Published in final edited form as:

Addict Biol. 2018 September ; 23(5): 1189–1199. doi:10.1111/adb.12549.

Neural Correlates of Tobacco Cue Reactivity Predict Duration to Lapse and Continuous Abstinence in Smoking Cessation Treatment

Max M. Owens¹, James MacKillop^{1,2,3}, Joshua C. Gray^{1,3}, Steven R.H. Beach¹, Michael D. Stein³, Raymond S. Niaura⁴, and Lawrence H. Sweet^{1,3}

¹The University of Georgia, Athens, GA

²Peter Boris Centre for Addictions Research, McMaster University/St. Joseph's Healthcare Hamilton, Hamilton, ON

³Brown University, Providence, RI

⁴Schroeder Institute at Truth Initiative, Washington, DC

Abstract

It has been hypothesized that neural reactivity to drug cues in certain limbic/paralimbic regions of the brain are an indicator of addiction severity and a marker for likelihood of success in treatment. To address this question, in the current study, 32 participants (44% female) completed a functional magnetic resonance imaging (fMRI) cigarette cue exposure paradigm two hours after smoking, and then enrolled in a 9-week smoking cessation treatment program. Neural activation to smoking cues was measured in five *a priori* defined limbic/paralimbic regions previously implicated with cue-reactivity across substances. These included regions of the ventral striatum, anterior cingulate cortex, and amygdala. Cox proportional hazards modeling was conducted to predict the number of days to first smoking lapse using neural activation in these regions. Greater neural activation during pretreatment exposure to smoking cues in the right ventral striatum, the left amygdala, and the anterior cingulate was associated longer periods of abstinence following cessation. A similar pattern was present for continuous abstinence for the full duration of treatment. While baseline levels of nicotine dependence were strongly associated with treatment outcome, activation in the right ventral striatum predicted duration of abstinence beyond level of nicotine dependence. These results suggest that pre-treatment reactivity to smoking cues in areas associated with cue-reactivity may be associated with successfully maintaining abstinence during treatment. This is consistent with models that propose that as addiction becomes more severe, motivational processing shifts

Corresponding Author: Max Owens, MS, Department of Psychology, University of Georgia, 125 Baldwin St., Athens, GA 30601, owensmax@uga.edu.

Preliminary results of this study were presented as a poster at the 2015 American Psychological Association annual convention in Toronto, Ontario (Canada).

AUTHOR CONTRIBUTIONS

All authors were involved substantively in the work leading to this report. Specifically, JM MDS RSN and LHS were involved in study design. MMO and JCG contributed to data collection and provision of smoking cessation treatment. JM and SRHB provided clinical supervision of treatment. Data analyses and drafting of manuscript were completed by MMO. Important intellectual contributions to data interpretation and manuscript preparation were provided by JM, JCG, SRHB, MDS, RSN, and LHS. All authors critically reviewed content and approved final version for publication.

from regions that subserve reward salience and learning to regions responsible motor behavior and habit learning.

Keywords

Cue-reactivity; Smoking Cessation Treatment; fMRI

INTRODUCTION

Smoking-related illness remains the leading preventable cause of death in the United States (National Institute on Drug Abuse 2014). Success rates for quitting smoking rarely exceed 25% at 6 months following treatment with the best evidence-based approaches (American Cancer Society 2014). Identifying pretreatment correlates of response to treatment may eventually be useful for assessment of relapse risk and to determine individualized treatment plans for smoking cessation. Additionally, understanding causes of treatment failure may help to enhance understanding of nicotine dependence. Given the role of environmental smoking cues in triggering craving in many models of addiction (West and Brown 2013), measuring a smoker's response to these cues has been a common strategy.

While evidence has been mixed about whether changes in self-reported craving to smoking cues is associated with later treatment outcome (Waters et al. 2004; Perkins 2009, 2012; Conklin et al. 2012; Wray et al. 2013), neural activity in response to smoking cues has been proposed as a predictor of treatment response and as a tool to improve understanding of the causes smoking cessation treatment failure. One meta-analysis of fMRI smoking cue-reactivity studies found a number of cortical regions to be activated in response to smoking cues, including the dorsolateral prefrontal cortex, the medial frontal cortex, the posterior cingulate cortex, cuneus, precuneus, and lingual gyrus (Engelmann et al. 2012). However, another meta-analysis focused on cue-reactivity across different addictive substances, including smoking, indicated that an interconnected group of limbic/paralimbic regions of the brain, specifically the ventral striatum, amygdala, and anterior cingulate cortex, to be mostly strongly associated with cue-reactivity (Kühn and Gallinat 2011). These limbic/paralimbic regions are closely connected to the mesolimbic dopamine system, which is critical to the reinforcing experience of addictive drugs and has been referred to as the 'final common pathway' of all reinforcing drugs (Pierce and Kumaresan 2006). Two alternative models have been proposed to explain how these regions' responsiveness to drug cue exposure relates to addiction severity and relapse risk. The incentive sensitization theory of addiction posits that as an individual becomes more severely addicted to a drug, neuroadaptive changes take place that create an augmented state of 'wanting' the drug, characterized by a shift to greater responding to drug cues in areas of the brain associated with incentive salience such as the nucleus accumbens (Robinson and Berridge 1993, 2001, 2008). This state is putatively independent of changes in drug 'liking.' An alternate model, referred to as the incentive-habit model, suggests that less addicted drug users will experience greater response to the presence of drug cues in these incentive salience brain regions, while the most addicted individuals primarily consume drugs in response to habitual and biological factors (such as blood nicotine levels) rather than in response to cues which

trigger craving. This reflects a transition from ventral striatal processing of incentive learning (nucleus accumbens) to dorsal striatal processing of habit learning as an individual becomes more severely addicted (Mogg et al. 2005; Everitt and Robbins 2013). Studies in nicotine dependent smokers have used self-report measures of nicotine dependence and their association with response in these brain regions during exposure to smoking cues to empirically test these two models. However, the results have been mixed, with some studies indicating that greater neural activation in response to smoking cues is associated with more severe nicotine dependence (e.g. McClernon et al. 2008) and others finding attenuated neural response to cues to be a sign of more severe dependence (e.g., Vollstädt-Klein et al. 2011).

Two studies have suggested that neural response in the limbic/paralimbic brain regions highlighted by Kuhn and Gallinat (2011) may also be associated with outcome in smoking cessation treatment, specifically that heightened neural response in these regions during cue exposure predicts failure in smoking cessation treatment (Janes et al. 2010; Versace et al. 2014). In one study, 21 nicotine-dependent women performed a functional magnetic resonance imaging (fMRI) cue-reactivity procedure prior to nicotine replacement therapy and a manualized behavioral smoking cessation intervention (Janes et al. 2010). Participants were grouped based on treatment success and their pre-treatment neural activity was compared using a whole-brain, voxelwise analysis. Results indicated response to cues was greater in the insula, dorsolateral prefrontal cortex, posterior cingulate, parahippocampal gyrus, putamen, thalamus, and cerebellum in the participants who lapsed at any point during a subsequent 9-week smoking cessation treatment. The second study took a different approach, using cluster analysis to divide 55 pre-quit-attempt smokers into two groups based on their neural response to smoking cues relative to pleasant images in a visual activation network (i.e., cuneus, precuneus, middle and inferior occipital gyri, superior parietal lobule, and middle temporal gyrus, and fusiform gyri) (Versace et al. 2011). Abstinence rates were compared between these groups following eight weeks of smoking cessation treatment with the group showing greater response in the visual network to pleasant images relative to smoking images being more likely to be abstinent following treatment. Follow-up voxelwise analyses revealed that the two groups also differed in activation in the right dorsal striatum, dorsomedial prefrontal cortex, and right dorsolateral prefrontal cortex.

These two studies provide preliminary evidence that an individual's neural response in limbic/paralimbic regions to smoking cues may be a marker of smoking cessation treatment prognosis. However, the studies used different designs and statistical analyses and neither was explicitly designed to test these regions; one study found greater activation in the putamen predicted lapse as part of an exploratory whole-brain voxelwise approach (Janes et al. 2010) and the other focused on differences in activation in the visual system between pleasant images and smoking cues and, as a follow-up analysis, found differences in dorsal striatum activation between groups formed according to activity in the visual system (Versace et al. 2014). *A priori* testing of only the regions shown to be most consistently activated by exposure to smoking (and other drug) cues would more conclusively address the possibility that response in these regions to smoking cues is a predictor of treatment outcome. It would also contribute to understanding the role of these regions in addiction to nicotine.

Thus, the goal of the current study was to test the hypothesis that neural reactivity to smoking cues specifically in the ventral striatum, the amygdala, and the anterior cingulate cortex serves as an indicator of lapse and continuous abstinence in smoking cessation treatment (Kühn and Gallinat 2011). A focus on the limbic/paralimbic regions highlighted by Kühn and Gallinat (2011) was chosen to reduce the number of tests conducted and to explicitly focus on the core motivational systems, which are the basis of the two competing models discussed above (incentive sensitization and incentive-habit). While a broader focus encompassing other neural systems involved in drug craving could have been used to obtain a more comprehensive picture of the prediction of lapse with brain activity during a CR paradigm (such as using the regions found in Engelmann et al. 2012), we elected to focus on a small set of regions which subserve common function to maximize power while avoiding excessive statistical tests. We hypothesized that the five regions identified by Kühn and Gallinat would be most associated with cue-reactivity across all substances (right and left ventral striatum, caudal and rostral anterior cingulate cortex, and amygdala) would significantly be associated with the duration participants remained abstinent after cessation in an organized smoking cessation program. In addition to its use of regions of interest defined *a priori* from prior meta-analytic research as predictors, this study differed from previous studies its focus on the contrast of images of smoking cues with neutral images and the use of a continuous measure of first lapse in treatment.

MATERIALS AND METHODS

Participants

Right-handed treatment-seeking smokers were recruited from the community using advertisements. Participants were required to be 18–60 years old, to smoke at least 10 cigarettes per day, and to report a motivation to quit of at least 5 on a scale of 1 to 10. Exclusionary criteria included major medical, psychiatric, or neurologic disorders; average consumption of more than six alcoholic beverages per day over the previous year; use of marijuana more than weekly over the previous three months; use of any other psychoactive drugs more than monthly over the previous three months; MRI contraindications; and IQ of less than 70. Of 52 participants who completed the initial fMRI assessment, one participant's data was lost due to a data transfer error, five were excluded for moving more than .35 millimeters during at least 33% of the brain volume acquisitions (i.e., excessive movement), and 14 did not initiate a quit attempt. Thus, 32 participants were included in the final analysis. The final sample is described in Table 1.

Procedures

All procedures were approved by the University of Georgia Institutional Review Board and were in compliance with the declaration of Helsinki. Participants were first screened by telephone to assess inclusion and exclusion criteria. Those with a positive screen were invited for an in-person eligibility assessment at which point smoking behavior was confirmed using exhaled carbon monoxide. Participants who met the inclusion and exclusion criteria were scheduled for an fMRI assessment session. To standardize exposure and rule out severe withdrawal effect, participants were instructed to smoke immediately prior to arriving for the session. Following an hour of pre-scan assessment and training, participants

completed a 90-minute MRI protocol consisting of the CR procedure, an anatomical scan, and other fMRI paradigms that are not the focus of the current report. Throughout this period, participants were not allowed to smoke and the CR procedure was conducted approximately two hours after participants smoked their last cigarette. Baseline craving ratings taken immediately prior to the CR paradigm indicate that participants were in a state of moderate deprivation during the CR procedure, endorsing slightly above 50% of the scale max on average (see Wilson and Sayette 2015 for review of the role of deprivation in fMRI CR procedures).

Following these sessions, participants completed a 9-week smoking cessation treatment protocol that combined in-person individual counseling sessions with a therapist and nicotine replacement therapy. A 90-minute treatment planning session was set approximately one week after the MRI protocol with a quit date being scheduled one week after that. Participants met individually with their smoking cessation therapist for 60 minutes on their quit date and then for 30 minutes weekly for the remainder of treatment. Thus, the total duration of treatment was one 90-minute session, one 60-minute session, and seven 30-minute sessions. The nine weekly counseling sessions followed evidence-based recommendations (Fiore et al. 2008) and comprised a motivational interviewing approach (e.g., engaging with clients, evoking individual motivation for quitting, facilitating change talk; Miller and Rollnick 2003), with elements of cognitive behavioral therapy (e.g., identifying antecedents of smoking; managing high-risk situations). The therapy manual and protocol adherence checklists are included in Supplemental Materials. Nicotine replacement was provided in the form of the nicotine patch with dosing following the manufacturer's instructions (4 weeks 21 mg, 2 weeks 14 mg, and 2 weeks 7 mg) and initiated on the quit date. Participants were paid for pre- and post-treatment research visits, but were not paid for treatment visits, which were provided without cost.

Treatment was provided by trained masters-level clinicians supervised by a licensed clinical psychologist. Therapy sessions were manualized and coded by another therapist for fidelity to the protocol using a checklist developed for the treatment manual, and for compliance with principles of motivational interview using the Global Rating of Motivational Interviewing Therapist (Moyers 2004). 75% of the initial therapy sessions and 66% of the second therapy sessions were coded for adherence to the treatment protocol, indicating 99% adherence to the stated protocol in sessions 1 and 2. Additionally, 59% of sessions 1 through 9 were coded for adherence to principles of motivational interviewing, indicating adherence to motivational interviewing principles among therapists was 96% of scale maximum.

fMRI Protocol—Imaging data were collected with a General Electric 16-channel fixed-site Signa HDx 3.0 Tesla MRI scanner. Structural images were acquired for anatomical reference using a high-resolution T1 SPGR sequence (voxel size = 1mm^3 , a field of view = 256^2 mm, matrix = 256^2 , and axial slice thickness = 1mm). Sufficient contiguous axial slices were acquired to obtain whole-brain coverage. Functional imaging used T2* echo planar imaging (EPI) with a single-shot gradient echo pulse sequence (TR = 2500 ms, TE = 25 ms, field of view = 225^2 mm, matrix = 64^2 , with 40 contiguous 3.5 mm slices collected axially, isometric voxel size = 3.5 mm^3). Two imaging runs of 215 and 220 brain volumes were acquired.

fMRI Cue Reactivity Procedure—The cue-reactivity (CR) procedure consisted of two imaging runs lasting 430 and 440 seconds during which participants viewed four blocks of smoking images (40 seconds per block), four blocks of neutral images (40 seconds per block), four blocks of rest (fixation cross presented for 20 seconds per block), and craving rating screens (10 seconds per block). Craving was rated three times: at the beginning and end of the experiment and once between the two imaging runs. Smoking and neutral blocks contained eight images that were presented for five seconds each in immediate succession. The order of these blocks was counterbalanced across runs. Smoking and neutral cue pictures were drawn from a set of pictures that has been used previously in fMRI smoking CR research (McClernon et al., 2007; McClernon, Hiott, Huettel, & Rose, 2005). They included images of cigarettes and people smoking. Neutral cue pictures included everyday objects (e.g., pencils, stapler) and people engaged in everyday activities (e.g., using the telephone). Participants were instructed to pay attention to the photographs on the screen and (when prompted) rate their craving for cigarettes. Prior to the scanning procedure, participants were instructed verbally how to use an MRI compatible button box to rate their craving for cigarettes on a scale from 0–8.

Measures

Fagerström Test of Nicotine Dependence (FTND)—This six-item questionnaire was used to measure participants' level of nicotine dependence. This measure is a widely used measure of nicotine dependence and has been shown to have good reliability and validity (Piper et al. 2006).

Treatment Response—The primary outcome was the number of days following their quit-date that participants did not smoke (i.e., “days to lapse”), defined via retrospective time line follow-back (Robinson et al. 2014) at every therapy session and confirmed using exhaled CO measured using a PiCO+Smokerlyzer (Bedfont Scientific Ltd., Rochester, UK). Exhaled CO was used to confirm self-reported smoking behavior with exhaled CO of 10 parts per million or greater used to indicate current smoking (Wald et al. 1981; Deveci et al. 2004). Smoking lapse was selected as the outcome of interest due to its consistent association with long-term treatment outcomes (Brandon et al. 1990; Kenford et al. 1994; Shiffman et al. 1996) and use of total abstinence (i.e., absence of lapse) by Janes et al. (2010) in a previous study investigating neural response to a cue-reactivity paradigm with smoking cessation treatment response. In order to maximize power, lapse was measured continuously as number of days to lapse, though continuous abstinence throughout treatment was also assessed for continuity with prior literature (i.e., Janes et al. 2010). Participants who dropped out of treatment following their quit date or had exhaled CO > 10 were considered to have lapsed and participants who did not lapse were coded as the total number of days assessed following their quit date.

Analyses

Data Processing—fMRI data processing and analysis was conducted using Analysis of Functional NeuroImages software (AFNI; Cox, 1996) as a block design experiment. Functional dataset volumes were registered and individually aligned to T1 anatomical datasets (corrected for head movement). Volumes including movement greater than 0.35mm

(i.e., 1/10 voxel) along the x, y, or z axes were censored from analyses and participants with greater than 33% of volumes censored were excluded from the study. Following motion correction, datasets were transformed into Talairach space (Talairach and Tournoux 1988) and individual volumes from each run were registered to a base volume (i.e., 3rd volume of the first CR imaging run) (Saad et al. 2009). The data were masked to exclude voxels outside the brain and spatially smoothed using a 7mm (i.e., two voxels) full width half-maximum (FWHM) Gaussian filter. Raw BOLD signal was scaled to percent signal change from mean signal intensity. For functional datasets, a GLM was completed using regressors relating to condition (smoking pictures and neutral pictures) and six nuisance regressors to account for motion (x, y, z, roll, pitch, yaw), as well as regressors for linear, quadratic, and cubic trends. The passive rest condition was not modeled and therefore served as a baseline.

Data Analysis—To test the hypothesis that the limbic/paralimbic regions associated with cue-reactivity across substances would predict smoking cessation treatment outcomes, a 4 mm radius sphere (268mm³) was drawn centered on the coordinates provided for each of the five limbic/paralimbic regions found to be associated with CR in the meta-analysis by Kühn and Gallinat (2011). The AFNI ROI draw plugin was used to translate MNI coordinates to Talairach space. The regions from this paper were the left and right ventral striatum, the left amygdala, and two regions of the ACC that crossed the midline (see Figure 1). Then the average beta value of the contrast of smoking and neutral images in each sphere was calculated for each participant. For the primary hypothesis tests, Cox proportional hazard regression analyses were conducted at the group level to determine if average beta values in these ROIs were associated with days to lapse. To provide an assessment of longer term lapse, continuous abstinence categorically defined (lapsed at all vs. did not lapse at all) was also tested as an outcome measure using logistic regression. For Cox and logistic regression models, independent variables were standardized to improve interpretability of results (i.e., no effect = hazard ratio of 1). Subsequently, as a follow-up analysis to clarify the role of FTND in this effect, each region in which response to CR was associated with days to lapse was run in a separate hierarchical cox regression model in which FTND score was first entered into the model followed by the region of interest. This was done to determine whether neuroimaging effects contributed uniquely to outcome prediction beyond another known predictor of treatment outcome. To determine if one condition was most important in predicting lapse or indicating nicotine dependence severity using the CR paradigm, Cox regression analyses were conducted testing activation in the five regions of interest during smoking cues (relative to baseline) and during neutral cues (relative to baseline) as predictors of lapse and Pearson correlations were used to assess the relationship of this activation with FTND. Using gender and age as covariates was considered, but ultimately was not done as neither was significantly associated with nicotine dependence, self-reported craving, or activation during the CR paradigm in regions of interest.

To complement these functional neuroimaging results, Pearson's correlations were conducted between the regions tested, FTND, and self-reported change in craving from before to after the CR paradigm and FTND. Self-reported craving ratings were not collected from two participants due to technical failure and these values were mean imputed. Additionally, FTND, baseline self-reported craving (i.e., pre-scan), and change in self-

reported craving in response to the CR paradigm (i.e., post-scan – pre-scan) were tested as predictors of days to lapse in independent Cox regression models.

RESULTS

Behavioral Findings

Participants attended an average of 7 out of 9 treatment sessions ($SD = 2.40$) with eight participants dropping out of treatment after their quit date and 15 participants completing all nine sessions. Participants who completed all nine sessions did not differ in age, gender, race, education, or income from those who did not ($p > .1$). Participants who completed all nine sessions had lower levels of nicotine dependence from those who did not ($t = -2.17$, $p = .04$), but did not differ on demographic variables. Participants averaged 17.5 days until first lapse ($SD = 20.30$) with six participants lapsing within the first 24 hours of their quit attempt and 9 participants remaining abstinent for the full 49 days of treatment. Participants who remained abstinent throughout treatment had lower levels of nicotine dependence than those who did not ($t = 2.66$, $p = .01$), but did not differ on any demographic characteristics ($p > .07$). In Cox regression analyses, pretreatment nicotine dependence as measured by the FTND predicted days until lapse (Hazard Ratio = 2.15, $p = .002$, 95% CI = 1.31 – 3.52).

On average participants rated their craving to smoke prior to the first run of the CR paradigm as 4.57 out of 8 ($SE = .42$), following the first run as 4.90 ($SE = .42$), and following the second run as 5.00 ($SE = .42$). Although directionally consistent, the change from the start to end of the CR paradigm was not significant ($t = 1.49$, $p = .15$). Days to lapse was not predicted by self-reported craving at baseline (Hazard Ratio = 1.23, $p = .32$, 95% CI = .81 – 1.85) or following the CR procedure relative to baseline (Hazard Ratio = 1.03, $p = .88$, 95% CI = .70 – 1.52).

Functional Neuroimaging Findings

In the study's primary hypothesis tests, Cox regression indicated that greater reactivity in the left amygdala, the caudal anterior cingulate, and right ventral striatum significantly predicted days to lapse (Table 2). In logistic regression, right ventral striatum ($WALD = 4.97$, $p = .03$, Odds Ratio = 4.87) and left amygdala ($WALD = 4.62$, $p = .03$, Odds Ratio = 2.76) significantly predicted whether participants maintained continuous abstinence throughout treatment, though caudal anterior cingulate fell short of significance ($WALD = 3.31$, $p = .07$, Odds Ratio = 2.36). Neither controlling for self-reported craving prior to the CR paradigm nor change in craving during the CR paradigm altered these regions prediction of lapse.

In secondary analyses controlling for FTND, the association with days to lapse remained significant in the right ventral striatum (Hazard Ratio = .64, $p = .05$, 95% CI = .41 – 1.00), though not for left amygdala (Hazard Ratio = .68, $p = .15$, 95% CI = .41 – 1.14) or caudal anterior cingulate cortex (Hazard Ratio = .77, $p = .20$, 95% CI = .52 – 1.14).

Supplemental correlation analyses indicated that neither baseline craving ($r = .32$, $p = .08$) nor change in craving ($r = .21$, $p = .25$) were associated with FTND. Activity in the left amygdala during smoking cues (relative to neutral cues) was inversely associated with FTND ($r = -.41$, $p = .02$; Figure 2). Change in craving was inversely associated with the left

($r = -.46$, $p = .009$) and right ventral striatum ($r = -.46$, $p = .02$) and the rostral anterior cingulate cortex ($r = -.41$, $p = .02$). There were no other significant associations between the predictor regions, FTND, and self-reported craving.

In supplemental Cox regression analyses investigating the importance of individual conditions in the CR paradigm to predicting lapse, in no region was activation during smoke or neutral cues relative to baseline significant as a predictor of days to lapse, suggesting that the difference between responses to smoking and neutral cues is the aspect that is associated with lapse. Activation during smoking cues (relative to baseline) in the right and left ventral striatum were significantly negatively correlated with FTND, as was activity in the right ventral striatum during neutral cues (relative to baseline). In no other regions was smoke or neutral relative to baseline significantly related to FTND.

DISCUSSION

This study examined whether pretreatment brain reactivity to smoking cues predicted duration to first lapse in smoking cessation treatment. Specifically, we examined whether neural response to smoking cues in five limbic/paralimbic regions of interest that have been shown in prior research to be activated by exposure to drug cues was associated with the number of days until lapse during an assisted cessation attempt. Greater neural response to smoking cues in the right ventral striatum, the left amygdala, and the caudal ACC was significantly associated with longer duration of abstinence following quit date.

Current models suggest the amygdala's and ventral striatum are critical to the process of assigning and experiencing of emotional and motivational salience to drug cues (Kühn and Gallinat 2011). The ACC has been associated with the cognitive modulation of emotion (Ochsner et al. 2004; Kalisch et al. 2006). These regions are all a part of what has been described as the 'final common pathway' of drug craving (Kalivas and Volkow 2005) which is a critical pathway to the reinforcing effects of different classes of drugs (Pierce and Kumaresan 2006). One model of the neural response to drug cues in addiction suggests that early stage use is characterized by deliberate hedonic use and associated with greater activity in limbic/paralimbic brain regions during cue exposure, while later stage drug use is characterized by craving occurring in response to internal cues, such as withdrawal, rather than environmental cues (Everitt and Robbins 2005; Everitt et al. 2008). The finding that increased ventral striatum, amygdala, and ACC reactivity to smoking cues was associated with greater duration of short-term abstinence in smoking cessation treatment may represent further support for this interpretation: that greater reactivity in these regions was associated with less difficulty quitting suggests their activity is an indicator of less severe risk for lapse. The inverse relationship of FTND with amygdala activation and the reductions in all regions' effect size as predictors when controlling for FTND is consistent with this interpretation, suggesting that some of these regions predictive ability is due to their relationship with severity of dependence. However, that the right ventral striatum was predictive beyond FTND suggests there may be other elements of lapse risk that are indicated by activity in these regions beyond self-report measures of nicotine dependence.

While this study found greater activity in these regions during smoking cues relative to neutral cues predicted better treatment response, prior studies using pretreatment fMRI to predict smoking cessation treatment outcomes have found evidence that greater neural responding in these regions is associated with treatment failure (Janes et al. 2010; Versace et al. 2014). It is possible that the discrepant findings might be explained by the influence of factors that moderate the degree of neural reactivity to smoking cues, such as individual demographic or smoking-related characteristics, or that the results could depend on study design features such as the specifics of the CR paradigm used. Another possibility is that the treatments in each of these studies played a role in this difference in directionality of the predictive findings. Although the interventions were ostensibly similar, there are still many potential differences, such as session duration, emphasis of treatment, treatment adherence, or therapist training. Thus, it is possible that the current findings indicate that relatively high-intensity treatment is helpful in individuals demonstrating high levels of limbic/paralimbic activity in response to smoking cues. More broadly, these results illustrate the need for larger studies designed to focus on determining moderating factors for predicting treatment outcomes using neuroimaging. Supplemental materials accompanying the current study provide the treatment manual and adherence materials to facilitate potential treatment modality influences in future studies. In addition to methodological moderators, some variability may be due to the inherent difficulty in using laboratory paradigms to predict complex, real-world behaviors such as quitting smoking. Despite its robustness in eliciting self-reported craving, cue-elicited subjective craving has not demonstrated a consistent relationship to outcome in smoking cessation treatment (Perkins 2012). In this study, self-reported craving in response to smoking cues was not associated with outcome, suggesting that fMRI may be more sensitive than self-reported craving, although this work is still in its early stages.

These findings should be considered within the context of their limitations and strengths. Strengths of the study included biochemical verification of smoking abstinence and a well-standardized treatment protocol using empirically-supported practices for the treatment of nicotine dependence, and a focused analysis strategy targeting a small network of brain regions that have been consistently shown to respond during exposure to drug cues across users of several addictive substances. Among the most important considerations was the choice to focus on the regions reported by Kuhn and Gallinat, which have previously been identified as associated with the mesolimbic dopamine pathway and critical to the hedonic experience of addictive drugs. This was done to limit the scope of the study, thereby reducing the likelihood of spurious findings, and increase the interpretability of findings by focusing on regions sharing a putative core function in cue-reactivity. Thus, this study had limited focus on one aspect of the neural response to drug cues. Studies addressing other neural systems involved in the response to drug/smoking cues (e.g., central executive network, default network) are needed to address questions about their efficacy in predicting treatment outcome. Another consideration is the metric of self-reported craving used. Since there has been substantially less research investigating neural response to CR paradigms as a predictor of outcome than self-reported craving as a predictor of outcome, in designing the cue-reactivity paradigm we focused on maximizing collection of neural response. As a result, subjective ratings were assessed at the beginning and end of each run, not at the end of each

block of smoking or neutral cues, preventing the calculation of average of smoking vs neutral cue block effects. Instead it yielded a craving assessment that included the pre- and post-CR effects of smoking cues and neutral cues combined. While the use of post-CR craving is supported by prior research that suggests that neutral cues have little to no effect on self-reported cravings to smoke and that drug cues generate increases in craving that persist through neutral cues (i.e., carryover effects; Monti et al. 1987), this approach does not capture self-reported craving at the same resolution as brain activation making its use as a comparator limited. Despite this limitation, the form of self-reported craving used in this study still provides preliminary evidence of unique value of using fMRI to predict lapse and offers useful contextual information through its association with activation in the ventral striatum and dorsal anterior cingulate. However, findings surrounding self-reported craving in this study should be interpreted with caution until replicated with higher resolution measures of self-reported craving. Lastly, while lower levels of activation during smoking cues relative to neutral cues predicted lapse in this study, at the group level significant differences in activation between smoking and neutral cues were found in only one of the three regions of interest that predicted lapse (caudal ACC). This may potentially be because the meta-analysis used to identify the a priori ROIs had substantially greater statistical power, indicating the value of using meta-analyses in ROI selection. In addition, in the context of treatment response, these patterns may be present because lapse-prone individuals exhibit diminished response to smoking cues in the striatum and amygdala and most participants in the current study lapsed at some point, leading to a lack of significant difference at the group level. However, hyperactivity during neutral cues in the striatum and amygdala in lapse-prone individuals may also play a role, as individual's exhibiting severe withdrawal may be triggered even by stimuli not overtly related to smoking. These interpretations are not mutually exclusive and both would be consistent with the incentive-habit model, which states that highly dependent individuals smoke in response to bodily cues (like withdrawal) rather than external stimuli. In fact, since no regional activations during individual conditions predicted lapse (i.e., smoke vs. baseline, neutral vs. baseline), both interpretations are likely true to some degree.

Acknowledging these considerations, this study nonetheless provides evidence that pre-treatment neural response to smoking cues in limbic/paralimbic brain regions typically associated with response to smoking cues and craving is positively associated with an individual's ability to abstain from smoking as part of an organized smoking cessation attempt. Consequently, this study's findings provide support to the incentive-habit model of drug addiction (Mogg et al. 2005; Everitt and Robbins 2013) by suggesting that reductions in neural responsivity to smoking cues in brain regions associated with incentive salience are associated with an inability to abstain from smoking in dependent smokers in treatment. Clinically, this implies that for smokers who have transitioned from incentive learning and more deliberative cognitive processing to having habit learning and automatized drug seeking, smoking cessation is more difficult. Refining these relationships and further disentangling the neural predictors of smoking cessation outcome remains a critical priority for future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to Francis Joseph McClernon, PhD at Duke University, who originally created the stimuli and provided them for this study. The authors thank the trainees involved in data collection and treatment provision for their contributions. This study was funded by NIH grant R21 DA031269-01, the Peter Boris Chair in Addictions Research, and the Gary R. Sperduto Professor in Clinical Psychology endowment. The funders had no role in the study design, data collection/analysis, or resulting manuscript.

References

- American Cancer Society. 2014A word about success rates for quitting smoking.
- Brandon TH, Tiffany ST, Obremski KM, Baker TB. 1990; Postcessation cigarette use: The process of relapse. *Addictive Behaviors*. 15:105–114. DOI: 10.1016/0306-4603(90)90013-N [PubMed: 2343783]
- Conklin CA, Parzynski CS, Salkeld RP, Perkins KA, Fonte CA. 2012; Cue Reactivity as a Predictor of Successful Abstinence Initiation Among Adult Smokers. *Experimental and Clinical Psychopharmacology*. doi: 10.1037/a0029599
- Cox RW. 1996; AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and biomedical research, an international journal*. 29(3):162–73.
- Deveci SE, Deveci F, Açık Y, Ozan AT. 2004; The measurement of exhaled carbon monoxide in healthy smokers and non-smokers. *Respiratory Medicine*. 98:551–556. DOI: 10.1016/j.rmed.2003.11.018 [PubMed: 15191041]
- Engelmann JM, Versace F, Robinson JD, Minnix JA, Lam CY, Cui Y, Brown VL, Cinciripini PM. 2012; Neural substrates of smoking cue reactivity: A meta-analysis of fMRI studies. *NeuroImage*. 60:252–262. DOI: 10.1016/j.neuroimage.2011.12.024 [PubMed: 22206965]
- Everitt BJ, Belin D, Economidou D, Pelloux Y, Dalley JW, Robbins TW. 2008; Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. *Philosophical transactions of the Royal Society of London Series B, Biological sciences*. 363(1507):3125–35. DOI: 10.1098/rstb.2008.0089 [PubMed: 18640910]
- Everitt BJ, Robbins TW. 2005; Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nature neuroscience*. 8(11):1481–9. DOI: 10.1038/nn1579 [PubMed: 16251991]
- Everitt, BJ, Robbins, TW. *Neuroscience & Biobehavioral Reviews*. Vol. 37. Elsevier Ltd; 2013. From the ventral to the dorsal striatum: Devolving views of their roles in drug addiction; 1946–1954.
- Fiore MC, Jaén CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, Dorfman SF, Froelicher ES, Goldstein MG, Heaton CG, Henderson PN, Heyman RB, Koh HK, Kottke TE, Lando HA, Mecklenburg RE, Mermelstein RJ, Mullen PD, Orleans CT, Robinson L, Stitzer ML, Tommasello AC, Villejo L, Wewers ME. 2008; A Clinical Practice Guideline for Treating Tobacco Use and Dependence: 2008 Update. :158–176. DOI: 10.1016/j.amepre.2008.04.009
- Janes AC, Pizzagalli DA, Richardt S, Frederick B deB, Chuzi S, Pachas G, Culhane MA, Holmes AJ, Fava M, Evins AE, Kaufman MJ. 2010; Brain Reactivity to Smoking Cues Prior to Smoking Cessation Predicts Ability to Maintain Tobacco Abstinence. *Biological Psychiatry*. 67:722–729. DOI: 10.1016/j.biopsych.2009.12.034 [PubMed: 20172508]
- Kalisch R, Wiech K, Critchley HD, Dolan RJ. 2006; Levels of appraisal: A medial prefrontal role in high-level appraisal of emotional material. *NeuroImage*. 30(4):1458–1466. DOI: 10.1016/j.neuroimage.2005.11.011 [PubMed: 16388969]
- Kalivas PW, Volkow ND. 2005; The Neural Basis of Addiction: A Pathology of Motivation and Choice. *American Journal of Psychiatry*. 162(8):1403–1413. DOI: 10.1176/appi.ajp.162.8.1403 [PubMed: 16055761]

- Kenford SL, Fiore MC, Jorenby DE, Smith SS, Wetter D, Baker TB. 1994; Predicting smoking cessation. Who will quit with and without the nicotine patch. *Journal of the American Medical Association*. 271(8):589–594. DOI: 10.1001/jama.271.8.589 [PubMed: 8301790]
- Kühn S, Gallinat J. 2011; Common biology of craving across legal and illegal drugs - a quantitative meta-analysis of cue-reactivity brain response. *European Journal of Neuroscience*. 33:1318–1326. DOI: 10.1111/j.1460-9568.2010.07590.x [PubMed: 21261758]
- McClermon FJ, Hiott FB, Huettel SA, Rose JE. 2005; Abstinence-induced changes in self-report craving correlate with event-related fMRI responses to smoking cues. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 30:1940–1947. DOI: 10.1038/sj.npp.1300780 [PubMed: 15920499]
- McClermon FJ, Hiott FB, Liu J, Salley AN, Behm FM, Rose JE. 2007; Selectively reduced responses to smoking cues in amygdala following extinction-based smoking cessation: Results of a preliminary functional magnetic resonance imaging study. *Addiction Biology*. 12:503–512. DOI: 10.1111/j.1369-1600.2007.00075.x [PubMed: 17573781]
- McClermon FJ, Kozink RV, Rose JE. 2008; Individual differences in nicotine dependence, withdrawal symptoms, and sex predict transient fMRI-BOLD responses to smoking cues. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 33:2148–2157. DOI: 10.1038/sj.npp.1301618 [PubMed: 17987060]
- Miller WR, Rollnick S. 2003; Motivational Interviewing: Preparing for change. *American Journal of Forensic Psychology*. 21:83–85.
- Mogg K, Field M, Bradley BP. 2005; Attentional and approach biases for smoking cues in smokers: An investigation of competing theoretical views of addiction. *Psychopharmacology*. 180(2):333–341. DOI: 10.1007/s00213-005-2158-x [PubMed: 15696322]
- Monti PM, Binkoff Ja, Abrams DB, Zwick WR, Nirenberg TD, Liepman MR. 1987; Reactivity of alcoholics and nonalcoholics to drinking cues. *Journal of abnormal psychology*. 96(2):122–126. DOI: 10.1037/0021-843X.96.2.122 [PubMed: 3584660]
- Moyers TB. The Global Rating of Motivational Interviewing Therapists. 2004
- National Institute on Drug Abuse. 2014DrugFacts: Cigarettes and Other Tobacco Products.
- Ochsner KN, Knierim K, Ludlow DH, Hanelin J, Ramachandran T, Glover G, Mackey SC. 2004; Reflecting upon feelings: an fMRI study of neural systems supporting the attribution of emotion to self and other. *Journal of cognitive neuroscience*. 16(10):1746–1772. DOI: 10.1162/0898929042947829 [PubMed: 15701226]
- Perkins KA. 2009; Does smoking cue-induced craving tell us anything important about nicotine dependence? *Addiction (Abingdon, England)*. 104:1610–1616. DOI: 10.1111/j.1360-0443.2009.02550.x
- Perkins K. 2012; Subjective reactivity to smoking cues as a predictor of quitting success. *Nicotine and Tobacco Research*. 14(4):383–387. DOI: 10.1093/ntr/ntr229 [PubMed: 22140145]
- Pierce RC, Kumaresan V. 2006; The mesolimbic dopamine system: The final common pathway for the reinforcing effect of drugs of abuse? *Neuroscience and Biobehavioral Reviews*. 30(2):215–238. DOI: 10.1016/j.neubiorev.2005.04.016 [PubMed: 16099045]
- Piper ME, McCarthy DE, Baker TB. 2006; Assessing tobacco dependence: a guide to measure evaluation and selection. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*. 8:339–351. DOI: 10.1080/14622200600672765 [PubMed: 16801292]
- Robinson TE, Berridge KC. 1993; The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Research Reviews*. 18(3):247–291. DOI: 10.1016/0165-0173(93)90013-P [PubMed: 8401595]
- Robinson TE, Berridge KC. 2001; Incentive-sensitization and addiction. *Addiction*. 96(1):103–114. DOI: 10.1046/j.1360-0443.2001.9611038.x [PubMed: 11177523]
- Robinson TE, Berridge KC. 2008; The incentive sensitization theory of addiction: some current issues. *Philosophical transactions of the Royal Society of London Series B, Biological sciences*. 363(1507):3137–46. DOI: 10.1098/rstb.2008.0093 [PubMed: 18640920]
- Robinson SM, Sobell LC, Sobell MB, Leo GI. 2014; Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use. *Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors*. 28:154–62. DOI: 10.1037/a0030992 [PubMed: 23276315]

- Saad ZS, Glen DR, Chen G, Beauchamp MS, Desai R, Cox RW. 2009; A new method for improving functional-to-structural MRI alignment using local Pearson correlation. *NeuroImage*. 44:839–848. DOI: 10.1016/j.neuroimage.2008.09.037 [PubMed: 18976717]
- Shiffman S, Hickcox M, Paty JA, Gnys M, Kassel JD, Richards TJ. 1996; Progression from a smoking lapse to relapse: prediction from abstinence violation effects, nicotine dependence, and lapse characteristics. *Journal of consulting and clinical psychology*. 64(5):993–1002. DOI: 10.1037/0022-006X.64.5.993 [PubMed: 8916628]
- Talairach, J, Tournoux, P. Co-Planar Stereotaxis Atlas of the Human Brain. 1. Thieme Medical Publishers; Stuttgart, Germany: 1988.
- Versace F, Engelmann JM, Jackson EF, Costa VD, Robinson JD, Lam CY, Minnix JA, Brown VL, Wetter DW, Cinciripini PM. 2011; Do brain responses to emotional images and cigarette cues differ? An fMRI study in smokers. *The European journal of neuroscience*. 34(12):2054–63. DOI: 10.1111/j.1460-9568.2011.07915.x [PubMed: 22097928]
- Versace F, Engelmann JM, Robinson JD, Jackson EF, Green CE, Lam CY, Minnix JA, Karamhage MA, Brown VL, Wetter DW, Cinciripini PM. 2014; Prequit fMRI responses to pleasant cues and cigarette-related cues predict smoking cessation outcome. *Nicotine and Tobacco Research*. 16:697–708. DOI: 10.1093/ntr/ntt214 [PubMed: 24376278]
- Vollstädt-Klein S, Kobiella A, Bühler M, Graf C, Fehr C, Mann K, Smolka MN. 2011; Severity of dependence modulates smokers' neuronal cue reactivity and cigarette craving elicited by tobacco advertisement. *Addiction Biology*. 16:166–175. DOI: 10.1111/j.1369-1600.2010.00207.x [PubMed: 20331560]
- Wald NJ, Idle M, Boreham J, Bailey A. 1981; Carbon monoxide in breath in relation to smoking and carboxyhaemoglobin levels. *Thorax*. 36:366–369. DOI: 10.1136/thx.36.5.366 [PubMed: 7314006]
- Waters AJ, Shiffman S, Sayette MA, Paty JA, Gwaltney CJ, Balabanis MH. 2004; Cue-provoked craving and nicotine replacement therapy in smoking cessation. *Journal of consulting and clinical psychology*. 72(6):1136–1143. DOI: 10.1037/0022-006X.72.6.1136 [PubMed: 15612859]
- West R, Brown J. 2013; A synthetic theory of motivation. *Theory of Addiction*. :192–228. DOI: 10.1002/9781118484890.ch8
- Wilson SJ, Sayette MA. 2015; Neuroimaging craving: Urge intensity matters. *Addiction*. 110(2):195–203. DOI: 10.1111/add.12676 [PubMed: 25073979]
- Wray JM, Gass JC, Tiffany ST. 2013; A systematic review of the relationships between craving and smoking cessation. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*. 15:1167–82. DOI: 10.1093/ntr/nts268 [PubMed: 23291636]

Figure 1.

A priori regions of interest. Pink = amygdala; yellow = left ventral striatum, blue = right ventral striatum, orange = rostral anterior cingulate cortex, green = caudal anterior cingulate cortex. Left = left. Panel A) Axial slices, left to right z coordinates: -14, -3, 8, 19. Panel B) Sagittal slice, x coordinate: -4. Panel C) Coronal slices, left to right y coordinates: 5, -3.

Figure 2.
Correlation between amygdala activation during smoking cues relative to neutral cues in percent signal change and Fagerström Test of Nicotine Dependence (FTND).

Table 1Demographics (*N*= 32)

Variable	<i>M (SD) or %</i>
Age	39.1 (11.9)
Gender (%female)	43.7%
Race (%)	
White	68.7%
Black/African-American	28.1%
Asian	3.1%
Ethnicity	
Hispanic or Latino	3.1%
Not Hispanic or Latino	96.9%
Annual Income (%)	
\$0–9,000	34.3%
\$10–19,000	31.2%
\$20–29,000	15.6%
\$30–39,000	18.8%
Education (years)	13.8 (2.2)
Cigarettes smoked per day	21.3 (11.7)
Exhaled carbon monoxide (parts per million)	21.8 (10.0)
Fagerström Test of Nicotine Dependence	4.8 (2.4)

Cox proportional-hazard regression models of *a Priori* Regions of Interest as Predictors of days to lapse. Regions of interest were transformed to Z-scores to enhance interpretability. Each model represents one of five separate regression analysis.

Table 2

A Priori ROIs		X	Y	Z	Hazard Ratio	95% CI	p
L	Ventral Striatum	-6	-4	-5	.82	.57 – 1.18	.29
R	Ventral Striatum	5	5	-6	.57	.38 – .86	.008
	Caudal Anterior Cingulate	-5	30	24	.61	.40 – .95	.03
L	Amygdala	-19	-4	-18	.53	.32 – .87	.01
	Rostral Anterior Cingulate	-4	42	10	.74	.49 – 1.13	.16

Significant findings are in bold.

X, Y, Z report center of mass of regions drawn from Kühn & Gallinat, 2011
Montreal Neurological Institute (MNI) coordinates