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Sex Differences in the Association of Cigarette Craving With Insula Structure

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ABSTRACT

Background: Cigarette craving, which can negatively impact smoking cessation, is reportedly stronger in women than in men when they initiate abstinence from smoking. Identifying approaches to counteract craving in people of different sexes may facilitate the development of personalized treatments for Tobacco Use Disorder, which disproportionately affects women. Because cigarette craving is associated with nicotine dependence and structure of the insula, this study addressed whether a person's sex influences these associations.

Methods: The research participants (n = 99, 48 women) reported daily cigarette smoking and provided self-reports of nicotine dependence. After overnight abstinence from smoking, they underwent structural magnetic resonance imaging scanning to determine cortical thickness of the left and right anterior circular insular sulcus, and self-rated their cigarette craving before and after their first cigarette of the day.

Results: Women reported stronger craving than men irrespective of smoking condition (i.e., pre- and post-smoking) ($P = .048$), and smoking reduced craving irrespective of sex ($P < .001$). A 3-way interaction of sex, smoking condition, and right anterior circular insular sulcus thickness on craving ($P = .033$) reflected a negative association of cortical thickness with pre-smoking craving in women only ($P = .012$). No effects of cortical thickness in the left anterior circular insular sulcus were detected. Nicotine dependence was positively associated with craving ($P < .001$) across groups and sessions, with no sex differences in this association.

Conclusions: A negative association of right anterior insula thickness with craving in women only suggests that this region may be a relevant therapeutic target for brain-based smoking cessation interventions in women.

Keywords: Craving, insula, nicotine dependence, sex differences, smoking

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Significance Statement

Cigarette craving undermines the success of smoking cessation. Compared with men, women report stronger cigarette craving when they initiate abstinence and greater relief when they resume smoking. Women also respond differently to treatments aimed at facilitating smoking cessation. Because nicotine dependence and insula structure have been associated with cigarette craving, this study addressed whether a person's sex influences these associations. Thickness in a region of the right anterior insula was negatively associated with craving in women only, suggesting that this brain region may be a relevant therapeutic target for brain-based interventions in women who want to stop smoking. There was no sex difference in the correlation of nicotine dependence with craving, indicating that reducing nicotine dependence could diminish craving in both women and men who initiate smoking cessation.

INTRODUCTION

Cigarette smoking continues to be the leading cause of preventable disease and death in the United States (Centers for Disease Control and Prevention, 2017; Creamer et al., 2019), linked to approximately 480 000–540 000 deaths per year (Jamal et al., 2018). With the current global pandemic, individuals who smoke face an unprecedented health risk, as they are 2.4 times more likely to die of complications from COVID-19 than those who do not smoke (Vardavas and Nikitara, 2020). Although smoking cessation is the most important health-promoting change that a person can undertake to reduce his or her risk of a variety of diseases (U.S. Department of Health and Human Services, 2010), currently available treatments are only partially effective, providing long-term cessation rates below 20% (Cahill et al., 2016; McKee et al., 2016; Hartmann-Boyce et al., 2018; Akanbi et al., 2019). Thus, more effective treatment strategies are needed to address this enormous public health concern.

Compared with men, women are disproportionately affected by certain serious smoking-related illnesses (U.S. Department of Health and Human Services, 2010), such as heart disease (Huxley and Woodward, 2011) and lung cancer (Kiyohara and Ohno, 2010), and they experience sex-specific effects of smoking, including menstrual dysfunction, infertility, ectopic pregnancy, miscarriage, stillbirth, birth defects, early menopause, and cervical cancer (U.S. Department of Health and Human Services, 2001, 2014). This disparity is especially concerning because, even though men are more likely to smoke than women (Centers for Disease Control and Prevention, 2017; Creamer et al., 2019), women are less likely to maintain long-term abstinence (Scharf and Shiffman, 2004; Perkins and Scott, 2008; Smith et al., 2016; Garey et al., 2018). Notably, sex differences have been observed in the efficacy of first-line treatments for smoking cessation, such as nicotine replacement (Weinberger et al., 2014; Garey et al., 2018) and varenicline (Gorelick, 2015; McKee et al., 2016). Therefore, the best treatment for a man who smokes may not be optimal for a woman, and "researchers risk drawing erroneous conclusions when they extrapolate outcome data from one sex to another" (Klein et al., 2015).

Understanding sex differences in the behavioral states, especially cigarette craving, that undermine the success of smoking cessation may inform the search for personalized, sex-specific treatments for people who want to stop smoking. Compared with men, women generally report greater withdrawal-related symptoms during early abstinence from smoking (12–24 hours) (Hogle and Curtin, 2006; Leventhal et al., 2007; Xu et al., 2008; Pang and Leventhal, 2013; Doran, 2014; Faulkner et al., 2018; Pang et al., 2019), including stronger craving (Field and Duka, 2004; Leventhal et al., 2007; Tong et al., 2007; Knott et al., 2008; Dickmann et al., 2009; Heishman et al., 2010; Perkins et al., 2013; DeVito et al., 2014; Doran, 2014). Women also report greater relief of craving (Eissenberg et al., 1999; Leventhal et al., 2007) and other withdrawal-related symptoms (Xu et al., 2008) when they resume smoking. Although there is a growing body of literature in support of sex differences in withdrawal-related distress and smoking-induced relief, some studies have reported no such differences (Herbert et al., 2001; Franklin et al., 2004; McClernon et al., 2008; Mendrek et al., 2014), suggesting that as-yet unidentified moderating factors account for these inconsistencies.

There is considerable literature demonstrating that smoking-related states are linked to the function and integrity of the insula. The findings are consonant with the insula representing the interoceptive effects of taking a drug, bringing information about bodily states into conscious awareness (Naqvi and Bechara, 2010; Zaki et al., 2012; Paulus and Stewart, 2014). Cue-induced cigarette craving is positively correlated with regional cerebral glucose metabolism, an index of local brain function (Brody et al., 2002), and damage to the insula can eliminate cigarette craving and promote smoking cessation (Naqvi et al., 2007). In addition, administration of nicotine reduces functional connectivity within insula-amygdala and insula-default mode network circuits in individuals who smoke and are tested when abstinent (Sutherland et al., 2013).

There is evidence for right lateralization of insular contributions to smoking-related states. In participants who smoke, cigarette craving after overnight abstinence is positively correlated with the difference between right insular perfusion in abstinence and satiety conditions (Wang et al., 2007). Craving is also correlated with connectivity between the right anterior insula and the anterior cingulate cortex during abstinence from smoking and is reduced along with this connectivity when smoking is reinitiated (Faulkner et al., 2019). Finally, young participants who smoke exhibit a negative correlation between right but not left insula thickness and cigarette craving (Morales et al., 2014).

Evidence of smoking-related structural differences also highlights the insula as a brain region involved in smoking-related states. One study reported that people who smoke have smaller cortical thickness of the insula compared with people who do not (Durazzo et al., 2018). Moreover, thickness of the right insular cortex was smaller in patients with Major Depressive Disorder who smoked compared with Major Depressive Disorder who did not (Zorlu et al., 2017). Lin et al. (2019) reported smaller thickness of the right anterior and superior segment of the circular sulcus of the insula in people who smoked heavily compared with healthy participants who did not smoke. The participants who smoked heavily also exhibited smaller cortical thickness in the left insular inferior segment of the circular sulcus as well as a negative correlation between thickness of the left insula and nicotine dependence (Lin et al., 2019). Another study, which

evaluated people with a substance dependence that was more generalized than cigarette smoking, found a sex-by-group (substance dependent vs controls) interaction on right insula thickness, as women with substance dependence had smaller right insula thickness than healthy control women, whereas men with substance dependence had larger right insula thickness than healthy control men (Tanabe et al., 2013). Together, these findings support the view that thickness of the right insula may play an important role in tobacco use disorder.

We therefore tested for sex differences in the associations of nicotine dependence and insula thickness with cigarette craving after overnight abstinence from smoking and with the smoking-induced relief of craving. The right anterior circular insular sulcus was selected as the region of interest. This region represents the most rostral and ventral aspect of the insula and was chosen because it closely overlaps with a subdivision of the insula where thickness was previously linked with craving (Morales et al., 2014) and because it exhibits smaller cortical thickness in people who smoke cigarettes heavily compared with people who do not (Lin et al., 2019). Based on previous findings, we hypothesized that women would report stronger craving than men and greater relief of craving after smoking. We also hypothesized that nicotine dependence would be positively related to craving, whereas right but not left insula thickness would be negatively related to craving and that these associations would vary with sex.

METHODS

Overview of Experimental Design

The participants were otherwise healthy adults who smoked cigarettes daily, were willing to maintain overnight abstinence (approximately 12 hours) from smoking before testing, and underwent structural magnetic resonance imaging (MRI) for measurement of insula thickness. Self-reports of cigarette craving were collected twice: before and after participants smoked their first cigarette of the day (pre- and post-smoking, respectively) after overnight abstinence from smoking. Data were pooled from 2 studies. Study 1 took place between April 2014 and August 2016 and included participants who were 18–25 years of age. The participants underwent testing on 5 days, when they smoked either a research cigarette with nicotine content of 0.027, 0.110, 0.231, or 0.763 mg or their preferred-brand cigarette. Only data from testing on the day when they smoked their preferred-brand cigarette were included in the analyses reported here. Other results from Study 1 are reported elsewhere (Faulkner et al., 2018, 2019). Study 2 took place between September 2017 and February 2021 and included individuals who were 18–45 years old. The participants underwent testing only on 1 day, when they smoked their preferred-brand cigarette. Both studies were conducted at the Semel Institute for Neuroscience and Human Behavior at the University of California, Los Angeles. All study procedures were approved by the University of California, Los Angeles Internal Review Board.

Participants

Ninety-nine participants across both studies were recruited via online and print advertisements. They attended an intake session where they received a detailed explanation of their respective study procedures, gave written informed consent, and were screened for eligibility. Fifty-one men (19 from Study 1 and 32 from Study 2) and 48 women (17 from Study 1 and 31 from Study 2) met all study criteria, completed all procedures, and were included in the final data analyses. Post-smoking craving data were not collected from 3 of these participants, but all of their other data, including pre-smoking craving, were included in the final analyses.

Inclusion criteria were age of 18–45 years (18–25 years for Study 1), generally good health, and self-reported smoking at least 4 cigarettes per day for at least 1 year. Exclusion criteria were positive urine tests for drugs of abuse other than nicotine or tetrahydrocannabinol, consuming >10 alcoholic beverages per week, any major current psychiatric or substance-use disorder for Study 1 assessed via a screening tool derived from the Structured Clinical Interview for DSM-IV (First and Gibbon, 2004); for Study 2, assessed via the Mini International Neuropsychiatric Interview for DSM-5 (Sheehan et al., 1998; Hergueta and Weiller, 2013, DSM-5 update)], history of neurological injury, and using electronic cigarettes, cigars, snuff, or chewing tobacco more than 3 times per month. Smoking status was verified during the intake session using a urine cotinine test (ACCUTEST NicAlert Urine and Saliva Screen, Jant Pharmacal Corp., Encino, CA, score ≥3 representing cotinine ≥100 ng/mL). Diagnoses of lifetime (i.e., prior history of) psychiatric or substance use disorders were not used for inclusion/exclusion.

Verification of Drug and Alcohol Abstinence

On the testing day, abstinence from cocaine, opiates, benzodiazepines, and amphetamines (and tetrahydrocannabinol for Study 1) was verified with a 5-panel urine drug test (Drugs of Abuse Test Insta-view, Alfa Scientific Designs Inc., Poway, CA). Alcohol abstinence was verified using a breathalyzer (Alco-Sensor FST, Intoximeters, Inc., St. Louis, MO). For Study 2, recent abstinence from tetrahydrocannabinol was verified with the Dräger DrugTest 5000 saliva test (Dräger, Inc., Houston, TX). Overnight (approximately 12 hours) smoking abstinence was verified with the Micro+ Smokerlyzer breath CO monitor (Bedford Scientific Ltd., Maidstone, Kent, UK), with a required CO level in expired air of <10 ppm.

Self-Report Measures

Nicotine dependence was measured during the intake session using the Heaviness of Smoking Index (HSI) (Borland et al., 2010). Scores on the HSI were derived from "time to first cigarette in the morning" and "cigarettes smoked per day," 2 items of the Fagerström Test for Nicotine Dependence (Fagerström, 2012). Each item was scored from 0 to 3 for a total possible sum score of 6, with higher scores indicating greater nicotine dependence. For the "time to first cigarette" item: 0 = after 60 minutes, 1 = 31–60 minutes, 2 = 6–30 minutes, and 3 = within 5 minutes. For the "cigarettes per day" item: 0 = 10 or less, 1 = 11–20, 2 = 21–30, and 3 = 31 or more. The HSI was used because it is shorter than the full 6-item Fagerström test and has comparable psychometric properties (Heatherton et al., 1989; Kozlowski et al., 1994; Etter et al., 1999).

Cigarette craving was measured using the craving subscale (mean score) of the 15-item version of the Shiffman-Jarvik Withdrawal Scale (Shiffman and Jarvik, 1976) before and after the participants smoked their first cigarette of the day (pre- and post-smoking, respectively). This subscale comprises 5 items (e.g., "If you could smoke freely, would you like a cigarette this minute?," "If you were permitted to smoking, would you refuse a cigarette right now?", etc.), each scored from 1 to 7, where 1 = definitely not and 7 = definitely, for a total possible score of 35.

Structural MRI Acquisition

Of the 99 participants, 84 (n = 24, 10 women, from Study 1; n = 60, 30 women, from Study 2) had MRI scans of the brain. MRI scans were collected both pre- and post-smoking, but only structural data from the pre-smoking scan were included in the analyses. In both studies, the structural T1-weighted images were acquired using a Magnetization Prepared Rapid Gradient Echo sequence with the following parameters: Study 1: 3T TRIO Siemens, isovoxel 1 mm^3, FOV = 256 × 256 mm^2, TE = 3.31 ms, TR = 2530 ms; flip angle = 7°; 176 sagittal slices; Study 2: 3T PRISMA Siemens, isovoxel 0.8 mm^3, FOV = 240 × 256 mm^2, TE = 2.24 ms, TR = 2400 ms; flip angle = 8°; 208 sagittal slices.

Structural MRI Processing

Anatomical MR images were processed using FreeSurfer 6.0.0 (http://surfer.nmr.mgh.harvard.edu), which generates a 3-dimensional model of the cortical surface and provides local cortical thickness measurements (Dale et al., 1999). Mean thickness within 72 automatically defined cortical parcels for each hemisphere were extracted from this model (Fischl et al., 2004; Desikan et al., 2006). Quality of the data was evaluated using the Qoala-T supervised learning quality control tool (Klapwijk et al., 2019), which flagged data from 3 participants for inspection. No errors in the segmentation and parcellation for these data were observed within the insular area or its vicinity. Data from all 84 participants were included in the structural analyses.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for Social Scientists (SPSS 27; IBM, Chicago, IL). General Linear Mixed Models (GLMMs) were used for testing associations between variables of interest. This analysis framework allows for direct testing of differences between the association of variables in different groups by including interaction terms and additionally because it allows for the inclusion of covariates, if necessary.

A GLMM was used to determine the main effects of sex (men vs women), smoking condition (pre- vs post-smoking), nicotine dependence (HSI), and their interactions on cigarette craving. To test for sex differences in the relationships of nicotine dependence with pre-smoking craving, as well as with the smoking-induced change in craving, the 3-way interaction between sex, smoking condition, and nicotine dependence was included in the GLMM. To determine whether to control for study (Study 1 vs Study 2) or age, preliminary GLMMs were conducted for craving, evaluating the main effects of study or age, sex, smoking condition, and their interactions. There were no main effects of study or age or significant interactions with the other variables on craving. Therefore, study and age were not included as covariates in the final analyses. Two additional GLMMs, corrected for multiple comparisons using the Bonferroni method (critical $Ps < .025$), were conducted to determine whether either of the 2 items of the HSI ("cigarettes per day" and "time to first cigarette") were driving the main effect of nicotine dependence on craving. For these GLMMs, the nicotine dependence score was replaced by the score for "cigarettes per day" or the score for "time to first cigarette," respectively.

The right anterior circular insular sulcus (Figure 2A) was tested to evaluate our main hypotheses. The left contralateral anterior circular insular sulcus was also tested to evaluate hemispheric specificity. To test for the existence of a relationship between anterior insula structure and cigarette craving as well as a sex difference in this relationship, GLMMs (one for the right hemisphere and another for the left hemisphere) were constructed to test for the main effects of sex (men vs women), smoking condition (pre- vs post-smoking), anterior circular insular sulcus thickness, and their interactions on craving. Interactions between sex, smoking condition, scanner, and age with insula thickness were included in the models. We also included participant age and scanner version in the models to control for their influence on cortical thickness measures (Dickerson et al., 2008; Tamnes et al., 2010).

To test for sex differences in the relationships of insula thickness with cigarette craving and the smoking-induced change in craving, the 3-way interaction between sex, smoking condition, and insula thickness was included in the model. Finally, to control for nonspecific effects of cortical thickness on craving, the main effect of mean hemispheric thickness, its interactions with sex, smoking condition, scanner, and age, and its 3-way interaction with sex and smoking condition were also included. The Bonferroni method was used to correct for multiple comparisons of the right and left hemispheres (critical $Ps < .025$). Two initial post hoc GLMM analyses, corrected for multiple comparisons using the Bonferroni method (critical $Ps < .025$), were conducted to aid in the interpretation of a 3-way interaction of sex-by-smoking condition-by-right insula thickness on craving. These 2 models tested for the effects of right insula thickness on the smoking-induced change in craving (i.e., 2-way interactions of right insula thickness and smoking condition on craving) in men and women, respectively. Four additional exploratory post hoc GLM analyses, corrected for multiple comparisons using the Bonferroni method (critical $Ps < .0125$), were conducted to aid the interpretation of the 3-way interaction of sex-by-smoking condition-by-right insula thickness on craving. These models tested for a relationship between right insula thickness and craving in (1) men after overnight abstinence, (2) women after overnight abstinence, (3) men after smoking, and (4) women after smoking.

ANOVA statistics computed using the GLMM parameter estimates as well as the unstandardized effect sizes (i.e., regression coefficients) and 95% confidence intervals from all primary and post hoc analyses are reported in the Results section below, and parameter estimates for each model are reported in tables in the Supplementary Materials section.

RESULTS

Participant Characteristics

Ninety-nine adults who smoked daily completed self-report measures of cigarette craving after overnight (approximately 12 hours) abstinence from smoking, before and after smoking their first cigarette of the day (pre- and post-smoking, respectively), and were included in the analyses (Table 1). The sample included relatively young individuals who smoked, with a mean age of 29.2 ± 7.9 years, who were mostly non-Hispanic/Latino (approximately 80%) and Caucasian (approximately 52%). They smoked a mean of 11.4 ± 5.2 cigarettes per day and had low-to-moderate levels of nicotine dependence (HSI scores of 2.2 ± 1.3). The majority (approximately 62%) smoked their first cigarette of the day within 30 minutes of waking up. On average, they used 1.0 ± 3.1 g of marijuana per week, with time of last use at least 2 days prior to testing, and reported having 3.8 ± 5.6 drinks of alcohol per week. Men

Table 1. Participant demographics and substance use statistics (behavioral analyses)

	Entire sample (n = 99)	Men (n = 51)	Women (n = 48)	Significance (*P* value)
Age (y)[a]	29.2 ± 7.9	29.2 ± 7.6	29.3 ± 8.3	.949
Ethnicity (% of participants)				
Hispanic/Latino	13.1	9.8	16.7	.616
Not Hispanic/Latino	79.8	82.4	77.1	
Unknown	7.1	5.9	6.3	
Race (% of participants)				
Caucasian	51.5	52.9	50.0	.971
African American	23.2	23.5	22.9	
Mixed	9.1	7.8	10.4	
Other	16.2	15.7	16.7	
Cigarette smoking[a]				
Nicotine dependence[b]	2.2 ± 1.3	2.3 ± 1.3	2.2 ± 1.2	.511
Cigarettes/d	11.4 ± 5.2	12.1 ± 6.1	10.6 ± 4.0	.160
Time to first cigarette[b] (% of participants)				
Within 5 min	17.2	19.6	14.6	.365
6–30 min	44.4	45.1	43.8	
31–60 min	24.2	17.7	31.4	
After 60 min	14.1	17.7	10.4	
Substance use[a]				
Marijuana (g/wk)	1.0 ± 3.1	1.0 ± 3.1	1.0 ± 2	.999
Alcohol (drinks/wk)	3.8 ± 5.6	3.5 ± 4.2	4.0 ± 6.8	.663

[a]Mean ± SD.
[b]Measured with the Heaviness of Smoking Index (HSI, Borland et al., 2010).
Men and women in these studies were well-matched and did not differ on any demographic or substance use variables measured. All differences were tested with unpaired *t* tests, with the exception of race, ethnicity, and time to first cigarette, which were tested with chi-square tests.

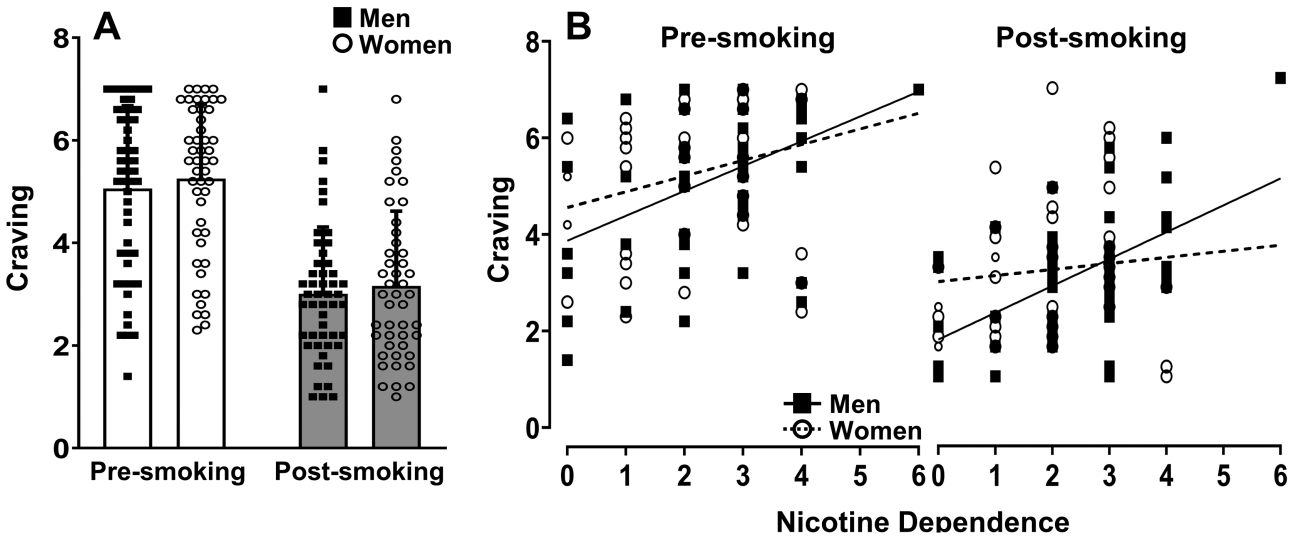

Figure 1. Effects of sex, resumption of smoking, and nicotine dependence on cigarette craving. Nicotine dependence (Heaviness of Smoking Index [HSI]) was measured in men (n = 51) and women (n = 48), and craving was measured after overnight (approximately 12 hours) smoking abstinence, before and after the first cigarette of the day. (A) There were main effects of sex (*P* = .048) (women reported greater craving than men) and smoking (*P* < .001) (men and women reported less craving after vs before smoking) on craving. (B) There was also a main effect of HSI on craving (*P* < .001) (individuals with greater nicotine dependence reported greater craving, irrespective of sex or smoking condition). Means ± SD shown.

and women were well matched, as there were no significant differences between the groups in any of the demographic or substance use variables (all *P*s > .05; see Table 1). With respect to demographic and substance abuse variables, the subsample that participated in MRI scanning (n = 84) was almost identical to the full sample and showed no sex differences in any of the variables (all *P*s > .05; see Supplementary Table 1 in Supplementary Materials).

Effects of Sex and Resumption of Smoking on Cigarette Craving

There was a main effect of sex on cigarette craving ($F[1,94] = 4.025$, $P = .048$; regression coefficient = −1.21; 95% CI = −2.34 to −0.07). Women reported greater craving than men, both before and after smoking (Figure 1A). There was also a main effect of smoking the first cigarette of the day on craving ($F[1,92] = 35.721$, $P < .001$;

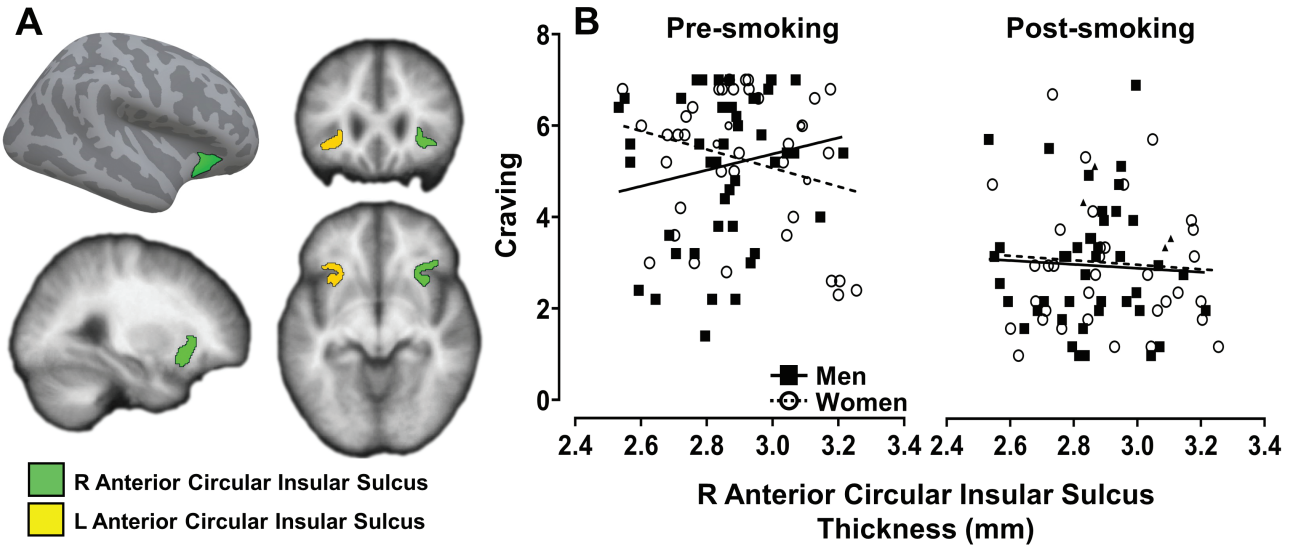

Figure 2. Sex differences in the relationship between insula thickness and cigarette craving. Mean thickness (mm) within the anterior insula, within each hemisphere, was measured in men (n = 44) and women (n = 40), and craving was measured after overnight (approximately 12 hours) smoking abstinence. (A) A rendered "inflated" brain (top left) as well as coronal (top right), transaxial (bottom left), and sagittal (bottom right) brain views, showing the FreeSurfer parcellations for which thickness was determined: the right (green) and left (yellow) anterior circular insular sulcus. (B) There was a 3-way interaction of sex, smoking condition, and right anterior circular insular sulcus thickness on craving ($P = .033$). Post hoc analyses showed that mean insula thickness was negatively associated with craving in abstinent women only ($P = .012$).

regression coefficient = 1.66; 95% CI = 0.74 to 2.59). Smoking reduced craving in both men and women (Figure 1A), but there was no significant interaction of sex and smoking condition on craving ($P = .415$).

Effects of Nicotine Dependence on Cigarette Craving

There was a main effect of nicotine dependence on cigarette craving ($F[1,94] = 16.944$, $P < .001$; regression coefficient = 0.14; 95% CI = −0.20 to 0.47). Participants with greater dependence reported greater craving, irrespective of sex or smoking condition. There were no significant dependence-by-sex or dependence-by-smoking interactions and no 3-way interaction of sex, smoking condition, and dependence on craving ($P > .05$).

When items on the HSI were evaluated separately, there was a main effect of cigarettes per day ($F[1,93] = 11.892$, $P = .001$; regression coefficient = 0.48; 95% CI = −0.27 to 1.23) and a slightly weaker main effect of time to first cigarette ($F[1,93] = 9.977$, $P = .002$; regression coefficient = 0.07; 95% CI = −0.40 to 0.54) on cigarette craving. Participants who smoked more cigarettes per day or smoked sooner after waking up reported greater craving, irrespective of sex or smoking condition. There were no 2-way interactions of sex with either cigarettes per day or time to first cigarette on craving, and no 3-way interactions of sex and smoking condition with either of these measures ($P > .025$).

Effects of Insula Structure on Cigarette Craving

Of the 2 insular regions examined, significant effects were found only for right anterior circular insular sulcus thickness (Figure 2A). No main effect of right anterior circular insular sulcus thickness on craving was found ($P = .852$), but there was a 3-way interaction of sex, smoking condition, and right anterior circular insular sulcus thickness on craving ($F[1,73] = 4.719$, $P = .033$; regression coefficient = −4.36; 95% CI = −8.36 to −0.36), which did not survive the Bonferroni correction for multiple comparisons ($P > .025$).

When men and women were tested separately, the 2-way interactions between right anterior circular insular sulcus thickness and smoking condition were not significant ($P > .025$). Additional exploratory post hoc analyses showed that thickness of the right anterior circular insular sulcus was negatively associated with craving in women in the pre-smoking condition ($F[1,31] = 7.103$, $P = .012$; regression coefficient = 8.87; 95% CI = −16.59 to −1.16) but not after smoking ($P = .945$) (Figure 2B). In men, thickness of the right anterior circular insular sulcus was not associated with craving under either smoking condition ($P > .0125$) (Figure 2B).

DISCUSSION

The findings support previous observations that women who smoke cigarettes report greater abstinence-induced craving than men (Field and Duka, 2004; Leventhal et al., 2007; Tong et al., 2007; Knott et al., 2008; Dickmann et al., 2009; Heishman et al., 2010; Perkins et al., 2013; DeVito et al., 2014; Doran, 2014) and that nicotine dependence is positively correlated with craving (Donny et al., 2008; Nesic et al., 2011). We add to these findings by demonstrating that the cigarettes per day item of the HSI is also positively correlated with craving, whereas the time to first cigarette item is negatively correlated with craving. The effect size for the effect of cigarettes per day on craving is larger than the effect size for time to first cigarette, suggesting that cigarettes per day may be a stronger contributor to the effect of dependence on craving.

The brain structural analyses performed here extend the previous observation that in a small sample of young individuals who smoked, there was a negative correlation between cortical thickness in the right anterior insula and cigarette craving (Morales et al., 2014). Whereas we did not observe a main effect of right insula thickness on craving per se, as did Morales et al. (2014), there was a sex difference in the relationship between right insula thickness and smoking condition on craving. Specifically, thickness of the right but not the

left anterior circular insular sulcus was negatively associated with abstinence-induced cigarette craving in women but not men (i.e., in our sample the relationship between right insula thickness and craving was specific to sex, not generalized to participants). Morales et al. (2014), the only other study reporting a negative correlation of right anterior insula thickness and craving, had a small sample of people who smoked (n = 18, 8 women) that precluded analysis of sex differences. Moreover, their sample was composed of much younger individuals (approximately 19-year-olds compared with 30-year-olds in our sample), which may suggest that the sex difference we observed could be affected by age, although we did not find a main effect or any 2-way or 3-way interactions of age with thickness on craving. The sex difference in the association of thickness and craving must be interpreted with caution because the significant 3-way interaction of sex-by-smoking condition-by-right insula thickness on craving did not survive Bonferroni correction for multiple comparisons when the left insula was included in the analysis. Future studies to validate and clarify this sex difference are necessary. Brain-based smoking cessation interventions, such as transcranial magnetic stimulation, have been evaluated for smoking cessation (Li et al., 2017) and reduced cigarette consumption and nicotine dependence after stimulation of the insula (Dinur-Klein et al., 2014) or the left dorsolateral prefrontal cortex (Li et al., 2020; Abdelrahman et al., 2021). Such interventions may improve their efficacy by targeting different brain regions, and perhaps different subregions of the insula, in men vs women. This study points to the right anterior circular insular sulcus as an important target for women.

Sex did not affect the association of nicotine dependence and craving, suggesting that targeting dependence to aid in smoking cessation would be equally beneficial for men and women. Possible avenues of reducing nicotine dependence include the use of nicotine replacement therapy (NRT) and reduced nicotine cigarettes (RNCs). NRT can help reduce the number of cigarettes smoked per day (see review by Hughes, 2002), but women appear to respond less favorably to NRT (Weinberger et al., 2014; Garey et al., 2018). RNCs that contain minimal or non-addictive levels of nicotine (Benowitz and Henningfield, 1994; Donny et al., 2015) have shown promise in helping people, especially men (Vogel et al., 2014), quit smoking. Use of RNCs can decrease nicotine intake with minimal withdrawal symptoms and without promoting compensatory over-smoking (Benowitz et al., 2015; Donny et al., 2015), thereby helping individuals quit smoking (Benowitz et al., 2017). However, noncompliance is common with RNCs, and people who smoke will often seek out other forms of nicotine (Benowitz et al., 2015; Donny et al., 2015). As such, these 2 treatment strategies represent options that, despite some limitations, can be clinically leveraged to reduce nicotine dependence, which may help lower craving and improve smoking cessation outcomes. The evidence that both of these treatment strategies are more beneficial for men further highlight the need for the development of treatments that especially benefit women.

Overall, this study provides promising evidence for sex differences in the influence of insula structure, but not nicotine dependence, on cigarette craving in early abstinence. A notable limitation is that, despite a relatively large sample (n = 99), statistical significance was not retained when correcting for the additional analysis of the left anterior insula (negative control region). Another limitation is that the correlational nature of the findings precludes drawing causal inferences. Future studies could expand on and clarify the nature of the observed relationships through interventions that target the right anterior insula, with a focus on sex differences in craving. Longitudinal studies of participants who have not yet started smoking may also be helpful in determining whether cortical thickness in the right anterior circular insular sulcus is a predictor of susceptibility for nicotine dependence. Moreover, measurements of ovarian hormones in women and androgens in men could help clarify the neuroendocrine mechanisms underlying these sex differences and whether they can be leveraged to improve smoking-cessation treatment outcomes.

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Interest Statement

As principal investigator of the project, Dr London takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have reviewed and approve the final version of this manuscript. Dr Tyndale has consulted for Quinn Emanuel and Ethismos Research Inc. All other authors declare no conflict of interest.

Data Availability

All demographic, self-report, and structural MRI data discussed in this manuscript, as well as the code used for statistical analyses, are publicly available at Open Science Framework under project title "Sex Differences in the Association of Cigarette Craving With Insula Structure" (https://osf.io/z3s9p/)."

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