



Caudate reactivity to smoking cues is associated with increased responding to monetary reward in nicotine-dependent individuals

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ABSTRACT

Quitting smoking is challenging in part because environmental smoking cues can trigger the desire to smoke. Neurobiological responses to smoking cues are often observed in reward-related brain regions such as the caudate and nucleus accumbens (NAc). While reward plays a well-established role in the formation of cue reactivity, whether general reward responsiveness contributes to individual differences in cue-reactivity among *chronic* smokers is unclear; establishing such link could provide insight into the mechanisms maintaining cue reactivity. The current study explored this relationship by assessing smoking cue reactivity during functional magnetic imaging followed by an out-of-scanner probabilistic reward task (PRT) in 24 nicotine-dependent smokers (14 women). In addition, owing to sex differences in cue reactivity and reward function, this same relationship was examined as a function of sex. Following recent smoking, greater reward responsiveness on the PRT was associated with enhanced left caudate reactivity to smoking cues. No relationship was found in any other striatal subregion. The positive relationship between reward responsiveness and caudate smoking cue reactivity was significant only in male smokers, fitting with the idea that males and females respond to the reinforcing elements of smoking cues differently. These findings are clinically relevant as they show that, following recent smoking, nicotine-dependent individuals who are more cue reactive are also more likely to be responsive to non-drug rewards, which may be useful for making individualized treatment decisions that involve behavioral reward contingencies.

1. Introduction

Quitting tobacco smoking continues to be a challenge for the majority of smokers (Chaiton et al., 2016; Piasecki, 2006), in part because environmental cues associated with smoking can evoke behavioral, emotional, and neurobiological responses (i.e., cue reactivity), which drive the desire to smoke (Carpenter et al., 2009; Carter and Tiffany, 1999, 2001; Engelmann et al., 2012; Shiffman et al., 2013). Interestingly, not all smokers show the same patterns of brain reactivity to smoking cues (Janes et al., 2010, 2017; Kang et al., 2012; McClernon et al., 2007; Tang et al., 2012; McClernon et al., 2008), supporting the notion that individual variance may influence how cues motivate smoking behavior (Janes et al., 2010, 2017). Biological (e.g., sex; Doran, 2014; Dumais et al., 2017; McClernon et al., 2007; Wetherill et al., 2013) and smoking-related factors (e.g., severity of dependence; Vollstädt-Klein et al., 2011) have been linked with heightened cue

reactivity, providing insights into which populations may be more prone to cue-induced relapse. It is critical to specify the cognitive mechanisms contributing to such variance in cue reactivity as this may enhance the ability to develop therapies targeting such underlying factors.

It is plausible that cue reactivity is directly influenced by one's level of reward responsivity, which can be operationalized as the tendency to adapt behavior based on the availability of rewards (Pizzagalli et al., 2005). The idea that reward plays a role in addiction and cue reactivity is not new as it has long been shown that reward-related brain regions such as the dorsal and ventral striatum (Delgado, 2007) also respond to smoking-related cues (David et al., 2005; Frederiksen Franklin et al., 2007; Janes et al., 2009; Yuan et al., 2017). Furthermore, our prior work showed that following acute nicotine administration there is a positive association between brain reactivity to reward-predictive stimuli and behavioral reward responsivity (Moran et al., 2017). Building

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on this finding, it is plausible that brain reactivity to smoking cues may also be related to behavioral reward responsivity. Additionally, the relationship between cue reactivity and reward responsivity may be mediated by other factors known to impact nicotine dependence such as biological sex (see Benowitz and Hatsukami, 1998 for review). Specifically, nicotine-related reinforcement appears to play a larger role in motivating smoking in males relative to females (Perkins et al., 1992; see Perkins, 1996 for review), which may be related to the finding that smoking induces a larger dopamine release in males (Cosgrove et al., 2014; Weinstein et al., 2016). Whether sex influences the relationship between cue reactivity and reward sensitivity is unclear and would help explain the noted sex differences in nicotine dependence.

To determine whether there is a link between striatal reactivity to smoking cues and reward responsivity, 24 nicotine-dependent smokers performed a smoking cue-reactivity task during concurrent functional magnetic resonance imaging (fMRI) ~ 1 h after smoking. After the scan, participants completed a probabilistic reward task (PRT), which quantifies behavioral responsivity to monetary rewards (Pizzagalli et al., 2005). Specifically, the relationship between striatal reactivity to smoking cues and PRT performance was assessed. The striatal regions of interest (ROIs) included the nucleus accumbens (NAc) and the caudate as these regions play a role in the establishment and expression of reward-related conditioned behavior (Knutson et al., 2001; Tricomi et al., 2004; Haruno, 2004). While dopamine release in the NAc underlies the reinforcing properties of abused substances such as nicotine (Brody et al., 2004; Pontieri et al., 1996; Di Chiara and Imperato, 1988), dorsal striatal regions such as the caudate play a larger role in cue-induced craving in chronic drug users (Volkow et al., 2006). Thus, cue-induced reactivity in the caudate may better reflect the relationship between reward responsivity and cue reactivity in established long-term smokers. Finally, we investigated whether the relationship between these measures differed between males and females.

2. Methods

2.1. Study sample

Twenty-four nicotine-dependent tobacco smokers (14 female) completed study procedures at McLean Hospital. Participants met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR) criteria for current nicotine dependence and was verified by the Fagerström Test for Nicotine Dependence (FTND; Fagerström, 1978) with an average score of 5.95 ± 1.20 (\pm SD). Participants reported smoking an average of 13.72 ± 3.85 cigarettes per day over the past 6 months and had an average expired air carbon monoxide (CO) of $22.29 \text{ ppm} \pm 12.34$ at screening. The average age of smoking onset for participants was 17.44 ± 2.01 with an average pack-year (cigarettes per day X years of smoking) of 6.57 ± 3.74 . All study procedures were approved by the Partners Human Research Committee. Prior to study procedures, participants provided written informed consent and were compensated for their participation. For full demographics, see Table 1.

Exclusionary criteria were evaluated using an amended version of the Structured Clinical Interview for DSM-IV (SCID-I; First et al., 2002) and included current medical illness, pregnancy, recent drug/alcohol use (confirmed by a QuickTox11 Panel Drug Test Card, Branam Medical Corporation, Irvine California; Alco-Sensor IV, Intoximeters Inc., St. Louis, MO), current drug or alcohol dependence other than nicotine, current or lifetime major depressive episode (current verified with The Beck Depression Inventory-II; Beck et al., 1996), and current or lifetime diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or psychotic disorders not otherwise specified.

Smoking time was standardized by instructing participants to smoke one of their own cigarettes in the laboratory 1 h before the functional magnetic resonance imaging (fMRI) procedure. Following fMRI, participants were administered the PRT approximately 3 h after scanning.

Table 1

Demographic characteristics. A. Demographic characteristics for all participants. B. Demographic characteristics breakdown by sex. No significant differences in demographic variables were observed between male and female participants $p > .05$.

A.					
Variable	M [n]		SD		
Age	27.63		6.05		
Females	[14]		-		
Males	[10]		-		
Education	15.00		2.15		
FTND	5.95		2.03		
Pack-year	6.57		3.74		
B.					
Variable	Males		Females		Statistics
	M	SD	M	SD	
Age	26.90	5.97	28.14	6.27	$p = 0.630$
Education	15.65	2.20	14.54	2.06	$p = 0.217$
CO	20.60	12.77	23.50	12.36	$p = 0.582$
FTND	5.80	1.22	6.07	1.21	$p = 0.595$
Pack-year	6.05	3.14	6.94	4.20	$p = 0.575$
Avg cigs/day	14.90	3.92	12.89	3.72	$p = 0.216$

2.2. Functional neuroimaging acquisition

Scanning procedures were consistent with our previous work in an overlapping sample where only imaging metrics were evaluated and the PRT was not assessed (Janes et al., 2016). Scans were acquired on a Siemens 3 T Trio scanner (Erlangen, Germany) with a 32-channel head coil. Multi-planar rapidly acquired gradient echo-structural images were acquired with the following parameters (TR = 2.1 s, TE = 3.3 ms, slices = 128, matrix = 256×256 , flip angle = 7° , resolution = $1.0 \times 1.0 \times 1.33 \text{ mm}$) and gradient echo-planar images were acquired during cue reactivity using the following parameters (TR = 2 s, TE = 30 ms, flip angle = 75° , slices = 37, distance factor = 10 %, voxel size = 3.5 mm isotropic, and GRAPPA acceleration factor = 2). Slice acquisition was aligned to the anterior and posterior commissures, and the phase encode direction was set to acquire from the posterior to anterior direction to prevent prefrontal signal loss.

2.3. Cue reactivity paradigm

Participants performed a cue reactivity task during fMRI. Across 5 blocks, participants were shown 50 smoking images that included smoking-related content (e.g. hand holding cigarette) and 50 neutral images without smoking stimuli, but otherwise matched for content (e.g. hand holding pencil). Smoking images were validated for their ability to elicit subjective craving in our previous work (Janes et al., 2015); as in our prior work, smoking cues in the current study were rated as inducing more craving than neutral cues ($t(23) = 5.89$, $p < .001$). Ten target images of animals were presented to verify that participants were paying attention. Participants were instructed to press a button every time they saw a target image. Consistent with our prior work (Janes et al., 2010, 2016), smoking, neutral, and target images were presented for 4 s in a pseudorandom order (with no more than two of the same picture-type occurring in a row) evenly across each 5-minute block. Images were separated by a jittered inter-trial-interval (ITI), in which participants were shown a fixation cross on a black screen. The ITI times ranged from 6 to 14 s in intervals of 2 s with a 10 s average across block.

2.4. fMRI preprocessing

The procedure for fMRI analysis was consistent with our previous

work (Janes et al., 2016). All analyses were conducted using tools from the Functional Magnetic Resonance Imaging of the Brain (fMRIB) Software Library (FSL; www.fmrib.ox.ac.uk/fsl) and FreeSurfer image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>). Using FSL, the first 5 volumes of each run were removed to allow for signal stabilization. Functional data pre-processing included motion correction, brain extraction, slice timing correction, spatial smoothing with a Gaussian kernel of 6 mm full-width half-maximum, and high-pass temporal filtering with Gaussian-weighted least-squares straight-line fitting with $\sigma = 100$ s. Motion artifacts and intensity spiking were analyzed and adjusted for using an in-house program (<https://github.com/bbfrederick/spikefix>). Subject specific data were registered to standard space using the MNI152 2 mm³ template (Montreal Neurological Institute, Montreal, QC, Canada).

2.5. Cue-reactivity neuroimaging analysis

Cue-reactivity analyses were also consistent with our prior work (Janes et al., 2016). First-level analysis was carried out separately for each of the participant's cue-reactivity runs. The first-level general linear model included 3 regressors corresponding to smoking, neutral, and target image presentation, which were convolved using the standard gamma hemodynamic response function. Confound regressors modeling motion effects (x, y, z translation and rotation motion) were also included. Consistent with our prior work (Janes et al., 2016), we included a regressor representing motion/intensity artifacts identified and removed prior to preprocessing using an in-house program (<https://github.com/bbfrederick/spikefix>). For each participant, contrasts maps of smoking versus neutral images were created and first-level results were combined (across the 5 blocks) using a second-level fixed-effects analysis to create average brain reactivity for each participant.

FreeSurfer's image analysis suite was used to identify and create subject-specific region of interest (ROI) masks for the left and right NAc and caudate, respectively. Output from the automated segmentation was converted to MNI space and used to create these masks. After each ROI was visually inspected for location accuracy, beta weights for each region were extracted from the second-level (subject specific) smoking > neutral contrast.

2.6. Probabilistic reward task

Similar to prior work (Pizzagalli et al., 2005), we used a computerized probabilistic reward task (PRT) to assess reward responsivity by measuring an individual's propensity to modify behavior based on reward feedback. Briefly, the PRT consisted of 2 blocks of 100 trials each, where participants were shown one of two faces with slightly different mouth lengths (short versus long) and asked to identify which mouth-type was presented. Correct responses were financially rewarded using an asymmetrical reinforcement schedule, where the correct identification of one mouth triggered the response "Correct!! You won 5 Cents" three times more frequently (rich) than the other mouth (lean), eliciting a response bias. Participants completed the PRT outside of the scanner ~4 h following smoking and ~2.5 h after completing a cue reactivity paradigm.

Following Pizzagalli et al.'s (2005) procedures, *response bias* (RB) was calculated for each block to measure the behavioral bias towards the rich stimulus, where higher values suggest greater responsivity to the stimulus more frequently paired with the reward. *Discriminability* (d) was also calculated for each block, which captures the individual's ability to perceptually distinguish between mouth types. Discriminability values were used as a control to ensure that any noted association was due to a response bias and not variance in perception. PRT measures were calculated using the following formulas:

Response Bias:

$$\log b = \frac{1}{2} \log \left(\frac{RICH_{correct} * LEAN_{incorrect}}{RICH_{incorrect} * LEAN_{correct}} \right)$$

Discriminability:

$$\log d = \frac{1}{2} \log \left(\frac{RICH_{correct} * LEAN_{correct}}{RICH_{incorrect} * LEAN_{incorrect}} \right)$$

Using procedures outlined in Pizzagalli et al.'s (2005), the validity of the PRT data was evaluated using four *a priori* criteria. Values for *response bias* and *discriminability* were calculated for each block using published formulas (Pizzagalli et al., 2005) and the change scores from blocks 1–2 were used in subsequent analyses as a way to capture reward learning that occurred from the first to the second block.

2.7. Data analysis

To assess for a relationship between cue reactivity and non-drug reward responsivity, we conducted multivariate regression analyses using ΔRB [= RB (Block 2) – RB (Block 1)] as the predictor, and the smoking > neutral beta weights extracted from the left and right NAc and caudate ROIs as dependent variables. To determine whether the overall ability to distinguish mouth types was driving any relationship between ΔRB and cue reactivity, we conducted the same multivariate regression again using Δd [= discriminability (Block 2) – discriminability (Block 1)] as the predictor.

To explore whether the relationship between ΔRB and striatal activation differed between males and females, the same multivariate regression was run for males (n = 10) and females (n = 14), separately. Pearson's correlation coefficients were calculated between ΔRB and striatal regions that were significant in the multivariate regression. To compare the association between striatal activation and ΔRB between men and women, correlation coefficients were converted to a Fisher's Z and statistically compared using Fisher's test for independent correlation (two-tailed; Fisher, 1915, 1921).

3. Results

3.1. Relationship between striatal ROIs and response Bias

Response bias. The multivariate regression model included the left and right NAc and caudate as dependent variables with ΔRB as the predictor. The overall model was significant ($F_{(4, 19)} = 3.64, p = .023$, partial $\eta^2 = .43$). When probing individual striatal brain regions, ΔRB significantly predicted left caudate smoking > neutral cue activation (Fig. 1a; unstandardized $B = 43.02$, Standard Error = 18.05, $p = .026$, partial $\eta^2 = .21$). Specifically, 16.9 % (adjusted R^2) of the variance in left caudate activation was accounted for by ΔRB . Change in RB approached significance for predicting right caudate activation (Fig. 1b; unstandardized $B = 36.19$, Standard Error = 19.03, $p = .070$, partial $\eta^2 = .14$). Using Steiger's Z-test for dependent correlations (Steiger, 1980), a direct comparison of the correlation coefficients of left ($r = 0.42, p = .039$) and right ($r = 0.27, p = .201$) caudate respectively with ΔRB did not reveal significant hemispheric differences ($z = 0.54, p = .59, two-tailed$).

For the NAc ROIs, ΔRB did not significantly predict left (Fig. 1c; unstandardized $B = -7.81$, Standard Error = 19.73, $p = .70$) or right (Fig. 1d; unstandardized $B = 29.13$, Standard Error = 22.21, $p = .20$) NAc activation.

Discriminability. There was no significant relationship (all p -values > .05) between discriminability and striatal regions, indicating that the relationship between response bias and caudate activation was not due to overall task perceptual difficulty.

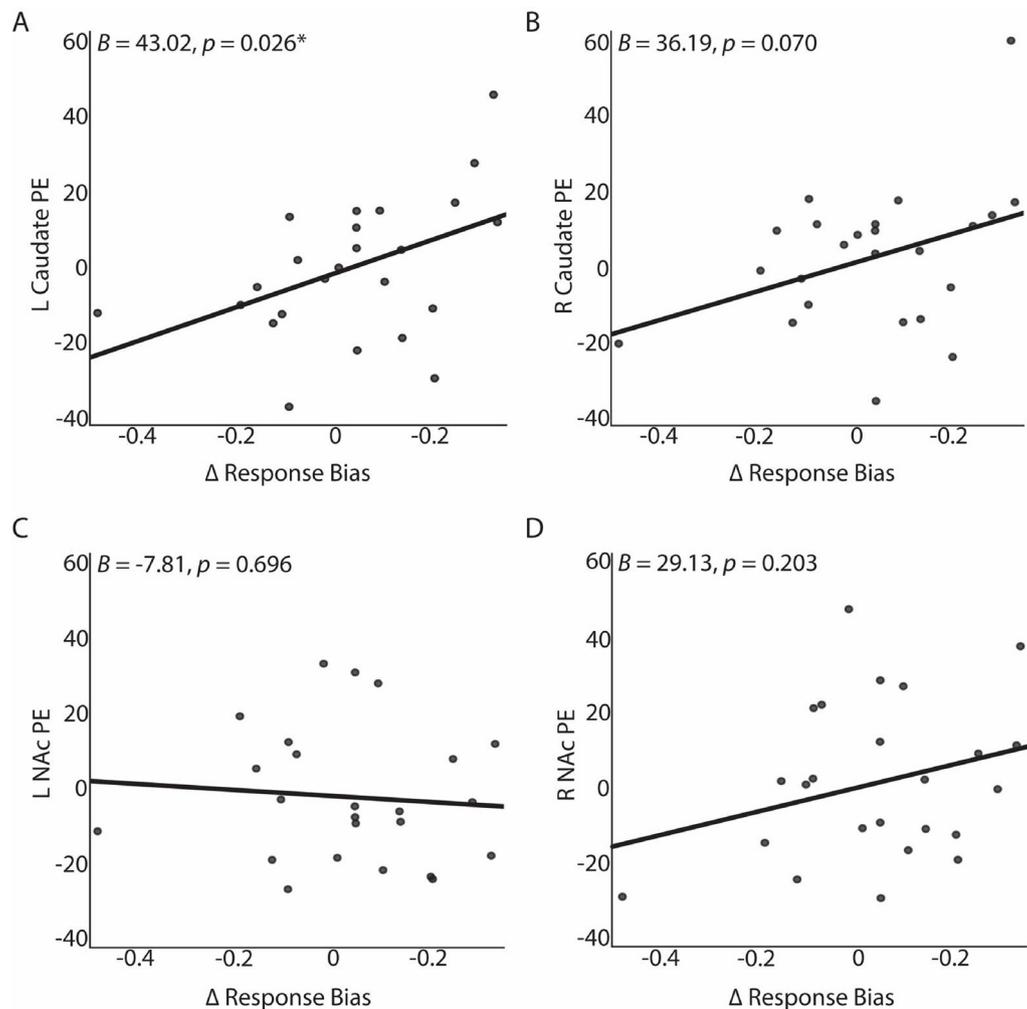


Fig. 1. Multivariate regression results for striatal ROIs and response bias for overall sample. **A, B.** Plots of left and right caudate beta weights from smoking > neutral contrast from cue reactivity paradigm against change in response bias in probabilistic reward task. Δ RB significantly predicted the left caudate in a positive direction. Δ RB approached significance for the right caudate. **C, D.** Plots of left and right NAc beta weights from smoking > neutral contrast from cue reactivity paradigm against change in response bias in probabilistic reward task. Δ RB did not significantly predict left or right NAc.

3.2. Relationship between striatal ROIs and response Bias based on sex

Multivariate regression models were run in males and females separately to evaluate whether the relationship between striatal reactivity to smoking cues and response bias differed based on sex. When considering male participants, the overall multivariate regression model was significant ($F_{(4, 5)} = 8.18, p = .020$, partial $\eta^2 = .87$). For males, Δ RB significantly predicted left caudate smoking > neutral cue activation (Fig. 2; unstandardized $B = 89.66$, Standard Error = 23.11, $p = .005$, partial $\eta^2 = .65$) and approached significance for right caudate cue activation (unstandardized $B = 62.59$, Standard Error = 27.50, $p = .052$, partial $\eta^2 = .39$). Specifically, 61.0 % (adjusted R^2) of the variance in left caudate activation was accounted for by Δ RB in males. No significant results were observed for left (unstandardized $B = -6.19$, Standard Error = 26.67, $p = .82$) or right (unstandardized $B = 36.33$, Standard Error = 25.88, $p = .20$) NAc cue activation. For females, the overall multivariate regression was not significant ($F_{(4, 9)} = 1.13, p = .40$).

To evaluate whether the Δ RB and left caudate relationship was significantly different between males and females, separate two-tailed Pearson's correlation analyses were run for males and females using Δ RB and left caudate. The resultant r -values were z-transformed and statistically compared using a Fisher's test for independent correlation (two-tailed; Fisher, 1915, 1921). This test confirmed that men had a

significantly stronger association between left caudate cue activation and Δ RB than females ($Z = 2.50, p = 0.024$).

4. Discussion

The current work shows that among smokers, those with greater caudate reactivity to smoking cues are also the most reward responsive. To our knowledge, this is the first study to directly link caudate cue reactivity with behavioral responsiveness to monetary reward in smokers. This relationship suggests that cue reactivity towards primary drug-related rewards does not necessarily occur at the expense of responsiveness to secondary conditioned reinforcers (e.g., money), which is in contrast to theories suggesting that addiction is characterized by a hypersensitivity to drug rewards and hyposensitivity to non-drug rewards (Goldstein and Volkow, 2002; Volkow et al., 2010). However, the current work focused only on individuals who recently smoked and it is unclear how this association may be impacted following periods of extended abstinence or in those abusing other substances. Our caudate-specific finding fits with prior work demonstrating the caudate's role in habitual responding, which is expected given that our study sample consisted of long-term established smokers (Porrino et al., 2004; see Everitt and Robbins, 2005 for review). Likewise, the lack of finding between NAc cue reactivity and reward responsiveness fits with our hypothesis and the purported role of the NAc in the initial phases of

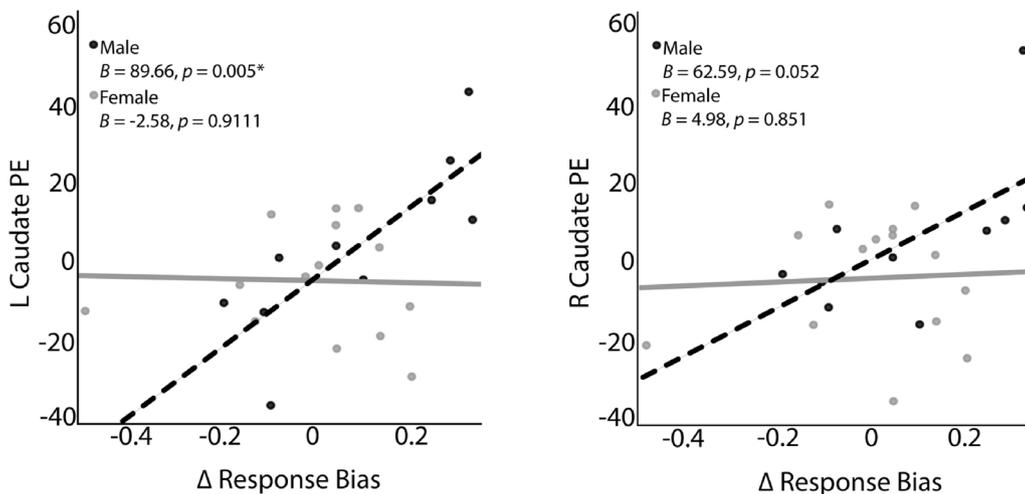


Fig. 2. Multivariate regression results for striatal ROIs and response bias based on Sex. Plots of smoking > neutral beta weights extracted from fMRI cue reactivity paradigm for left and right caudate for male and female subsamples. For male participants, Δ RB showed a significant association with left caudate smoking > neutral cue activation and approached significance for right caudate cue activation.

learning (e.g., Parkinson et al., 2002). Specifically, the NAc plays an important role in action-outcome learning of goal-directed behaviors, while the caudate's role is associated with facilitating cue-induced habitual behaviors (see Everitt and Robbins, 2005 for review; Tricomi et al., 2004) following established learning.

A follow-up analysis on the caudate finding showed that this positive association between caudate cue reactivity and reward responsivity was present only in males. This finding fits with the notion that there are sex-specific mechanisms contributing to nicotine dependence (Becker, 1999; Munro et al., 2006). For instance, previous work has reported that men show more smoking-induced dopamine release relative to females in areas of the striatum (Cosgrove et al., 2014; Weinstein et al., 2016), such as the caudate (Weinstein et al., 2016). While findings are mixed on sex differences in brain reactivity to smoking cues (Dumais et al., 2017; McClernon et al., 2008; Wetherill et al., 2013; Zanchi et al., 2016), the present study focused on the relationship between brain reactivity to smoking cues and behavioral reward responsivity. Our findings suggest that behavioral reward responsivity may influence smoking cue-reactivity more so in males relative to females, lending support to prior work showing that in comparison to females, males are characterized by more smoking cue reactivity in reward-related brain regions (Dumais et al., 2017; Wetherill et al., 2013). Additionally, preclinical research has demonstrated that repeated nicotine exposure enhances reward-association learning in males but not females (Quick et al., 2014), which fits with the notion that nicotine use impacts male and female brains differently (Beltz et al., 2015; Cosgrove et al., 2014; Fallon et al., 2005). While we did not administer nicotine in the current study, our sample reported long-term nicotine use and it is therefore plausible that our results suggest sex differences in the relationship between reward learning and cue reactivity possibly resulting from extended nicotine use. While this specific conjecture requires further testing, our results contribute to the extant literature on sex differences in reward function and cue reactivity by highlighting a stronger relationship between these two concepts for males relative to females.

This study contributes to the field by shedding light on behavioral reward-related characteristics that underlie cue reactivity, however the study has limitations worth noting. First, the current work focused on individuals who recently smoked and therefore it is plausible the association between caudate and reward responsivity may change if participants were evaluated following extended abstinence. Second, while reward responsivity to monetary rewards was used as a predictor in the linear regression, our study design precludes us from drawing directional conclusions about whether variance in non-drug reward responsivity prior to nicotine exposure directly influenced the establishment of cue reactivity. Third, the sample size for sex-specific

analyses was relatively small but we were reassured by the sizable effect size for the finding in males (partial $\eta^2 = 0.65$). However, future studies should try to replicate our findings in a larger sample. Fourth, although in this initial evaluation we chose to focus on clear *a priori* ROIs that have been strongly linked to reward and cue-reactivity, larger subsequent studies should be powered to conduct a whole-brain analysis, which may reveal a relationship between areas mediating executive functions, cue reactivity, and reward responsivity (Bi et al., 2017). Finally, it is plausible that hormonal variations in women may have influenced our findings (Franklin et al., 2015; Diekhof and Ratnayake, 2016), as certain hormonal phases have been shown to increase smoking cue reactivity (Franklin et al., 2015) and reward sensitivity (Diekhof and Ratnayake, 2016) in females, which should be taken into consideration by future studies.

Based on our results, we conclude that individuals who show more caudate cue reactivity are also more reward responsive to non-drug reinforcers. Extrapolating from these results, it is plausible that therapies targeting reinforcement, such as contingency management, may be useful in such reward-responsive individuals. The fact that the relationship between reward and cue reactivity was noted only in males fits with the growing literature highlighting the need to consider sex differences when trying to understand and ultimately treat nicotine dependence.

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Contributors

ACJ designed the study. ACJ and ALP conceptualized the project. EM conducted analyses and wrote initial draft with ALP and ACJ. KSW assisted with draft revisions and figure production. DAP provided feedback on study design and expertise on reward task used.

Declaration of Competing Interest

Dr. Pizzagalli has received consulting fees from Blackthorn Therapeutics, Boehringer Ingelheim, Compass, Takeda and an honorarium from Alkermes for activities unrelated to the current research.

Dr. Pizzagalli has a financial interest in BlackThorn Therapeutics, which has licensed the copyright to the Probabilistic Reward Task through Harvard University. Dr. Pizzagalli's interests were reviewed and are managed by McLean Hospital and Partners HealthCare in accordance with their conflict of interest policies. All other authors report no biomedical financial interests or potential conflicts of interest.

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