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Sex differences in tobacco smokers: Executive control network and frontostriatal connectivity

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ABSTRACT

Background: Women experience greater difficulty quitting smoking than men, which may be explained by sex differences in brain circuitry underlying cognitive control. Prior work has linked reduced interhemispheric executive control network (ECN) coupling with poor executive function, shorter time to relapse, and greater substance use. Lower structural connectivity between a key ECN hub, the dorsolateral prefrontal cortex (DLPFC), and the dorsal striatum (DS) also contributes to less efficient cognitive control recruitment, and reduced intrahemispheric connectivity between these regions has been associated with smoking relapse.

Therefore, sex differences were probed by evaluating interhemispheric ECN and intrahemispheric DLPFC-DS connectivity. To assess the potential sex by nicotine interaction, a pilot sample of non-smokers was evaluated following acute nicotine and placebo administration.

Methods: Thirty-five smokers (19 women) completed one resting state functional magnetic resonance imaging scan. Seventeen non-smokers (8 women) were scanned twice using a repeated measures design where they received 2 and 0 mg nicotine.

Results: In smokers, women had less interhemispheric ECN and DLPFC-DS coupling than men. In non-smokers, there was a drug x sex interaction where women, relative to men, had weaker ECN coupling following nicotine but not placebo administration.

Conclusions: The current work indicates that nicotine-dependent women, versus men, have weaker connectivity in brain networks critically implicated in cognitive control. How these connectivity differences contribute to the behavioral aspects of smoking requires more testing. However, building on the literature, it is likely these deficits in functional connectivity contribute to the lower abstinence rates noted in women relative to men.

1. Introduction

Tobacco smoking remains the principal cause of preventable illness and death in the United States (U.S. Department of Health and Human Services (USDHHS, 2014). Despite available evidence-based smoking cessation treatments, the majority of people who attempt to quit relapse within 8 days (Hughes et al., 2004). This highlights the need to better understand biological factors enhancing substance use vulnerability. One such biological factor is sex, as women have greater difficulty maintaining long-term abstinence than men (Bjornson et al., 1995; Perkins and Scott, 2008; Scharf and Shiffman, 2004; Smith et al., 2016). Given the serious health consequences of smoking and the challenges of quitting for women, it is especially important to understand how sex impacts the brain circuitry related to smoking cessation. While resting state functional connectivity studies in nicotine dependence have identified sex differences in networks associated with self-referential processing, affect, and reward (Beltz et al., 2015; Wetherill et al., 2014), sex differences in cognitive control networks remain relatively unexplored. This is critical, as cognitive control is necessary for maintaining abstinence (Powell et al., 2010).

The executive control network (ECN; Seeley et al., 2007), also known as the frontoparietal control network (Smith et al., 2009), is one of the primary resting state networks associated with cognitive control. Disrupted ECN connectivity is linked to cognitive control deficits (Dong et al., 2015) and relapse in addiction, such as any heroin or methamphetamine use during treatment (Li et al., 2018). For instance, smokers have reduced ECN connectivity compared to non-smokers (Li et al., 2016; Wu et al., 2015), which has been found to predict earlier

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substance use relapse (Camchong et al., 2013). More specifically, interhemispheric ECN coupling (i.e., the correlation of spontaneous activity between the left and right hemispheres) is a marker of substance use and related cognitive control. Reduced interhemispheric ECN coupling is linked to worse executive functioning, earlier relapse in cocaine use disorder (any cocaine or amphetamine use post-treatment discharge; McHugh et al., 2017), and more severe heroin use (Qiu et al., 2017). The link between interhemispheric ECN coupling and substance abuse-related behavior makes this network a critical target for evaluating sex differences, which have thus far been unexplored.

Due to the fact that increased cognitive or self-control can inhibit smoking behavior (Muraven, 2010), connectivity between ECN hubs and regions associated with conditioned behavior may also underlie sex differences in smokers. The dorsolateral prefrontal cortex (DLPFC) is a key ECN hub important for cognitive control (Buhle et al., 2014; Casey et al., 1997; MacDonald et al., 2000), but smokers display deficits in DLPFC activity during cognitive control compared to non-smokers (Nestor et al., 2011). The DLPFC facilitates top-down control over goal-directed behavior (Robinson et al., 2012) through a structural and functional frontostriatal loop with the dorsal striatum (DS) (Choi et al., 2012; Di Martino et al., 2008; Jarbo and Verstynen, 2015). The DS, including the caudate and putamen, is involved in the formation and maintenance of substance use behaviors (Everitt and Robbins, 2013). Stronger structural frontostriatal connectivity is associated with better cognitive control (Liston et al., 2005). However, smokers have weaker structural intrahemispheric DLPFC-DS connectivity than non-smokers, whereas stronger structural DLPFC-DS connectivity is associated with the ability to maintain abstinence (Yuan et al., 2018a, b). Smokers also have weaker resting state intrahemispheric DLPFC-DS connectivity, which is related to impaired cognitive control (Yuan et al., 2016), consistent with parallel findings in internet gaming disorder (Yuan et al., 2017). Despite this network's role in addiction, sex differences in nicotine-dependent individuals have not been examined.

To fill this gap, in the present study, we assessed whether chronic smokers displayed sex differences in resting state networks involved in cognitive control by probing: 1) interhemispheric ECN coupling and 2) intrahemispheric DLPFC-DS coupling. To start disentangling the potential sex by nicotine interaction, coupling strength was also evaluated in an exploratory independent cohort of non-smokers following placebo and nicotine administration. This manipulation will provide evidence for how sex and nicotine interact during initial exposure, which may aid in explaining how sex differences develop in chronic smokers.

2. Materials and methods

2.1. Participants

2.1.1. Nicotine-dependent smokers

Thirty-five nicotine-dependent individuals (19 women, 16 men; aged 28.64 ± 6.06, age range 18–41) participated in all study procedures at McLean Hospital's Imaging Center. Secondary data analyses were conducted with participants combined from two independent smoking studies: a) N = 19, 10 women (Janes et al., 2015a), b) N = 17, 9 women (Janes et al., 2015b) to conduct the sex-based functional connectivity analyses novel to the present study. All participants reported smoking daily for at least 6 months prior to the study start date and were nicotine-dependent as assessed by the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991). Smoking was biologically verified via expired carbon monoxide (CO; Micro Smokerlyzer II, Bedfont Scientific Instruments, Kent, UK) at the start of the study.

Participants were recruited via online advertisements, local list serves, and locally posted fliers. The Structured Clinical Interview for DSM IV-TR (SCID; First et al., 2002) was used to exclude participants who had current substance use disorders (other than nicotine dependence), organic mental disorder, bipolar disorder, schizophrenia spectrum disorder, current depressive episode, or psychotropic drug use. Participants were also excluded if they were pregnant, had a history of head trauma or injury causing loss of consciousness lasting greater than three minutes, or had other MRI contraindications. Participants were also required to have a breath blood alcohol level of zero (Alco-Sensor IV, Intoximeters, St Louis, MO). All procedures were performed in compliance with relevant laws and institutional guidelines and in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants, and research was approved by the McLean Hospital Institutional Review Board and Partners Human Research Committee (the institutional review board of Partners Healthcare hospitals).

2.1.2. Non-smokers

Non-smokers were 17 healthy control participants (8 women, 9 men; aged 26.06 ± 6.09, age range 18–38) from a separate study on the effects of acute nicotine that had not examined sex differences (Janes et al., 2018). Participants in the acute nicotine study were recruited with the same exclusion criteria as smokers, but they could not have nicotine use disorder as assessed by participant history and the SCID. Non-smokers also reported < 20 lifetime uses of nicotine (reflecting no regular lifetime cigarette use), no nicotine use in the past year, and had expired CO < 5 ppm, thus confirming their non-smoking status.

2.2. Study procedures

2.2.1. Nicotine-dependent smokers

During the study visit, participants smoked their own cigarettes *ad lib* 1.5 h prior to scanning while being observed by study staff to normalize recency of smoking, and expired CO was measured immediately prior to scanning. Craving for cigarettes and negative affect were assessed before scanning with the Questionnaire of Smoking Urges - Brief (QSU-brief; Cox et al., 2001) and the Positive and Negative Affect Schedule (PANAS; Watson et al., 1998), respectively. Participants completed a 6-min resting state functional magnetic resonance imaging (fMRI) scan, and they were asked to remain awake with their eyes open. The resting state scan was the first functional sequence run during the scanning session.

2.2.2. Non-smokers

Participants received a 2-mg nicotine lozenge or placebo lozenge 1 h prior to scanning in a double-blind randomized cross-over design with each participant completing the nicotine and placebo conditions on average 10.5 days apart (one lozenge type per study visit) (Janes et al., 2018). The nicotine lozenge (Nicorette Lozenge, GlaxoSmithKline, Brentford London) and placebo (Tums antacid, GlaxoSmithKline, Brentford London) were both mint flavored and similar in size, shape, and color. The lozenges dissolved next to the cheek in approximately 15 min without chewing. Plasma nicotine levels for the 2-mg lozenge peak at 1 h with a 2.3-hour half-life (Choi et al., 2003), and scanning took place within this window. This dose yields approximately 1-mg of systemic nicotine (Choi et al., 2003) and is similar to smoking one cigarette (Benowitz and Jacob, 1984). The resting state scan was the first functional sequence run, and resting state instructions for the non-smoker and smoker cohorts were identical. Blood draws were collected immediately post scanning to quantify the concentration of cotinine, the main metabolite of nicotine. One female and two male participants were unable to provide serum samples; thus, urine measurements were taken to verify the effect of the nicotine lozenge.

2.3. Imaging parameters

2.3.1. Nicotine-dependent smokers

Imaging was conducted on a Siemens Trio 3 T scanner (Erlangen, Germany) with a 32-channel head coil. Multiecho multi-planar rapidly

acquired gradient echo (MPRAGE) structural images were collected using the following parameters: repetition time (TR) = 2.1 s, echo time (TE) = 3.3 ms, slices = 128, flip angle 7°, and resolution = 1.0 × 1.0 x 1.33 mm. For the resting state scan, data were collected using a gradient echo-planar sequence with the following parameters: TR = 2.5 s, TE = 30 ms, flip angle = 90°, slices = 42, voxel size = 3.5 mm isotropic.

2.3.2. Non-smokers

Imaging data were collected on the same scanner with the same parameters as the smokers except for the resting state scan: TR = 720 ms, TE = 32 ms, flip angle = 66°, slices 64, voxel size = 2.5 mm isotropic, and a multi-band acceleration factor of 8.

2.4. fMRI processing and data analyses

Resting state scans across all studies were processed using tools from the fMRI of the Brain (FMRIB) Software Library (FSL; http://fmrib.ox.ac.uk/fsl). The first 5 volumes were removed to allow for signal stabilization. Preprocessing included motion correction with MCFLIRT, slice timing correction, brain extraction, 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 were then affine-registered to the MNI152 2 mm^3 standard space template (Montreal Neurological Institute, Montreal, QC, Canada) using FLIRT (Jenkinson and Smith, 2001). Participant data were then denoised using FSL's multivariate exploratory linear decomposition into independent components (MELODIC) to limit motion and noise from affecting analyses. MELODIC was first used to identify all independent components (ICs) for each participant. ICs representing noise were identified by visually inspecting all spatial maps and associated time courses for each IC (Janes et al., 2015a; McCarthy et al., 2017). Those ICs representing noise were then regressed out of the fMRI data using FSL's fsl regfilt function.

To assess interhemispheric coupling in the ECN, average time courses for the right and left ECN were extracted from the denoised resting state data. The right and left ECN were defined using a fronto-parietal ROI from Smith et al. (2009; Fig. 1) with no overlap with the opposite hemisphere (McCarthy et al., 2017). The selected DLPFC and DS ROIs have shown changes in frontostriatal coupling strength as a result of acute nicotine in individuals with major depressive disorder (Janes et al., 2018). The right and left DLPFC ROIs were defined by a 5-mm sphere based on MNI coordinates +/- 42, 38, 28 that were highlighted in the Curtis and D'Esposito (2003) review and overlap with Brodmann's area 9/46 (Petrides, 2005). The right and left DS ROIs were defined as the striatal regions functionally connected to the ECN, including the DLPFC, using resting state fMRI (Choi et al., 2012). As a negative control to determine whether sex differences are widespread beyond interhemispheric ECN coupling and coupling between the DLPFC and DS, we conducted a follow-up analysis examining the primary visual cortex (V1) as a control region. Despite a dearth of data on sex differences in DLFPC-V1 coupling, the V1 has not been associated with sex-related differences in interhemispheric coupling (Viswanath et al., 2015; Zuo et al., 2010). Thus, we did not expect sex differences in interhemispheric V1 coupling or intrahemispheric coupling with the DLPFC. The right and left V1 ROIs were created from the occipital pole of the Harvard-Oxford Cortical Structural Atlas with a 50% probability threshold (see Supplementary Material). The average time courses for each ROI were then demeaned, detrended, Hamming windowed, and correlated, accounting for possible signal time lags, resulting in one maximum correlation value (r) per participant (Janes et al., 2018; McCarthy et al., 2017). Correlation values were subsequently Fisher z transformed and analyzed in SPSS 24.

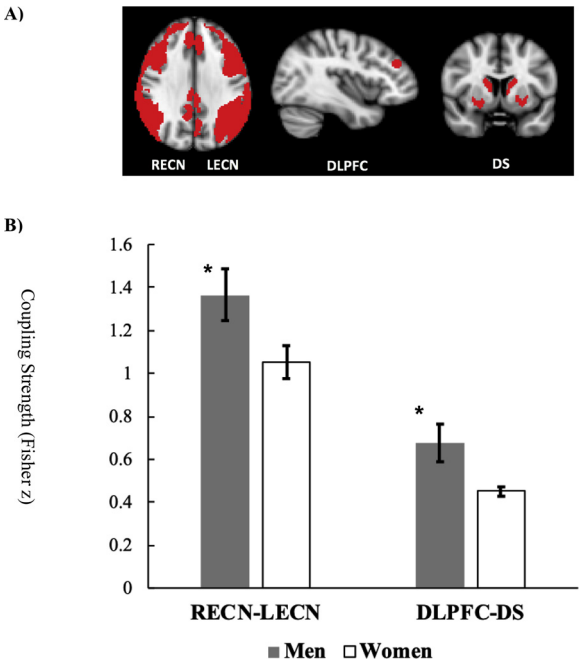

Fig. 1. Coupling: Nicotine-dependent smokers.

2.5. Demographic, clinical, and coupling statistical analyses

All analyses were conducted in SPSS 24. Independent sample t-tests and chi-square tests were used to compare demographic variables (age, education, handedness, body mass index) and smoking characteristics (cigarettes per day [CPD], pack-years [CPD/cigarettes in a pack x years smoking], FTND, and pre-scan expired CO, pre-scan smoking craving and negative affect), cotinine, and depressive symptoms between men and women. While current depression was excluded, subclinical depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II; Beck et al., 1996). This control was included because nicotine has been shown to modulate DLPFC-DS coupling differently in individuals with and without depression (Janes et al., 2018). Sex differences in interhemispheric ECN and DLPFC-DS coupling controlling for putative sex differences in demographic, smoking, or clinical variables were examined with one-way and repeated measures ANCOVAs. Lastly, to investigate whether sex differences in coupling were driven by smoking variables, Pearson correlations examined the relationship between coupling strength and smoking variables (CPD, pack years, FTND, CO, craving, negative affect) within each sex. To protect against false positive findings, a Bonferroni adjusted alpha of 0.008 (0.05/6) was used for each set of ROIs (interhemispheric ECN and DLPFC-DS).

3. Results

3.1. Nicotine-dependent smokers: demographic, smoking, and clinical characteristics

Demographic, smoking, and clinical characteristics are presented in Table 1. Men and women did not significantly differ by age, education, handedness, pack-years, nicotine dependence (FTND), expired CO, tobacco craving, negative affect, or depression ($ps > 0.05$). Men reported smoking significantly more cigarettes per day than women ($t(33) = 2.52$, $p = .017$, Cohen's $d = 0.85$), which is expected (Jamal et al., 2016). As a result, cigarettes per day was included as a covariate in subsequent analyses.

3.2. Nicotine-dependent smokers: ECN interhemispheric coupling

Women had significantly lower ECN interhemispheric coupling than men ($F(1, 32) = 7.74$, $p = 0.009$, $\eta_p^2 = 0.20$) (Fig. 1). This sex

Table 1
Demographic, smoking, and clinical characteristics.

	Nicotine-dependent Smokers		Non-Smokers	
	Men n = 16 # (%)	Women n = 19 # (%)	Men n = 9 # (%)	Women n = 8 # (%)
Race				
Caucasian	10 (62.5)	9 (47.4)	6 (66.7)	2 (25.0)
African American	1 (6.3)	4 (21.2)	2 (22.2)	1 (12.5)
Asian	2 (12.5)	3 (15.8)	–	3 (37.5)
Hispanic	1 (6.3)	3 (15.8)	–	2 (25.0)
More than one race	2 (12.5)	0 (0.0)	1 (11.1)	–
Right-handed	11 (68.8)	16 (84.2)	7 (77.8)	7 (87.5)
	M (SD)	M (SD)	M (SD)	M (SD)
Age*	27.75 (6.42)	29.11 (5.87)	29.22 (6.36)	22.50 (3.34)
Education*	15.47 (1.82)	14.53 (2.41)	17.22 (2.17)	14.69 (1.89)
Average daily cigarettes+	15.53 (3.76)	12.53 (3.30)	–	–
Pack-years	7.67 (5.25)	7.57 (3.98)	–	–
FTND	5.69 (1.54)	5.84 (1.17)	–	–
CO pre-scan	23.31 (11.55)	24.84 (10.87)	1.11 (0.78)	1.75 (1.17)
Craving pre-scan	20.94 (8.66)	17.37 (6.59)	–	–
Negative affect pre-scan	11.53 (2.35)	11.00 (1.89)	–	–
Serum cotinine post scan	–	–	13.56 (6.59)	16.9 (6.66)
Body mass index (BMI)	–	–	24.42 (2.99)	25.28 (4.57)
Depression (BDI-II)	4.18 (3.30)	2.79 (2.96)	1.44 (3.01)	1.63 (3.16)

FTND = Fagerström Test of Nicotine Dependence; CO = expired carbon monoxide (parts per million); BDI-II = Beck Depression Inventory-II. Non-smoking men and women completed both placebo and nicotine conditions. Serum cotinine levels are reported for non-smokers during the nicotine study visit, as cotinine levels were zero during the placebo condition.

* Sex difference for non-smokers ($p < 0.05$).

\+ Sex difference for smokers ($p < 0.05$).

difference was not widespread, as there was no significant effect of sex on interhemispheric V1 coupling.

3.3. Nicotine-dependent smokers: DLPFC-DS coupling

The main effect of sex was significant ($F(1, 32) = 7.08$, $p = 0.012$, $\eta_p^2 = 0.18$) with women having significantly weaker DLPFC-DS coupling than men (Fig. 1). The main effect of hemisphere and sex x hemisphere interaction was not significant. This sex difference does not necessarily generalize globally, as coupling between the DLPFC and V1 did not significantly differ between women and men.

3.4. Nicotine-dependent smokers: correlations between smoking variables and coupling

To investigate whether the coupling patterns described above were further modulated by smoking and nicotine dependence variables, Pearson correlations were performed between the four smoking variables and coupling strength within each sex separately. Average cigarettes smoked per day, pack-years, nicotine-dependence (FTND), CO, smoking craving, and negative affect were not significantly associated with interhemispheric ECN coupling or DLPFC-DS coupling strength in either sex ($ps > 0.064$).

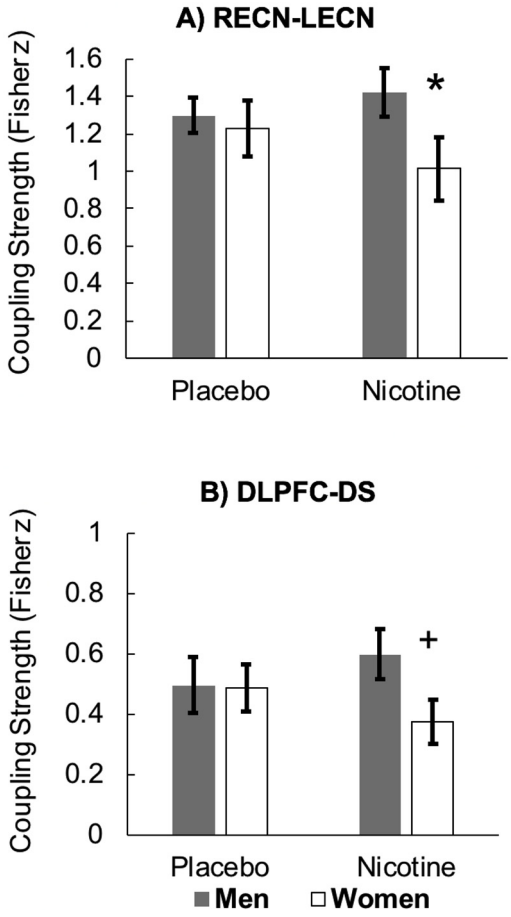

Fig. 2. Coupling: Non-smokers.

3.5. Non-smokers: demographic and clinical characteristics

Demographic and clinical characteristics are presented in Table 1. The positive cotinine values verified the presence of nicotine during the nicotine condition. Sex differences were not noted, except men were significantly older ($t(15) = 2.77$, $p = .017$, Cohen's $d = 1.32$) and had more years of education than women ($t(15) = 2.56$, $p = .022$, Cohen's $d = 1.24$). Therefore, age and education were included as covariates in the analyses below.

3.6. Non-smokers: ECN interhemispheric coupling

The interaction between sex and drug (nicotine vs. placebo) was significant ($F(1, 13) = 8.71$, $p = 0.011$, $\eta_p^2 = 0.40$). The main effects of sex and drug were not significant. As a follow-up to the sex by drug interaction, a one-way ANCOVA indicated that women had less ECN coupling than men ($F(1, 13) = 7.44$, $p = 0.017$, $\eta_p^2 = 0.36$) following nicotine, not placebo ($F(1, 13) = 0.15$, $p = 0.710$, $\eta_p^2 = 0.01$), administration (Fig. 2). Within-sex, coupling strength was not significantly different between placebo and nicotine conditions. Highlighting regional specificity, the sex x drug interaction did not extend to the V1.

3.7. Non-Smokers: DLPFC-DS coupling

The sex x drug interaction was a trend approaching significance ($F(1, 13) = 3.79$, $p = 0.073$, $\eta_p^2 = 0.23$). Given the sex differences found in the smoking sample, we evaluated whether the two sexes differed in the nicotine condition, but this was not the case ($F(1, 13) = 1.68$, $p = 0.218$). The main effects of sex, drug, and hemisphere were not

significant, and the interactions between these variables were not significant. When performing the control analysis (DLPFC-V1 coupling), there were also no significant sex differences overall, within drug condition, or by hemisphere.

4. Discussion

The present study demonstrated that in chronic smokers, women had *less* interhemispheric ECN coupling at rest compared to men. Weak ECN connectivity has been linked to worse cognitive control (Camchong et al., 2013) and heightened risk for earlier cocaine use post-treatment discharge (McHugh et al., 2017), suggesting that reductions in cognitive control mediated by ECN communication impair the ability to remain abstinent. Building on these prior findings, the current work suggests that weaker interhemispheric ECN connectivity in women may contribute to the lower tobacco abstinence rates noted in women relative to men (Perkins and Scott, 2008).

With respect to frontostriatal connectivity, nicotine-dependent women also had reduced DLPFC-DS coupling, which may reflect top-down cognitive control deficits (DLPFC to DS). The prefrontal cortex is thought to drive top-down control mechanisms in frontostriatal circuits (Morein-Zamir and Robbins, 2015) with increased frontostriatal connectivity reflecting better cognitive control (Vink et al., 2014). In smokers, reduced structural integrity of the DLPFC-DS circuit is tied to worse cognitive control and compromised ability to refrain from smoking during abstinence (Yuan et al., 2018a, b). Smokers also have weaker resting state DLPFC-DS connectivity, which is linked to more cognitive control errors (Yuan et al., 2016). Furthermore, reduced DLPFC-DS coupling has been associated with more treatment dropout in individuals with alcohol use disorder (Kohno et al., 2017), suggesting that the reduced DLPFC-DS coupling currently noted among female smokers may contribute to diminished ability or motivation to persist in treatment.

The exploratory data from nicotine vs. placebo exposure in the independent sample of non-smokers indicate that women had less interhemispheric ECN coupling and a trend for less DLPFC-DS coupling than men following acute nicotine administration, reflecting similar sex differences noted in chronic smokers. Critically, and highlighting the specificity of these findings, sex differences in coupling were not evident following placebo administration. These preliminary results shed light on the reduced ECN and frontostriatal coupling in women who smoke in that early nicotine exposure evokes sex differences in ECN coupling strength. We know that stronger interhemispheric ECN coupling has been linked to better cognitive performance (McHugh et al., 2017; Wang et al., 2013), and men have stronger interhemispheric ECN coupling than women with exposure to acute and chronic nicotine. Accordingly, if nicotine-induced interhemispheric ECN connectivity contributes to cognitive performance impairments in a sexually dimorphic manner, this may start to explain why men quit smoking more easily than women when using a nicotine replacement patch (Perkins and Scott, 2008; Vogel et al., 2014). In contrast, women are more likely to quit smoking when using low nicotine cigarettes, as these cigarettes primarily address the sensory aspects of smoking rather than purely nicotine replacement (Vogel et al., 2014). While preliminary, the current work in non-smokers suggests a sexually dimorphic effect of nicotine during *early* nicotine exposure, which may precede the sex difference found in the chronic smokers. How acute nicotine impacts chronic smokers requires further testing, as acute nicotinic effects will be impacted by a history of use. It is also unclear whether these sex differences would abate during more prolonged abstinence.

One unanswered question is: *why* do these sex differences exist? It is possible that sex differences in nicotine and/or dopamine function may contribute to the current findings. Nicotine increases or upregulates nicotinic acetylcholine receptors (nAChRs; Govind et al., 2009). Human studies indicate that smokers have more frontostriatal nAChR availability than non-smokers (Staley, 2006), which appears to be true for men but not women (Cosgrove, 2012). When nicotine binds to such receptors, it releases dopamine in the dorsal striatum more quickly for women compared to men, though men exhibit more rapid dopamine release in the ventral striatum (Cosgrove et al., 2014). During nicotine withdrawal, preclinical models show larger drops in striatal dopamine in females than males (Carcoba et al., 2017), reflecting faster nicotine metabolism observed in women relative to men who are non-smokers (Benowitz and Clinical, 2006). Disrupting nAChRs in dopaminergic neurons also interferes with the behavioral effects of acute nicotine in males but not females in preclinical research (Zhang et al., 2016), suggesting that nicotine-induced dopaminergic activity and behavior is sex-dependent. Given that there was not a significant relationship between brain connectivity and expired CO or self-reported smoking variables in the present study, it is plausible that sex differences in nicotinic and/or dopamine function also contribute to the sex-specific differences in brain connectivity. However, the role of underlying neurochemistry was not directly tested in the current work and requires further evaluation.

Though the results of this study are informative, they must be interpreted in the context of several limitations. One limitation is that we cannot rule out potential effects of hormonal changes over the menstrual cycle. This may be crucial, as lower sex hormone levels among naturally cycling women have been linked to increased ECN communication with other cognitive control regions, such as the anterior cingulate cortex (Petersen et al., 2014). Within smokers, hormonal variation can impact frontostriatal coupling, attentional bias to smoking cues (Wetherill et al., 2016), and cognitive ability (Sofuoglu et al., 2011). Future studies of cognitive control circuits in female smokers would benefit from a comprehensive examination of menstrual cycle phase and hormone levels to determine appropriate timing of smoking cessation interventions. Irrespective of this limitation, the current work defines sex differences independent of hormonal variation, which is an important first step.

A second limitation is that quantitative cotinine levels were only available for the non-smokers, so we were unable to compare potential differences in nicotine between the smokers and non-smokers. It could be that different amounts of nicotine are required to evoke the observed sex differences in coupling strength over time following chronic exposure to nicotine. Acute and chronic nicotine exposure can also have different effects on cognitive performance (Anderson and Diller, 2010; Leach et al., 2013) and the brain (Ettinger et al., 2009). Sex differences in response to acute nicotine may vary between people with a history of chronic or no nicotine exposure, as smokers and non-smokers often differ in baseline resting state ECN connectivity (Weiland et al., 2015). Within smokers, there may also be sex differences in connectivity measures depending on abstinence status as well as nicotine vehicle (lozenge, patch, cigarette). To gain a more complete understanding of how sex differences manifest in smokers, it will be critical to study potential effects of sex under abstinent, sated, and acute nicotine conditions in chronic smokers. However, the goal of this work was not to directly compare the smoking and non-smoking samples but rather to examine sex differences within each group. Despite potential differences in how smokers and non-smokers respond to nicotine, the sex differences following acute nicotine administration mirrored those in the chronic smokers. The persistence of such sex differences in chronic smokers over the course of abstinence and treatment remains to be explored.

Additionally, we did not comprehensively assess withdrawal symptoms for smokers beyond craving for cigarettes and negative affect before scanning. Sex differences in withdrawal symptom severity could impact our results, as women have reported more withdrawal symptoms than men (Faulkner et al., 2018; Leventhal et al., 2007). However, there were no significant sex differences in craving or negative affect, consistent with prior reports (Svikis et al., 1986). This suggests that these facets of withdrawal may not fully explain the neurobiological sex differences found in the present study, though further exploration may

prove enlightening. Another limitation is that the non-smoking sample size was limited. Since the smoking and non-smoking cohorts represent independent studies that could not be evaluated together, directly determining whether there is an interaction between smoking status (smoker/non-smoker) and nicotine administration needs to be tested. Finally, a larger sample of non-smokers may have led to a significant, instead of a trend level, sex by drug interaction on DLPFC-DS coupling within that group. Given the preliminary yet informative nature of the non-smoking data, further study on the effects of sex and nicotine on frontostriatal connectivity is warranted.

4.1. Conclusions

Despite these limitations, the current work identifies sex differences in cognitive networks critical to the maintenance of addictive disorders. Further, the significant sex by drug interaction in non-smokers suggests that early nicotine exposure elicits sex differences in cognitive network connectivity. This current finding is clinically relevant and, if acute nicotine has a similar sex-specific effect in chronic smokers, it may explain why women are less likely to achieve and maintain abstinence when aided by nicotine replacement therapy (Perkins and Scott, 2008; Vogel et al., 2014). Specifically, nicotine's effect through replacement therapy may reduce brain coupling in women and make it more difficult to engage the cognitive resources necessary to quit long-term. Future work is needed to determine the behavioral repercussions of these noted sex differences in brain circuitry.

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Contributors

J.M.M. completed data analysis/interpretation and drafted the manuscript. K.M.D. assisted with data interpretation and manuscript preparation. M.Z. contributed to data collection and management. D.A.P., D.P.O., and L.V.M. contributed to research study design and manuscript preparation. A.C.J. oversaw research study design, data collection, data analysis/interpretation, and drafting the manuscript. All authors approved of the final version of the manuscript.

Conflict of interest

D.A.P. has received consulting fees from Akili Interactive Labs, BlackThorn Therapeutics, Boehringer Ingelheim, Posit Science, and Takeda for activities unrelated to the current research. J.M.M., K.M.D., M.Z., D.P.O., L.V.M., and A.C.J. declare no biomedical financial conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2018.11.023.

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