Segregation of default mode from frontoparietal system protects against smoking lapse

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Abstract

Background. Quitting smoking is notoriously difficult. Models of nicotine dependence posit that deficits in cognitive control contribute to failures to maintain smoking abstinence during smoking cessation attempts. We examine the role for large-scale functional brain systems associated with cognitive control in smoking lapse. **Methods.** We use data from 70, five-minute functional magnetic resonance imaging (fMRI) scans in 17 daily smokers (5 female) undergoing a smoking lapse paradigm after 12 hours of smoking abstinence. **Results.** Cox regression results indicate that decreased segregation of the default mode system from the frontoparietal system undermine the ability to resist smoking. **Conclusions.** Results lend support to the hypothesis that large-scale functional brain systems associated with cognitive control are implicated in smoking lapse behavior and point to the importance of cognitive control as a mechanism underlying smoking relapse.

Keywords: nicotine; tobacco; fMRI; lapse; connectivity

INTRODUCTION

Quitting smoking is notoriously difficult, with the majority of cessation attempts ending in relapse (i.e., return to regular smoking) (1). Models of nicotine dependence posit that deficits in cognitive control contribute to continued smoking after a quit attempt in two key ways. A reduced ability to override impulses to smoke can bias decisions towards smoking over alternative reinforcers (2,3) and can promote a return to smoking in order to ameliorate abstinence-related cognitive control deficits (4). In line with these proposals, smokers exhibit impaired inhibitory control and working memory relative to non-smokers (5,6); smokers show impaired cognitive control performance during smoking abstinence relative to smoking satiety (7,8); and poorer performance on working memory tasks and inhibitory control tasks is associated with more rapid smoking resumption following smoking abstinence (9,10). Here, we extend research on the role of cognitive control in smoking cessation by examining how functional brain systems associated with cognitive control are correlated with smoking lapse.

One of the best predictors of relapse (11) following a smoking cessation attempt is experiencing a lapse (i.e., any smoking after initial cession) (12). Although lapses can represent just a single puff on a cigarette (13), the majority of participants who lapse go on to relapse and resume regular smoking (14,15). The first lapse during a cessation attempt, then, often represents a gateway towards relapse (16,17). Findings that cognitive control is associated with relapse provide initial evidence that limitations in cognitive control are implicated in smoking lapses (10,18).

Yet, the nature of lapses, as defined by discrete moments embedded within cessation attempts, challenges the identification of their precipitants. A second challenge for studying smoking lapses is that the precipitants of lapses may themselves change from moment to

moment. Indeed, in the case of cognitive control processes such as working memory, inhibitory control, and sustained attention, substantial day-to-day (19) and even moment-to-moment (20,21) fluctuations in performance have been observed. Within-person fluctuations have also been observed in the functional brain organization of systems involved in cognitive control (22,23). Observations of fluctuations in cognitive control and cognitive control-relevant functional brain systems encourage a consideration of functional brain systems in the moments immediately preceding lapses given that the status of processes (e.g., negative affect) in moments more proximal to lapses are more predictive of smoking lapses than data collected further back in time (e.g., hours before lapse versus day before lapse) (24).

Laboratory smoking lapse paradigms represent an efficient and cost-effective way to overcome the difficulty of isolating lapse behaviors as they occur (25). In an increasingly used lapse paradigm, smokers are exposed to known precipitants of smoking relapse behavior, including nicotine deprivation, alcohol, and stress (26-28). Smokers are then given the option of beginning tobacco self-administration or delaying self-administration by 5-minute increments for up to 50 minutes in exchange for monetary reinforcement. The delay period models smokers' ability to resist smoking, with shorter relative to longer times to lapse reflective of lower abilities to resist smoking. This lapse paradigm demonstrates validity, showing sensitivity to the effects of medications with known clinical efficacy for smoking cessation (29) and, to date, has supported the role of alcohol, stress, nicotine and food deprivation, exposure to smoking environment cues, and the devaluation of monetary rewards in facilitating lapse behavior in the laboratory (26,28,30-33).

In the present study, we overcome the challenges associated with identifying the role of cognitive control-relevant functional brain systems in smoking lapses by observing participants

as they engage in a laboratory smoking lapse paradigm, accompanied by functional Magnetic Resonance Imaging (fMRI). Our goal is to provide insight into the role of cognitive control-relevant functional brain systems in efforts to resist the urge to smoke. We focus on interactions between two large-scale functional brain systems that are known to support cognitive control. The frontoparietal system is comprised of regions with roles in response selection (34), response suppression (35), working memory (36), and attentional control (37), processes shown to be relevant for changes in smoking behavior (9,10,18). The default mode system is characterized by a tendency to deactivate during many cognitive tasks and to activate at rest, as well as during self-referential and social tasks (38,39). Evidence suggests that the integrity of functional connectivity of the default mode and frontoparietal systems, as well as their interactions, is fundamental to cognitive control. In particular, greater strength of connectivity among the default mode and frontoparietal systems, indicating reduced segregation of activity between the two systems, is associated with poorer working memory and inhibitory control performance (40-42). Given the association between cognitive control and the segregation of the default mode from the frontoparietal system, we hypothesized that greater segregation of the default mode from the frontoparietal system would protect against lapses during a smoking lapse paradigm. Notably, by taking continuous fMRI measurements during the course of the lapse task, we also capture potentially time-varying changes in functional connectivity of the systems theorized to be associated with lapse behavior.

METHODS AND MATERIALS

Participants

Participants were 20 individuals (8 female) recruited using newspaper, radio, and internet advertisements, and flyers posted in the community. To be eligible for the study, individuals were required to be right handed, to be between the ages of 18 and 45 years, to report that they smoked at least 10 cigarettes per day for the past 24 months, to indicate that they were not currently planning to quit smoking or actively pursuing any form of smoking cessation treatment, and to have a baseline expired-air carbon monoxide (CO) level greater than 10 parts per million (ppm); the latter criterion was chosen in order to verify smoking status (BreathCo, Vitalograph, Lenexa, Kansas). Individuals were excluded if they reported any of the following: current heavy use of illicit substances (defined as illicit drug use on 10 or more days in the past 30 days), current use of prescription medications that have been found to affect blood flow responses in the brain, current psychiatric diagnoses, chronic cardiovascular or respiratory problems, and/or any contraindications for magnetic resonance imaging (MRI). All procedures were approved by the Pennsylvania State University Institutional Review Board, and written informed consent was obtained from all participants.

Procedures

Demographic and smoking-related variables were collected at an initial baseline session. Participants then completed an fMRI session on a subsequent day. They were instructed to abstain from smoking and from using any nicotine-containing products for at least 12 hours prior to the scan session. Upon arriving for the fMRI experiment, participants reported the last time they smoked a cigarette and a CO sample was obtained to verify compliance with these instructions; compliance was defined as < 8 ppm or $\geq 50\%$ reduction from their baseline CO level. Participants then completed the following surveys to assess affective state, nicotine withdrawal symptoms, and the urge to smoke: the Positive and Negative Affect Schedule (43),

the Wisconsin Smoking Withdrawal Scale (44), and the Questionnaire of Smoking Urges-Brief (45).

After completion of the surveys and before being placed in the scanner, participants were given instructions for an fMRI reward task not reported on here. Following the acquisition of anatomical data, participants then completed a 3.5-minute resting baseline scan and six runs of the reward task, each lasting approximately 5 minutes. Next, participants performed an fMRI task modeling smoking lapse behavior adapted from prior behavioral research (27), which is the focus of the current study.

At the beginning of the fMRI smoking lapse task, participants were informed that they would be given the opportunity to smoke immediately after being removed from the scanner, but that they would be given the chance to earn extra money by delaying their removal to complete additional scans. Specifically, they were told that they could choose to remain in the scanner for up to 50 additional minutes, earning \$1 for every five minutes that they remained in the scanner (i.e., up to \$10 total), and that they would be asked to indicate via button press whether or not they would like to remain in the scanner before each five-minute scan began. After receiving instructions, participants provided visual analog scale ratings of their affect (from “unpleasant” to “pleasant”), their level of arousal (from “sleepy” to “aroused/activated”), and their urge to smoke (from “no urge at all” to “strongest urge ever”), with each scored on a 0-100 range.

Participants then completed the following sequence for each of up to 10 five-minute runs. First, participants pushed one of two buttons to signify whether they would like to start the subsequent 5-minute run of the smoking lapse task or be removed from the scanner. Next, those who elected to remain in the scanner completed a 5-minute run of the task, during which they were asked to relax and remain as still as possible with their eyes open. (If the participant instead

chose to be removed from the scanner, they were taken out of the MRI at that point and did not complete any additional runs of the task.) Finally, immediately after the run ended, participants used visual analog scales to rate their affect, level of arousal, and urge to smoke, as well as to rate how much they were trying to change or resist their urge to smoke during the previous run (from “not at all” to “very much”). Participants were given the opportunity to smoke after being removed from the scanner and were paid the money that they earned during the smoking lapse task in cash at the conclusion of the experimental session.

Data Preparation

A summary of our preparation and analysis of the functional imaging data from the smoking lapse task is as follows: we preprocessed and denoised the BOLD time series, after which we created an association matrix representing the functional connectivity among regions of the brain for each participant and each 5-minute block. We then quantified the segregation of the default mode from the frontoparietal system for each association matrix. We provide additional detail below.

Data acquisition. Scanning was conducted at the Penn State Social, Life, and Engineering Sciences Imaging Center using a 3-Tesla Siemens Trio scanner (Siemens Corporation, NY). Prior to functional scanning, a high-resolution T1-weighted (T1w) anatomical image was acquired (256x256 matrix; FOV=256 mm²; 160 1-mm sagittal slices). During functional scanning, 34-slice oblique-axial functional images (3x3x3 mm voxels) were acquired using a standard echo-planar imaging pulse sequence [TR=2000 ms, TE=25 ms, FOV=192 mm, flip angle=80°].

Data preprocessing. Initial preprocessing of the brain imaging data was performed using fMRIPrep 1.4.1rc1 (46), which is based on Nipype 1.2.0 (47,48). A detailed overview of the

steps taken is provided in the supplement. We then denoised the fMRI data with a protocol based on studies that evaluated the performance of a wide variety of denoising pipelines in mitigating motion artifact in studies of BOLD functional connectivity (49,50) using the publicly available eXtensible Connectivity Pipeline (XCP) software (51). Six head motion regressors and three matter regressors (global signal, white matter, and cerebrospinal fluid), as well as their derivatives, quadratic terms, and the squares of their derivatives (36 regressors in total) were regressed from the time series. We also conducted despiking – identifying outliers in the intensity of each voxel’s detrended BOLD time series and interpolating over these outliers.

Creating an association matrix. Using the preprocessed and denoised BOLD fMRI data, we created an association matrix representing the strength of functional connectivity between pairs of brain regions. We defined regions of the default mode and frontoparietal systems on a commonly applied parcellation scheme (52), the coordinates of which can be found in the Supporting Information. For each region, we extracted a time series of the BOLD signal separately for each individual. All regions were modeled as 10mm diameter spheres around the center coordinates. The extracted time series were the average time series for all voxels within the sphere. The spherical regions represented nodes in functional connectivity networks. Pairwise Pearson correlation coefficients between node time series were used as network edge weights. Similar to previous functional connectivity studies (e.g., 53,54), negative correlations were set to 0 to eliminate potential misinterpretation of negative edge weights.

Default mode and frontoparietal system segregation measure. We calculated the strength of default mode system segregation from the frontoparietal system as follows (55):

$$\text{Default Mode System Segregation} = \frac{\bar{z}_w - \bar{z}_b}{\bar{z}_w}, \quad (1)$$

where $\bar{z}_w$ is the mean connectivity strength of edges between all pairs of nodes in the default mode system and $\bar{z}_b$ is the mean connectivity strength of edges between all pairs of nodes that spanned the default mode and the frontoparietal systems. Higher values of the default mode system segregation indicate greater segregation of the default mode system from the frontoparietal system.

Data Analysis

We hypothesized that segregation of the default mode from the frontoparietal system would be protective against deciding to leave the scanner in order to smoke a cigarette rather than remaining in the scanner in order to earn a monetary incentive. We adopted a survival analysis framework, a framework in which the outcome variable is the timing of an event (56), to test this hypothesis. Participants who experience an event during the observational period experience a “death”, whereas participants not experiencing an event “survive” (the terminology comes from survival analysis’ legacy in epidemiology). In the current analyses, the relevant event is the decision to leave the scanner. In the present study, there were 9 event times, or moments at which a participant could decide to leave the scanner during the smoking lapse task (i.e., at the end of blocks 1 through 9). Of the 20 participants enrolled in the study, three did not choose to leave the scanner at any point during the 10 blocks. Survival analysis was developed in part to handle right-censored cases and, as such, these three right-censored cases are readily accommodated (57). Three participants decided to smoke rather than to begin the smoking lapse task. These left censored cases, in which the event occurred prior to or coincident with the start of the observation period, were not included in the analysis as they provided no fMRI data for the smoking lapse task.

A participant's likelihood of survival may be associated with different types of predictors, both time-invariant (e.g., age) and time-varying (e.g., segregation of the default mode from the frontoparietal system within each scanning block). We estimate the survival function, reflecting the cumulative loss of all participants in the sample. Formally, the survival function is expressed as

$$S(t) = \Pr(T > t), \quad (2)$$

and gives the probability that a participant will survive past time t . We also estimate the hazard rate, which is the risk of experiencing the event of interest given that the participant has survived up to a specific time, and we determine whether the function differs systematically in relation to predictor variables. We use a Cox regression model to examine how the hazard rate is related to default mode segregation from the frontoparietal system during each scanning block of the smoking lapse task. We fit a cox regression model specified as

$$h_i(t) = h_0(t) \exp(\beta_1 \text{Age}_i + \beta_2 \text{Segregation}_i(t)), \quad (3)$$

where the hazard of deciding to leave the scanner at time t depends on the product of the baseline hazard $h_0(t)$ and an exponentiated linear function of q predictors that may be time-invariant or time-varying. We include the time-invariant predictor of age, β_1 , and the time-varying predictor of default mode segregation from the frontoparietal system during each scanning block directly preceding the decision, β_2 , the value of which varies from scanning block to block.

Of greatest interest was the test of whether the parameter β_2 was different than 0 (i.e., that there is an association between default mode-frontoparietal system segregation and the hazard of choosing to leave the scanner to smoke a cigarette). Parameters were transformed into a more easily interpreted hazard ratio metric ($\text{HR} = \exp[\beta]$), which can be interpreted as the change in the risk of leaving the scanner if the parameter in question rises by one unit: $\text{HR} = 1.00$

indicates no association between the predictor and outcome variable, $HR > 1$ indicates higher hazard of event occurrence for higher values of the predictor, and $HR < 1$ indicates lower hazard of even occurrence for higher values of the predictor (58). HRs can also be interpreted as percent change in hazard as $100 \times [HR-1]$. We included age as a time-invariant covariate because previous work indicates that default mode and frontoparietal system segregation decreases with age (e.g.,59).

We fit the model using PROC PHREG (60) by implementing the counting process style of input (61). The discrete nature of event quantification (block by block) resulted in tied times during which participants decided to leave the scanner. We used the “tie = exact” option in SAS Proc PHREG to accommodate these tied events (62).

RESULTS

Participant characteristics and descriptive statistics

As detailed above, 17 participants (5 female) provided data for the survival analysis. The mean age of these participants was 24.41 years ($SD=6.90$). The self-identified racial composition of the usable sample was as follows: 82% White, 6% Asian, and 12% unreported. Participants reported smoking an average of 13.41 ($SD=3.62$) cigarettes per day and had a baseline CO level of 19.53 ppm ($SD = 7.19$). Additional characterization of the sample may be found in Table S1.

We provide descriptive statistics of key model variables in Table 1. Figure 1 shows the survival times for each participant (presence of square on horizontal lines) grouped by scanning block, in addition to the value of default mode frontoparietal system segregation within each block for each participant. Right censored cases ($n=3$) do not have Xs at the end of their rows to indicate that the event of interest (smoking lapse) was not observed in these participants.

Segregation of the default mode from the frontoparietal system protects against lapse

The baseline survival function estimated from an unconditional (baseline hazard) model is shown in Figure 2. We then added age and the default mode frontoparietal system segregation variable to the model. Goodness of model fit was tested using a likelihood ratio test that compared the fit of the model with age and default mode frontoparietal system segregation as predictors relative to the unconditional model. The likelihood ratio test was significant, $\chi^2(2)=7.02, p=0.03$, indicating that the model with age and default mode frontoparietal system segregation fit the data better than the unconditional model.

Results of the model (Table 2) indicate that the extent of default mode frontoparietal system segregation in the scanning block immediately preceding the decision to stay or leave the scanner was associated with the choice to leave the scanner in order to smoke a cigarette, $\beta_2=-5.84, p=0.04$. As hypothesized, with one unit increase in the segregation variable, participants were 0.003 times (HR=0.003) as likely, or 99.7% less likely (percent change = $100 \times [0.003 - 1.00] = -99.7\%$), to choose to leave the scanner in order to smoke a cigarette.

Results are robust to participant motion

Follow-up analyses indicate that the association between default mode frontoparietal system segregation and the choice to leave the scanner was robust to including participant motion (Table S2). Examining the independent associations between the components that make up the default mode frontoparietal system segregation variable revealed that connectivity between the default mode and frontoparietal systems was the biggest driver of the observed association (Table 3), relative to within-system functional connectivity of the default mode system and the frontoparietal system.

No association is observed between self-reports and smoking lapse

Time-varying self-reports of affect, arousal, and urge to smoke prior to each scan block, and post scan block self-ratings of how much participants were trying to change or resist their urge to smoke during the previous run, were not significantly associated with the choice to leave the scanner in order to smoke (Table S4). Repeated measure correlations between the default mode frontoparietal system segregation measure and the self-report scales indicated no significant associations between segregation and urge to smoke, $r(52)=0.09, p=0.54$, arousal, $r(52)=0.09, p=0.52$, or efforts to resist smoking urges, $r(52)=-0.07, p=0.61$. However, affect was significantly correlated with segregation, $r(52)=0.33, p=0.02$, such that greater segregation of the default mode and frontoparietal systems was associated with more positive affect prior to the scan block.

DISCUSSION

One of the best predictors of smoking relapse is the experience of a lapse during a cessation attempt (14,16). To provide insight into the precipitants of smoking lapses, we examined the association between cognitive control-relevant functional brain systems and smoking lapse behavior. In line with our hypothesis, decreased segregation of the default mode system from the frontoparietal system undermined the ability to resist smoking in a sample of daily smokers who were deprived of nicotine for over 12 hours.

The current study extends a laboratory paradigm modeling smoking lapse behavior (27) into the neuroimaging setting. Capturing BOLD fMRI during an attempt to resist smoking to earn a monetary incentive allowed us to test the role for large-scale functional brain networks associated with cognitive control in prompting lapse behavior. Our focus on connectivity among the default mode and frontoparietal systems reflects the importance of these systems in cognitive

control abilities, with findings that segregation of these systems from one another supports accurate cognitive control performance (40-42). In the context of cigarette-smoking specifically, improvements in cognitive withdrawal symptoms after nicotine replacement are associated with increased inverse coupling between default mode and frontoparietal systems (63). Our findings are consistent with behavioral studies indicating that poorer cognitive control task performance is associated with more rapid smoking resumption following smoking abstinence (9,10), and further build upon them by considering brain dynamics in real time during decisions to resist smoking.

Interestingly, self-ratings of affect, arousal, and urge to smoke prior to scan blocks and post-scan block ratings of how much participants resisted the urge to smoke were not significantly associated with decisions to leave the scanner in order to smoke a cigarette. These findings add to a body of literature indicating the promise of neural activity in predicting smoking-related behaviors (64-68). For example, existing work has observed associations between BOLD activity in the left dorsolateral prefrontal cortex and posterior cingulate during an N-back working memory task and the ability to remain abstinent during a 7-day quit attempt (69). With these findings, neuroimaging is emerging as a tool to predict behavior, providing an alternative to efforts to predict future behavior through self-reports that may contain biases stemming from social desirability effects (70) or that may fail to predict behavior due to a lack of conscious access to factors implicated in behavior (71).

Although self-ratings were not associated with lapse behavior, a correlation was observed between self-ratings of affect and default mode frontoparietal system segregation. More positive affect was reported prior to scans during which segregation between the default mode and frontoparietal systems was greater than usual. Positive affect has been theorized to inhibit

craving by facilitating self-regulation (72) and, consistent with this perspective, high positive affect is associated with reduced cravings during tobacco, alcohol, and opioid withdrawal (73,74). Results of the present study, coupled with findings that positive mood is associated with increased flexibility in large-scale brain networks (75), are consistent with the perspective that positive mood facilitates self-regulation via modulating functional connectivity associated with cognitive control. Notably, however, functional connectivity predicted lapse behavior above and beyond self-rating of affect (Table S5) suggesting that while positive affect may modulate the extent of segregation between the default mode and frontoparietal systems, it is not sufficient to predict lapse behavior on its own.

Conclusions

In summary, segregation of the default mode system from the frontoparietal system was associated with a reduced risk of lapsing during a laboratory smoking lapse task. Results lend support to the hypothesis that large-scale functional brain systems associated with cognitive control are implicated in smoking lapse behavior and point to the importance of cognitive control as a mechanism underlying smoking relapse.

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Disclosure of Biomedical Financial Interests and Potential Conflicts of Interest

The authors have no conflicts of interest to disclose.

Citation diversity statement

Recent work in neuroscience and other fields has identified a bias in citation practices such that papers from women and other minorities are under-cited relative to the number of such papers in the field (76-81). Here we sought to proactively consider choosing references that reflect the diversity of the field in thought, form of contribution, gender, and other factors. We used automatic classification of gender based on the first names of the first and last authors (79,82), with possible combinations including male/male, male/female, female/male, and female/female. Excluding self-citations to the first and last authors of our current paper, the references contain 38.10 % male/male, 15.87% male/female, 23.81% female/male, 17.46% female/female, and 4.76% unknown categorization. We look forward to future work that could help us to better understand how to support equitable practices in science.

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Table 1

Correlations and Descriptive Statistics of Key Study Variables

Variables	1	2	3	4	5	6	7
1. Default Mode Segregation^a	-						
2. DMN-FPN Connectivity^a	-0.76***	-					
3. DMN WN Connectivity^a	0.61**	0.04	-				
4. FPN WN Connectivity^a	-0.24	0.54*	0.32	-			
5. Age	-0.59*	0.46	-0.31	0.10	-		
6. Cigarettes Per Day	-0.15	-0.04	-0.30	-0.12	-0.15	-	
7. Motion^a	-0.06	-0.02	-0.15	0.03	0.01	0.25	-
<i>Mean</i>	0.34	0.09	0.14	0.15	24.41	13.41	1.08
<i>Standard Deviation</i>	0.10	0.01	0.10	0.03	6.90	3.62	0.04

Notes: ^aIntraindividual mean of the time series (up to 10 scan blocks per person); $N=17$; *** $p<0.001$; ** $p<0.01$; * $p<0.05$.

Table 2.

Cox regression results testing association between default mode frontoparietal system segregation and age on hazard of choosing to leave the scanner to smoke

Predictor	Estimate	Standard Error	<i>p</i>	Hazard Ratio	95% Confidence Interval of Hazard Ratio
Default Mode Segregation	-5.84	2.82	0.04	0.003	0.00 – 0.74
Age	-0.12	0.07	0.07	0.89	0.78 – 1.01
-2 Log Likelihood	40.92				
AIC	46.20				

Note: AIC= Akaike Information Criteria. $N = 17$ persons. Likelihood ratio test: $\chi^2(2)=7.02$, $p=0.03$.

Figure Captions

Figure 1. Survival times (x-axis) for each participant (separate lines on y-axis). Event times (leaving the scanner to smoke a cigarette) are indicated by an X. Three participants remained in the scanner for the entire 50 minutes. Each scan block for each participant is colored to indicate the magnitude of default mode frontoparietal system segregation. Lighter colors indicate greater segregation.

Figure 2. Estimated baseline survival function.

Figure 1 is a bar chart illustrating the distribution of DMN-FPN Segregation scores across 10 scan blocks for 15 participants. The y-axis represents the 'Participant' (1 to 15), and the x-axis represents the 'Scan Block' (1 to 10). A color scale on the right indicates the 'DMN-FPN Segregation' score, ranging from 0.0 (dark blue) to 0.6 (light blue). Each bar represents a participant's scores across the 10 scan blocks. The scores generally decrease from block 1 to block 10, with some participants showing a more gradual decline than others.

Figure 2.