Examining Brain Responses Linked to Emotion in Individuals Who Smoke Cigarettes

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Study Protocol

Study Background and Rationale

Functional neuroimaging methods have played an increasingly important role in the study of drug use and addiction (Heitzeg, Cope, Martz, & Hardee, 2015; Parvaz, Alia-Klein, Woicik, Volkow, & Goldstein, 2011). Functional neuroimaging has had a particularly large impact in the field of research on cigarette smoking (McClernon & Gilbert, 2004). Much of the research using neuroimaging to examine smoking and other addictive behaviors has focused on brain activity associated with drug craving, which can be defined as a strong desire or motivation to use drugs (Wilson & Sayette, 2015). This emphasis reflects widespread agreement that craving is a clinically significant feature of drug addiction (Tiffany & Wray, 2012).

The neuroimaging methods used to study drug craving have improved in several ways over the past three decades. On the quantitative front, data analysis techniques have become far more sophisticated in recent years, paving the way for a deeper understanding of the relationship between complex aspects of brain functioning and the craving to use drugs. For example, researchers have used cutting-edge functional connectivity approaches to examine how activity within and between large-scale brain networks changes under conditions designed to increase or decrease craving (Sutherland, McHugh, Pariyadath, & Stein, 2012). The tools that are available to addiction researchers have grown substantially in many other ways. For instance, investigators can now take advantage of a diverse array of methods for inducing craving while collecting neuroimaging data (e.g., using multisensory cues; Yalachkov, Kaiser, & Naumer, 2012), creative strategies for connecting craving-related brain activity to subsequent behavior (e.g., combining fMRI and experience sampling methods; Berkman & Falk, 2013), and emerging technologies for producing targeted changes in brain activity to help reduce urges (e.g., real-time neurofeedback; Hartwell et al., 2013).

In contrast to the advances described above, progress in the functional neuroimaging of craving has lagged in one crucial domain – the methods used to assess subjective affective experience. Other than self-report measures, which have been available since the earliest days of neuroimaging craving research, investigators currently have few options when it comes to measuring subjective affect in brain imaging studies. Self-report can provide very useful information about what participants are experiencing. However, self-report measures typically lack the sensitivity and precision needed to relate momentary affective responses to simultaneous brain activity. This stems in part from the compromises that researchers often must make to collect self-report data in neuroimaging studies. In our fMRI studies of craving, for example, participants commonly rate their affect before and after, but not during, the scan to reduce unwanted movement (e.g., Wilson, Sayette, & Fiez, 2013). This asynchrony is far from ideal, as meaningful relationships may be missed if initial affective responses fade or otherwise change with passing time. Even when self-report measures are administered while brain imaging data are being acquired, ratings are frequently made using devices with a very small number of possible responses (e.g.,

handheld units with five buttons). As a result, researchers routinely find it necessary to rely upon coarse Likert scales that fail to fully capture the continuous nature of affective experience.

The lack of objective, sensitive methods for measuring affective experience in neuroimaging craving research is an important limitation given the strong evidence that craving and affect are closely interrelated (Tiffany, 2010). Indeed, some have argued that craving is essentially an affective process (Baker, Morse, & Sherman, 1986; Giuliani & Berkman, 2015). Regardless of whether craving and affect are separate but tightly connected or craving is inherently an affective state, it is clear that the field needs alternative strategies for assessing affect – particularly nonverbal methods – that can serve as a complement to self-report measures.

This project is based on the premise that neuroimaging craving research has been hindered in important ways by having to rely exclusively on self-report measures of affect, and that an alternative approach that involves using facial coding analysis to assess affective responses holds substantial promise for addressing this barrier to progress. Successful completion of the aims of the project would provide valuable data regarding the feasibility of measuring affect during brain imaging using facial coding. This comprehensive and multimodal assessment approach has the potential to make a significant impact on the field by providing addiction researchers with a powerful new tool for characterizing the relationship between craving-related brain activity and affect. More broadly, facial coding would serve as a potent supplement to self-report in any area using neuroimaging to study affective responses (e.g., studies of depression, basic research on emotion and decision making).

Study Objectives

The goal of this project is to combine functional magnetic resonance imaging (MRI) and facial expression analysis to examine associations between moment-to-moment changes in brain activity and emotional responses in individuals who smoke cigarettes. These associations will be assessed under conditions designed to increase the motivation to smoke. The specific aims of the project are: 1) to demonstrate the feasibility of measuring affect by coding facial expressions displayed during functional MRI; and 2) to demonstrate that moment-to-moment changes in affect are meaningfully associated with ongoing brain activity in individuals who are motivated to smoke. It is hypothesized that facial coding will be effective for quantifying the positive and negative affect exhibited by smokers in the MRI scanner. It is also hypothesized that emotional responses will be associated with brain activity in areas previously linked to cigarette craving (e.g., the ventromedial prefrontal cortex and anterior cingulate cortex). If successful, the proposed project will provide a foundation for using this new method to explore a variety of questions that are currently very difficult to address (e.g., characterizing how affect changes dynamically in relation to brain activity when smokers attempt to regulate their craving).

In addition to these primary objectives, the study also includes behavioral testing with the following goals: finalizing initial study procedures and subsequent modifications required due to the COVID-19 pandemic through pilot testing; allowing progress toward the aims of the project while research was initially shut down and then subsequently restricted due to the COVID-19 pandemic; and troubleshooting technical challenges. This includes behavioral testing to identify a subset of stimuli from the set that reliably elicit affective facial expressions for use during fMRI scanning. To facilitate the ability to interpret the emotional facial expressions exhibited by participants experiencing cigarette craving, we will also examine the facial reactions that they exhibit during basic positive and negative emotional states induced by experimental stimuli. Various methods have been used to induce emotions in the laboratory, but relatively little is known about the relative effectiveness of these approaches. This is particularly true when it comes to produce target emotional states in individuals who smoke cigarettes and who are experiencing a craving to smoke. As a result, it is not clear which method for inducing emotion would be best to include in the fMRI study. To address this gap, behavioral testing will be conducted to evaluate the effectiveness of the following types of stimuli: "neutral" pictures and videos designed to elicit minimal changes in the urge to smoke; smoking-related pictures and videos designed to elicit increases in the urge to smoke; smoking-unrelated pictures and videos designed to elicit strong negative affect; and smoking-unrelated pictures and videos designed to elicit strong positive affect. Participants' facial reactions will be recorded and coded to determine which stimuli elicit more robust affective facial expressions.

Participant Identification and Recruitment

Participants will be recruited using the following methods: radio advertisements, newspaper advertisements, posted flyers at approved locations on PSU campuses (including branch campuses) and businesses (local and in surrounding townships), website ads, social media (e.g., Facebook and Twitter), and email listservs. In addition to being placed directly by the study PI or other study personnel, the project will use the services of a company called BuildClinical to post recruitment ads that will be run across many different digital platforms (e.g., Facebook, Instagram, Google, Bing, WebMD, YouTube, Snapchat, Reddit, Twitter, and banner ads). We will also advertise the study on www.researchmatch.org and StudyFinder.

Advertisements posted directly by the study PI or other study personnel will invite potential participants to email or phone the PI's laboratory. Or, as an alternative when relevant (e.g., for posted flyers), individuals can scan a QR code with their smartphone and fill out a very brief REDCap prescreening questionnaire (REDCap_PrescreeningForm.pdf). If they qualify based on the preliminary screening, they will then be called by the lab for additional information and, if interested, to see if they are eligible. In addition, we will contact individuals who have expressed interest in being contacted for future studies conducted by our laboratory by answering "yes" to a question asking them whether or not they would like to be contacted for future studies during a telephone screening and/or by giving permission for such contact on an informed consent form.

Study Design

The primary study is comprised of two parts: (1) a screening/baseline session and (2) a functional MRI experimental visit. This is a between-groups experimental design in which participants will be randomly assigned to two conditions (Expect-Yes and Expect-No). The study will use the following modified design while revised standards are in place due to the COVID-19 pandemic: (1a) remote screening/baseline session; (1b) an abbreviated in-person visit to biochemically verify smoking status, and (2) a functional MRI experimental visit. The study will also include behavioral testing using a within-subjects experimental design with one independent variable: (1) stimulus type (neutral vs. smoking-related pictures and videos, negative vs. positive pictures and videos).

Study Procedures

<u>Screening/baseline session</u>

- Upon arrival, participants will be asked to turn off or silence their cell phone and/or any other personal electronic devices and to refrain from using them during the session, except for during breaks or to record pertinent information (e.g., entering the date and time for the next scheduled visit into a calendar). (They will be given similar instructions at the start of the functional MRI experimental visit.)
- After informed consent is obtained, participants will be asked to complete a brief Demographics questionnaire and the Fagerström Test for Nicotine Dependence.
- Next, participants will be asked to provide a carbon monoxide sample, which is a screening procedure that is used to verify their smoking status. To provide a CO sample, participants will be asked to hold their breath for 20 seconds and then exhale into a disposable mouthpiece attached to a carbon monoxide device. The device will produce a CO reading in parts per million immediately.
- Next, participants will be given an overview of the key information covered in the informed consent form to ensure that they fully understand the timeline and requirements of the study. They will be given a chance to ask any questions that they have about the study.
- Next, participants will be administered a battery of baseline measures.
- Following screening, they will be introduced to MRI through an orientation conducted in the Mock Scanner room of the 3T MRI Facility in the basement of Chandlee Lab. The participant will be asked to lie on a table and slid into the mock scanner to become accustomed to the size of the bore, as well as the sounds of the magnet. They will also be informed about the importance of remaining still while in the scanner.
- After completing the practice, participants will be removed from the mock scanner. They will then be told to abstain from smoking cigarettes or using any other nicotine products for 12 hours and from using alcohol/recreational drugs for 24 hours before the functional MRI experimental visit. Participants will also be asked to bring at least one of their cigarettes with them to the experimental visit because they may be given an opportunity to smoke during the session.

- The screening/baseline session will then conclude, and participants will be compensated via cash payment.

Functional MRI experimental visit

- Participants will complete one functional MRI experimental visit, which will be held on a separate day.
- At the start of each session, participants will be asked to report the last time that they have used any of the following: cigarettes, other nicotine products, alcohol, and recreational drugs. They will also provide a CO sample to verify 12-hour abstinence from cigarettes, based upon a cutoff derived from prior research (Cropsey et al., 2014; Javors, Hatch, & Lamb, 2005).
- Participants will then complete computerized measures assessing nicotine withdrawal, craving, and state affect.
- Next, participants will be told that they will be given a 15-minute break immediately following the functional MRI portion of the session and that they will be informed whether or not they will be given the opportunity to smoke during the break shortly before it begins.
- Next, participants will be escorted to the SLEIC and placed in the MRI scanner.
- While in the MRI scanner, participants will complete the following functional tasks (in addition to the collection of anatomical images). First, participants will be shown several video clips (each approximately 20-30 seconds). Participants will be instructed to watch and respond naturally to the videos, and they will be asked to rate how they are feeling after each clip. These videos consist of short clips of real-life situations from a research database recently developed by Samson et al. (2016). Some of these videos are designed to produce negative affect (mostly painful accidents). The remaining videos are designed to produce positive affect (e.g., children dancing). Next, participants will be randomly assigned to two groups. Specifically, one group (those assigned to the Expect-Yes condition) will be informed that they will be given an opportunity to smoke during a 15-minute break immediately following the functional MRI portion of the session. The other group (those assigned to the Expect-No condition) will be informed that they will not be given an opportunity to smoke during the study and will therefore have to wait until after the session has concluded before having a chance to smoke (although they will still be given a 15-minute break immediately following the functional MRI portion of the session).
- Next, participants will be presented with two additional types of short videos (each approximately 20-30 seconds): (1) half designed to elicit minimal changes in affect and the urge to smoke ("neutral" videos); and (2) half designed to elicit significant changes in affect and the desire to smoke (smoking-related videos). Participants will be instructed to watch and respond naturally to the videos, and they will be asked to rate how they are feeling after each clip. These videos were developed and validated by Tong et al. (2007) for use in smoking research.

- Participants' faces will be video recorded during functional MRI scanning using a commercially available MRI-compatible camera system (MR-Cam 12M-I, MRC Systems, Heidelberg, Germany) that was developed for various applications (e.g., patient monitoring, eye tracking). The cameras will be mounted to the head coil during fMRI data collection. The cameras contain an integrated LED for illumination and can be equipped with different lenses to optimize the magnification, field of view, and working distance. All parts and connections are shielded to prevent the camera from introducing artifacts into the MRI/fMRI data (and vice versa). The 50-Hz analog output from the cameras will be transmitted to a computer in the control room, where it will be converted to a digital signal using a frame grabber and recorded for subsequent facial coding analysis.
- After completing the MRI scan, participants will be removed from the scanner and will be escorted to 308 Chandlee for a 15-minute break. The suite in 308 Chandlee houses the Penn State Smoking Behavior Research Facility, a shared resource at the University Park campus dedicated to facilitating the University's developing strength in interdisciplinary tobacco-related research. The Smoking Behavior Research Facility contains four independently ventilated rooms that allow research participants to light and smoke cigarettes during research sessions while the remaining areas of the laboratory remain smoke-free. Participants assigned to the Expect-Yes condition (those told earlier that they would be given the opportunity to smoke before the end of the study), will be permitted to smoke one cigarette while in the testing room during this break. They will be offered a cigarette of their preferred brand from a supply kept by the lab, although they will also be free to smoke one of their own as an alternative. Participants assigned to the Expect-No condition (those told earlier that they would not be given the opportunity to smoke before the end of the study) will also be given a 15-minute break, but they will not be given the opportunity to smoke during the break.
- Participants will be asked to remain in the lab after the break before being excused. This is designed to maintain the integrity of the smoking expectancy manipulation, as participants often learn about the study through word-of-mouth. During this period, participants will be asked to provide ratings of how they are feeling and their urge to smoke periodically, as well as a questionnaire assessing personality traits.
- The functional MRI experimental visit and study will then conclude, and participants will be compensated via cash payment.

<u>Behavioral testing only</u>

A subset of participants was asked to complete behavioral testing only for initial piloting, to allow progress toward the aims of the project while research was initially shut down and then subsequently restricted due to the COVID-19 pandemic, and to troubleshoot technical challenges. They completed the following procedures:

- Participants will be presented with stimuli designed to elicit positive and negative affect. Stimuli will consist of the following:

    - Videos of still photos from the International Affective Picture System (IAPS; Lang, 1988), with mood-congruent instrumental music played throughout the presentation of the images. Half of the videos contain images designed to produce negative affect (e.g., children and adults looking upset and/or with serious injuries, dead animals). The remaining half of the videos contain images designed to produce positive affect (e.g., romantic couples [there are no erotic images], smiling babies).
    - Video of short clips of real-life situations from a research database recently developed by Samson et al. (2016). Half of the videos contain images designed to produce negative affect (mostly painful accidents). The remaining half of the videos contain images designed to produce positive affect (e.g., children dancing).
    - Videos developed and validated by Tong et al. (2007) for use in smoking research. Half of the videos contain scenes designed to elicit significant changes in affect and the desire to smoke (smoking-related videos). The remaining half of the videos contain scenes designed to elicit minimal changes in affect and the urge to smoke ("neutral" videos).
- Participants will be instructed to watch and respond naturally to the videos, and they will be asked to rate how they are feeling after each clip.
- Participants' faces will be recorded as they watch the videos.
- After the completion of the video task, behavioral testing will conclude, and participants will be compensated via cash payment.

Statistical Analysis Plan

Recordings of participants' facial movements will be analyzed using FaceReader software (Noldus Information Technology). FaceReader processes facial data using three automated steps. First, the software detects the presence of a face using a robust cascaded classifier algorithm [61]. Second, an algorithm based on the Active Appearance method [62] is applied to create a three-dimensional model with over 500 points capturing the shape and texture of the face. Third, using this network of points, the software classifies facial expressions using a three-layer feed-forward neural network trained on more than 10,000 facial images depicting basic emotions that were coded manually by trained experts.

FaceReader will be used to derive a time course (at a 50 Hz sampling rate) quantifying the valence of participants' affect during stimulus exposure (ranging from highly positive to highly negative). Valence will be calculated based on automated analysis of facial expressions linked to "felt" affect for each video frame spanning the run in which the evocative stimuli are presented.

Functional MRI data will be preprocessed using standard steps (including motion correction, non-brain removal, spatial smoothing, grand-mean intensity normalization, and high-pass temporal filtering). Following preprocessing, statistical analysis of the functional MRI data will be conducted within the framework of the general linear model (GLM). Following model fitting, subsequent analyses will compare the effects of stimulus

condition (e.g., smoking-related versus neutral cues) on brain activation as a function of smoking expectancy condition (Expect-Yes vs. Expect-No). As a primary outcome, we will focus on effects in two *a priori* regions of interest (ROIs). The first is the ventromedial prefrontal cortex (vmPFC), as there is strong evidence that vmPFC activity positively correlates with the subjective value of stimuli and actions, including during the anticipation of imminent rewards. We will create an ROI in the vmPFC ROI by generating a 10-mm sphere centered at the following MNI coordinates taken from a meta-analysis of 206 fMRI studies examining subjective valuation: x = -1, y = 46, z = -7 (Batra et al., 2013). The second region we will focus on is the dorsal anterior cingulate cortex (dACC), as research indicates that it is consistently activated under conditions that produce negative affect, such as when there is a conflict between current and desired states. We will create an ROI in the dACC by generating a 10-mm sphere centered at the following MNI coordinates taken from a meta-analysis of 59 fMRI studies of negative affect: x = -2, y = 10, z = 38 (Shackman et al., 2011).

Risks

More than a million MRI studies have been performed around the world. We will be following standard MRI procedures. High magnetic field inside of the scanner can be hazardous in the presence of some metallic devices, specifically: magnetic fields may dislodge metallic implants, causing bleeding and disruption of adjacent tissues. Magnetic fields may also cause problems for electrical pacemakers and stimulators. In addition, radio waves may heat the body and metallic objects within or on the body, possibly resulting in burns. Finally, certain metallic objects may move toward the magnet at very fast speeds if attracted by the magnetic field. Although highly unlikely, participants might experience dizziness, mild nausea, or tiny flashing lights while in the magnet. These sensations are mostly due to movement while inside the magnet and can be minimized by holding still. All of these sensations should stop shortly after leaving the magnet. Additionally, because of the small space in the magnet, and the length of the study, some people find the experiment to be uncomfortable. However, since participants will have a visual screen to look at, they are unlikely to experience such feelings. There are no known risks from MRI apart from those described above. However, there is always the possibility that there are unknown risks associated with this procedure. It is important that a baby (fetus) developing in the uterus not be exposed to any unnecessary risks. Therefore, to participate in this study, female participants must report that they are not pregnant.

There is a risk that participants will be uncomfortable about answering some of the questions they are asked. Participants will be informed that they do not have to answer any questions that they do not wish to during both the phone screen and during the first visit when consent is obtained.

Some of the questions that participants will be asked during the study concern potentially illegal behavior, such as using illegal drugs. This information could potentially be a risk if it became known and could be linked to the participant's identity. While participants are asked to answer questions regarding their drug and alcohol use, all information gathered

from participants will be kept completely confidential. Participants' names and identifying information will not appear on any data forms to ensure confidentiality. The identity of participants will be indicated by a case number on collected records. Participant data files will be accessible only to the PI and trained research staff.

Participants may be given the option of smoking during the experimental session. The use of nicotine and tobacco products during pregnancy poses well-known risks to fetal development. However, participants will not be required to smoke a cigarette as a part of the study; that is, they are free to decline the opportunity to smoke. In addition, participants will already have indicated that they are not pregnant as a part of the standard MRI safety form that is administered as a part of SLEIC SOP before the fMRI portion of the session. Thus, we do not believe that this aspect of the study (i.e., providing participants with the option of smoking) involves any increase in risk in relation to pregnancy.

Participants may experience symptoms of nicotine withdrawal (e.g., irritability, fatigue, difficulty concentrating) when attempting to refrain from smoking before the functional MRI experimental visit. Participants are free to resume smoking at any time, however, which should eliminate any withdrawal symptoms. In sum, we do not anticipate that participants will experience any risks that are above what people experience in everyday life.

Finally, there is a risk of loss of confidentiality if participants' information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening (as described below).
The following steps will be taken to minimize risks:

- Participants will fill out a screening form to determine if they have any implants that would endanger them in the MRI (e.g., if a participant has a pacemaker or stimulator implanted, they will not be eligible to participate in this research).
- Participants will be carefully checked by the experimenter or technologist for the presence of any metallic objects such as body piercings or items in pockets.
- Participants will be asked to let the experimenter or technologist know if they feel any unusual warmth during the MRI scan.
- Participants can discontinue the study at any time without penalty (e.g., to smoke a cigarette to alleviate symptoms of nicotine withdrawal).
- As noted above, participants' names and identifying information will not appear on any data forms to ensure confidentiality; the identity of participants will be indicated by a case number on collected records; and participant data files will be accessible only to the PI and trained research personnel.
- A list that matches participants' names with their code number will be kept in a password-protected file on a secure computer server.
- All task and questionnaire data files (including MRI data files) will be coded with a unique ID number and all names or other personal identifiable information will be removed. Only this code (and never participants' names) will be used when analyzing or reporting data.

- All data files will be stored and secured in Penn State Addiction Smoking and Health Lab of the Pennsylvania State University in a locked cabinet in a locked office (in Moore or Chandlee Building) or, for computer files, in a password-protected file on a secure computer server. Only members of the research team will have access to this information.
- In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.
- The confidentiality of electronic data will be maintained to the degree permitted by the technology used.

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