The requests will be reviewed and approved by the investigators and by the relevant IRBs. Data that may be difficult to de-identify (including geolocation data) will be shared at an aggregate level, with restrictions as developed in consultation with the IRB, to protect participant privacy. The requested research data files will be accompanied by a description of variables and how they were collected. We will also share protocols relevant to data collection procedures, as useful and in consultation with other interested researchers.

Imaging data files will be made available to researchers following the procedures outlined above through a secure file-sharing interface once the main findings have been published, in consultation with the relevant IRBs; alternative requests regarding format of imaging data will also be considered and honored to the extent possible within practical constraints.

Study tasks and code to reproduce analyses will be made available on the Falk Lab GitHub account (https://github.com/cnlab/).

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Study background

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