Utilizing Augmented Reality as an Adjunct for Smoking Cessation; Development and Initial Validation

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TITLE: Utilizing Augmented Reality as an Adjunct for Smoking Cessation; Development and Initial Validation

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RESEARCH STRATEGY

A. SIGNIFICANCE

A.1. Smoking, Smoking Cessation, and Emerging Technology

Cigarette smoking is the leading preventable cause of morbidity and mortality in the U.S. and accounts for 30% of all cancer deaths (ACS, 2014; USDHHS, 2014). Although tobacco use has declined over the past 50 years, smoking prevalence was 15.5% in the U.S. among adults in 2016 (Jamal et al., 2018). As such, developing more effective cessation interventions remains a public health priority.

There is a specific need for cessation interventions that reduce barriers to dissemination and implementation, and mHealth interventions hold particular promise in this regard (Abroms et al., 2012; Free et al., 2011; Rodgers et al., 2005; Vinci et al., in press). Moreover, harnessing recent advances in technology may increase the uptake of cessation treatment, while also targeting identified roadblocks to cessation. For example, in 2016, 77% of Americans owned a smartphone, more than double the percentage only 5 years earlier, with over 60% ownership even among low-income populations (PEW Research, 2018). Further, among all smartphone owners in 2014, 62% reported using their phone to access information about a health condition (Smith, 2015). Thus, novel interventions that leverage advances in technology may be an ideal way to increase the reach and efficacy of smoking cessation.

Augmented reality (AR) is a recent and rapidly-advancing mobile technology with potential utility for smoking cessation. Through the display of virtual smoking cues superimposed upon smokers' natural environment, AR appears ideal for improving the long-term effects of extinction-based intervention strategies (i.e., cue-exposure). Cue-exposure typically consists of presenting a drug cue (e.g., cigarette) to individuals multiple times, while not allowing them to engage in the typical drug behavior (in this case smoking), in order to extinguish the urge to smoke. As described in more detail below, cue-exposure treatments have demonstrated efficacy for decreasing craving in the laboratory, but these effects are often short-lived as they do not generalize well beyond the extinction setting (e.g., lab) into the real-world environment (Bouton, 2000*). AR allows the entire cue exposure session to take place in the real-world, which could greatly enhance the efficacy of cue exposure treatment. (An introduction to AR from CNNMoney can be seen here: https://www.youtube.com/watch?v=_EfMCTOQd6A.)* The current proposal aims to capitalize upon emerging AR technology to create and validate a novel treatment adjunct for smoking cessation.

A.2. Digital Environments

The last two decades have brought tremendous advances in the creation of artificial or altered environments via digital technology. *Virtual reality* creates a simulated, full digital environment. In contrast, *augmented reality* affects the perception of the real-world environment by "augmenting" it with computer-generated digital objects.

A.2.1. Virtual Reality (VR) combines 3D computer-generated graphics with motion trackers, vibration platforms, and audio in head-mounted displays to create immersive and interactive environments. The ability to create alternative, digital environments has made VR attractive for use in mental health treatments. A recent review of VR technology use within psychiatric disorders (Maples-Keller et al., 2017) found support for the efficacy of VR interventions—either alone or in conjunction with traditional therapy components—in treating anxiety disorders, schizophrenia, pain management, eating disorders, and addiction. VR interventions most often incorporate cue-exposure and social skills training, two components to which interactive, naturalistic virtual environments are well suited. Advantages of VR cue-exposure compared to in vivo cue-exposure include better stimulus control and lower risk. For example, treating a snake phobia using VR does not require the presence of an actual snake; and treating an addictive behavior does not require the actual presence of tempting and potentially illegal or harmful substances. Studies have found that VR exposure compared favorably to in vivo exposure (e.g., Powers & Emmelkamp, 2008). Patient acceptability of VR is high with low refusal (Garcia-Palacios, 2007) and treatment dropout rates (Lahiri et al., 2015).

Thus far, VR in smoking cessation has been primarily incorporated as one element (e.g., cue-exposure or coping skills) in a more comprehensive treatment approach. VR smoking cue-exposure has successfully elicited nicotine cravings (Bordnick et al., 2004; Choi et al., 2011; Pericot-Valverde et al., 2014; Thompson-Lake et al., 2015) and effectively reduced physiological arousal after cue-exposure trials (Choi et al., 2011). Cue-exposure via VR combined with nicotine replacement therapy (NRT) has been found to produce greater smoking cessation and reduction, better coping skills, and greater cessation self-confidence than NRT alone (Pericot-Valverde et al., 2015).

Although existing research using VR suggests its potential as a smoking cessation tool, VR also has several disadvantages that reduce its clinical utility: (1) The development of full virtual environments is time-consuming and costly; (2) Although constantly improving, the VR scenes are often low in realism, which may limit their effectiveness and generalizability; (3) Because of the limited number of VR scenes, they do not capture the range of smoking contexts of the typical smoker. This also limits their generalizability, as described below (A.3.).

A.2.2. Augmented Reality (AR) is a rapidly-emerging technology that could provide a novel and exciting treatment strategy for smoking cessation. AR inserts virtual, digitally-created objects into the real-world environment as viewed on a screen (i.e., smartphone or tablet; see Figure 1), with emerging options for head-mounted displays as well. AR is similar to VR in that the user is immersed in a particular environment. However, whereas VR presents an artificial, computer-generated environment, AR inserts digital objects into the user's actual environment in real-time. To be considered AR, a system must (1) combine real and virtual objects in a real environment; (2) run interactively, and in real-time; and (3) align real and virtual objects with each other (Azuma et al., 2001; Baus & Bouchard, 2014). In summary, whereas VR brings the user into a digitally-created world, AR brings a digitally-created object into the user's own world. As such, AR addresses the three weaknesses of VR described above: (1) Because only an object rather than an entire environment is digitally created, AR requires a small fraction of the time and cost to develop; (2) Because objects are much simpler than full environments, AR objects can be created with a high degree of realism, either through digital artistry, digital photography, or a combination; (3) Because VR objects are superimposed upon the user's natural environment, an infinite number and range of smoking contexts are possible, with personal relevance to each user.

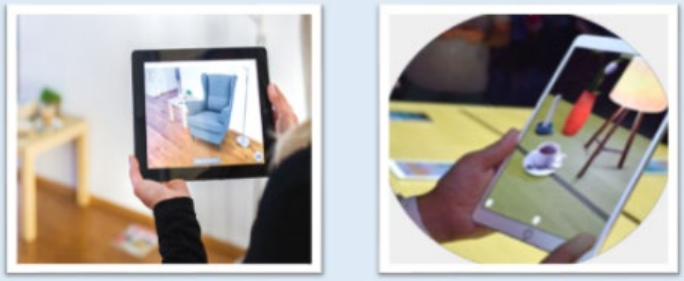

Figure 1: A live view of a physical, real-world environment whose elements are "augmented" by computer-generated real-world sensory graphical input.

Rudimentary forms of AR have been developed long before the term "augmented reality" was coined in 1990. However, with the exponential increase in computer power in mobile devices, AR hardware and software have been advancing particularly fast over the past decade (Baus & Bouchard, 2014). The first mass awareness of AR occurred with the Pokémon Go gaming app, released in 2016, which used smartphones' GPS, gyroscopes, compass, and camera to superimpose primitive (by today's standards) AR "creatures" in the users' natural environment. In the two years since, the technology has improved dramatically and has developed more mainstream uses in education, entertainment, architecture, and retail. As an example of the last, the furniture store, IKEA, has an app that allows the user to place and view digital depictions of their products placed within the user's own home, similar to Figure 1. Once a digital AR object has been placed within a user's natural environment, the digital object closely approximates the perceptual qualities of a real object in that location. For example, the user can approach or view the object from any direction, distance, or angle while maintaining a realistic perspective. The object also maintains its apparent position even when the user turns away from it and then returns to it. Motion can also be included within an AR object; for example, an AR cigarette can include smoke actively rising from it. Note that the latest model of Apple's iPhone (Model X) was designed to optimize AR applications. Indeed, the two camera lenses were switched from horizontal to vertical positions in part for better depth mapping and determination of planes upon which to place AR images. In parallel, the Apple operating system iOS 11 is optimized for AR, and Apple's ARKit is a mobile platform for

simplifying the development of AR apps. *iOS 12 will add further AR functionality, including the ability for multiple users to see and interact with the same AR object.* Similarly, Google's Tango AR platform is available for development of AR apps on Android devices.

Like VR, AR offers stimulus control and safety advantages over in vivo exposure for clinical use, but with the additional advantages listed above. Unlike VR, however, there has been relatively little clinical use of AR to date. The vast majority of AR application in healthcare has been in the arena of professional training, particularly surgical training. In contrast, a recent systematic review identified only 13 published studies of AR within the domain of clinical psychology (Giglioli et al., 2015). Although the potential of AR for cue-exposure therapies has been recognized (Baus & Bouchard, 2014), these have been mostly limited to small animal phobias—cockroaches, in particular (e.g., Botella et al., 2016). We believe that AR will be useful for improving the efficacy of cue-exposure therapies for addictive behaviors, including tobacco use. Unlike VR, it does not yet appear that AR has been utilized in this manner*, except in superficial ways (see B. Innovation).*

A.3. Cue-Reactivity and Cue-Exposure Therapy

Most theories of addiction include a prominent role for conditioned cue-reactivity—the idea, based on Pavlovian conditioning, that during substance self-administration, otherwise neutral stimuli become paired or associated with the unconditioned, pharmacological effects of the drug (e.g., tachycardia or euphoria). Over time, the previously neutral conditioned stimuli (CSs) develop the capacity to elicit physiological conditioned responses (CRs) in the absence of drug ingestion (Stewart et al., 1984; Siegel, 1983; Wikler, 1965). Data have consistently suggested that environmental CSs (e.g., drug paraphernalia) can cause cue-reactivity in alcoholics, opiate addicts, and smokers (Brandon et al., 1995a; Rohsenow et al., 1992), and these CRs are subjectively experienced as cravings to use the drug. CRs (craving in particular) contribute to drug use maintenance and relapse, and cue-reactivity is predictive of future smoking cessation (Brandon et al., 2007; Conklin et al., 2012; Ditre et al., 2012). The role of conditioned cue-reactivity in addictive behaviors has been incorporated into most of the major contemporary influential models of addiction, including models with primary perspectives that are psychosocial (e.g., Witkiewitz & Marlatt, 2004), cognitive (Tiffany, 1990), and neurological (Kalivas & Volkow, 2005; Robinson & Berridge, 1993).

The logical clinical implication of cue-reactivity theory and research is that cue-reactivity can be extinguished through the repeated presentation of drug-related cues (CSs) in the absence of the unconditioned stimulus (UCS; the ingested drug). To the extent that post-cessation relapse is initiated by conditioned craving, this treatment—called cue-exposure with response prevention, or cue-exposure therapy—should have clinical efficacy (Monti & Rohsenow, 1999).

Cue-exposure treatment studies do indeed demonstrate post-treatment declines in drug cravings or consumption (Childress et al., 1986; Drummond et al., 1994; McLellan et al., 1986; Monti et al., 1993; Sitharthan et al., 1997; Unrod et al., 2014). However, long-term clinical outcomes remain modest. A meta-analysis of cue-exposure treatments for addictions found that their overall effect size (d = 0.09) was small (Conklin & Tiffany, 2002). Learning and addiction theorists have argued that the limited efficacy of cue-exposure therapies can be attributed to the minimal attention paid to context effects (Bouton, 2000; Brandon, 2001; Brandon et al., 1995a; Childress et al., 1986; Conklin & Tiffany, 2002; Powell, 1995; Rodriguez et al., 1999). That is, cue-exposure therapy is typically provided via extinction trials that take place in either a laboratory or clinic setting. Based on considerable animal and human research, extinction that occurs in these contexts does not appear to generalize to contexts in the user's natural environment (i.e., the renewal effect; Bouton, 2002; Collins & Brandon, 2002). Therefore, considerable effort has been spent in testing alternative approaches for expanding the context of extinction to smoking cues.

A.4. Expanding the Extinction Context

The most straight-forward approach would be to provide cue-exposure therapy in multiple contexts within the smoker's natural environment. However, smoking takes place in a multitude of locations, and it is not feasible for a smoking cessation counselor to accompany the smoker throughout his/her naturalistic environments to have cue-exposure therapy sessions. Consequently, researchers have been creative in developing alternative ways to expand the context of cue-reactivity, which could then be used to expand the context and generalizability of extinction/cue-exposure therapies. Attempts to expand the cue-reactivity context have included (1) increasing the realism of the laboratory/clinic context via photos taken by smokers of their natural environment and large-scale projections of environmental scenes (Conklin et al., 2010); (2) having

smokers bring video images of smoking cues into their natural environment (Wray et al., 2011); and (3) providing smokers with "extinction cues" for them to bring into their natural environment (Unrod et al., 2014; Collins & Brandon, 2002). More recently, researchers have attempted to harness advances in VR to create pseudo-natural exposure environments in the laboratory/clinic setting (Pericot-Valverde et al., 2015). Although this approach has been effective at provoking cravings and has the advantage of providing multiple, three-dimensional and interactive environments for cue-exposure sessions, it has the limitations noted above: (1) the VR environments are costly to produce, so only a limited number are available for use; (2) the VR environments are often not graphically realistic; and (3) the VR environments do not represent each smoker's actual smoking environments.

A.5. The Potential of Augmented Reality

The rapid and ongoing development of AR systems presents the opportunity to harness the technical advances of VR, while overcoming the limitations listed above. AR requires the development of only the specific smoking cues (e.g., cigarettes, lighters, people smoking), rather than the entire smoking environment. These cues are then inserted into the smoker's actual, naturalistic environments as seen through their smartphone (e.g., different locations in the home, work, outdoors, and other settings). Thus, with respect to the limitations of VR: (1) the production costs are much lower and an infinite number of natural environments can be used; (2) the environments are realistic because they are (3) the actual, real-time environments at the smoker's current location.

When compared to current cue-exposure therapies, AR has the potential to extend the short-term gains produced in the laboratory. Importantly, cue-exposure via AR would take place entirely in the real-world environment, circumventing current limitations of existing cue-exposure treatments. That is, AR provides the unique opportunity to conduct extinction trials in the natural environment of the smoker, which should dramatically increase the sustained efficacy of cue-exposure therapy, based on the contemporary models of extinction described above.

We conceptualize AR-based cue-exposure as an extinction-based *adjuvant* to a more comprehensive smoking-cessation intervention. That is, we are not proposing AR-based cue-exposure per se as a *sufficient* intervention for treating tobacco dependence. However, because cue-reactivity appears to be a proximal determinant of smoking maintenance and post-cessation relapse, cue-extinction is a logical, theory-based treatment component aimed toward improving cessation and reducing risk of relapse. Moreover, because of its portability and presentation of stimuli in the users' natural environments, AR has the potential to break through the contextual barrier associated with previous extinction-based therapies for treating addiction—i.e., the renewal effect. Our goal is to systematically develop and validate a smartphone app that could be used as an adjuvant to a wide variety of smoking cessation interventions, including traditional cessation counseling, telephone quitlines, online cessation websites, text messaging (SMS) interventions, and/or pharmacotherapy. It could also be incorporated into other mobile smoking cessation apps. Note too that AR has other therapeutic potential in addition to cue-exposure. For example, AR stimuli could be used to train smokers to execute cognitive and behavioral coping responses when confronted by smoking cues, or, alternatively, AR stimuli could be incorporated into mindfulness-based (e.g., Brewer et al., 2011; Davis et al., 2014; Vidrine et al., 2016) or Acceptance and Commitment (Bricker et al., 2014) therapies to train appropriate responses to smoking urges. These alternative uses would also be dependent on the ability of AR stimuli to elicit cravings to smoke (i.e., cue-reactivity). Thus, although in this initial stage of development, we will focus on testing AR for cue-reactivity and extinction, this research will also be relevant to alternative therapeutic uses of the technology.

The proposed research represents a systematic and **scientifically rigorous** process in the development of an evidence-based adjunctive therapy. Indeed, it represents Stage I of behavioral intervention development (Rounsaville et al., 2001); that is, the "proof of concept" research necessary to demonstrate that AR has potential that warrants testing in subsequent efficacy studies. Thus, the proposed research will create the AR images within a basic software app (Aim 1), and then test the stimuli's ability to initially elicit and then extinguish cue-provoked craving responses in the laboratory (Aim 2). Finally, we will begin the translation to Stage II intervention development by upgrading the app and pilot testing its utility and acceptability when used in smokers' natural environment (Aim 3). At the end of this project, we expect that the AR app will be ready to test as an adjuvant therapy for smoking cessation in a fully-powered randomized, controlled trial, representing Stage II and III research. Importantly, the proposed research is not driven solely by the availability of new technology, but by a sound **scientific premise** derived from both the theory-based and empirically-supported

role of cue-reactivity in the maintenance and cessation of addictive behaviors, and consequently, the potential value of extinction-based cue-exposure approaches in the treatment of addiction.

B. INNOVATION

The proposed research is innovative in numerous ways, capitalizing on the recent and still-emerging advances in AR technology. Searches on NIH Reporter and PubMed revealed that AR has begun to be utilized for training purposes (e.g., for training physicians), but there is little literature and no ongoing grants utilizing AR psychotherapeutically. Although there is a small literature on AR for extinction-based treatment of phobias (primarily cockroaches), there are not yet any published studies of AR for treatment of addictive behaviors. *The only uses of AR for smoking cessation that we could find include a British AR tool for physicians that, when pointed at a patient, illustrates organ damage caused by smoking, and a phone app created by the British Health Foundation that, when pointed at a cigarette pack, illustrates what the smoker could do with the money saved by quitting smoking (e.g., movie tickets, vacation)*. Thus, our proposed research would appear to be among the first to use established scientific methods to capitalize upon AR technology to (A) develop therapeutic uses of any kind, (B) including extinction-based approaches, (C) particularly for treating addictive behaviors, (D) notably tobacco dependence. The emergence of AR provides a new opportunity to solve the therapeutic dilemma of the renewal effect that has long been thought to limit the real-world efficacy of cue-exposure therapy.

C. APPROACH

C.1. Preliminary Studies

The study team (Drs. Vinci, Brandon, Drobes, and Sutton) is ideally suited for the proposed line of research, with relevant experience and expertise in cue-reactivity and cue-exposure among tobacco users, development of novel treatments for tobacco dependence, and the use of novel technologies. Drs. Vinci and Brandon are multiple principal investigators (MPIs) of the current application and demonstrate complimentary expertise that strengthens the project. Drs. Drobes and Sutton have an established history of working with Dr. Brandon on multiple tobacco use and cessation studies at the Tobacco Research and Intervention Program (TRIP) at Moffitt Cancer Center. *Our primary catchment area for recruitment includes three counties (Hillsborough, Pinellas, and Pasco) with a population of approximately 3 million residents and a smoking prevalence slightly above the national average (Florida County Health Rankings, 2018). This population base has yielded efficient accrual of smokers for both our treatment and laboratory studies, including those involving multiple lab sessions (e.g., Brandon et al., 2011; Donny et al., 2015; Drobes & Tiffany, 1997).*

C.1.2. Cue-Reactivity and Cue-Exposure Research

MPI, Thomas Brandon, Ph.D., has studied cue-reactivity and cue-exposure processes in the laboratory and has translated this research into clinical application. Innovations include: demonstrating that the pairing of neutral cues with smoking produced classically conditioned cravings to smoke (Lazev et al., 1999); delineating moderators of cue-reactivity, including drug availability (Juliano & Brandon, 1998) and medication effects (Brandon et al., 2011); and expanding the domain of cues that provoked craving, including affect, cognition, pain, and body image (Ditre & Brandon, 2008; Lopez et al., 2008; Litvin & Brandon, 2010; Heckman et al., 2015; 2017). Of particular relevance to the proposed research, he has studied the role of context in the generalizability of extinction (i.e., the renewal effect) through the translation of basic animal learning research into human studies and applications (Brandon et al., in press; Collins & Brandon, 2002; Stasiewicz et al, 2007; Unrod et al., 2014). He has also contributed to the theoretical conceptualization of smoking maintenance, cessation, and relapse, incorporating the role of cue-reactivity (Baker et al., 2004; Brandon, 1994; Brandon et al., 1995b, 2007; Ditre et al., 2012).

Co-Investigator, David Drobes, Ph.D., in addition to his collaborations with Dr. Brandon, has independently dedicated much of his career to understanding the mechanisms and implications of cue-reactivity. He has used diverse laboratory methods for eliciting subjective and psychophysiological reactions to smoking and other drug/appetitive cues (Drobes et al., 2001; Drobes & Tiffany, 1997; Saladin et al., 2002); including studies of contextual learning in the development and expression of drug tolerance (Tiffany et al., 1990, 1992); the impact of affective cues on smoking urges (Tiffany & Drobes, 1990); the relationship between smoking and alcohol cue-reactivity (Drobes, 2002; Oliver & Drobes, 2015); effects of medications on smoking cue-reactivity and cessation outcomes (Ditre et al., 2012); neural response to drug cues (Bloom et al., 2013;

George et al., 2001; Myrick et al., 2004; Oliver et al., 2016); smoking/alcohol cue-reactivity among adolescents (Thomas et al., 2005; Upadhyaya et al., 2004, 2006); and use of attentional bias paradigms to capture implicit processes in smoking cue-reactivity (Drobes et al., 2006; Evans et al., 2011; Oliver & Drobes, 2012).

MPI, Christine Vinci, Ph.D., has studied the effects of affect-based cue-exposure in smokers (Vinci et al., 2012); predictors of response to affect-based cue-exposure in smokers (Vinci et al., 2015); the role of mindfulness in response to negative affect cues among problematic alcohol users (Vinci et al., 2014); and the role of image vividness during cue-exposure treatment for posttraumatic stress disorder (Mota et al., 2015).

C.1.3. Development of Treatments for Tobacco Dependence

The investigators have considerable experience developing novel interventions for smoking cessation, including cue-exposure based treatments (Brandon et al., in press; Stasiewicz et al, 2007; Unrod et al., 2014), behavioral counseling (Brandon et al., 1987; Zelman et al., 1992), self-help interventions (e.g., Brandon et al., 2000, 2012, 2016; Meltzer et al., 2017), and pharmacotherapy (Ditre et al., 2012). Importantly, Dr. Sutton has led the statistical analysis on many of these projects (e.g., Brandon et al., in press, 2012, 2016; Meltzer et al., 2017; Unrod et al., 2014).

C.1.4. Use of Emerging Technologies

Finally, the team has embraced new technologies to advance tobacco research and treatment. Dr. Vinci is currently using human sensing technology (AutoSense*;* Ertin et al., 2011; Hovsepian et al., 2015) to evaluate a just-in-time adaptive intervention for smokers, by objectively and unobtrusively collecting data on behavioral (i.e., smoking) and physiological (e.g., heart rate) measures in the real-world environment during a quit attempt (R00MD010468). This project is also using ecological momentary assessment (EMA) to collect self-report data on response to the intervention. Dr. Brandon and his team developed the first telemetric (cable-free) instrument for measuring smoking topography (Kashinsky et al., 1995); he tested an early mobile therapy device (Brandon et al., 1995a); and he has recently been using eye-tracking to study attentional processes among smokers (Correa & Brandon, 2016). Meanwhile, along with his history of studying psychophysiological responses to smoking-related cues, Dr. Drobes has recently been collaborating on innovative and influential research using reduced nicotine-content cigarettes (e.g., Donny et al, 2015; Tidey et al., 2017). He is currently conducting a trial using these cigarettes to facilitate extinction processes during smoking cessation (Florida Biomedical Research Program grant #6JK02). Although the proposed project will be the first use of AR technology by the research team, we are collaborating with an experienced AR-development firm, Haneke Design. Further, given our experience in using emerging technologies, we are prepared and equipped to handle issues that often arise when incorporating new technology into a program of research (e.g., communicating with inter-disciplinary teams; incorporating technological advances; iterative adaptations).

In summary, the research team, led by Drs. Vinci and Brandon as MPIs, with Drs. Drobes and Sutton as co-investigators, has both the theoretical and research background on the mechanisms underlying the therapeutic potential of AR, as well as the experience and energy to capitalize upon this emerging technology.

C.2. Aim 1: AR Development and Pilot Testing

C.2.1. Project Overview

We will collaborate with an AR software specialist to develop sets of 6 smoking and 6 neutral AR stimuli that are embedded within a basic digital application. These stimuli will be piloted on a small group of smokers (*N*=10) to receive their feedback and modify as needed.

C.2.2. Participants

Aim 1 will recruit 10 participants. To ensure that we are recruiting a similar population for each Aim, inclusion and exclusion criteria will be similar for all three aims (*with a minor exceptions for Aim 2 and Aim 3*). Inclusion criteria for Aim 1 will be ≥ 18 years of age; currently smoking ≥ 3 cigarettes per day for the past year; breath carbon monoxide (CO) level ≥ 5 ppm; motivated to quit smoking; valid home address in the Tampa Bay area; functioning telephone number; and can speak, read, and write in English. Exclusion criteria will be regular use (e.g., no more than 1/3 of month) of other tobacco products (cigars); and a household member already enrolled in the study. *The criterion of ≥ 3 cigarettes per day for the past year was selected to obtain a wide range of smokers who would have developed both sufficient cue-reactivity and motivation to quit (Shiffman et al., 2014).*

C.2.3. Recruitment

Research will be conducted at Moffitt Cancer Center's Tobacco Research and Intervention Program (TRIP), which has exceptional facilities created specifically for human tobacco research. Participants will be recruited through referrals from other studies, print and media ads (e.g., radio, social media) within the Tampa Bay area, and flyers distributed throughout the community, such as to primary care offices and physicians. ResearchMatch.org will also be utilized as a recruitment tool for this protocol. ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University as an IRB-approved data repository **(*see IRB #090207*)**. These methods mimic the successful recruitment strategies for this population in past laboratory studies at TRIP conducted by the investigative team (e.g., Correa & Brandon, 2016; Ditre & Brandon, 2008; Heckman et al., 2017).

C.2.4. Procedures

Based on our discussion with the AR developer, Haneke Design, we anticipate the development of the AR stimuli and app to be completed within 4-8 weeks. We will base the stimuli on the existing cue-reactivity literature and commonly-used cues in these types of studies. We have chosen to focus on proximal smoking cues for this study (e.g., cigarettes, lighters, ashtrays), whereas future research will also likely extend to distal AR cues (e.g., coffee, alcohol; Conklin & Perkins, 2002). Examples of neutral cues are a pencil, eraser, and keys (Carpenter et al., 2009; Conklin et al., 2010; Conklin & Perkins, 2002; LaRowe et al., 2007; Wray et al., 2011).

After creating the stimuli, we will recruit interested participants as described above, who will complete an initial phone screen to assess eligibility. Those eligible based on the phone screen will be invited to attend an in-person session. At this session, study personnel will provide a detailed description of the study, answer questions, obtain written informed consent, and finalize eligibility. Individuals who are ineligible will be thanked and compensated for their time, and offered smoking cessation resources.

Eligible participants will then be brought to a private room, where they will provide a breath CO sample in order to confirm smoking status, complete a brief survey of demographics, smoking history, and familiarity with augmented reality, and view and provide feedback on each of the AR stimuli. Likert scale questions will assess urge and reality/co-existence (how realistic the item looks, and its integration into the environment), along with general feedback on the stimuli (discussed in further detail below). We anticipate this session taking approximately 1 hour, and participants will be compensated $35 for their time. We will then work with the AR developer to make any needed adjustments to the stimuli or the app. We anticipate that these adjustments will be minor and not require further piloting. However, we will have the flexibility to conduct additional piloting, if deemed necessary. Once the app and stimuli are finalized, we will begin recruiting for Aim 2 (see C.3.).

C.2.5. Measures

C.2.5.a. Demographics, tobacco use, and AR familiarity. Participants will complete a survey of demographics (age, Ethnicity, Race, sex, gender identity, sexual orientation, marital status, education, and income), Tobacco use and motivation (frequency and quantity, other types of tobacco use, dependency, motivation to quit smoking and confidence in quitting), and two questions about familiarity with augmented reality.

C.2.5.b. Urge. Participants will rate their urge (craving) to smoke on a 10-point Likert scale from 1 (absolutely no urge to smoke) to 10 (strongest urge to smoke). Single-item scales, such as this one, reduce participant burden when multiple ratings are required by the protocol, and they have been found to be reliable and valid in assessing urge to smoke (Kozlowski et al., 1996). They have also been used in prior work by the investigators (e.g., Brandon et al., 2011; Drobes & Tiffany, 1997; Vinci et al., 2012).

C.2.5.c. Reality/Co-existence. Three items are recommended to assess the quality of the AR experience (Baus & Bouchard, 2014). *Reality* refers to the perceived realism of the AR object ("How real did the object seem to you?"). *Environment co-existence* refers to the integration of the object into the surrounding environment, as seen on the smartphone screen ("How well did the object appear to be part of the scene?). *User co-existence* refers to the perceived degree to which the user feels in the presence of the object ("How much did you feel the object was right there in front of you?"). Of the three, user co-existence, is likely to improve the most with the development of AR headsets, which will eliminate the need to view the environment through handheld screens. Nevertheless, we will assess all three using 10-point Likert scales.

C.2.5.d. Additional Feedback on Stimuli. Participants will be asked for their feedback on a variety of other features of the stimuli including color, size, texture, as well as any characteristics that elicited strong positive or negative reactions, and any other images that we did not include that might elicit cravings (e.g., "Did anything about the object immediately turn you off or bother you?").

C.2.6. Data Management and Statistical Considerations

See Statistical Design and Power attachment, as per new instructions for Clinical Trial applications.

C.3. Aim 2: Laboratory Validation of AR Stimuli

C.3.1. Project Overview[1]

The primary goal of Aim 2 is to validate the AR stimuli developed in Aim 1 with respect to eliciting cue-reactivity and extinction in the laboratory. Pre-Covid-19 participants (*N*=17) will attend two lab-based sessions (Session 1 and Session 2). Although the same participants will attend both sessions, each session is independent with its own study design. Post-Covid-19 participants will attend only Session 2. Session 1 will test cue-reactivity, and Session 2 will test extinction. Session 1 will utilize a cue-reactivity paradigm using a 2x2 within-subjects factorial design crossing stimuli type (AR vs in vivo) with stimuli content (smoking vs neutral) as shown in Figure 2. The primary outcome will be urge to smoke, with reality/co-existence scales as secondary measures in the AR cells. Session 2 (N = 128) will evaluate extinction of urge to smoke through repeated presentations of the AR smoking stimuli (vs AR neutral stimuli). A secondary outcome will be latency to smoke an available cigarette following the presentation of AR stimuli.

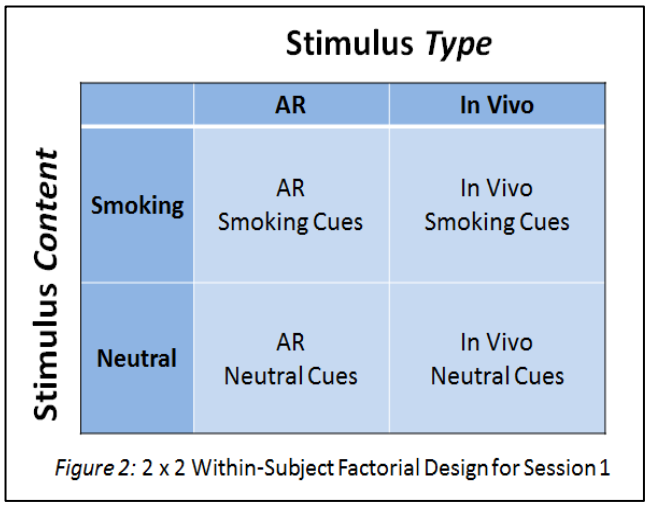

Figure 2: 2 x 2 Within-Subject Factorial Design for Session 1

C.3.2. Participants and Recruitment

Recruitment strategies and inclusion/exclusion criteria for the 17 pre-Covid-19 participants and the 128 post-Covid-19 participants will be identical to those outlined in Aim 1 (C.2.2., C.2.3.) with the additional exclusion criteria of self-reported pregnancy or lactation (due to expected smoking in a laboratory session) and currently not actively trying to quit smoking (e.g., enrolled in a cessation program). *We have allotted 15 months for recruitment, which would result in consenting an average of about 2 participants per week. As noted above (C.1.), our population base and smoking prevalence allow for efficient accrual of smokers to a range of studies. For example, for the multi-site Donny et al. (2015) study of reduced-nicotine cigarettes, our site recruited 84 smokers within 10 months (2 per week) to a more complex and extensive project with multiple visits. We also recently recruited 130 adult e-cigarette users (a much lower prevalence group) over 6 months (5 per week) for a behavioral lab study (Palmer & Brandon, 2018). Thus, we are confident that our proposed accrual goal is feasible.*

C.3.3. Phone Screening

Potentially eligible participants will be assessed via phone to determine whether they meet initial eligibility requirements. If eligible and interested, participants will be invited to Session 1 (pre Covid-19) or Session 2 (post Covid-19). They will be asked to abstain from smoking and all nicotine products (e.g., e-cigarettes) for 3 hours prior to attending this session, and told that confirmation of smoking status will be taken via a breath carbon monoxide (CO) measurement. There is no validated CO cut-off to confirm 3 hours of abstinence, so this is a "bogus pipeline" procedure, which has been found to improve accuracy of reported smoking behavior (Adams et al., 2008; Aguinis et al., 1993).

[1] Due to Covid-19 disruptions, after 3/13/20 additional safety precautions including minimizing participant contact were implemented. Aim 2 was powered for Session 2 (extinction), and cue reactivity was sufficiently demonstrated with the 17 participants who completed session 1 before the Covid-19 disruption in participant involvement. Thus, pre-Covid-19, participants attended both Sessions 1 and 2. Post-Covid-19, participants attend only Session 2 (extinction) and procedures were modified to accommodate a single session.

C.3.4. Procedure Overview for Session 1 and Session 2

At the beginning of Session 1 for pre-Covid-19 participants or Session 2 for post-covid participants, study staff will answer any questions the participants may have and the informed consent process will be completed. Participants will provide a breath CO sample and asked when they smoked their last cigarette, to confirm that they had abstained for 3 hours. Eligible participants will then complete a series of self-report questionnaires described below. We anticipate the informed consent and questionnaire phase will take approximately 45 minutes. Next, Session 1 pre-Covid-19 participants will complete the cue-reactivity procedures (about 45-60 minutes). Thus, Session 1 should take under 2 hours. Following this session, participants will be scheduled for Session 2 (extinction) within 120 days. Participants will be given similar pre-session abstinence instructions and asked to bring a pack of their own cigarettes. Again, this session will begin with self-report and CO assessment, and the full session is anticipated to last approximately 1.25 hours for pre-Covid-19 participants and 1.5-2.5 hours for post-Covid-19 participants.

If, at the beginning of either session, a participant self-reports smoking within the past 3 hours, s/he will be rescheduled. *Further, smoking status will be assessed at the beginning of Session 2; any participant who indicates that s/he has quit smoking for 24 hours or more will be ineligible for Session 2 (as participants will be asked to smoke during this session).* Otherwise, participants will then complete each respective session as described below. Participants will complete all procedures in a private laboratory room at TRIP. The procedures will be video-recorded from a central control room. The recordings will be reviewed to confirm study fidelity, and they will be used to score latency to smoke after Session 2.

C.3.5. Randomization

Session 1 will utilize a 2 x 2 within-subject design. Session 2 participants will be randomly assigned to either the extinction or control condition after stratifying by sex and cigarettes per day (cut point = 10). Block size will be 8 given the target sample size of 64 per condition (see below) and the 4 stratification cells.

C.3.6. Lab-based sessions: Descriptions of AR and In Vivo Cues

C.3.6.a. AR Cues. All AR cues will be presented via a smartphone provided to participants during the lab session. Six AR smoking cues and six AR neutral cues will be presented to participants. Although these cues can be presented individually (e.g., a single cigarette), we will have the ability to combine cues (e.g., cigarette in an ashtray). Further, movement of components of the cues (e.g., smoke coming up out of a cigarette, ash falling) will also be utilized whenever possible. Finally, participants will be encouraged to move around the stimuli to interact with the cue, as AR allows for the individual to see a stimulus from various angles. Urge to smoke and reality/co-existence questions will appear on the smartphone screen with response options. The AR app will allow for experimenters to select the order of the cues, as described below.

C.3.6.b. In vivo Cues. Presentation of in vivo cues will generally follow procedures used in the existing cue-reactivity literature (e.g., Wray et al. 2011; LaRowe et al., 2007). To match the AR cues for complexity and overall content, we will use 6 smoking and 6 neutral cues with matching content (e.g., if we use a pink eraser as a neutral cue for AR, a similar eraser will be used as an in vivo cue). Cues will be placed under numbered, opaque covers, and participants will be instructed when to uncover and re-cover each one during the trials. To control for assessment modality across Stimulus Type (AR vs in vivo), participants will answer urge questions via a smartphone app, similar to the AR app. Participants will also be encouraged to interact with the in vivo cues in a similar manner to the AR cues (e.g., walk around the cues to view from different distances and angles).

C.3.7. Session 1: Cue-reactivity

Session 1 will utilize a within-subjects design, so all participants will receive all cue presentations (see Figure 2 above). Because it would be difficult for participants to switch repeatedly between AR and in vivo cues, Stimulus Type (AR vs in vivo) will be presented in counterbalanced blocks. Within each block, we will randomize the presentation of smoking vs neutral cues. Figure 3 is a visual depiction of the stimulus-presentation strategy. Each cue will be presented for 15 seconds. Participants will complete the urge question at baseline and will then complete the urge question and reality/co-existence questions (for AR only) immediately following each cue presentation. To reduce carryover effects, each stimulus presentation will be

separated by 1 minute, during which participants will engage in a neutral activity (e.g., solving easy word search puzzles). The general procedures are similar to those commonly found within the literature (e.g., Carpenter et al., 2009; LaRowe et al., 2007; Wray et al., 2011). In sum, participants will complete baseline urge questions, view a cue for 15 seconds, complete urge and/or reality/co-existence questions, complete the word search for 1 minute, view another cue, and so on, until all 24 cues have been presented. The cue-reactivity procedures should last under 1 hour.

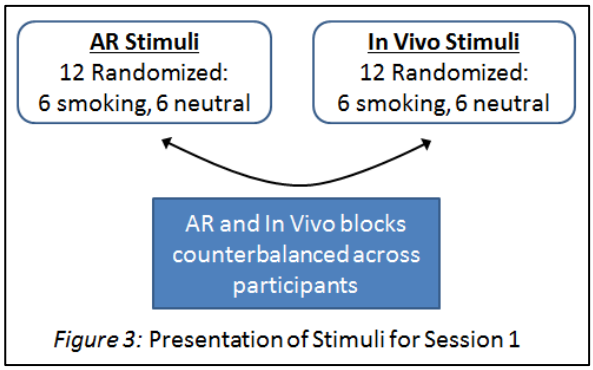

Figure 3: Presentation of Stimuli for Session 1

C.3.8. Session 2: Extinction

The extinction session will use only the AR cues (smoking and neutral). As noted above, participants will be randomized to either the extinction or control group. Twenty-eight trials of cues will be presented for each group. Both groups will receive the same neutral cue in Trial 1 (to establish baseline urge) and the same smoking cue in Trial 2 (for pre-test cue-reactivity). Then, the extinction group will receive smoking cues for trials 3-26, whereas the control group will receive neutral cues. Both groups will receive matched smoking cues for the second to last trial (27) followed by matched neutral cues for the final trial (28), for post-test cue-reactivity. Each cue will be presented for 1 minute and will be shown 4 times in trials 3-26. Figure 4 shows a visual representation of cue presentation for each group. With respect to the order of the cues, we will create 4 quasi-random orders for each condition (each comprising 4 blocks of 6 images, with no image repeated twice over a series of three images), which will be varied across participants. *We derived these procedures from the existing cue-exposure literature (e.g., Carpenter et al., 2009; Collins et al., 2011; Conklin & Tiffany, 2002; Kamboj et al., 2012; LaRowe et al., 2007; Vinci et al., 2012), and although no specific guidelines exist, these studies typically exposed participants to cues for up to 60 minutes total (54 minutes in the current study); utilize one to nine cues (6 smoking and 6 neutral in the current study); and utilize various amounts of time for exposure to each individual cue, often ranging from 10 seconds to 5 minutes (1 minute in the current study). For this study, we wanted each cue to be presented multiple times to allow sufficient time and exposure for extinction to occur, which ultimately resulted in 28 trials.*

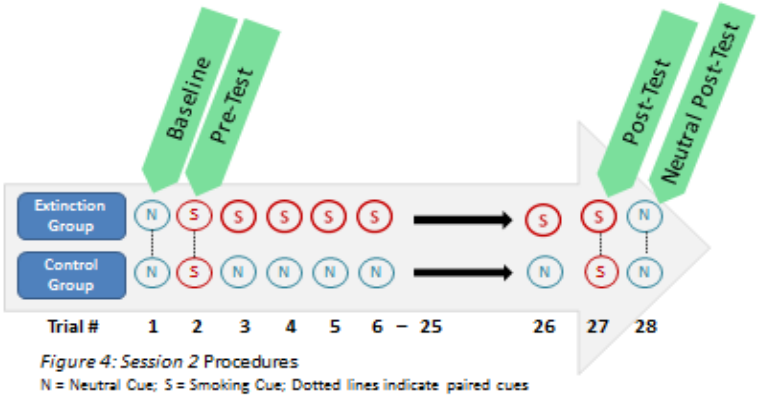

Figure 4: Session 2 Procedures
N = Neutral Cue; S = Smoking Cue; Dotted lines indicate paired cues

Following each cue, participants will complete the single-item measure of urge (primary outcome). Following the final trial (28) for both groups, participants will be presented with one of their own cigarettes and asked to take at least one puff. Latency to smoke will later be determined (using time stamps on the video-recording) and used as a secondary outcome as a behavioral measure of smoking motivation (e.g., Ditre et al., 2010; Kovacs et al., 2014; Shiffman et al., 2013; Stevenson et al., 2017). TRIP is equipped with 8 "negative pressure" rooms, compliant with state law regarding indoor smoking for research purposes that allow for the efficient removal of smoke between participants. Session 2 is expected to last 1.25 hours for pre-Covid-19 participants, and 1.5 to 2.5 hours for post-Covid-19 participants.

C.3.9. Compensation and Retention

Pre-Covid-19 participants will be compensated for Session 1 ($40) and Session 2 ($50). Post-Covid-19 participants will be compensated $60 for Session 2. To aid in retention, the following procedures will take place: reminder phone calls prior to all study visits, flexible scheduling for sessions, reminder cards, requiring a functioning phone number and home address to contact participants by phone or mail as needed, and obtaining the name, address, and phone number of at least 2 collaterals (i.e., relatives, friends) who can provide contact information for the participants, should we be unable to reach them during the study.

C.3.10. Additional Measures

Aside from those already described, the following measures will be administered at Session 1 for pre-Covid-19 participants and at Session 2 for post-Covid-19 participants . *Demographics and Smoking History* will collect data on variables including gender, age, race, marital status, income, education, and smoking history (e.g., number of quit attempts, years smoked). *Fagerström Test for Nicotine Dependence* (FTND; Heatherton et al., 1991) is a widely used measure of nicotine dependence. *Wisconsin Smoking of Withdrawal Scale* (WSWS; Welsch et al., 1999) is a well-validated measure used to assess various facets of nicotine withdrawal. *Positive and Negative Affect Schedule* (PANAS; Watson et al., 1988) is a self-report measure that assesses an individual's positive and negative affect at a given point in time. We will also administer the *Brief Wisconsin Inventory of Smoking Dependence Motives* (WISDM-38), a multidimensional assessment of motivational factors associated with smoking behavior (Smith et al., 2010). We are particularly interested in the Cue Exposure/Associative Processes scale, which assesses the degree to which a participant's smoking is driven by cue-reactivity. Therefore, we will include the full subscale from the original WISDM-68 (Piper et al., 2014), due to its superior psychometrics (Smith et al., 2010). Aside from their descriptive value, these additional measures will allow for testing moderators of cue-reactivity and extinction.

Summary of Changes Pre and Post-Covid-19		
	Pre-Covid-19	Post-Covid-19
N	17	128
Session(s)	Session 1 and Session 2	Session 2 only
Consent and Survey administration (demographics, smoking history, etc.)	Session 1	Session 2
Length of Session(s)	1.25 hours	1.5-2.5 hours
Compensation	$40 Session 1; $50 Session 2	$60

C.3.11. Data Management and Statistical Considerations

See Statistical Design and Power attachment, as per new instructions for Clinical Trial applications.

C.4. Aim 3: Initial Translation into Intervention-Ready App

C.4.1. Project Overview

Aim 3 will consist of the beginning phases of Stage II intervention development by (1) refining the app for intervention (rather than laboratory) use, (2) pilot testing the app for utility and acceptability in the smokers' natural environment, *and (3) examining proxies of behavior change for quitting smoking and smoking status.* Although we will use the same general components of the app developed for Aim 2, we anticipate that improvements to the app will be necessary to enhance its sophistication and usability by smokers *attempting to quit* in the field. When Aim 3 is complete, we expect the app and study team to be ready to conduct a fully-powered, randomized controlled trial using AR as an adjuvant therapy for smoking cessation. Finally, given the rapid pace of technology, it is very possible that by the time of Aim 2 completion, AR headsets/eyewear will be available at a reasonable cost. (Note that AR contact lenses are also under development.) If so, we will also pilot test these AR systems for utility and acceptability as part of Aim 3.

C.4.2. App Refinement

We will work with our AR software developers to refine the app based on (1) experimenter observation and participant feedback from Aim 2; (2) advances in AR capabilities since Aim 1; and (3) additional requirements for field use. In terms of the last, the app will be adjusted to deliver the cues over a longer period of time, as described below, and modified to allow bidirectional data transfer between the device in the field and the lab. This will allow the research team to alter or correct stimulus presentation, if necessary, and to download data on app use and response variables at regular intervals. We will also be able to add additional AR smoking cues, including distal cues (e.g., alcohol, coffee), which have been shown to be potent precipitators of smoking urge and relapse (e.g., Brandon et al., 1990; Conklin et al., 2008). Other user-friendly modifications will also be made (e.g., colors, fonts). Finally, versions of the app will be created for both IOS and Android operating systems, which will capture the vast majority of smokers.

C.4.3. Participants and Recruitment

We will recruit a small group of participants (*N*=50) using similar strategies and inclusion/exclusion criteria as Aim 1. *However, additional inclusion criteria will be having a smartphone that they are willing to use during the study, and being motivated to quit smoking within the next month (i.e., "preparation" stage of the Transtheoretical Model; Prochaska et al., 1992).* Because participation will be entirely remote, participants will not need to have a local address. If deemed eligible, they will be asked to provide verbal informed consent via telephone or video conferencing.

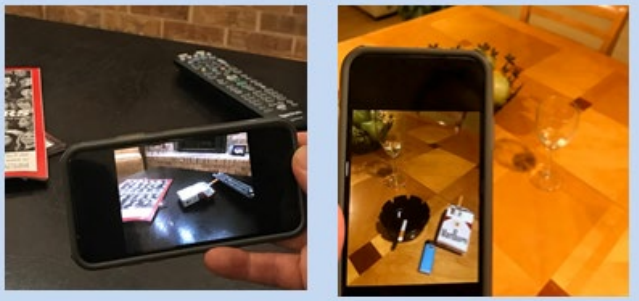

Figure 5: Simulated examples of AR stimuli in a smoker's home setting, including a single stimulus (left) and a three-object compound stimulus (right).

C.4.4 Procedures

After consenting, enrolled participants will be sent a link to complete an online baseline survey. Once the completed baseline survey has been returned, the participants will be sent a code or instructions to download the free app. They will also be sent a user/training manual for the AR app use. *Given that all participants will be motivated to quit smoking, basic cessation assistance will be provided, including Tobacco Free Florida's Quit Tips smoking cessation manual and the FL state tobacco quitline phone number and website.* A few days after the app and quitting materials are sent, research staff will call participants to explain the materials and answer questions. Participants will be instructed to use the AR app over the next 7 days in locations and situations where they smoke (e.g., home, bar; see Figure 5), with the goal of at least 5 uses per day. Usage and rating data will be collected in real-time. After the 7-day app use period, participants will be sent a link to an online follow-up survey that includes feedback on the app, smoking within the prior 7 days and smoking cessation motivation. Within approximately 7-14 days of completing the 7 day app use, participants will complete a brief telephone interview with study staff on their perceptions of the app as a potential cessation adjuvant and cigarette use over the course of the study. Participants will be compensated with electronic gift cards with value totaling up to $80. Participants will receive $10 for each of the completed baseline and follow-up surveys and the follow up phone interview. Participants can also receive a bonus of $5 for each online survey completed within 24 hours of being sent the link and a bonus of $5 if the follow up phone interview is completed within 10 days of completing the app use period. Participants will also receive $5 for each day that they use the AR app at least one time (for up to $35). Participants must use the app on at least four occasions to be eligible for the follow-up survey and interview.

C.4.5. Measures

To assess usability and acceptability, we will use both an established questionnaire, as well as questions developed for this study. Questions developed for this Aim are derived from Dr. Vinci's experience with implementing mHealth procedures among smokers, as well as the existing literature on usability testing (e.g., Harrison et al., 2013; Nayebi et al., 2012). We will also track how often participants use the app over the course of the week. The *System Usability Scale* measures participants' perception of usability and learnability (Brooke et al., 1996; Lewis & Sauro, 2009). To assess other components of usability and acceptability, we will develop a questionnaire with Likert scale items to capture the following areas: *reality/co-existence* (same items as in Aims 1 and 2), *usefulness* (Would this app appeal to you if you were currently attempting to quit smoking?), *ease of use* (How easy/difficult did you find using the app?;), *ease of learning* (How many days did it take to get comfortable using the app?); and *satisfaction* (Would you recommend this app to a friend or family member to help them quit smoking?; Overall, how satisfied were you with the app?).

Participants will also be asked questions by a trained interviewer on their perceptions of the phone app as a potential adjuvant for smoking cessation. Specifically, participants will be queried with open-ended questions such as, "What type of changes would you make to the app to increase the likelihood of using it, or, to make it more enjoyable to use?; What features would you add to the app?; What was the easiest part of using the app?; What was the most difficult part of using the app?; What was the most interesting part of using

the app?". These interviews will be recorded, transcribed and coded for analysis (described in more detail in the Statistical Design attachment).

Proxies of behavior change will be collected pre- and post-app testing, including motivation to quit and self-efficacy for quitting. For motivation, we will use the Contemplation Ladder*, which provides a visual image of a 10-rung ladder for participants to indicate their current motivation to change their smoking behavior (Biener & Abrams, 1991). We will also use the short form of the* Abstinence-Related Motivational Engagement *scale (ARME; Simmons et al., 2010), which provides a more sensitive index of current motivation. For self-efficacy, we will use the short form of the* Self-efficacy Scale–Smoking*, which is a 9-item measure that determines an individual's level of confidence for not smoking in positive/social situations, negative affect situations, and out of habit (Velicer et al., 1990).*

Data on smoking urges and smoking status will also be collected. Throughout testing, participants will rate their urge to smoke each time they use the app, which will allow us to observe any changes over time in this variable. Smoking status will be collected daily on the app and at follow-up, and abstinence will be defined as a self-report of no smoking in the past seven days (Perkins et al., 2013). Given the limited-time frame of this grant, we will only have short-term abstinence outcomes (7 days post-quit).

C.4.6. Statistical Considerations

See Statistical Design and Power attachment, as per new instructions for Clinical Trial applications.

C.5. Design Considerations

Choice of Comparison Stimuli Type for Aim 2, Session 1. Laboratory studies have historically used a variety of modalities for presenting cues to participants including in vivo, imaginal, video, photos, and audio (Conklin & Perkins, 2002). For this proof-of-concept study, we chose to compare the AR cues to *in vivo* cues for two reasons. First, in vivo cues are one of the most commonly used cues in the cue-reactivity literature (Conklin & Perkins, 2002). Second, using in vivo smoking cues sets the bar high for the AR comparison group, as they are the cues that smokers would typically see in their natural environment. Indeed, all other cue modalities are attempts at approximating in vivo cues. Thus, we believe comparing AR to real-world stimuli is ideal. Evidence that AR cues produce similar reactivity as do in vivo cues will provide strong support for this program of research.

Temporality of Session 1 (cue-reactivity test) and Session 2 (extinction test). We considered two options for these two critical proof-of-concept tests of AR stimuli. We could have conducted these as two separate, sequential studies, using different participants, with the second study dependent on findings from the first. The primary advantage would be the possibility of making major revisions to the AR app based on findings from the first study prior to conducting the second. However, sequential studies would have required a much longer time frame and the recruitment of many more participants, which presents challenges with respect to this grant mechanism. Therefore, we opted to conduct the two tests simultaneously for each participant (as two sessions), using the same research participants. This decision was bolstered by our high degree of confidence based on the existing cue-reactivity literature that AR stimuli will produce significant cue-reactivity. Despite this confidence, we believe it is necessary in a systematic line of research to subject this confidence to an empirical, documented test. Moreover, using the same participant sample allows us to use data collected in Session 1 (e.g., cue-reactivity, reality/in-presence) as moderator variables in Session 2.

Three-Hour Period of Abstinence. For both studies in Aim 2, we will ask participants to refrain from smoking for 3 hours prior to the session and will rely on self-report of no smoking to gauge compliance, along with "bogus-pipeline" collection of breath CO. These decisions were made for multiple reasons. First, because participants will have a range of smoking dependence, there are no valid CO cut-points to verify abstinence within the past 3 hours. We considered adding an initial session to collect baseline CO, but this would entail participants attending 3 sessions, which would increase attrition. Second, we could have asked for overnight abstinence and confirmed abstinence with CO the following day. However, again, due to the variability in smoking dependence, CO would not be accurately captured among light smokers. Compliance with overnight abstinence would likely be lower, and we would have less flexibility for scheduling the experimental sessions. Further, the bogus pipeline of CO should further increase compliance. Third, cue-reactivity is often elevated during acute deprivation, and 3 hours of abstinence should demonstrate substantial increases in craving/withdrawal (Hendricks et al., 2006).

Modality for AR presentation. The current study will evaluate cue-reactivity and extinction via a smartphone. We also considered using headgear/eyewear (i.e., AR glasses) as another modality. On the one hand, eyewear should allow the participant to be more immersed in his/her environment with greater co-existence. However, at this time AR eyewear is extremely expensive and less scalable than if we present AR via smartphone. As such, we decided to begin this line of research using a smartphone, with the intention of testing eyewear in the future, as the technology advances and the price drops.

Go vs No-Go Thresholds and Alternative Strategies. Aims 1 and 3 are developmental in nature and already have a built-in iterative process that allows us to incorporate feedback from participants and address potential issues as they arise. It is possible that Aim 2 might not result in the hypothesized cue reactivity and extinction, limiting our ability to advance to Aim 3. Although we do not anticipate this occurring due to the strong theoretical and empirical foundation of Aim 2, if this does happen, we will explore potential reasons for the unexpected outcomes (e.g., number of trials, reality/co-existence outcomes), including examination of the potential moderator variables. Based on those findings, we will modify the protocol (e.g., increase number of trials) and retest the key elements on new participants. Although we believe this is unlikely, if necessary we would defer Aim 3 in favor of resolving problems with Aim 2.

C.6. Timeline

Please see Study Timeline attachment, as per new instructions for Clinical Trial applications.

C.7. Implications and Future Directions

The primary goal of this study is to validate AR as an effective way to present smoking stimuli to elicit cue-reactivity and subsequent extinction. If successful, these findings have immediate implications for the use of cue-exposure as an adjunct to smoking cessation treatment. Indeed, AR has the potential to solve the extinction generalizability challenge presented by the renewal effect, which has limited the potential of cue-exposure treatments to date. Next steps would include taking our extinction paradigm into the real-world and conducting a larger, randomized controlled trial testing the efficacy of adding AR cue-exposure to an existing evidence-based smoking cessation program. Although the current study examines smoking stimuli (i.e., proximal cues), future research can also evaluate the role of AR for extinction of urge provoked by distal cues (e.g., alcohol, coffee; Conklin et al., 2008), which are also potent precipitants of smoking relapse. Beyond cue-exposure treatment, AR stimuli could be incorporated into other intervention protocols (e.g., coping skills training; mindfulness). This research could also inform the development of treatments for other mental health conditions that utilize extinction as part of treatment (e.g., other substance use disorders, social anxiety, PTSD). Exploring potential moderators (e.g., sex, nicotine dependence, initial cue-reactivity) will also allow us the ability to determine for whom this type of treatment may be most efficacious, consistent with a personalized medicine approach for treatment.

C.8. Participant Confidentiality

In the event, and only in the event, that study staff must work from home due to mandated orders (e.g., COVID-19 stay home orders), documents that contain protected health information may be temporarily kept at a personal residence for data entry and analysis. Documents will be secured in such a manner that they will be protected from being accessed by other individuals and pets who live in or visit the home. Any remote meetings (e.g., zoom meeting) or conference calls where protected health information may be discussed will be performed in a location that does not have listening devices (e.g., amazon echo) and are not likely to be overheard by those who live in or visit the personal residence.

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STATISTICAL DESIGN AND POWER

Aim 1.

For urge and reality/co-existence questions, descriptive analyses will be conducted to confirm that responses are in the expected direction (e.g., smoking stimuli result in higher urge reports than neutral stimuli; co-existence for smoking stimuli are rated ≥6 on the Likert scale). For questions asked in C.2.5.c., responses will be written down by an experimenter to be later analyzed. Using hand coding, the key themes/textual units related to the stimuli will be identified from these responses. Content analysis (via hand coding) will be conducted using an “intuitive” or “immersion/crystallizing” analysis plan, whereby the investigators review all the data and pull out those aspects most relevant to the research questions (Sandelowski & Barroso, 2003). Modifications to the stimuli will then be made based on these findings.

Aim 2.

The 2x2 within-subject design for Session 1 will provide measures of urge to smoke and reality/co-existence (for AR only) for analysis. Smoking cue-reactivity will be computed for both the AR and the in vivo conditions by subtracting the average urge to smoke (1-10 scale) following smoking cues from the average urge to smoke following neutral cues; higher scores represent greater smoking cue-reactivity. Based on the existing literature (Carter & Tiffany, 1999), we expect in vivo smoking cue-reactivity equivalent to a Cohen's *d* = 1.0, a very large effect. In terms of urge to smoke, this approximates an average difference score of 2.0 units with a standard deviation of 2.0.

Support for the effectiveness of AR to generate smoking cue-reactivity will be evaluated in two ways. First, average AR smoking cue-reactivity will be tested against a minimal threshold of Cohen's *d* = 0.5 (i.e., expected 1 unit on the urge to smoke scale) using a single-sample t-test. Second, the equivalence of the AR and in vivo stimuli toward generating smoking cue-reactivity will be evaluated using two one-sided tests (TOST) for equivalence.

The 142 participants completing Session 1 will be randomly assigned to the extinction or control condition in Session 2. With an estimated attrition of 10%, 128 are expected to complete Session 2. One measure of extinction will be the difference in urge to smoke at Trial 27 from urge to smoke at Trial 2, such that more positive values represent greater extinction of AR smoking cue-reactivity. Extinction based on this measure will be evaluated using a between-groups t-test. In addition, growth curve modeling will be used to compare the trajectories of urge to smoke using each self-report during the presentation of stimuli with the hypothesis of a greater negative slope for the extinction condition. Finally, the secondary measure of latency to smoke following the extinction trials will also be evaluated using a between groups t-test.

Sample size was driven by the power required for Session 2. Power was estimated using PASS 15 (2017). With 128 participants in Session 2 (64 per condition), alpha = .05, and a two-sided test, Power will ≥ .80 to detect a Cohen's *d* ≥ .50 (a medium effect size) using the t-test. *A medium effect size is consistent with most of the existing cue-exposure treatment literature on cravings to smoke despite variations in population, types of cues (e.g., visual, audio, in vivo), number of exposures, massed or spaced exposures and number of participants. Cohen's ds = .20, .45, .52, .75, 1.15 for studies with reported effect sizes or with effect sizes that could be easily calculated for smoking urges (Niaura et al, 1999; Corty and McFall, 1984; Lowe et al., 1980; Kamboj et al., 2012; Unrod et al, 2014). Although an effect size was not reported, Collins et al. (2011) found significant reductions in cravings following repeated cue exposure despite having a substantially smaller sample size (N = 42). Studies that did not find an exposure effect were severely underpowered with Ns ranging from 7 to 32 (Gotestam & Melin, 1983; Raw & Russel, 1980; Lee et al 2004; Vinci et al, 2012; Miranda et al. 2008; and LaRowe et al. 2007).* Growth curve modeling of urge to smoke will have greater power presuming reliable measurement. The 142 participants completing Session 1 will yield power > .95 to detect a small-medium (*d* =.35) AR smoking cue-reactivity effect that is greater than the minimal threshold (1 scale unit, *d* = 0.5). This *N* will also yield power > .80 using TOST with alpha = .05 to detect an average AR reactivity within 0.25 standard deviations of the average in vivo reactivity (expected 2 scale units, *d* = 1.0).

The target sample size is not adequate for fully-powered tests of moderators or mediators. Nevertheless, we will conduct exploratory analyses attempting to identify potential influences on or boundary conditions of AR smoking cue-reactivity and extinction. Key theory-based moderators are sex, nicotine dependence, and cue-reactivity (self-reported via the WISDM subscale). For Session 2, cue-reactivity and reality/co-existence measures from Session 1 also will be evaluated. Each moderator will be tested individually using the interaction term in a regression model (e.g., Cue Type x Sex in Session 1 and Group x Sex in Session 2). For example, if sex were a small-medium moderator of extinction in Session 2 (i.e., $\beta \sim .2$), the current sample size provides Power = .67 to detect an interaction of Group x Sex. The key theory-based mediators will be the reality/co-existence measures within the same session. Mediation will be tested using methods developed by Preacher and Hayes (e.g., 2008a, 2008b).

Aim 3.

For Aim 3, we will calculate descriptive statistics to examine a priori benchmarks regarding the usability and acceptability of the app. If any of these benchmarks are not achieved, the app will be adjusted accordingly and re-tested in additional field studies (beyond the present proposal). *For motivation to quit, self-efficacy for quitting, smoking urge, and quit status, we will also derive descriptive outcomes. Given the small sample size, we will not be powered to detect significant changes over time. Nonetheless, we will examine these data for*

trends in the expected directions (e.g., increases in motivation and self-efficacy). Smoking status will be collected post-app testing to determine what percentage of the sample successfully quit smoking. A priori benchmarks for each measure are presented in Table 1.

Qualitative analysis of interviews will be conducted. Interviews will be audio-recorded and verbatim transcripts created for content analysis (Charmez, 2006). Using hand coding, the goal will be to identify key themes/textual units related to the phone app. Content analysis will be conducted using an "intuitive" or "immersion/crystallizing" analysis plan, whereby the researcher reviews all data and pulls out those aspects most relevant to the research questions (Sandelowski & Barroso, 2003). The research team will identify key themes as they read through the interview transcripts. These findings will supplement quantitative data in order to identify potential changes/improvements for future iterations of the app.

Item	Scale	A Priori Benchmark
Usability and Acceptability Outcomes		
Daily use	From real-time data	≥ 80% of participants will use the app on ≥ 80% of days
System Usability Scale	Likert	≥ 80% will "strongly agree" that the app is usable (i.e., ratings ≥ 4 on 5-point scale)
Reality/co-existence	Likert	≥ 75% will rate these variables as ≥ 8 on 10-point scale
Usefulness	Dichotomous (Y/N)	≥ 75% will respond "yes"
Ease of Use	Likert	≥ 75% will indicate the app was easy to use
Ease of Learning	Days to learn (ratio); Dichotomous (Y/N)	≥ 75% will indicate 1-3 days for learning to use the app; ≤ 30% will contact staff for additional help using the app
Satisfaction	Dichotomous (Y/N); Likert	≥ 75% would recommend the app; ≥ 75% will indicate being very satisfied
Smoking Behavior		
Motivation to Quit	*Contemplation Ladder/ARME*	*≥ 80% of the sample will increase on motivation to quit smoking*
Cessation Self-Efficacy Scale	*Likert Scale*	*≥ 80% of the sample will increase on self-efficacy for quitting*
Urge to Smoke	*Likert*	*≥ 75% of the sample will have lower urges to smoke in the last 2 days of app testing, when compared to the first 2 days of app testing*
Smoking Abstinence	*Dichotomous (Y/N)*	*None. Collected for descriptive purposes only.*

Table 1. Benchmarks of Aim 3 Usability and Acceptability Testing.