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Nicotine and Non-Nicotine Smoking Factors Differentially Modulate Working Memory and Associated Brain Function

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Abstract

Background—Smoking abstinence impairs executive function, which may promote continued smoking behavior and relapse. The differential influence of nicotine and non-nicotine (i.e. sensory, motor) smoking factors and related neural substrates is not known.

Methods—In a fully factorial, within-subjects design, 33 smokers underwent fMRI scanning following 24-h of wearing a nicotine or placebo patch while smoking very low nicotine content (VLNC) cigarettes or remaining abstinent from smoking. During scanning, blood oxygenation level-dependent (BOLD) signal was acquired while participants performed a verbal N-back task.

Results—Following 24-h placebo (vs. nicotine) administration, accuracy on the N-back task was significantly worse and task-related BOLD signal lower in dorsomedial frontal cortex. These effects were observed irrespective of smoking.

Conclusions—Our data provide novel evidence that abstinence-induced deficits in working memory and changes in underlying brain function are due in large part to abstinence from nicotine

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Authors Contribution

FJM and JER were responsible for the study concept and design. FJM, BF and RK oversaw data collection and analysis. BF and RK conducted the data analysis. BF, RK, MAA, and MMS assisted with interpretation of findings. ECW served as study physician. DMVW collected study data and managed the study database. FJM drafted the manuscript. BF, RK, MAA and MMS provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

compared to non-nicotine factors. This work has implications both for designing interventions that target abstinence-induced cognitive deficits and for nicotine-reduction policy.

Keywords

addiction; fMRI; neuroimaging; nicotine; smoking; working memory

INTRODUCTION

Cessation of tobacco smoking results in a constellation of withdrawal signs and symptoms including subjective reports of difficulty concentrating and objective worsening of attention and working memory performance (Falcone et al., 2013a; Gilbert et al., 2004; Heishman, 1998; Heishman et al., 1994; Hendricks et al., 2006; Mendrek et al., 2006). These effects on cognition emerge within minutes of abstinence (Hendricks et al., 2006), persist for weeks following quitting smoking among some smokers (Gilbert et al., 2004) and are predictive of relapse (Patterson et al., 2010). Understanding the unique and interactive influence of various sensory, behavioral and pharmacological aspects of smoking on abstinence-induced cognitive impairments can guide the development of interventions that specifically target these deficits. The current study systematically investigates the effects of nicotine and non-nicotine factors on working memory performance and related brain function with the goal of delineating the role of these factors.

Smoking abstinence results in cessation of self-delivered nicotine—the primary psychoactive substance in cigarette smoke—and also non-nicotine factors including the sensory (e.g. taste, smell) and behavioral (e.g. ritualistic) aspects of smoking; and any of the potentially psychoactive, non-nicotine components of smoke (Caggiula et al., 2002; Rose, 2006). Research on the effects of nicotine (administered in the absence of smoking) or smoking denicotinized or very low nicotine content (VLNC) cigarettes (administered in the absence of nicotine) suggest a greater role for nicotine in modulating cognition. Nicotine administration compared to placebo has been shown to improve cognitive performance among abstinent smokers (Atzori et al., 2008; Beaver et al., 2011; Foulds et al., 1996; Froeliger et al., 2009) including one large and well-controlled study in which performance on a working memory N-back task was improved following administration of a 21 mg nicotine versus placebo patch to overnight-deprived smokers (Kleykamp et al., 2011). Consistent with these findings, administration of VLNCs has been shown to perpetuate abstinence-induced impairments in cognition (Gilbert et al., 1997; Wesnes and Warburton, 1983).

Neuroimaging studies of smokers performing tasks that require sustained attention and working memory suggest that frontal brain regions are modulated in conjunction with abstinence-induced performance deficits (Falcone et al., 2013b; Kozink et al., 2010; Xu et al., 2006). In a prior study, we observed decreased BOLD signal in dorsolateral prefrontal cortex (dlPFC) following 24-h abstinence during a task requiring sustained attention and working memory (Kozink et al., 2010). In another study of the effects of 24-h abstinence on working memory, abstinence decreased activation in working memory-related regions including dlPFC and dorsal medial frontal cortex (Falcone et al., 2013b). In both studies,

effects were observed regardless of memory load suggesting they were due to disruption of non-working memory specific processes (e.g. sustained attention). Acute nicotine (compared to placebo) administration to overnight abstinent smokers has been shown to both increase (Beaver et al., 2011) and decrease (Ernst et al., 2001) cortical activation. The effects of longer-term smoking/nicotine manipulations have not been evaluated nor has there been systematic investigation of the effects of nicotine vs. non-nicotine factors on the neural substrates underlying cognition.

This investigation sought to evaluate the effects of nicotine and non-nicotine factors on neurocognition. In a 2x2, within-subjects design, adult dependent smokers underwent scanning after 24-h of wearing a 21 mg/d nicotine or placebo patch while either smoking VLNCs or remaining abstinent from smoking. Blood oxygenation-level dependent (BOLD) signal was acquired during scanning. We hypothesized that performance on the placebo patch would be worse than performance on the nicotine patch, irrespective of smoking. Moreover we hypothesized that nicotine abstinence would decrease task-related BOLD signal in brain regions identified *a priori* that support working memory and sustained attention including dlPFC, dorsomedial frontal cortex (dmFC) and the parietal cortex. Based on research reviewed above in which smoking and nicotine were manipulated in the absence of the other factor, we hypothesized that smoking would have a relatively weaker or no impact on brain activation compared to nicotine, or would only modulate outcomes in interaction with nicotine.

METHODS AND MATERIALS

Participants

Thirty-five smokers between the ages of 18–55 were recruited from the community and completed all aspects of the study. Inclusion criteria for all subjects included being right-handed, free of serious health problems (e.g., hypertension), not currently undergoing treatment for a psychiatric illness, free of medications altering CNS functioning, not having any conditions making MRI research unsafe, testing negative for illicit drug use, and among females, having a negative serum pregnancy test.

Smokers were required to smoke 10 cigarettes/day of a brand delivering > 0.5 mg nicotine according to the standard Federal Trade Commission (FTC) method for at least 2 years, have an expired CO concentration of at least 10 ppm or a positive urine cotinine test (Nicalert™) of 100 ng/mL or greater, not currently use any nicotine products other than cigarettes and have no interest in quitting.

Procedures

All participants read and signed an IRB-approved informed consent form. Participants completed a 1.5-hr screening session during which they provided breath and saliva samples, underwent a medical evaluation that included a review of systems, EKG and vitals, and completed questionnaires regarding mood, smoking history, and suitability for MRI research. Participants who passed screening completed a training session during which they practiced a verbal working memory task (N-back, see below) while lying in a mock scanner.

Participants were required to achieve at least 40% accuracy on the 2-back condition within 4 practice attempts. In a 2 (PATCH)×2 (SMOKE) design, smokers underwent four separate fMRI scanning sessions following 24-h wearing a nicotine (NIC) or placebo (PLAC) transdermal patch during which time they smoked either VLNC cigarettes *ad libitum* or remained abstinent (ABST). Participants were provided with all study-related materials: 21 mg Nicoderm CQ® patches, placebo patches, and Quest 3 brand VLNC cigarettes (Vector Tobacco Co.; nicotine delivery < .05 mg/cigarette; FTC method). Patches were repackaged so that neither the experimenter nor the participant was aware of the patch condition. Results from a post-session questionnaire indicated that more than half of participants (52%) were not able to correctly guess their patch condition more than 50% of the time across the four sessions. The order in which participants completed conditions was random. Menthol or non-menthol VLNC cigarettes were provided based on participant preference (43% = menthol smokers). For conditions in which smoking was prescribed, participants were required to smoke the assigned cigarette immediately before entering the hospital (i.e. < 30 min prior to scanning). Abstinence was verified by expired CO on the scan day. Each scanning session was held at least 4 days apart (mean=8.6 days, SD=3.5). During all scanning sessions, participants completed the N-back task.

Nicotine Dependence

At screening, participants completed the Fagerström Test of Nicotine Dependence (FTND) (Heatherton et al., 1991).

N-back task

A verbal N-back task was comprised of 60 sec blocks during which participants were presented with a series of letters on a screen at a rate of 1/sec. Participants were required to identify whether the current stimulus was the same as the stimulus presented N-back. In 1-back blocks, participants identified whether the current letter was the same as the letter that preceded it (i.e. 1 letter back). In the 2-back block, participants identified whether the letter was the same as the letter presented 2 letters back. During the '0-back' blocks, participants pressed a button whenever they saw the letter 'X'. Nine targets per block were presented (mean inter-target-interval = 6 sec) and each block level (0-, 1-, 2-back) was presented four times over the course of 2 runs (total task time = 18 min). N-back blocks were separated by 25 sec rest periods.

Imaging Methods

Scanning was performed on a 3.0 T GE EXCITE HD scanner equipped with 40 mT/m gradients (Waukesha, WI). BOLD images were collected for 30 contiguous slices (3.8 mm thick) parallel to the horizontal plane connecting the anterior and posterior commissures. An inverse SENSE spiral pulse sequence sensitive to BOLD contrast was used, with TR=1.5 s, TE=30 ms, FOV=25.6 cm, matrix=64×64, flip angle=60°, and in-plane resolution=4 mm². After completion of the functional data collection, a T1-weighted 3D fast spoiled gradient-recalled (FSPGR) structural image was collected for 166 slices (1 mm thick), with TR=7.5 ms, TE=3 ms, FOV=25.6 cm, matrix=256×256, flip angle=12°, and in-plane resolution=1 mm².

Analysis of Behavioral Data

Two participants were excluded from the behavioral data analyses due to non-compliance (high CO on non-smoking day, $n=1$; < 50% accuracy on the 0-back, $n=1$). Analyses of the effects of condition on N-back task accuracy, reaction time (RT) and reaction time standard deviation (RTSD) were conducted using general linear mixed models in SAS 9.3 with subject-level Gaussian random effects. The models included SMOKE (VLNC, ABST), PATCH (NIC, PLAC) and N-back LEVEL (0,1,2) as factors.

Analysis of Brain Data

Preprocessing—Preprocessing was conducted using SPM8 to attenuate noise and artifacts. The first four volumes of each run were discarded to allow for T1 stabilization. All functional images underwent correction for acquisition timing and for head motion using rigid-body rotation and translation (Friston et al., 1994). Each participant's data was then subsequently warped into a standard stereotaxic space (Montreal Neurological Institute) with an isotropic 2 mm voxel size and smoothed with a 6 mm FWHM Gaussian filter. As in our previous work (Sweitzer et al., 2013), artifact detection tools implemented in SPM (ART; www.nitrc.org/projects/artifact_detection) were used to identify and adjust for image artifacts related to intensity spiking and motion (Chai et al., 2014; Redcay et al., 2013; see Supplement for details). In addition to those excluded from the behavioral analyses, participants were excluded from imaging analyses if > 10% of the total volumes were identified as outliers ($n=3$); or signal loss/other artifact ($n=2$).

Statistical Analysis—Participant's data from each session was entered into a first-level, whole-brain analysis using the General Linear Model (Friston et al., 1994) to examine BOLD response to each of the 3 N-back trial types (0-back; 1-back, 2-back). Blocks of each trial type were modeled as a box car function (60 sec) convolved with the canonical hemodynamic response function (HRF). Problematic volumes were removed from the analysis by including regressors generated by the ART program. A high-pass filter (128 seconds) was applied to remove slow signal drift.

Our method of selecting ROIs was patterned after prior studies of smoking and executive function (Falcone et al., 2013b; Loughead et al., 2010; Loughead et al., 2009) and consisted of identifying functional ROIs in our dataset that matched *a priori*-specified working memory areas: First, main effects of working memory were explored in a whole-brain repeated measures analysis of variance that identified activation across working memory load (2-0 and 1-0) and conditions. ROIs were functionally defined using a voxel threshold of $p < 0.05$ FWE-corrected and a cluster extent threshold of $k=200$. Five functional clusters, each matching *a priori* regions of interest associated with working memory were selected from among activation clusters (location of peak cluster listed, see Figure S1): dmFC comprised of the dorsal anterior cingulate cortex (dACC), supplementary motor area (SMA) and pre-supplementary motor area (preSMA) ($x=0$, $y=2$, $z=60$), bilateral dorsolateral prefrontal cortex (R/L dlPFC; $x=32$, $y=-2$, $z=58$ and $x=-44$, $y=6$, $z=32$, respectively), and bilateral parietal lobule (R/L PL; $x=34$, $y=-60$, $z=46$ and $x=-32$, $y=-46$, $z=42$ respectively). Regions were identified via visual inspection and in comparison with regions identified in prior meta-analyses (Owen et al., 2005; Wager and Smith, 2003) and prior studies of

smoking and working memory (Falcone et al., 2013b; Loughead et al., 2010; Loughead et al., 2009).

Average percent signal change was extracted from these regions for each participant during each condition for each working memory load condition using MarsBar (Brett et al., 2002). As with behavioral analyses, percent signal change in each of the ROIs was included in a general linear mixed model with subject-level Gaussian random effects. Patch condition, smoking status, and working memory load were used to predict percent signal change. Since different working memory loads and pharmacological conditions result in variable RTs, as in previous working memory studies (Loughead et al., 2010) we sought to control for the amount of time spent processing and responding to stimuli by controlling for RT at each working memory load level and condition in analyses of BOLD signal. Effect sizes (Cohen's *d*) were calculated for significant main effects of nicotine condition based on means, pooled variance and the correlation between measurements.

RESULTS

Participant Characteristics

Participant characteristics are presented in Table 1 for the full sample ($n=33$) and the sample that provided analyzable fMRI datasets ($n=28$).

Biochemical Assessment

Breath CO levels were compared as a function of experimental condition using a general linear mixed model with Gaussian random level subject effects. Across patch conditions, CO levels were significantly lower in the ABST (mean=3.6 ; SD=2.7) as compared to the DENIC (mean=15.3; SD=10.4) condition ($F_{1,96}=126.82$, $p < .0001$) suggesting a high level of compliance. CO levels did not vary as a function of nicotine (as compared to placebo) patch administration.

N-back Task Performance

Across conditions, increased task difficulty was associated with decreased accuracy (% correct) ($F_{2,352}=222.89$, $p < .0001$) and longer RTs ($F_{2,352}=260.15$, $p < .0001$) and greater variability in RT (SD of RT) ($F_{2,352}=182.03$, $p < .0001$); see Table S1 for means and SDs. As shown in Figure 1, wearing a placebo (vs. nicotine) patch was associated with significantly worse accuracy (main effect of PATCH, $F_{1,352}=11.04$, $p=.001$; $d = .38$). Placebo patch administration was also associated with increased variability in RTs ($F_{1,352}=11.28$, $p=.0009$; $d = .4$). Effects of SMOKE or interactions involving SMOKE and/or LEVEL were not observed.

Imaging Results

In each of the five ROIs, main effects of LEVEL were observed (2-back > 1-Back > 0-Back; p 's < 0.0001). In dmFC, BOLD signal was lower following 24 h placebo (compared to nicotine) administration across LEVEL and SMOKE factors (main effect of PATCH; $F_{1,296}=5.01$, $p=0.026$; $d = .26$; see Figure 2). In the R PL, a significant SMOKE×PATCH interaction ($F_{1,296}=4.17$, $p=0.042$) was observed. This interaction was characterized by

lower BOLD signal in the PLAC+VLNC condition compared to the NRT+VLNC and PLAC+ABST conditions (p 's < .05). An evaluation of whether FTND score moderated the effects of nicotine patch on performance or BOLD signal did not reveal any significant findings.

DISCUSSION

This behavioral and fMRI study provides novel evidence that nicotine and non-nicotine factors associated with smoking have differential effects on working memory performance and underlying brain function. This was achieved by systematically evaluating the effects of administering nicotine (vs. placebo) while smoking very low nicotine content cigarettes (or maintaining abstinence) in the 24 h prior to scanning. As hypothesized, placebo, compared to nicotine, was associated with worse working memory performance and lower BOLD signal in dmFC, irrespective of smoking condition. Less expectedly, smoking and nicotine interacted to modulate parietal BOLD signal. For both behavioral and brain outcomes, effects were observed across working memory load levels. Collectively, our data confirm that cognitive impairments associated with smoking abstinence are due in large part to abstinence from nicotine and the loss of signaling in a brain region associated with distraction resistance (see below). These findings have important implications for treating smoking abstinence-induced cognitive performance deficits and for policies aimed at reducing cigarette nicotine levels.

Whereas the current study is the first to systematically evaluate the effects of nicotine and non-nicotine factors on functional neuroanatomical correlates of working memory, our hypotheses were informed by prior studies investigating the effects of nicotine and non-nicotine factors on cognitive performance. Previous studies have shown that nicotine, when administered to overnight deprived smokers improves working memory performance (Atzori et al., 2008; Beaver et al., 2011; Foulds et al., 1996; Kleykamp et al., 2011) whereas smoking VLNC cigarettes induces or perpetuates working memory deficits (Gilbert et al., 1997; Wesnes and Warburton, 1983). The results of the present study, which systematically evaluated the effects of nicotine and smoking in a single sample of smokers, are consistent with these prior studies in that we observed better accuracy and decreased RT variability following 24 h nicotine administration, irrespective of smoking condition.

The observation of greater BOLD signal during nicotine (compared to placebo) administration in dmFC—a region comprised of the dorsal anterior cingulate (dACC) and supplementary motor area (SMA) and pre-SMA—is consistent with prior neuroimaging studies and the known role of dorsal midline structures in executive function. In a study of 63 smokers who were scanned during a visual n-back task, greater sustained activation was observed in frontal ROIs including the dmFC under smoking compared to a 24 hr abstinence condition (Falcone et al., 2013b). These effects were not observed to vary across working memory load levels (discussed below). Activation in dmFC is nearly ubiquitous across studies of working memory (Nee et al., 2013; Owen et al., 2005; Wager and Smith, 2003). In a recent meta-analysis of fMRI studies (Nee et al., 2013) in which various components of executive function during working memory were investigated, the dmFC was implicated in decreasing or mitigating interference of working memory processes from external distractors (i.e. distractor resistance). This proposed role for the dmFC and our data are consistent with

previous literature suggesting that nicotine enhances attention to task-relevant targets by decreasing distraction (Gilbert et al., 2005; Gilbert et al., 2007; Kassel, 1997; Kassel and Shiffman, 1997; Tsiora et al., 2013). Likewise, research with rodents and non-human primates suggests that nicotine decreases the influence of distractors on task performance (Bain et al., 2003; Hahn et al., 2002) and that this effect is mediated via the $\alpha 4\beta 2$ nicotine receptor system (Howe et al., 2010; Prendergast et al., 1998). Future neuroimaging studies in which distraction is manipulated will be needed to test the hypothesis that the dmFC is specifically involved in this effect of nicotine/nicotine withdrawal.

It is noteworthy that the observed effects of nicotine and smoking on behavior and BOLD signal did not interact with level of difficulty on the N-back task. This finding is consistent with previous studies of the effects of smoking abstinence on tasks requiring sustained attention and with varying working memory loads. In a previous study in which we examined the effects of smoking abstinence on a sustained attention task that required working memory (Kozink et al., 2010), we observed disruption of performance regardless of working memory load. Similarly, in a prior neuroimaging study employing the N-back task, memory load level did not interact as a function of smoking (Falcone et al., 2013b). Given that nicotine $\times$ memory load interactions have been more pronounced in human laboratory studies (Kleykamp et al., 2011; Mendrek et al., 2006), the lack of load effects in our and other imaging studies may be due to methodological factors.

Related to this, it is also noteworthy that we did not observe effects in dlPFC given that prior research has observed modulation of working memory activation in this region by smoking abstinence (Falcone et al., 2013b; Kozink et al., 2010; Xu et al., 2006). This may have been due to a lack of a 3-back condition which might have further taxed dlPFC-dependent processes and revealed an effect. Future studies that include a wider ranges of task difficulties and also assess the effects of acute nicotine and/or smoke administration following abstinence (as in Xu et al., 2006) might lead to a more precise understanding of the role of dlPFC in nicotine abstinence-induced changes in cognitive performance.

In addition to the predicted effects of nicotine, we also observed an unanticipated interaction between nicotine administration and smoking on BOLD signal in the superior part of the right parietal cortex. Like the dmFC, the SPL is a core component of sustained attention and working memory networks (Owen et al., 2005; Wager and Smith, 2003). However, the observed interaction in right SPL is difficult to interpret, especially in the absence of an interactive effect of these factors on task performance measures. As such, this finding suggests that non-nicotine factors may have only subtle effects on working memory and/or sustained attention.

Our findings have implications for clinical practice and policy. Initial data reports suggest that the magnitude of abstinence-induced cognitive deficits including attention and working memory may be predictive of cessation outcomes (Patterson et al., 2010) and remediation of cognitive deficits has been proposed as an intervention to improve cessation outcomes (Ashare and Schmidt, 2014). Our data suggest that these deficits are due in large part to cessation of nicotine and thus support the use of nicotine replacement therapies in order to remediate these effects; they also provide evidence that the dmFC is modulated by nicotine

abstinence and as such, abstinence-induced deficits may be reversed by targeting this region (e.g. with rTMS). It is also worth noting that in this same sample, we observed effects of smoking (versus abstinence) on withdrawal symptoms that were substantially more robust than the effects of nicotine (versus placebo)(Addicott et al., 2014). This, and previous literature, strongly support the notion that nicotine and non-nicotine factors have differential influence on a range of clinically relevant outcomes and as such, clinical intervention should be designed to target both of these factors.

At a policy level, passage of the Family Smoking Prevention and Tobacco Control Act in 2009 provided the FDA with regulatory authority to reduce the nicotine content of cigarettes to levels that would decrease the addictive potential of cigarettes (Congress, 2009; Hatsukami et al., 2010). Our results suggest that enacting such a policy, particularly if nicotine levels were reduced substantially and rapidly, could negatively impact neurocognition of a substantial number of smokers. While the impact of such a policy on real-world cognitive function and outcomes is unknown, further research on this topic is warranted.

Strengths of our study include a fully factorial, within-subjects design in which smoking behavior was crossed with nicotine administration over 24 h periods. One potential limitation of our study was the lack of a smoking as usual condition. Although we attempted to replicate smoking as usual by providing smokers with their preferred cigarette type (menthol vs. nonmenthol) and nicotine replacement, sensory and pharmacological differences between our manipulation and smoking as usual may have accounted for some effects. To address this question we compared withdrawal symptoms between the training (when participants could smoke freely) and NRT+DENIC sessions. No significant differences were observed suggesting that, while not a perfect analogue, the nicotine patch + VLNC condition replicated important aspects of smoking as usual.

In summary, the results of our study provide novel evidence that abstinence from nicotine factors associated with smoking result in worse cognitive performance and decreased BOLD signal in dmFC, a brain region involved in distractor resistance. Our finding of differential effects of nicotine and non-nicotine factors on neurocognition suggest that treatment of abstinence-induced deficits will require targeting abstinence from nicotine (e.g. via nicotine replacement therapy) and to a lesser extent abstinence from non-nicotine factors. Future research will be required to evaluate the effects of these factors on other forms of cognition, correlates of everyday cognitive outcomes and relations with clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. N-back task accuracy as a function of working memory load, nicotine administration and smoking

A main effect of PATCH ($p < .001$) was characterized by greater accuracy when smokers were wearing a nicotine (shaded in blue) as compared to placebo (shaded in orange) patch, irrespective of smoking behavior. See text for additional statistical details and the online Supplement for means and SDs.

a. dmFC: Main effect of PATCH

b. rPL: PATCH x SMOKE Interaction

Figure 2. Task-related BOLD signal as a function of nicotine administration and smoking in dACC/preSMA and right PL

In dmFC (upper panel), 21 mg/d nicotine administration in the 24 h prior to scanning resulted in greater BOLD % signal change compared to placebo administration (main effect of PATCH, $p=.026$), irrespective of smoking behavior. In right PL, a PATCH $\times$ SMOKE interaction ($p=.042$) was characterized by lower % signal change following smoking VLNCs and wearing a placebo patch for 24 h prior to scanning relative to other conditions. $* = p < .05$; see text for additional statistical details.

Table 1

Demographic data for the full sample (n=33) and the subsample available for fMRI analysis (n=28).

	Full Sample (n=33)	fMRI Sub- Sample (n=28)
	<i>Mean (SD)</i>	
Age	36.6 (9.2)	37.7 (9.2)
Cigarettes/Day	16.5 (5.1)	17.0 (4.9)
Years Smoked	18.0 (9.0)	19.2 (8.6)
FTND	5.0 (2.1)	5.3 (2.0)
	<i>n (%)</i>	
Female	17 (51.5)	14 (50.0)
Non-White	15 (45.5)	13 (46.4)