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Revisiting the role of the insula and smoking cue-reactivity in relapse: A replication and extension of neuroimaging findings

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Abstract

Introduction—The ability to direct smoking cessation treatment based on neuroscientific findings holds incredible promise. However, there is a strong need for consistency across studies to confirm neurobiological targets. While our prior work implicated enhanced insula reactivity to smoking cues in tobacco smoking relapse vulnerability, this finding has not been confirmed.

Method—Using functional magnetic resonance imaging (fMRI), we evaluated the pre-cessation brain reactivity to smoking vs. neutral cues in nicotine dependent smokers who were and were not able to maintain subsequent abstinence.

Results—Of the 23 (7 women) individuals assessed, 13 relapsed and there were no demographic differences between those who did and did not relapse. However, smokers who relapsed showed enhanced reactivity to smoking cues in the right insula and dorsal striatum, showing significant overlap between our current and prior work despite methodological differences, including the fact that our previous work only included women.

Conclusion—The current work supports our prior results and builds on the concept that the insula and dorsal striatum work in concert to maintain nicotine dependence. Specifically, dorsal

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Contributors

Conceived and designed the experiments: JMG, AEE, MF. Performed the experiments: MR JMG. Oversaw clinical aspects: GP, Analyzed the data: JMG ACJ. Wrote the paper: ACJ. All authors have approved the final article.

Conflict of Interest

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striatal-mediated habitual responding may be triggered both by the external drug-associated cues, and the insula-mediated internal states that provide additional context motivating drug use. This replicated finding also mirrors preclinical work that finds the same individualized distinction, as only some rodents attribute incentive salience to drug cues and are more likely to reinstate drug seeking after extinction. To effectively treat addiction, these individual characteristics and their underlying neurobiological foundations must be considered.

Keywords

insula; tobacco smoking; relapse; dorsal striatum; fMRI; smoking cues

1. Introduction

The persistence of nicotine dependence despite available treatments effective for initial abstinence has driven the search for the neurobiological basis of relapse vulnerability. Such research holds promise in terms of paving the way for effective neuroscience-directed therapies. However, defining a single neurobiological locus is difficult because drug use is impacted by numerous factors with distinct neurobiological pathways (i.e., cue-reactivity, stress, affect). Even when focusing on a single factor, such as reactivity to drug-related cues, no consistent brain activation pattern has been confirmed across studies (Courtney et al., 2016).

What is clear when evaluating the link between relapse and brain reactivity to drug cues is that reward- and emotion-related regions are typically implicated (Courtney et al., 2016). When considering nicotine dependence, a preliminary study suggested that greater smoking cue-reactivity in the ventral striatum and thalamus predicted relapse (McClernon et al., 2007). Our own past work shows that insula reactivity to smoking cues predicts smoking cessation outcome with 73% accuracy (Janes et al., 2010). However, a follow-up exploratory whole brain analysis also showed that individuals who relapsed had greater cue-reactivity in additional regions, such as the thalamus and putamen. While there is some concordance between studies, the differences suggest the need for additional work.

Recently, there has been much focus on the need for reproducible neuroimaging research given the identification of flaws in functional magnetic resonance imaging (fMRI) statistics leading to overinflated findings (Eklund et al., 2016). Beyond this specific issue, numerous sources of variance can influence reproducibility across neuroimaging studies. For example, any two studies are likely to differ on design elements such as task parameters, scanner platform, and subject samples. Consistency across studies despite such differences suggests the validity of a finding, which is critical when developing treatment based on neuroimaging.

With the call for reproducibility in mind, we sought to replicate and extend our prior work linking insula reactivity to smoking cues with relapse vulnerability. Despite the lack of a prior confirmation study, the insula's role in addiction has become clear. For instance, the insula is commonly reactive to smoking cues (Engleman et al., 2011), and has been linked with nicotine use in clinical (Naqvi et al., 2007) and preclinical research (Contreras et al., 2012; Forget et al., 2010). However, a strong case could also be made for other brain

regions, such as the dorsal/ventral striatum and thalamus regions, that also have been linked with relapse vulnerability. Thus, we scanned nicotine dependent individuals during a smoking cue-reactivity paradigm and evaluated brain reactivity within these regions between individuals who were and were not able to maintain abstinence during a subsequent quit attempt.

2. Methods

2.1 Participants

Twenty-three otherwise healthy nicotine-dependent smokers were enrolled from a smoking cessation clinical trial (MGH; NCT01480232). Smokers met DSM-IV criteria for current nicotine dependence, reported smoking 5 cigarettes per day within the last six months and had expired air carbon monoxide (CO) 10ppm at screening (Bedfont Micro IV Smokerlyzer, Bedfont Scientific, Kent, England). Participants were excluded who had current unstable medical illness, substance-use disorder other than nicotine in the prior 6 months, positive ten-panel urine screen for recent use of addictive drugs (Medimpex United Inc), current major depressive disorder, lifetime diagnosis of bipolar disorder or schizophrenia, self-reported use of psychotropic medications, or positive pregnancy test. This study was approved by the Partners Human Subjects Committee. All participants were consented and compensated.

2.2 Assessments

Baseline smoking behavior was characterized by measuring expiratory CO levels, urine cotinine levels, and assessing pack-years of tobacco smoking, and severity of nicotine dependence (Fagerstrom Test for Nicotine Dependence (FTND); Heatherton et al., 1991) and craving (Tiffany Questionnaire of Smoking Urges (TQSU). After the fMRI assessment, all participants attempted to quit smoking. Smoking cessation took place in the context of the parent clinical trial, which assessed the efficacy of an Alpha-7 nicotinic acetylcholine receptor antagonist (EVP-6124). The study medication was administered with or without nicotine replacement therapy (NRT) in addition to 15 mins manualized individual cognitive behavioral therapy. Thus, there were four possible groups: EVP + NRT, EVP + placebo, placebo + NRT, placebo + placebo. Given the small sample size and the lack of an association between medication groups and cessation outcome, participants were split into two groups regardless of medication: abstinent and relapse. Criteria for abstinence were: **1.** Self-report of 2-week abstinence using timeline follow back (Harris et al., 2009), **2.** CO<10ppm, **3.** Cotinine<50ng/mL.

2.3 Cue Reactivity Task

Concurrent with fMRI, participants viewed 30 smoking-related and 30 neutral images (Okuyemi et al., 2006). Smoking images included paraphernalia such as cigarettes or people engaged in smoking behavior. Neutral images depicted everyday objects (i.e., staplers and telephones) or people engaged in everyday activities (i.e., reading). Images were presented in a block design (5 images/block displayed for 4 seconds each) with six blocks per cue type. A 14-second fixation was displayed between each of the 12 blocks. Blocks were

presented in pseudo-random order with no more than two blocks of the same cue type appearing consecutively. Total task length: 6 minutes and 48 seconds.

2.4 Acquisition Neuroimaging Data

All smokers were permitted to smoke prior to the scan to minimize withdrawal. They were scanned using a 3 T Siemens (Erlangen, Germany) Skyra scanner with a 32-channel head coil at the Martinos Center for Biomedical Imaging. Whole-brain T1-weighted 1 mm isotropic structural scans were collected using a 3D multiecho MPRAGE sequence (176 sagittal slices, 256 mm FoV, TR 2530 ms, TI 1200 ms, 2× GRAPPA acceleration, TE 1.64/3.5/5.36/7.22 ms). Functional scans were collected using a 2D gradient echo EPI sequence (31 slices, 3 mm thick, 0.6 mm gap, TR 2 s, TE 30 ms).

2.5 Functional Magnetic Resonance Imaging Analysis

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) within FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Pre-processing included: motion correction with McFLIRT, brain extraction using BET, slice time correction, spatial smoothing with a Gaussian kernel of full-width half-maximum 5mm, and highpass temporal filtering Gaussian-weighted least-squares straight line fitting, with sigma=50.0 s).

The first-level general linear model included regressors corresponding to smoking and neutral image presentation convolved with the gamma hemodynamic response function. Nuisance regressors for the 6 motion parameters also were included and contrasts were conducted between the smoking and neutral conditions. Higher-level group analysis was carried out using FSL's non-parametric permutation method (FSL Randomise; Nichols and Holmes, 2002) with cluster-based thresholding corrected for multiple comparisons using a cluster forming threshold of $z = 2.3$ and a family-wise error corrected threshold of $p < 0.05$. The smoking > neutral contrast was compared between smokers who did and did not maintain abstinence within an anatomically defined mask (Harvard-Oxford cortical structural atlas) comprised of the bilateral insula, striatum (nucleus accumbens, putamen, caudate), and thalamus.

3. Results

3.1 Participants

Of the 23 participants scanned, 10 remained abstinent while 13 relapsed. All demographic and smoking measures are shown in table 1. These two groups did not differ on basic demographic measures (sex, age, education) or smoking-related measures (cigarettes smoked per day, pack years, FTND, craving).

3.2 fMRI

Relative to those who maintained abstinence, individuals who relapsed had greater brain reactivity to smoking cues in the right insula, dorsolateral putamen, and a small portion of the dorsal caudate (figure 1 top panel). This cluster of activation was comprised of 1,280 voxels with peak activation located at $x = 29$, $y = 55$, $Z = 27$ (MNI coordinates).

4. Discussion

The current work replicates and extends our prior finding linking relapse vulnerability with enhanced insula reactivity to smoking cues (Janes et al., 2010). Both studies show greater insula, but also dorsal striatal reactivity to smoking cues in individuals who relapse. As shown in figure 1, there is significant overlap between our current findings and our past exploratory whole brain analysis. Such overlap is remarkable given the methodological differences between the two studies, including the use of more advanced imaging techniques in the current work, different task parameters, and the fact that only women were evaluated in the initial report. Further, co-activation of the insula and dorsal striatum in both studies allows for an update of our prior discussion on the insula's role in relapse vulnerability.

The insula's and dorsal striatum's role in addiction is well founded (Everitt and Robbins, 2013; Naqvi and Bechara, 2009), with the current findings supporting recent evidence suggesting these regions work in concert to maintain addiction. In a follow-up to their original paper linking insula damage with spontaneous smoking cessation (Naqvi et al., 2007), the same group showed that basal ganglia damage, primarily encompassing the putamen, disrupted smoking addiction (Gaznick et al., 2014). However, individuals with both basal ganglia and insula damage had the largest sustained rates of smoking cessation, suggesting the involvement of both regions in the maintenance of addiction. Our findings mirror this work, as relapse vulnerable individuals have greater smoking cue reactivity in the insula and dorsal striatum, primarily in the dorsolateral putamen.

The fact that cue induced activation is localized to the dorsolateral putamen, the sensory-motor subdivision of the striatum, suggests that cue-responding in relapse-vulnerable individuals is under habitual control (Gremel et al., 2017; Everitt and Robbins 2013). Such responding is likely triggered by the external drug-associated-cues, and the insula-mediated internal states, which provide additional context motivating drug use. While the right dorsolateral putamen activation reported here is linked to cue-induced habit formation (Tricomi et al., 2009), there is evidence suggesting that that this region plays a critical role in cue-induced incentive salience, which gives drug-related cues a strong motivational force (DiFeliceantonio and Berridge, 2016).

Our prior and current findings support the idea that the insula and dorsal striatum play a strong role in relapse vulnerability within a subset of individuals; those who activate these systems in response to cues are more likely to relapse. The finding that there are cue vulnerable and invulnerable subpopulations reflects preclinical work showing that only some animals attribute incentive salience to cues (Saunders and Robinson, 2013). Such cue-reactive animals, termed "sign-trackers" can be differentiated from "goal-trackers", who do not assign incentive properties to drug/reward cues. While both groups learn that cues predict reward, it is the sign-trackers who are more vulnerable to the motivating properties of cues and have greater difficulty resisting the behavioral influence of cues (Meyer et al., 2012; Flagel et al., 2007, 2008) even after extinction (Saunders and Robinson, 2010).

Persistence of drug-cue responding begs the question: "How do we treat cue-vulnerable populations?". In addition to reducing the motivational influence of drug cues, down/

upstream brain regions contributing to enhanced cue-reactivity may be a viable target. For instance, disrupted prefrontal function is found in sign-tracking rodents, leading to the inability to suppress attention to reward cues (Paolone et al., 2013). This finding is consistent with our prior work showing that highly cue-reactive individuals had greater difficulty ignoring smoking words task (Janes et al., 2010), which was associated with reduced prefrontal gamma-aminobutyric acid (GABA; Janes et al., 2013). Reduced communication between prefrontal brain regions and cue-reactive areas such as the insula and striatum contribute to relapse vulnerability (Addicott et al., 2015; Janes et al., 2010; Sweitzer et al., 2016; Zelle et al., 2016). In contrast, striatal smoking cue reactivity is reduced when individuals employ cognitive regulation strategies that upregulate prefrontal activity (Kober et al., 2010), suggesting that highly cue reactive smokers may benefit from such therapeutic techniques. In the current work, participants were not asked to resist craving and thus future work is needed to evaluate the PFC's specific role in heightened cue reactivity.

One limitation of the current work is the small sample size, which is due to the difficulty of recruiting and maintaining the enrollment of individuals seriously attempting to quit tobacco smoking. Second, because participants were enrolled in a clinical trial, not all participants received the same cessation aid. Medication group assignment did not affect outcome, indicating that, within this sample, cessation success was not mediated by the medication being studied. While this may be due to the small sample size, it still indicates that the brain reactivity measured prior to the cessation attempt was not influenced by either nicotinic pharmacotherapy. This finding is in line with our prior work showing that greater brain reactivity to smoking cues predicts relapse despite treatment with NRT. These findings are consistent despite variability between our two studies in task design (prior: event-related design, current: block design) and differences in group demographics, as the past study only included women. When comparing the two studies further, the prior sample of relapse vulnerable participants had higher FTND scores (6.8 vs. 5.7) while abstinent participants were younger in the current cohort (35 vs. 44.4). Another difference in task was that our prior event-related design involved a behavioral component allowing us to assess task engagement. This aspect was not part of our current block design. These differences highlight the robustness of our findings and support the idea that heightened cue reactivity is not necessarily directly linked to other clinical variables but is likely clinically relevant, independent of these other factors. Thus, factors such as cue-vulnerability along with additional aspects known to influence nicotine use such as nicotine dependence severity, sex, psychiatric disorders, and others may converge to create a specific risk profile driving an individual's relapse vulnerability. Despite these limitations, our current finding shows substantial overlap with our prior work linking insula and dorsal striatal smoking cue reactivity with cessation outcome, supporting the need of neuroscience based personalized therapy.

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Highlights

- Relapse-vulnerable smokers have greater insula reactivity to smoking cues prior to cessation.
- Dorsal striatal smoking cue reactivity also predicted relapse vulnerability.
- The current findings overlap with our prior work providing much needed replication.

Figure 1. Brain reactivity to smoking vs. neutral cues comparing smokers who relapsed to those who maintained abstinence

Smokers who subsequently relapsed had greater brain reactivity to smoking vs. neutral cues prior to a quit attempt in the right insula and dorsal striatum (putamen). The current findings were calculated using non-parametric permutation methods (FSL's randomize) and cluster corrected to $p < 0.05$. There is substantial overlap in the pattern of brain activation in the current sample (top panel) and our prior exploratory whole brain analysis (bottom panel).

Participant Demographics

Table 1

Following a cessation attempt, all participants were divided into an abstinent or relapse group based on their smoking cessation success. No significant differences were found between the groups on any demographic or smoking-related behavioral measures. Data represented as mean $\pm$ SD.

	All <i>n</i> = 23	Abstinent <i>n</i> = 10	Relapse <i>n</i> = 13	<i>p</i>
Sex % (n)				
Women	30.4 (7)	20 (2)	38.5 (5)	
Men	69.5 (16)	80 (8)	61.5 (8)	0.36
Age	39.7 $\pm$ 11.9	35 $\pm$ 11.3	43.2 $\pm$ 11.6	0.1
Education	14.4 $\pm$ 1.7	13.9 $\pm$ 1.7	14.7 $\pm$ 1.7	0.24
Cigarettes per day	18.2 $\pm$ 8.8	15.5 $\pm$ 9.4	20.2 $\pm$ 8.2	0.21
Expired CO (ppm)	22.4 $\pm$ 14.8	15.8 $\pm$ 11.8	27.5 $\pm$ 15.2	0.06
Pack years	21.9 $\pm$ 17.3	16.8 $\pm$ 16.7	25.9 $\pm$ 17.4	0.22
FTND scores	5.3 $\pm$ 2.5	4.4 $\pm$ 1.9	5.9 $\pm$ 2.7	0.15
Age of Smoking Onset	16.7 $\pm$ 2.9	15.5 $\pm$ 2.7	17.7 $\pm$ 2.7	0.08
Total Craving Score (TQSU)	38 $\pm$ 12.5	39.3 $\pm$ 14.7	37 $\pm$ 11.1	0.67
Days Abstinent	19.9 $\pm$ 29.6	45.2 $\pm$ 29.57	0.38 $\pm$ 0.65	< 0.001