Drug and Alcohol Dependence 178 (2017) 469–476

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Multi-site exploration of sex differences in brain reactivity to smoking cues: Consensus across sites and methodologies

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ARTICLE INFO

Keywords:
Sex differences
fMRI
Smoking cue
Nicotine
Striatum
Nicotine dependence

ABSTRACT

Background: Biological sex influences cigarette smoking behavior. More men than women smoke, but women have a harder time quitting. Sex differences in smoking cue (SC) reactivity may underlie such behavioral differences. However, the influence of sex on brain reactivity to SCs has yielded inconsistent findings suggesting the need for continued study. Here, we investigated the effect of sex on SC reactivity across two sites using different imaging modalities and SC stimulus types.

Methods: Pseudo-continuous arterial spin-labeled (*p*CASL) perfusion functional magnetic resonance imaging (fMRI) was used to assess brain responses to SC versus non-SC videos in 40 smokers (23 females) at the University of Pennsylvania. BOLD fMRI was used to assess brain responses to SC versus non-SC still images in 32 smokers (18 females) at McLean Hospital. Brain reactivity to SCs was compared between men and women and was correlated with SC-induced craving.

Results: In both cohorts, males showed higher SC versus non-SC reactivity compared to females in reward-related brain regions (i.e., ventral striatum/ventral pallidum, ventral medial prefrontal cortex). Brain activation during SC versus non-SC exposure correlated positively with SC-induced subjective craving in males, but not females.

Conclusions: The current work provides much needed replication and validation of sex differences in SC-reactivity. These findings also add to a body of literature showing that men have greater reward-related brain activation to drug cues across drug classes. Such sex differences confirm the need to consider sex not only when evaluating SC-reactivity but when examining nicotine dependence etiology and treatment.

1. Introduction

Nicotine dependence remains a major public health concern, with cigarette smoking being the leading cause of preventable death in the United States (CDC, 2014). To fully assist all smokers attempting to quit, cessation aids that account for individual differences may need to be considered. For instance, biological sex plays a large role in nicotine use patterns and cessation outcomes, with higher smoking rates among men than women (Jamal et al., 2014), and women having greater difficulty quitting smoking than men (Cepeda-Benito et al., 2004; Perkins and Scott, 2008; Smith et al., 2016). Further, women have shown a smaller decline in smoking rates (CDC, 2011), and suffer more severe smoking-related consequences (Allen et al., 2014; Kiyohara and Ohno, 2010; Laviolette et al., 2007) than men. Given that sexual dimorphism begins at inception and is modified across the lifespan by both the natural hormonal milieu and by societal norms, a critical next step is clearly defining the underpinnings of these and other smoking-related sex differences.

Exposure to nicotine-associated or smoking cues (SCs) modulates nicotine seeking and/or smoking behavior (Caggiula et al., 2001; LeFoll and Goldberg, 2005; Rose, 2006). This interaction is often modulated by sex (Chaudhri et al., 2005; Perkins et al., 2001). However, literature examining sex differences in SC reactivity is mixed. Some studies show that SC-elicited subjective craving is greater in women compared to men (Carpenter et al., 2014; Doran, 2014; Field and Duka, 2004; Waters et al., 2004), yet others report no differences between men and women

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http://dx.doi.org/10.1016/j.drugalcdep.2017.05.044
Received 24 March 2017; Received in revised form 4 May 2017; Accepted 25 May 2017
Available online 08 July 2017
0376-8716/

(Colamussi et al., 2007; Franklin et al., 2004; Saladin et al., 2012; Shiffman et al., 2013). Sex differences in brain reactivity to SCs also is mixed, which may be due to the paucity of existing literature. The few prior studies investigating sex differences in brain reactivity to SCs are acknowledged pilot studies, and thus, focused on small sample sizes, leading to variable results (McClernon et al., 2008; Mendrek et al., 2014; Zanchi et al., 2016). Our prior work has also examined sex differences in brain reactivity to SCs, and showed that men have greater brain reactivity to SCs relative to women (Wetherill et al., 2013). While our work was not preliminary, the inconsistencies between our work and the work of others needs to be addressed. Given that biological sex is the most fundamental difference among human beings there is a need to determine consistency in the field to gain a more thorough understanding of how sex influences SC reactivity.

To further investigate brain reactivity to SCs in both men and women, we examined the effect of sex on brain responses to SCs in two new cohorts from two different institutions (University of Pennsylvania and McLean Hospital). This multi-site investigation utilized different neuroimaging modalities and different SC stimuli, allowing us to assess sex effects independent of methodological differences. The University of Pennsylvania cohort was scanned during SC exposure using *pseudo*-continuous arterial spin-labeled (pCASL) perfusion functional magnetic resonance imaging (fMRI). The SCs were presented within a short video containing appetitive smoking-related content, and were compared to a similarly-valenced video devoid of smoking-related material. pCASL has the advantage of providing a quantitative measure of cerebral blood flow (CBF) by using arterial water as an endogenous tracer. pCASL fMRI provides an average value for each prolonged stimulus presentation (SC video and non-SC video), allowing for a strong SC and non-SC signal with minimal 'carryover' arousal and/or craving. The McLean Hospital cohort was scanned during SC exposure using blood oxygenation level dependent (BOLD) fMRI, and used smoking-related still images versus non-smoking still images. BOLD fMRI has the advantage of providing a high magnitude of signal change during rapid stimulus presentation (i.e. when using an event-related design). For both cohorts, we used the *a priori* region of interest (ROI) analysis approach that was used in our prior investigation (Wetherill et al., 2013), to investigate sex-specific brain responses in regions known to be involved in SC reactivity (i.e., ventral striatum (VS), ventral pallidum (VP), ventral medial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC), anterior ventral insula, amygdala, and parahippocampus; Brody et al., 2002; Franklin et al., 2007; Janes et al., 2015). Collectively, our goal was to determine whether we would replicate our prior findings of higher SC reactivity in men relative to women (Wetherill et al., 2013) in these independent cohorts that also account for methodological variability. Findings from the current study will provide a broader understanding of the impact of sex on brain reactivity to SCs.

2. Materials and methods

2.1. Study 1

2.1.1. Participants

Study 1 was conducted at the University of Pennsylvania, and participants were recruited via radio or online advertisements and local listserves. The MINI International Neuropsychiatric Interview (Sheehan et al., 1998) was used to exclude participants who had substance use disorder other than nicotine dependence, current Axis 1 DSM IV psychiatric diagnoses, or significant medical conditions. Participants were also required to have a breath blood alcohol level of zero (Alco-Sensor IV, Intoximeters, St Louis, MO), and were excluded if they were pregnant, had irremovable metal in or within their body, had a history of head trauma or injury causing loss of consciousness lasting greater than three minutes or associated with skull fracture or intracranial bleeding, or had other contraindications for MRI (Dill, 2008). One male participant was removed due to abnormally enlarged ventricles and one female participant was removed for having smoking behavioral characteristics > 3 standard deviations from the mean. Final study participants were 40 smokers (23 females; aged 35.6 ± 2.5; age range 21–56). Severity of nicotine dependence was determined from a laboratory-developed Smoking History Questionnaire (SHQ) that includes a modified Fagerström Test for Nicotine Dependence (FTND; Fagerström, 1978; Heatherton et al., 1991; to view modified version, see Supplementary Methods). All participants were moderately nicotine dependent and reported smoking ≥ 6 cigarettes per day (CPD) for at least 6 months prior to the study start date. Smoking was biologically verified via expired CO levels, with all participants having a CO level of ≥ 10 ppm prior to scanning. Informed consent was collected from all eligible participants, and research was approved by the University of Pennsylvania Institutional Review Board.

2.1.2. Study procedures

Brain activation in response to SC exposure was assessed by *p*CASL perfusion fMRI, which is a quantitative assessment of CBF and an indirect measure of brain activity (Floyd et al., 2003). While being observed by study staff, participants smoked their own cigarettes *ad lib* approximately 25 min before the scanning session. During each session, participants completed brain scans in the following order: a high resolution structural scan, a 5 min resting perfusion baseline scan, a 5 min BOLD resting baseline scan, a 9 min non-SC *p*CASL scan, and a 9 min SC *p*CASL scan. The SC and non-SC presentations each consisted of one audio-visual clip that included actors differing in race, age, and sex. For the SC video, actors were smoking and using explicit language designed to induce appetitive desire for a cigarette (e.g., "I'm really enjoying this cigarette!"). For the non-SC video, content was similar, in which actors related interesting stories while handling a pen or similar non-arousing object, but did not include smoking or smoking reminders. Using the Craving and Withdrawal Questionnaire (CWQ; Franklin et al., 2007; Wetherill et al., 2013), subjective craving (i.e., "How much do you desire a cigarette right now?") was assessed on a 7-point Likert-type scale before and after SC stimulus presentation during the scanning session.

2.1.3. Imaging parameters

Imaging was conducted on a Siemens Trio 3T whole body scanner (Erlangen, Germany) using an 8-channel head coil. Structural images were collected using a T1-weighted three-dimensional (3D) high resolution MPRAGE scan with field of view (FOV) = 250 mm, repetition time (TR) = 1620 ms, echo time (TE) = 3.09 ms, matrix = 192 × 256, and slice thickness = 1 mm. A *p*CASL perfusion fMRI sequence was used for resting baseline, SC and non-SC data acquisition. Interleaved images with and without labeling were obtained using a gradient echo echo-planar sequence with a delay of 1.5 or 1 ms inserted between the end of the labeling pulse and image acquisition (FOV = 220 mm, matrix = 64 × 64 × 18, TR = 4000 ms, TE = 17 ms, flip angle = 90°, slice thickness = 6 mm with a 7.2 mm gap).

2.1.4. fMRI processing and data analyses

An SPM-based arterial spin labeling (ASL) data processing toolbox (Wang et al., 2008) was used for *p*CASL perfusion data analyses (described previously in Franklin et al., 2009, 2011). Briefly, ASL image pairs were realigned to the mean of all control images and spatially smoothed with a 3D isotropic Gaussian kernel at 9 mm full width at half maximum (FWHM). For both SC and non-SC scans, 68 CBF image series were generated from the 136 label/control ASL image pairs using a simplified two-compartment model with the sinc interpolation method for CBF calculations (Wang et al., 2008). The mean control image of each subject's data was co-registered to the structural image using SPM8's mutual information based co-registration algorithm. The same transformation parameters were applied to co-register the CBF maps to each subject's anatomical image. Anatomical images were then registered to the MNI152 2 mm^3 standard space template (Montreal

Neurological Institute, Montreal, QC, Canada), and the resulting transformation matrix was used to align the CBF images to MNI space. A binary brain mask was used to exclude any non-brain areas in the CBF maps.

Contrasts between SC versus non-SC stimuli were defined in the general linear model (GLM) to assess the voxel by voxel CBF difference for each subject. Using the corresponding parametric contrast maps, random effects analysis was used to test for a significant main effect of condition (SC versus non-SC) in each sex with a statistical parametric map of the *T*-statistic at each voxel for population inference within our ROI mask. Based on our previous studies of SC-reactivity in nicotine dependent smokers (Franklin et al., 2007, 2009, 2011; Wetherill et al., 2013), the ROI mask included the following regions: vmPFC, VS/VP, hippocampus, extended amygdala (i.e., amygdala, bed nucleus of stria terminalis), ACC, and anterior ventral insula. The ROI mask was created using the Harvard–Oxford probabilistic anatomical atlas provided with the fMRI of the brain (FMRIB) software Library (FSL; Smith et al., 2004) and is available for viewing at http://franklinbrainimaging.com/. Significant voxels passed a voxel-wise statistical threshold of $p < 0.005$. To control for multiple comparisons, significant voxels were also required to be part of a cluster > 55 voxels, as determined by a Monte-Carlo simulation, resulting in a 5% probability (corrected) of a cluster surviving due to chance. All coordinates listed are in MNI space. To examine the association between SC-induced craving and SC-induced neural activation, linear regression analysis was used to correlate post-SC craving and the change from pre- to post-SC craving with brain activity (SC > non-SC) at each voxel within the ROI mask. Correlations were conducted in males and females separately. For regions showing a correlation, data were extracted from the functional cluster and plotted as a function of change in craving from pre- to post- SC exposure.

2.1.5. Demographic and behavioral statistical analyses

Independent sample *t*-tests were used to compare demographic variables (age, education, CPD, pack years [lifetime tobacco use calculated by (CPD/cigarettes in a pack) x years smoking], and FTND score) between males and females. To determine the effect of SC exposure on subjective craving, paired samples *t*-tests compared pre-SC craving scores and post-SC craving scores for all subjects and within each sex. To determine the effect of sex on subjective craving, independent sample *t*-tests were used to compare pre-SC craving, post-SC craving, and the change from pre- to post-SC craving (post-SC craving score minus pre-SC craving score) between males and females.

2.2. Study 2

2.2.1. Participants

Study 2 was conducted at McLean Hospital's Imaging Center, and participants were recruited via online advertisements, local listserves, or locally posted fliers. The structured clinical interview (SCID) for DSM IV-TR was used to exclude participants who had substance use disorder other than nicotine dependence, organic mental disorder, bipolar disorder, schizophrenia spectrum disorder, current depressive episode, or psychotropic drug use. Other exclusion criteria for Study 2 were identical to that of Study 1 (see section 2.1.1 for exclusion criteria). Final study participants were 32 smokers (18 females; aged 29.03 ± 1.05, age range 18–41). Participants were combined from two independent studies executed at McLean Hospital, in which nicotine dependent individuals were exposed to SCs vs. non-SCs (N = 18, 10 females; Janes et al., 2015) or exposed to SCs vs. non-SCs within the context of a working memory task (N = 14, 8 females; Janes et al., 2015). All participants were moderately nicotine dependent as assessed by the FTND (Fagerström, 1978) and reported smoking ≥ 10 CPD for at least 6 months prior to the study start date. Smoking was biologically verified via expired CO levels. All participants had a CO level of ≥ 10 ppm prior to scanning, except for one participant that had a CO level of 6 ppm who had self-reported smoking their last cigarette the night before their scan. This participant's brain reactivity to SCs was within the normal range (1 standard deviation of the mean), and therefore was included in all analyses. Informed consent was collected from all eligible participants, and research was approved by the McLean Hospital Institutional Review Board or Partners Human Research Committee (the institutional review board of Partners Healthcare hospitals).

2.2.2. Study procedures

Brain activation in response to SC exposure was assessed using BOLD fMRI. While being observed by study staff, participants smoked their own cigarettes *ad lib* approximately 1.5 h before the scanning session. Participants completed either the traditional cue reactivity task or a working memory task for SCs (described previously in Janes et al. (2015a, 2015b)). The same SCs and non-SCs were used in both tasks. SC images included smoking-related content such as people smoking, people holding cigarettes, or cigarettes alone. Non-SC images were matched for content such that they included people, hands, or objects (e.g., pens, paintbrushes) but did not include cigarettes. The traditional cue reactivity task also included target images (pictures of animals) in which participants were instructed to press a button to ensure that they were awake and attending to the task. In the traditional cue reactivity task, participants were shown 60 SCs, 60 non-SCs, and 12 target images divided evenly across 5 blocks. Images were presented for 4 s in a pseudorandom order so that no more than 2 of the same image type occurred consecutively. Images were divided by a jittered inter-trial interval (white fixation cross on a black screen) ranging from 6 to 14 s in intervals of 2 s with a 10 s average across block. For the working memory task, participants were presented with 48 SCs and 48 non-SCs in the context of the delay-match-to-sample task (LoPresti et al., 2008; Schon, 2004). For each match to sample trial, participants were presented with either a SC or non-SC image for 2 s ("sample period") that they would have to match to a subsequent image following a 10 s delay. There were 96 trials divided evenly across 6 blocks, with each trial divided by the same jittered inter-trial interval described above. For the purpose of this study, only the sample period of each match to sample trial was analyzed. Because the sample period allows for the SC versus non-SC contrast to be analyzed without involving the working memory components of the task, the sample period corresponds closely to our traditional SC reactivity task. Indeed, we have replicated our traditional SC reactivity task results using the working memory task (Janes et al., 2016). Subjective craving (participants' rating response to the phrase "desire to smoke") was assessed on a 5-point Likert-type scale before and after the scanning session.

2.2.3. Imaging parameters

Imaging was conducted on a Siemens Trio 3T scanner (Erlangen, Germany) using a 32-channel head coil. Acquisition parameters were identical for the two tasks. Multiecho 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 × 1.0 × 1.33 mm). For task-related fMRI, data was collected using a gradient echo-planar sequence with the following parameters: TR = 2 s, TE = 30 ms, clip angle = 75°, slices = 37, distance factor 10%, voxel size = 3.5 mm isotropic and a GRAPPA acceleration factor of 2.

2.2.4. fMRI processing and data analyses

Data were processed using FSL (http://fmrib.ox.ac.uk/fsl). The first 5 vols were removed for all analysis to allow for signal stabilization. Preprocessing included motion correction, brain extraction, slice time correction, spatial smoothing with a Gaussian kernel for a FWHM of 6 mm, and a high-pass temporal filter with Gaussian-weighted least-squares straight-line fitting with 100 s. Each participant's data was then registered to the MNI152 2 mm^3 standard space template (Montreal Neurological Institute, Montreal, QC, Canada). An in-house program was used to detect and adjust for artifacts generated by intensity spiking

(see Janes et al., 2015a, 2015b). First-level analysis was conducted on each participant's individual task runs separately. All task-related regressors were convolved with the gamma hemodynamic response function. Confound regressors representing motion were included in the model. Contrasts were conducted between SC and non-SC conditions. Lower level individual runs were then combined for second level analysis to generate the average brain reactivity for each participant across runs.

Beta weights from the same ROI mask used in Study 1 (see Section 2.1.4) were extracted using FSL's featquery from each individual for the SC versus non-SC contrast. Because individuals had participated in one of two different SC reactivity tasks (see Section 2.2.2), SC reactivity was assessed by extracting mean beta weights. Data from both tasks were combined as the male:female ratio was similar across tasks, and there were no differences in cue reactivity between the two tasks within males ($t_{(12)} = -0.44$, $p = 0.67$, *t-test*) or females ($t_{(16)} = -0.58$, $p = 0.57$, *t-test*). Two-tailed independent sample *t*-tests compared SC versus non-SC beta weights between males and females. Given the results of Study 1, we also performed a post-hoc analysis to compare beta weights between males and females within individual ROIs that showed a sex difference in Study 1. Therefore, beta weights from the left and right vmPFC and left and right VS for the SC versus non-SC condition were extracted separately, and sex differences were analyzed using one-tailed independent sample *t*-tests.

2.2.5. Demographic and behavioral statistical analyses

Males and females were compared on the same demographic and craving measures as described in Study 1 Section 2.1.5. To examine the association between SC-induced craving and SC-induced neural activation, Pearson's correlation was used to correlate post-SC craving and the change from pre- to post-SC craving with ROI mask beta weights (SC versus non-SC). Correlations were conducted in males and females separately.

3. Results

3.1. Study 1

3.1.1. Participant characteristics

Table 1 provides participant demographics and smoking history characteristics. There were no significant sex differences in age and years of education. As is commonly observed in the literature, males had higher pack years than females ($t_{(38)} = -2.5$; $p < 0.02$) and there was a nonsignificant trend for males to have higher FTND scores ($t_{(38)} = -1.9$; $p = 0.07$) and smoke more CPD ($t_{(38)} = -1.8$; $p = 0.08$) compared to females (Niaura et al., 1998; Wetherill et al., 2013, 2014). FTND scores ranged from 1.65 to 7.0.

3.1.2. Smoking cue reactivity

Relative to females, males showed higher SC versus non-SC brain activity in the VS/VP (t = 3.83; 3, −3, −19) and vmPFC (t = 4.03; 3, 43, −11; Fig. 1). Covarying for pack years, which was significantly greater in males than females, had minimal impact on the data leading to a stronger vmPFC sex difference and weaker VS/VP sex difference (reduced voxelwise statistical threshold of $p < 0.01$ and cluster size > 25 for VS/VP). Within males, greater brain responses to SCs relative to non-SCs were observed in the VS/VP (t = 3.84; 3, 5, −15), vmPFC (t = 3.52; 13, 31, −19), ventral anterior insula (t = 3.27; 45, −11, 3), and parahippocampus (t = 4.12; 29, −21, −23). In females, there were no regions that showed greater responses to SCs relative to non-SCs. No brain region showed greater activation to SCs versus non-SCs in females compared to males, or to non-SCs relative to SCs in either sex. Data are reported using a corrected voxelwise statistical threshold of $p < 0.005$ and cluster size > 55.

Table 1
Participant Characteristics.

Study 1: pCASL fMRI and SC videos				
	All	Males	Females	p[a]
	n = 40	*n = 17*	*n = 23*	
Race% (n)				
White	38 (15)	29 (5)	43 (10)	
Black	60 (24)	71 (12)	52 (12)	
Other	2 (1)	0 (0)	5(1)	
Age	37.7 ± 1.8	40.5 ± 2.4	35.6 ± 2.5	0.18
Education	14.3 ± 0.4	14 ± 0.7	14.5 ± 0.4	0.48
Cigarettes per day	13.6 ± 1.0	15.7 ± 1.6	12.1 ± 1.2	0.08
Pack years[b]	12.5 ± 1.7	17.1 ± 2.8	9.2 ± 1.8	0.02
FTND scores	4.8 ± 0.3	5.4 ± 0.4	4.3 ± 0.3	0.07
Pre-SC craving scores	3.4 ± 0.3	3.2 ± 0.4	3.5 ± 0.4	0.72
Post-SC craving scores	4.2 ± 0.3	4.4 ± 0.5	4.1 ± 0.4	0.6
Δ Craving scores[c]	0.9 ± 0.2***	1.2 ± 0.3**	0.6 ± 0.3*	0.16
Study 2: BOLD fMRI and SC still images				
	All	Males	Females	*p*[a]
	n = 32	*n = 14*	*n = 18*	
Race (%)				
White	59 (19)	64 (9)	56 (10)	
Black	12 (4)	7 (1)	17 (3)	
Other	28 (9)	29 (4)	28 (5)	
Age	29.0 ± 1.1	28.9 ± 1.6	29.2 ± 1.4	0.89
Education	15.0 ± 0.4	15.7 ± 0.5	14.6 ± 0.6	0.17
Cigarettes per day	13.8 ± 0.7	15.4 ± 1.0	12.5 ± 0.8	0.03
Pack years[b]	7.9 ± 0.8	8.4 ± 1.4	7.5 ± 1.0	0.59
FTND scores	5.8 ± 0.2	5.9 ± 0.4	5.8 ± 0.3	0.87
Pre-SC craving scores	2.4 ± 0.2	2.7 ± 0.3	2.1 ± 0.3	0.17
Post-SC craving scores	3.3 ± 0.2	3.6 ± 0.2	3.1 ± 0.3	0.23
Δ Craving scores[c]	0.9 ± 0.2**	0.9 ± 0.2*	1.0 ± 0.3**	0.74

Paired *t*-tests were conducted on the Δ craving scores: * $p < 0.02$; ** $p < 0.001$ *** $p < 0.0001$

pCASL = pseudo-continuous arterial spin-labeled; BOLD = blood oxygenation level dependent; fMRI = functional magnetic resonance imaging; FTND = Fagerström Test for Nicotine Dependence

Data depicts average ± SEM

[a] Unpaired *t*-test p value between males and females.

[b] Pack years calculation: Cigarettes per day (÷) cigarettes in a pack (x) years smoking.

[c] Change (Δ) in craving scores calculation: Post-SC craving score (–) Pre-SC craving score.

3.1.3. Correlations with craving

Craving measured immediately before SC exposure (baseline craving [pre-SC]), craving measured post-SC exposure, and the change in craving from pre- to post- SC exposure (post-SC (minus) pre-SC) did not differ between males and females (ps > 0.1; Table 1). Craving scores increased from pre- to post- SC exposure in all participants ($t_{(39)} = 4.5$, $p < 0.0001$) as well as in males ($t_{(16)} = 4.3$, $p < 0.001$) and females ($t_{(22)} = 2.5$, $p < 0.02$) separately. VS/VP activity positively correlated with the change in craving from pre- to post- SC exposure in males (cluster size = 258 contiguous 2 × 2 × 2 voxels; $t_{(16)} = 5.9$, $r = 0.77$; Fig. 2). This correlation was significantly greater in males relative to females ($p = 0.015$, two-tailed) as there was no association between VS/VP activity to SCs and change in craving in females. There were no correlations between the change in craving from pre- to post- SC exposure with any other brain region in either sex, or between post-SC craving with any brain region in either sex. Data are reported using a corrected voxelwise statistical threshold of $p < 0.005$ and cluster size > 55.

An interactive visual display of all brain data and unmasked data at a reduced threshold can be found at http://franklinbrainimaging.com

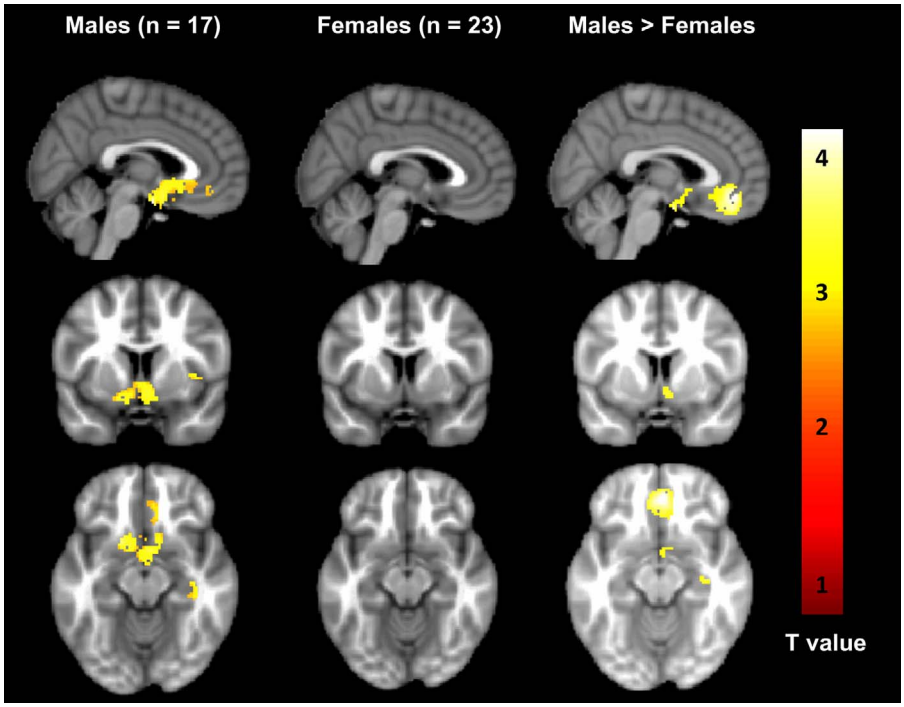

Fig 1. Smoking cue (SC)-induced brain reactivity in Study 1. Sagittal, coronal and axial images (shown at MNI coordinates x, y, z = 3, 7, −13) of brain responses to SC relative to non-SC exposure in males, females, and males compared to females. Note the distinct response to SCs in males within the ventral striatum/ventral pallidum (VS/VP; t = 3.84), the lack of response in females, and the greater response in males compared to females in the ventral medial prefrontal cortex (vmPFC; t = 4.03) and VS/VP (t = 3.83). Data were analyzed in SPM8 and overlain on the MNI brain, cluster corrected at $p < 0.005$. Images are displayed neurologically (left is left). An interactive visual display of all brain data in all three planes can be found at http://franklinbrainimaging.com.

3.2. Study 2

3.2.1. Participant characteristics

Participant demographics and smoking history characteristics are provided in Table 1. There were no significant sex differences in age, years of education, pack years, or FTND scores, but males smoked more CPD compared to females ($t_{(30)} = -2.3$, $p < 0.05$). FTND scores ranged from 3 to 8.

3.2.2. Smoking cue reactivity

Beta extractions from the ROI mask (Fig. 3A) revealed higher brain responses to SCs relative to non-SCs in males compared to females ($t_{(30)} = 2.5$; $p < 0.05$; Fig. 3B). This sex difference remains significant when covarying for CPD, which was significantly higher in males than females ($F_{(1,29)} = 7.6$, $p < 0.05$, ANCOVA). Post-hoc analyses revealed higher SC versus non-SC brain responses in males compared to females in the left and right vmPFC (left: $t_{(30)} = 2.3$, $p < 0.05$; right: $t_{(30)} = 2.3$, $p < 0.05$; Supplementary Fig. 1). A trend toward a sex difference was observed in the right VS ($t_{(30)} = -1.4$, $p = 0.09$), while no sex difference was observed in the left VS ($t_{(30)} = -0.2$, $p = 0.42$; Supplementary Fig. 1).

3.2.3. Correlations with craving

Beta extractions from the ROI mask were correlated with subjective craving scores. Craving measured immediately before SC exposure (baseline craving [pre-SC]), craving measured post-SC exposure, and the change in craving from pre- to post- SC exposure (post-SC (minus) pre-SC) did not differ between males and females (ps > 0.1; Table 1). Craving scores increased from pre- to post- SC exposure in all participants ($t_{(31)} = -4.5$, $p < 0.001$) as well as in males ($t_{(13)} = -4.2$, $p < 0.01$) and females ($t_{(17)} = -2.9$, $p < 0.01$) separately. Brain activity positively correlated with post-SC craving in males ($r = 0.65$, $p < 0.05$; Fig. 3C). There was no correlation between brain activity and post-SC craving in females or between the change in craving from pre- to post- SC exposure in either sex.

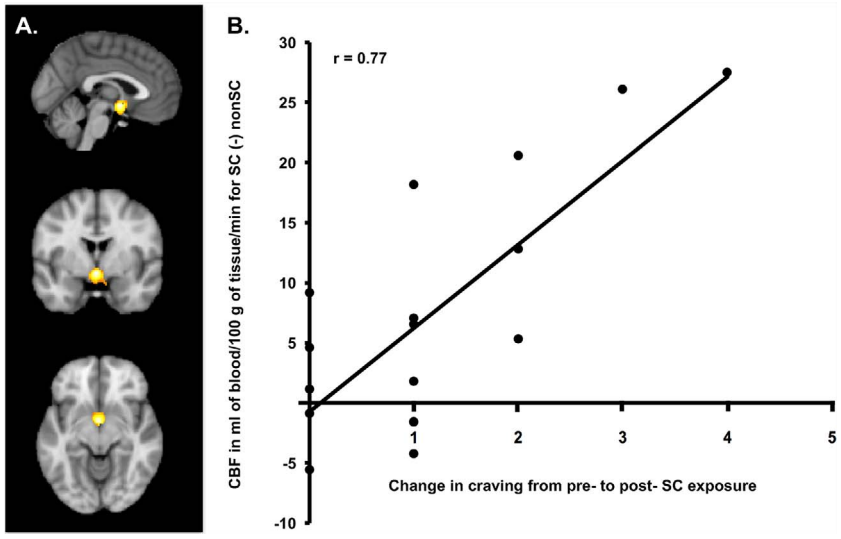

Fig. 2. Correlation between smoking cue (SC)-induced brain reactivity and subjective craving in Study 1. A., Sagittal, coronal and axial images showing a positive correlation between craving and brain responses in the ventral striatum/ventral pallidum (VS/VP) during SC relative to non-SC exposure in males (t = 5.93). Data were analyzed in SPM8 and overlain on the MNI brain, cluster corrected at $p < 0.005$. Images are displayed neurologically (left is left). B., Data were extracted from the functional VS/VP cluster and plotted as a function of change in craving from pre- to post- SC exposure. An interactive visual display of all brain data in all three planes can be found at http://franklinbrainimaging.com.

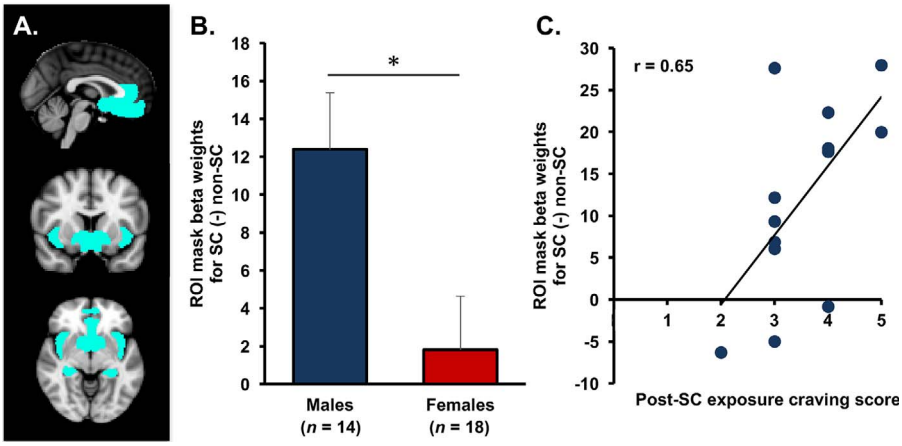

Fig. 3. Smoking cue (SC)-induced brain reactivity and correlation with subjective craving in Study 2. A., Sagittal, coronal and axial images showing the location of the ROI mask (encompassing the ventral medial prefrontal cortex, ventral striatum/ventral pallidum, hippocampus, amygdala, anterior cingulate cortex, and anterior ventral insula) overlain on the MNI brain from which beta weights were extracted. B., Brain activity during SC relative to non-SC exposure is significantly higher in males compared to females ($t = -2.55$). Bars indicate mean + SEM; *$p < 0.05$, *t*-test, two-tailed. C., Extracted beta weights from the ROI mask in males were plotted as a function of post-SC exposure craving scores. ROI mask activation in males is positively correlated with post-SC craving scores ($r = 0.65$, $p < 0.05$).

4. Discussion

Our prior data demonstrated that men have greater brain reactivity to SCs relative to women (Wetherill et al., 2013). However, several studies of sex differences in SC-induced brain reactivity have not provided consistent results, suggesting the need for continued study. In both independent cohorts reported in the current work, we found that men had greater brain reactivity to SCs in our *a priori* ROI in comparison to women. Importantly, these findings were consistent despite significant methodological variability between the two sites.

This current work is in line with our prior study indicating that men have significantly greater brain reactivity to SCs relative to women (Wetherill et al., 2013). In evaluating the sexes individually, we also replicated the finding of high SC reactivity in men (Wetherill et al., 2013), but failed to find any significant SC-related activation in women. This is inconsistent with our prior studies showing heightened SC-induced brain reactivity in women (Janes et al., 2009, 2010, 2012; Wetherill et al., 2013). However, this variability *is* consistent with the idea that circulating gonadal hormones in women impact women's responses to SCs potentially leading to variability across studies (Franklin et al., 2015; Mendrek et al., 2014; for review see Wetherill et al., 2016). Therefore, the lack of observable SC-reactivity in women in the current study may be due to greater variability in brain responses in women due to hormonal fluctuations. However, we are unable to test this directly as women in both samples varied widely in hormonal status (i.e., naturally menstruating, taking birth control, *peri-* or post-menopausal). Addressing this issue is a current area of research in our laboratories.

Regardless of the influence of hormonal variability within our female cohorts, our data confirm that, relative to women, men show significantly greater SC reactivity. In Study 1, men show greater SC reactivity compared to women in the VS/VP and vmPFC. Study 2 largely confirmed this finding as men showed greater brain reactivity to SCs relative to women when evaluating the entire *a priori* ROI, which included the VS/VP, vmPFC, and other brain regions typically reactive to reward and emotionally valenced stimuli. The finding of enhanced SC reactivity in men relative to women in these brain regions is consistent not only with our previous study of SC reactivity (Wetherill et al., 2013) but with studies of cue-reactivity to other abused substances, such as cocaine and alcohol (Kilts et al., 2004; Petit et al., 2013; Potenza et al., 2012). For example, while men exhibited cocaine cue-elicited reactivity across reward-related brain regions, cocaine cue reactivity in women was either absent (Potenza et al., 2012) or primarily restricted to frontal cortical regions (Kilts et al., 2004). Beyond cue reactivity, men also show greater reward-related brain reactivity during consumption of nicotine (Cosgrove et al., 2014) and alcohol (Urban et al., 2010). For example, in comparison to women, men have greater VS activity and dopamine release during cigarette smoking as determined by positron emission tomography (Cosgrove et al., 2014). Collectively, these studies indicate that men may be more responsive to drug-related stimuli across drug classes.

While both men and women experienced SC-elicited craving, this craving was only correlated with brain reactivity in men. Correlations in men were found in regions that showed significant SC-induced reactivity (i.e., the VS/VP in Study 1 and the ROI mask that included the VS/VP in Study 2), suggesting a direct link between neural and subjective responses to SCs. This sex-specific correlation is consistent with our prior study in cannabis users showing a positive association between striatal activation and cannabis cue-induced craving in men only (Wetherill et al., 2015). As the VS plays a key role in addictive processes including drug-cue associations (Koob and Volkow, 2010; Robinson and Berridge, 2003), it is not surprising that striatal activity is associated with cigarette craving. Why VS activity is not correlated with craving in women, however, remains unclear. It is possible that variability in women's hormonal state is masking our ability to observe this effect or that women's craving could be modulated by brain regions other than those present within our *a priori* ROI.

In addition to our initial examination of sex differences in neural responses to SCs (Wetherill et al., 2013), three other groups have conducted similar experiments, but with varying results (e.g., greater reactivity in females and/or males (McClernon et al., 2008; Zanchi et al., 2016) or no sex differences (Mendrek et al., 2014)). However, these pilot studies had extremely small sample sizes (McClernon et al., 2008; Zanchi et al., 2016), which has the potential to profoundly impact studies of sex differences given the known influence of hormonal variability on women's responsivity to SCs. One must also recognize that 'smoking cue exposure' is a broad term for any type of stimulus that includes cigarettes or smoking. There is a wide variety of valence and salience across different stimulus types, which may interact with sex. While the current work used appetitive SCs, at least one of the prior studies showing enhanced SC reactivity in women presented SCs in the context of a stressful scenario (Zanchi et al., 2016). Given women's enhanced reactivity to stressful stimuli (Li et al., 2005; Potenza et al., 2012), considering sex differences in SC reactivity under appetitive vs. stressful conditions may be an important avenue of future research.

In summary, we report the consistent and reproducible finding of greater reward-related brain reactivity to SCs in men relative to women. Similar results were observed despite multiple differences between the studies not only in imaging techniques and SC stimuli, but also in design (time since last cigarette relative to scanning) and in cohort characteristics (Study 1 cohort being slightly older and having smoked for longer). The results also showed consistency despite our inability to evaluate the impact of hormonal variability in women. This consistency is likely due to the fact that both samples included women in various hormonal states, providing a picture of women "on average". However, as stated above, considering hormones is a critical next step, which will enhance the reproducibility of findings. While our sample size is a

significant improvement from the existing literature, it is still relatively modest. Although Study 2 largely replicates results of Study 1, future studies with larger sample sizes are required for further replication and to assess potential interactions of other factors, such as the influence of hormones and behavioral smoking characteristics. Despite this limitation, our findings add to a body of literature supporting the idea that, relative to women, men have greater brain reactivity primarily in reward-related brain regions in response to drug cues across abused substances (Kilts et al., 2004; Petit et al., 2013; Potenza et al., 2012). Such sex differences confirm the need to consider sex not only when evaluating SC reactivity but when examining nicotine dependence etiology and treatment. Although future research is required to more fully understand how SCs impact brain reactivity in women, our data suggest that men may benefit from treatment strategies aimed at devaluing the rewarding properties of SCs.

Role of funding source

This research was supported by the National Institute on Drug Abuse grants R01DA029845, R01DA040670, R01DA030394, and K23AA023897to RRW, K01029645 to ACJ, and T32DA015036-15 to S. Lukas. The funding organizations had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Contributors

KMD, ACJ, RRW, and TRF conceptualized the experiment and analyzed and interpreted the data. KMD wrote the manuscript, and ACJ, RRW, and TRF provided substantial manuscript feedback. KJ and NH assisted in data analysis. MG assisted in clinical assessments. NH, JB, SF, EG, and HP organized study days and collected data. All authors have approved the final manuscript.

Conflict of interest

No conflict declared

Acknowledgements

Study 1: The authors wish to thank Drs. John Detre and Ze Wang for optimization of the perfusion fMRI technique. We also thank the clinical and nursing staff at the Center for the Studies of Addiction for conducting psychological and physical evaluations; and the MRI technicians at the Hospital of the University of Pennsylvania for conducting the scanning sessions. The authors also wish to thank the lab manager Ms. Melanie Maron for her assistance in all study-related matters and Sarah Sivilich for her role as the franklinbrainimaging.com website administrator. Study 2: The authors wish to thank Dr. Blaise Frederick for his role in setting up the BOLD fMRI sequence. We also thank Dr. Scott Lukas for his guidance and for manuscript feedback.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2017.05.044.

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