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

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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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(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