Published in final edited form as:

Biol Psychiatry. 2010 April 15; 67(8): 722–729. doi:10.1016/j.biopsych.2009.12.034.

Brain Reactivity to Smoking Cues Prior to Smoking Cessation Predicts Ability to Maintain Tobacco Abstinence

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Abstract

Background—Developing means to identify smokers at high risk for relapse could advance relapse prevention therapy. We hypothesized that functional magnetic resonance imaging (fMRI) reactivity to smoking-related cues, measured prior to a quit attempt, could identify smokers with heightened relapse vulnerability.

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Disclosures

The following authors reported no biomedical financial interests or potential conflicts of interest. ACJ, BBF, SR, SC, GP, MC, AH, DAP: has received research support from GlaxoSmithKline and ANT North America Inc. (Advanced Neuro Technology), consulting fees from ANT North America Inc. (Advanced Neuro Technology) and AstraZeneca for projects unrelated to the current study, and honoraria from AstraZeneca.

AEE: Research Product Support from Pfizer, and Speaker Honoraria from Reed Medical Education.

MF: Research Support: Abbott Laboratories, Alkermes, Aspect Medical Systems, Astra-Zeneca, Bio Research, BrainCells, Inc., Bristol-Myers Squibb Company, Cephalon, Clinical Trial Solutions, Eli Lilly & Company, Forest Pharmaceuticals Inc., Ganeden, GSK, J & J Pharmaceuticals, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, NARSAD, NCCAM, NIDA, NIMH, Novartis, Organon Inc., PamLab, LLC, Pfizer Inc, Pharmavite, Roche, Sanofi-Aventis, Shire, Solvay Pharmaceuticals, Inc., Synthelabo, Wyeth-Ayerst Laboratories

Advisory/Consulting: Abbott Laboratories, Amarin, Aspect Medical Systems, Astra-Zeneca, Auspex Pharmaceuticals, Bayer AG, Best Practice Project Management, Inc, BioMarin Pharmaceuticals, Inc., Biovail Pharmaceuticals, Inc., BrainCells, Inc, Bristol-Myers Squibb Company, Cephalon, Clinical Trials Solutions, CNS Response, Compellis, Cypress Pharmaceuticals, Dov Pharmaceuticals, Eisai, Inc., Eli Lilly & Company, EPIX Pharmaceuticals, Euthymics Bioscience, Inc., Fabre-Kramer, Pharmaceuticals, Inc., Forest Pharmaceuticals Inc., GSK, Grunenthal GmbH Janssen Pharmaceutica, Jazz Pharmaceuticals, J & J Pharmaceuticals, Knoll Pharmaceutical Company, Labopharm, Lorex Pharmaceuticals, Lundbeck, MedAvante Inc. Merck, Methylation Sciences, Neuronetics, Novartis, Nutrition 21, Organon Inc., PamLab, LLC, Pfizer Inc, PharmaStar, Pharmavite, Precision Human Biolaboratory, PsychoGenics, Roche, Sanofi-Aventis, Sepracor, Schering-Plough, Solvay Pharmaceuticals, Inc., Somaxon, Somerset Pharmaceuticals, Synthelabo, Takeda, Tetrigenex, Trancept Pharmaceuticals, TransForm Pharmaceuticals, Vanda Pharmaceuticals, Inc., Wyeth-Ayerst Laboratories. Speaking/Publishing: Adamed Co., Advanced Meeting Partners, American Psychiatric Association, American Society of Clinical Psychopharmacology, Astra-Zeneca, Belvoir, Boehringer-Ingelheim, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithKline, Imedex, Novartis, Organon Inc., Pfizer Inc, PharmaStar, MGH Psychiatry Academy/Primedia, MGH Psychiatry Academy/Reed-Elsevier, UBC, Wyeth-Ayerst Laboratories. Equity Holdings: Compellis

Royalty/patent, other income: patent applications for SPCD and for a combination of azapirones and bupropion in MDD, copyright royalties for the MGH CPFQ, SFI, ATRQ, DESS, and SAFER

MJK: Research Support: GSK, Organon, Varian Inc., BioPAL; Advisory/Consulting: Amgen, Novartis.

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Methods—Twenty-one nicotine-dependent women underwent fMRI prior to quitting smoking, during which smoking-related and neutral images were shown. These smokers also were tested for possible attentional biases to smoking-related words using a computerized emotional Stroop (ES) task previously found to predict relapse. Smokers then made a quit attempt and were grouped based on outcomes (abstinence versus slip: smoking 1 cigarette after attaining abstinence). Pre-quit fMRI and ES measurements in these groups were compared.

Results—Slip subjects had heightened fMRI reactivity to smoking-related images in brain regions implicated in emotion, interoceptive awareness, and motor planning and execution. Smoking cue-induced insula and dorsal anterior cingulate cortex (dACC) reactivity correlated with an attentional bias to smoking-related words. A discriminant analysis of ES and fMRI data predicted outcomes with 79% accuracy. Additionally, smokers who slipped had decreased fMRI functional connectivity between an insula-containing network and brain regions involved in cognitive control, including the dACC and dorsal lateral prefrontal cortex, possibly reflecting reduced top-down control of smoking-related cue-induced emotions.

Conclusions—These findings suggest that the insula and dACC are important substrates of smoking relapse vulnerability. The data also suggest that relapse-vulnerable smokers can be identified prior to quit attempts, which could enable personalized treatment, improve tobacco-dependence treatment outcomes, and reduce smoking-related morbidity and mortality.

Keywords

Insula; Dorsal anterior cingulate cortex; fMRI; emotional Stroop task; tobacco; relapse

Introduction

Tobacco-related illness is estimated to cause over 5 million yearly deaths in the developed world (1). By 2030, the yearly smoking-related death toll is expected to rise to 8 million unless current smoking trends are reversed (1). Although most smokers would like to quit (2) and nicotine dependence treatments exist (3–5), relapse rates remain high (6–8). Since relapse vulnerability is strongly influenced by smoking cue reactivity (9), developing a better understanding of neurobiological mechanisms underlying smoking cue reactivity may lead to new treatments. From a clinical perspective, developing means to identify relapse-vulnerable smokers prior to smoking cessation would allow for personalized treatment, possibly reducing smoking relapse and associated morbidity and mortality.

Functional MRI (fMRI) may be useful for identifying brain regions and circuits underlying relapse vulnerability. Functional MRI studies of smokers have reported a number of brain areas that are reactive to smoking-related cues (10–12). However, it is unknown whether fMRI reactivity to smoking cues can predict relapse vulnerability. Therefore, we determined whether fMRI smoking-cue reactivity before a smoking cessation attempt relates to smoking outcomes, by assessing smoking cue brain reactivity in smokers about to quit smoking. The clinical outcome of interest by which smoking cue-reactivity data was grouped was smoking any part of a cigarette after attaining at least 24 hours of abstinence (a “slip”). Slips occur early in the course of smoking cessation attempts, are triggered by exposure to smoking-related cues (13), and are highly predictive of relapse in naturalistic (8,14–17) and controlled studies (18). It was hypothesized that fMRI reactivity to smoking-related cues would differ based on short-term cessation outcomes.

We investigated whether slip subjects exhibited different group level whole brain fMRI activation patterns. To develop a neuroanatomical model predictive of individual smoking cessation outcomes, individual subject data were used to examine the effects of smoking-related cues on specific brain regions including the insula, dorsal anterior cingulate (dACC),

dorsal lateral prefrontal cortex (DLPFC), and amygdala. The insula was a main focus since it is reactive to smoking-related cues (19), it may mediate cue-induced craving (20), and it is thought to be critical for maintaining tobacco dependence (21). The anterior insula may be particularly important since it is thought to be the site of interoceptive awareness and it is active during a range of subjective feeling states (22). The ACC was targeted since it is anatomically connected to the insula (22), both regions co-activate in studies of interoceptive awareness, and the dACC activates when smokers attempt to resist cue-induced craving (10), possibly reflecting an effort to exert cognitive control (23). Functional MRI reactivity in the left DLPFC was assessed since high-frequency transcranial magnetic stimulation over the left DLPFC reduces cigarette craving and consumption (24). The amygdala also was investigated because it plays a role in initial responses to emotionally salient stimuli (e.g., (25)), including smoking cues (11). Because interactions between brain regions may be important in regulating smoking cue reactivity (26), a functional connectivity analysis was conducted on the same fMRI data. We evaluated whether functional connectivity of a network containing the anterior insula and dACC differed as a function of the ability to maintain abstinence.

Behavioral performance on an emotional Stroop (ES) task, which has been shown to identify recently-abstinent smokers with heightened relapse vulnerability (27), was assessed. It is unknown whether an attentional bias for smoking-related words, measured with the ES *prior* to smoking cessation, can predict relapse vulnerability.

It was hypothesized that, prior to quitting smokers who would slip would have greater fMRI reactivity to smoking-related images and disrupted functional connectivity of the insula/dACC network. We also hypothesized that an attentional bias for smoking-related words on the ES task would correlate with fMRI reactivity to smoking-related images in the insula, dACC, left DLPFC, and amygdala, and these measures would predict smoking cessation outcomes.

Methods

Subjects

Twenty-one women underwent neuroimaging at McLean Hospital before participating in a smoking cessation clinical trial at Massachusetts General Hospital (MGH, NCT00218465). Subjects met DSM-IV criteria for current nicotine dependence, reported smoking 10 cigarettes/day in the last 6 months, and had expired air carbon monoxide (CO) >10 ppm at screening. Smokers with current unstable medical illness, pregnancy, recent drug/alcohol use (QuickTox 11 Panel Drug Test Card, Branan Medical Corporation, Irvine California; Alco-Sensor IV, Intoximeters Inc., St. Louis, MO), major depressive disorder, alcohol use disorder in the prior 6 months, current psychotropic drug use, or lifetime diagnosis of organic mental or psychotic disorders were excluded. Only women were enrolled since the parent clinical trial involved an investigational medication not approved for use in men. Institutional Review Boards at MGH and McLean Hospital approved this study. Subjects provided written informed consent and were compensated for participation.

Baseline smoking behavior was characterized by recording/measuring pack-years of tobacco smoking, expiratory CO levels (Bedfont Micro IV Smokerlyzer, Bedfont Scientific, Kent, England), the number of cigarettes smoked the morning prior to imaging, and by administering the Fagerstrom Test for Nicotine Dependence (FTND) (28). Group differences (slip versus abstinence) were assessed with two-sided Student's t-tests.

Emotional Stroop Task

Nineteen subjects performed a computerized ES task (27) prior to smoking cessation, in which smoking-related and neutral words, matched for length and use frequency in English language, were displayed in red, green, or blue fonts, using Eprime software (Psychology Software Tools, Inc., Pittsburgh, PA). Subjects were instructed to report (via button press) word color as quickly and accurately as possible, and ignore word meaning. After a 96-trial practice block of letter strings, four 33-trial experimental blocks separated by 5-second breaks were run in the following word order: neutral, smoking, smoking, neutral. To replicate prior studies and avoid smoking-related word carryover effects, analyses were restricted to the first 2 blocks (as per (27,29,30)). Analyses considering all four blocks yielded similar findings (see Results).

Each trial began with a fixation cross (500 ms), followed by word presentation until a response was made, followed by a 500-ms inter-trial interval. If no response occurred within 3 seconds, the word disappeared and a new trial started after 500 ms. A 500-ms tone was presented after incorrect/absent responses. Reaction times (RT) and accuracies were recorded by computer.

To minimize outlier response effects, outlier trials ($150 \text{ ms} > \text{RT} > 1500 \text{ ms}$) were excluded as were trials with natural log-transformed RT falling outside the range of mean ± 3 SD. Mixed analyses of covariance (ANCOVAs) were run separately on accuracy and RT scores entering *Group* (slip, abstinent) as between-subject factors, *Condition* (Neutral vs. Smoking-related words) as repeated measures, and FTND scores as covariates (subjects who eventually slipped had higher baseline FTND scores; see Results). *Group* $\times$ *Condition* interactions indicated significant group differences in ES task interference effects, computed as $\text{Accuracy}_{\text{Neutral}} - \text{Accuracy}_{\text{Smoking}}$ and $\text{RT}_{\text{Smoking}} - \text{RT}_{\text{Neutral}}$. Higher RT/accuracy values indicated smoking-related interference effects.

Neuroimaging

Smoking was not restricted until shortly before imaging. During fMRI, subjects viewed smoking-related (people smoking, hands holding cigarettes, or cigarettes alone) or neutral (general content-matched but no smoking cues) images (11,31). Animal images were shown to prompt subjects to press a response button and were included to ensure subjects attended to stimuli, but were not used in data analyses. A total of 42 smoking-related, 40 neutral, and 8 animal images were presented in six equal length blocks. Each image was presented pseudo-randomly for 4 seconds with no more than two of the same stimulus type appearing consecutively. A fixation cross appeared for 14 seconds between images.

Scans were acquired on a Siemens Trio 3 Tesla scanner (Erlangen, Germany) with a circularly polarized (CP) head coil. Multiplanar rapidly acquired gradient-echo structural images (TR=2.1 sec, TE=2.7 msec, slices=128, matrix=256 $\times$ 256, flip angle=12, resolution=1.0 $\times$ 1.0 $\times$ 1.33 mm) and gradient echo echo-planar images (TR=2 sec, TE=30 msec, matrix=64 $\times$ 64, field of view=224, flip angle=75, slices=30, resolution=3.5mm isotropic with 0mm gap) were acquired.

fMRI Analyses

Images were analyzed using Brain Voyager QX 1.10.4 (Brain Innovation, Maastricht, Netherlands). Images were slice-time corrected, motion corrected, spatially smoothed (6mm Gaussian kernel), resampled to 3 $\times$ 3 $\times$ 3mm isotropic voxels, and spatially normalized into Talairach space. To reduce motion-related variability, a program (based on (32)) was used to model out time points (1.2% of all data points) exhibiting motion $> 1.75\text{mm}$ ($\frac{1}{2}$ voxel size).

A whole-brain fixed-effects general linear model (GLM) was run using image regressors (smoking, neutral, animal images) and motion confound regressors. The 2-gamma hemodynamic response function was convolved with square waves defined by the onset/offset of each image presentation. Beta maps comparing smoking to neutral images were created for each subject. These maps were used to compare fMRI activity between slip and abstinent subject groups using a random-effects ANOVA.

Multiple comparisons were cluster level corrected (33). To determine the cluster extent necessary to correct for multiple comparisons, a Monte Carlo simulation (a standard method used to correct multiple comparisons (34), was run with Matlab script Cluster_threshold_beta (35). In a single simulation, the minimum size of each contiguous voxel cluster was determined by modeling the functional image matrix (64×64×30 voxels), by assuming an individual voxel type 1 error of $p=0.01$, and by smoothing the activation map by a 3-dimensional 6mm FWHM Gaussian kernel. Following 10,000 simulations, the cluster size probability was determined and the cluster extent that yielded $p=0.005$ (thirty-one 3mm resampled isotropic voxels, $\sim 837 \text{ mm}^3$) was selected, which is more conservative than accepted threshold levels (36).

Region-of-interest (ROI) Analyses: Relation to Cessation Outcome and Emotional Stroop Performance

Beta weights for the smoking image>neutral image contrasts were extracted from the anterior insula, dACC, DLPFC, and amygdala, using the Brain Voyager ROI analysis tool. Beta weights were averaged across all voxels within each ROI. The insula and amygdala ROIs were defined anatomically and the DLPFC and dACC were defined based on the functional connectivity analysis (see Figure S1 in Supplement 1). A Pearson's correlation coefficient was calculated to evaluate possible relationships between ROI fMRI activation and ES task performance. To determine whether pre-quit fMRI and ES findings could discriminate slip from abstinent subjects, a discriminant analysis using a cross-validation approach was performed. The cross-validation used a leave-one-out classification strategy, in which each case was iteratively classified based on all other cases, in order to minimize the possible effects of single subjects on the discriminant function.

Independent Component Analysis (ICA)

The ICA was performed on cue-reactivity fMRI data to determine functional connectivity between insula and frontocingulate areas. ICA was chosen rather than a seed region-based approach because ICA more effectively removes artifacts stemming from functional connectivity analyses based on seed regions (37). Additionally, ICA is superior for separating independent functional networks, allowing the selection of a network containing the bilateral insula, the anterior cingulate and other frontal brain structures, from other networks in which the insula may be involved.

The Group ICA fMRI Toolbox v1.3e (GIFT, (38)) was used to identify the independent component containing insula and ACC. Since group ICA requires that all data be analyzed simultaneously, a principal component analysis data reduction step was run to load all data into memory. Data then were concatenated into a matrix and a group spatial ICA was performed using the infomax algorithm. ICA splits fMRI data into independent components, which are temporally correlated groupings of fMRI signals that represent independent functional networks. The GIFT minimum description length algorithm determined that 25 optimal components existed. All 25 maps representing average connectivity for all 21 subjects were visually inspected. Based on our *a priori* hypothesis, component #2 containing bilateral insula and anterior cingulate (but not spurious connectivity signal in white matter or ventricles) was selected for further analysis.

Next, each participant's component #2 time course was converted into a Brain Voyager-compatible regressor and a random-effects GLM was run containing the component #2 time course and motion confound regressors. The component #2 activation map for all 21 subjects was Bonferroni corrected to $p < 0.01$ and compared between slip and abstinence subjects, using a random-effects ANOVA. Multiple comparisons were corrected to $p = 0.005$ with the Monte Carlo procedure described above.

Smoking Cessation

After pre-quit imaging and other assessments, all subjects quit smoking during the 8-week smoking cessation phase of the clinical trial. Interventions included a weekly, manualized individual behavioral intervention, nicotine patch (21 mg/day for 4 weeks, 14 mg/day for 2 weeks, 7 mg/day for 2 weeks), and 2 mg nicotine polacrilex gum or lozenge, up to 12 mg/day, to be used as needed. All participants quit smoking for at least 24 hours. Following 24 hours abstinence, participants who smoked any cigarettes during the NRT treatment period were considered to be at high risk for relapse (slip group), and those who did not smoke during this period were considered at low relapse risk (abstinence group). Our criteria were based on a Society for Research on Nicotine and Tobacco's working group definition of relapse as smoking 7 or more consecutive days or more than once/week for 2 or more consecutive weeks, and a slip as smoking any amount less than this following at least 24 hours abstinence (39). Smoking status was established by weekly self-report of smoking behavior in the prior 7 days using the Time Line Followback Method (40,41) and weekly expired CO measurements. Subjects who self-reported abstinence and had an expired $\text{CO} < 9\text{ppm}$ were considered abstinent.

Results

Of the 21 subjects who completed pre-quit neuroimaging, 9 slipped while on NRT. Slips took place on average 17.4 days (range: 1–49 days) after established abstinence. Slip and abstinence groups only differed on FTND scores ($t_{19} = 2.6$, $p < 0.02$; Table 1) and not on any other demographic variable. Of the 19 subjects completing the ES task, 8 slipped. In the entire clinical trial cohort ($N = 126$) from which study subjects were recruited, slips were strong predictors of relapse (Odds Ratio = 4.25, 95% Confidence Interval: 1.41–12.79, $p < 0.01$).

Functional MRI Results

Whole-Brain Analysis—A whole-brain mixed-effects analysis revealed that, relative to the abstinent group, the slip group had greater smoking-related versus neutral image reactivity in the bilateral insula, ACC, posterior cingulate cortex, amygdala, primary motor cortex, premotor cortex, inferior parietal cortex, parahippocampal gyrus, thalamus, putamen, cerebellar hemispheres and vermis, prefrontal cortex, and striate and extra-striate cortex ($t_{19} = 2.86$, cluster corrected $p \leq 0.005$, Fig. 1; see also Table S1 in Supplement 1).

Emotional Stroop Task—A mixed *Group* (slip, abstinence) $\times$ *Condition* (neutral vs. smoking-related words) analysis of covariance (ANCOVA), adjusting for FTND scores, was conducted. For both reaction time ($F_{1,16} = 9.98$, $p < 0.006$) and accuracy ($F_{1,16} = 9.61$, $p < 0.007$), the *Group* $\times$ *Condition* was significant, due to significantly higher smoking-related interference effects ($\text{RT}_{\text{Smoking}} - \text{RT}_{\text{Neutral}}$ and $\text{Accuracy}_{\text{Neutral}} - \text{Accuracy}_{\text{Smoking}}$) in slip subjects ($n = 8$) relative to abstinent subjects ($n = 11$; Table 1). Highlighting the specificity of these findings, there was no main effect of *Group* either for accuracy ($F_{1,16} = 0.37$, $p > 0.55$) or reaction time ($F_{1,16} = 0.01$, $p > 0.94$). *Group* $\times$ *Condition* effects were replicated for the reaction time measure when considering all four blocks (reaction time: $F_{1,16} = 7.05$, $p < 0.02$; and accuracy: $F_{1,16} = 3.64$, $p = 0.074$).

Correlations Between fMRI and Emotional Stroop Data—Right and left anterior insula fMRI reactivity was strongly correlated ($r=0.93$, $p<0.001$); accordingly, the mean bilateral anterior insula activity was used for correlation analyses. In subjects undergoing both fMRI and the ES task ($n=19$), mean anterior insula ROI Beta weights were significantly correlated with task interference effects (accuracy: $r=-0.62$, $p<0.006$; RT: $r=0.51$, $p<0.03$), as were the Beta weights for the dACC (accuracy: $r=-0.53$, $p<0.025$; RT: $r=0.41$, $p<0.083$). For the left DLPFC and amygdala, no correlations emerged (all $p>0.11$). Thus, participants with the strongest anterior insula and dACC fMRI activation to smoking-related images showed the largest interference effects. Hierarchical regression analyses confirmed that ES interference effects predicted mean insular and dACC activity after controlling for FTND scores (mean insula: accuracy: $\Delta R^2=0.38$, $\Delta F_{1,16}=9.76$, $p<0.007$; RT: $\Delta R^2=0.25$, $\Delta F_{1,16}=5.43$, $p<0.04$; dACC: accuracy $\Delta R^2=0.37$, $\Delta F_{1,16}=10.43$, $p<0.005$).

Given group differences in ES effects and insula/dACC activation, a discriminant analysis was conducted to determine whether pre-quit data could discriminate slip from abstinent subjects. Stroop interference RT (Wilks' $\lambda=0.71$) and accuracy effects (Wilks' $\lambda=0.60$) as well as mean anterior insula fMRI reactivity (Wilks' $\lambda=0.73$) were all significant outcome predictors (all $F_{s,17}>6.21$, $ps<0.025$), whereas dACC fMRI reactivity was not (Wilks' $\lambda=0.95$). Further, when all four predictors were included, the overall model was significant ($\chi^2(4)=10.44$, $p<0.035$), and correctly classified 5 of 8 slip and 10 of 11 abstinent subjects (78.9% correct classification rate). A model including only the ES interference effects and the mean insula reactivity also was significant ($\chi^2(3)=9.23$, $p<0.026$) and correctly classified 73.7% of cross-validated grouped cases (8 of 11 abstinent and 6 of 8 slip subjects).

Functional Connectivity Results—In light of our *a priori* hypothesis concerning the insula and the ACC (22), a network containing the insula and ACC was identified from the ICA functional connectivity analysis. This network included temporal and frontal cortical regions, the rostral and dACC, surrounding frontal regions (including pre- and primary motor cortex and prefrontal cortex), and primary and association visual areas within the occipital and parietal cortex. The network also included the thalamus, amygdala, caudate nucleus, putamen, brainstem, and cerebellar hemispheres ($t_{20}=7.80$, Bonferroni corrected $p=0.01$, Fig. 2; see also Table S2 in Supplement 1). When comparing this network between subjects who slipped and maintained abstinence, slip subjects showed decreased functional connectivity between this network and the left insula, adjacent inferior frontal gyri, prefrontal cortex, ACC, primary and premotor cortex, primary somatosensory cortex, cerebellum, superior and middle temporal gyrus, putamen, and primary visual and visual association cortices ($t_{20}=2.85$, cluster corrected $p=0.005$, Fig. 2; see also Table S3 in Supplement 1).

Discussion

Smokers who slipped during the quit attempt exhibited increased pre-quit brain fMRI reactivity to smoking-related images in the insula, amygdala, and several other brain areas. Insula and amygdala activation might imply that smoking-related images are more emotionally salient and may induce interoceptive awareness to a greater extent than neutral images in smokers vulnerable to relapse. The current insula findings coincide with evidence suggesting that this region is involved in maintaining smoking behavior and processing smoking- and other drug-related cues (19,21). Slip subjects also had increased reactivity to smoking-related images in motor control and planning areas such as ACC, prefrontal cortex, and others involved in motor behavior (e.g. premotor cortex, cerebellum, (42)), replicating data indicating that smoking cues enhance brain reactivity in regions related to tool use (43). This enhanced reactivity raises the possibility that, in the presence of smoking-related

stimuli, vulnerable subjects may be more likely to prepare for or initiate motor responses geared toward reducing interoceptive sensations related to craving.

Functional Connectivity Findings

The functional connectivity analysis identified a network including the insula and ACC, which are structurally connected and co-activate in studies of interoceptive awareness (22). This network included brain regions involved in emotional processing (e.g. amygdala, insula; (25)) and in reactivity to smoking-related cues (amygdala, thalamus, cuneus, insula; (11,12,44)). Slip subjects had reduced pre-quit connectivity between this network and brain regions involved in response inhibition (45), such as the dACC and DLPFC. Slip subjects also had less connectivity between the overall network and the left insula, an interesting finding since the left insula may bridge communications between the executive-control and interoceptive networks (46). The connectivity findings along with impaired ES performance suggest that slip subjects may have decreased top-down control of emotion regulation. This could result in increased interoceptive awareness of smoking-related cues, leading to enhanced smoking cue-reactivity, ES interference effects, and relapse vulnerability.

Correlation Analyses

The mean bilateral insula fMRI activation to smoking-related images was correlated with indexes of increased attentional bias to smoking-related words, possibly reflecting a behavioral phenotype of relapse vulnerability (27). This correlation may result from the insula's role in interoceptive awareness (22). Attention to internal states such as craving upon exposure to smoking cues/words could increase attentional bias toward smoking-related words and thus be associated with increased interference scores on the ES task. These findings suggest that the insula is an important brain substrate of relapse vulnerability. Additionally, dACC activation was found to correlate with decreased accuracy to name the color of smoking-related words. Dorsal ACC activation increases when smokers try to resist cue-induced craving (10), which may reflect greater effort to maintain cognitive control over craving responses (47). We found decreased functional connectivity between the dACC and insula, suggesting that the ability of the dACC to regulate insula and interoceptive states may be disrupted in subjects who will eventually slip. One interpretation is that slip subjects, with reduced dACC functional connectivity, may exhibit greater dACC activity in response to smoking-related cues, as an attempt to maintain top-down control of interoceptive and emotional states.

We conclude that increased smoking-related anterior insula and dACC reactivity and ES attentional bias may reflect potentiated relapse vulnerability. Consistent with this assumption, a discriminant analysis including mean bilateral insula and dACC fMRI reactivity and ES interference effects predicted, with high accuracy, which smokers would slip after attaining initial smoking abstinence. Our model remained predictive after controlling for nicotine dependence severity, using the FTND. The FTND accounts for some, but not likely all residual variance, suggesting that other aspects of dependence-related variance including plasma nicotine/cotinine levels may have contributed to group differences. The ability of fMRI and ES to predict short-term outcomes warrants confirmation in an independent sample to determine whether these measurements have utility as a clinical prediction tool. Such a tool could be used to personalize treatment and enrich clinical trials of novel smoking relapse prevention treatments with subjects more likely to relapse, potentially reducing variability and accelerating drug discovery.

Limitations

An important caveat is that this study only included women. Since smoking cue-reactivity and craving differ by sex (44,48), it is unclear whether our findings generalize to men.

However, no sex differences were reported for the effects of insular lesions on smoking behavior (21) and no sex differences in insula reactivity to smoking cues have been reported (44), suggesting that sex differences minimally influence study findings. In addition, menstrual cycle phase was not controlled for, and we cannot rule out a possible influence of menstrual cycle on the current findings. One argument against this possibility is that participants underwent fMRI and the ES task, and quit smoking, over different time intervals that span menstrual cycle phases (8.2 ± 4.7 days apart), with no difference between slip and abstinence groups. Thus, we believe our findings, and in particular, the correlation between anterior insula fMRI smoking cue reactivity and ES interference effects, are not attributable to menstrual cycle effects. We intend to examine the effects of sex and menstrual cycle phase in future fMRI cue reactivity studies.

Future Directions

Follow up studies are needed to validate our observation that fMRI and ES can predict short-term cessation outcomes. Such information should help prospectively identify smokers who would benefit from standard therapies (e.g., NRT) as well as those who may benefit from tailored relapse-prevention treatments, including treatments that may modulate insula reactivity to smoking-related cues. For example, the macaque insula is enriched in corticotrophin-releasing factor-1 (CRF-1) receptors (49) and in rodent work, a CRF-1 receptor antagonist reduced deficits in brain reward function induced by nicotine withdrawal and stress-induced relapse (50). Thus, CRF-1 antagonists may be a useful therapy for smokers with heightened insula reactivity to smoking-related cues. As another example, infusion of the hypocretin-1 receptor-selective antagonist (SB-334687) into the insula of rodents reduced nicotine self-administration (51), and systemically SB-334687 reduced motivation for nicotine and other positive reinforcers (52). Thus, hypocretin receptor antagonists may represent another pharmacological approach to modulate insula reactivity to smoking-related cues (53) in relapse-vulnerable smokers. We plan to use fMRI to study how different pharmacological treatments modulate insula smoking cue reactivity and how such effects relate to relapse vulnerability.

Conclusions

We conclude that pre-quit brain reactivity to smoking-related images is greater in smokers who eventually slip after attaining brief abstinence with NRT and that anterior insula and dACC fMRI cue reactivity correlate with an attentional bias to smoking-related words. The functional connectivity findings suggest that slip subjects had reduced pre-quit top-down control over interoceptive awareness and may have been less able to regulate emotional responding to smoking-related images. While these findings pertain directly to smokers, the roles played by the insula in interoceptive awareness (22) and dACC in cognitive control (47) suggest that insula, dACC, and ES assessments may be useful for identifying vulnerable individuals with other disorders influenced by incentive-related cues, including other addictive disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported in part by National Institute on Drug Abuse grants U01DA019378, R01DA022276, R01DA014674, R01DA09448, K02DA017324, T32DA015036, by funding from the Counter-Drug Technology Assessment Center (CTAC), an office within the Office of National Drug Control Policy (ONDCP) via Army Contracting Agency contract BK39-03-C-0075, and by research support from GlaxoSmithKline. We thank Dr.

David Schoenfeld (Massachusetts General Hospital) for his contributions to this study. The authors are grateful to Drs. Robert S. Ross, Bruce M. Cohen, and Elizabeth Quattrocki-Knight for comments on the manuscript.

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Figure 1.

Whole-brain analysis of pre-quit brain reactivity to smoking-related versus neutral images compared between subjects who did and did not slip. Subjects who slipped exhibited greater fMRI reactivity in several brain areas (see Table S1 in Supplement 1), including the right anterior insula ($t_{(19)}=2.86$, cluster corrected, p 0.005). Talairach (55) coordinates: $x=35$, $y=18$, $z=0$. A = anterior, S = superior, R = right.

Figure 2.

Functional connectivity analyses. Top: The pre-quit network was identified in 21 subjects and contained bilateral insula and anterior cingulate cortex (cross hairs positioned in the anterior insula; Talairach (57) coordinates: $x=-38$, $y=13$, $z=-6$, $t_{(20)}=7.80$, Bonferroni corrected $p=0.01$; Table S2 in Supplement 1). Bottom: pre-quit network connectivity difference between slip ($N=9$) versus abstinence ($N=12$) subjects in dorsal anterior cingulate and other brain areas (Table S3 in Supplement 1. Talairach (55) coordinates for the dACC: $x=0$, $y=13$, $z=26$, $t_{(20)}=2.85$, cluster corrected, $p=0.005$). A = anterior, S = superior, R = right.

Table 1
Demographic Information

Subject Demographics and Emotional Stroop Data. Age, carbon monoxide (CO) levels and cigarettes smoked prior to scan were measured on the fMRI scan day. “Cigarettes smoked prior to scan” refers to the number of cigarettes subjects smoked on the fMRI scan day. FTND, HAM-D (54) and Pack Years were assessed at screening prior to the fMRI scan day. Days on NRT are the total number of days subjects were treated with NRT during their quit attempt. Emotional Stroop Accuracy_{Neutral} – Accuracy_{Smoking} represents the difference in response accuracy for neutral minus smoking words. RT_{Smoking} – RT_{Neutral} represents the difference in reaction time for responding to neutral minus smoking words. Two neuroimaging participants (one in each group) did not perform the Emotional Stroop Task.

Group	Eventual Slip Subjects (n = 9)	Abstinence Subjects (n = 12)
Age (years)	47.7 ± 8.6	44.4 ± 12.3
CO (ppm)	19.2 ± 9.2	21.4 ± 8.2
Cigarettes Smoked Prior to Scan	4.4 ± 2.1	4.3 ± 2.0
FTND	6.9 ± 1.2	5.0 ± 1.9*
HAM-D	3.6 ± 3.3	1.2 ± 1.7
Pack Years	33.0 ± 24.8	25.8 ± 17.2
Days on NRT	46.9 ± 20.9	48.7 ± 11.8
Emotional Stroop Interference Effect (accuracy: % correct)	0.016±0.030 ^a	0.020±0.019 ^{b,**}
Emotional Stroop Interference Effect (reaction time; ms)	71.03±59.67 ^a	-0.14±58.06 ^{b,**}

Data are represented as mean ± SD.

* Groups differ at p<0.02;

** Groups differ at p<0.01.

^a n = 8,

^b n=11.