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Nicotine Effects on White Matter Microstructure in Young Adults

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Abstract

Objective: Nicotine use is widely prevalent among youth, and is associated with white matter microstructural changes as measured by diffusion tensor imaging (DTI). In adults, nicotine use is generally associated with lower fractional anisotropy (FA), but in adolescents/young adults (≤30 years), microstructure appears healthier, indicated by higher FA. This cross-sectional study examined associations between nicotine use and white matter microstructure using fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) in young adults.

Methods: Fifty-three participants (18 nicotine users [10 female]/35 controls [17 female]) ages 18–25 underwent MRI scan, neuropsychological battery, toxicology screening, and drug use interview. Nicotine group associations with FA and MD were examined in various white matter tracts. In significant tracts, AD and RD were measured. Exploratory correlations were conducted between significant tracts and verbal memory and sustained attention/working memory performance.

Results: Nicotine users exhibited significantly lower FA than controls in the left anterior thalamic radiation, left inferior longitudinal fasciculus, left superior longitudinal fasciculus—temporal, and left uncinate fasciculus. In these tracts, AD and RD did not differ, nor did MD differ in any tract. White matter quality was positively correlated with sustained attention/working memory performance.

Conclusions: Cigarette smoking may disrupt white matter microstructure. These results are consistent with adult studies, but inconsistent with adolescent/young adult studies, likely due to methodological and sample age differences. Further studies should examine longitudinal effects of nicotine use on white matter microstructure in a larger sample.

Keywords: Nicotine; Cigarette; Young adult; White matter; Diffusion tensor imagning; Magnetic resonance imaging

Introduction

Prevalence of Nicotine Use

Tobacco smoking remains the leading cause of preventable and premature death in the United States (U.S. Department of Health and Human Services, 2014). Nicotine cigarette use is surprisingly widespread among young adults. In 2016, 23.5% of young adults ages 18–25 report current (past month) cigarette use (Center for Behavioral Health Statistics and Quality, 2017), while 12.5% of 12th graders and 6.0% of young adults report use of electronic vaporizers (Schulenberg et al., 2017). Since 98% of individuals who try cigarettes do so by age 25 (U.S. Department of Health and Human Services, 2014), characterizing the effects of nicotine use in adolescence and young adulthood on the developing brain is critically important.

Psychopharmacology of Nicotine

Nicotine, the psychoactive component of tobacco, activates nicotinic acetylcholine receptors (nAChRs), which are found throughout the brain, including in the thalamus, basal ganglia, cortex, hippocampus, and cerebellum (Brody et al., 2006).

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Desensitization of nAChRs results from chronic exposure (Benowitz, 2009; Wang & Sun, 2005). This desensitization leads to nAChR up-regulation, which may be implicated in nicotine dependence (Benowitz, 2009). Additionally, cigarette smoke is widely known to cause neuroinflammation, and oxidative damage and stress in the brain (Durazzo, Gazdzinski, & Meyerhoff, 2007; Khanna, Guo, Mehra, & Royal, 2013; Swan & Lessov-Schlaggar, 2007); however, the exact mechanisms by which cigarette smoke damages the brain have yet to be fully elucidated (Durazzo, Meyerhoff, & Nixon, 2010; Khanna et al., 2013).

Effect of Nicotine on Brain Structure

White matter microstructure can be measured by diffusion tensor imaging (DTI), a non-invasive magnetic resonance imaging (MRI) technique that measures the diffusion of water within white matter (Le Bihan, 2003; Mori & Zhang, 2006). The most commonly used measure of the amount of anisotropic diffusion—diffusion that is direction-dependent, perhaps determined by a physical barrier (Beaulieu, 2002)—is fractional anisotropy (FA; Alexander, Lee, Lazar, & Field, 2007; Basser & Pierpaoli, 1996), although mean diffusivity (MD—diffusion in all directions), axial diffusivity (AD—diffusion parallel to the fiber), and radial diffusivity (RD—diffusion perpendicular to the fiber) are also measured. Higher FA is usually considered indicative of better white matter health (Alexander et al., 2007). White matter microstructure has been fairly well studied in adult smokers with generally consistent results. Adult smokers demonstrate lower FA in the corpus callosum (Lin, Wu, Zhu, & Lei, 2013; Savjani et al., 2014; Umene-Nakano et al., 2014), *left* prefrontal cortex (Zhang et al., 2011), and anterior limb of the internal capsule (ALIC; Savjani et al., 2014). FA is typically negatively correlated with nicotine dependence (Hudkins, O'Neill, Tobias, Bartzokis, & London, 2012; Zhang et al., 2011), duration of smoking (Savjani et al., 2014), and cigarettes per day (Hudkins et al., 2012; Umene-Nakano et al., 2014). In contrast, two studies found *higher* FA in adults in the corpus callosum (Hudkins et al., 2012; Paul et al., 2008), right prefrontal areas, and middle cingulum (Hudkins et al., 2012); however, both of these studies are limited by very small sample sizes. Only three adult studies have examined MD in smokers; two found no difference from controls (Lin et al., 2013; Paul et al., 2008), while one (Savjani et al., 2014) discovered higher MD within the corpus callosum and ALIC. Lower AD and higher RD are also seen in the corpus callosum (Lin et al., 2013; Savjani et al., 2014) and ALIC (Savjani et al., 2014). Fortunately, most of these studies contain a relatively even number of male and female participants (Hudkins et al., 2012; Paul et al., 2008; Savjani et al., 2014; Zhang et al., 2011), and exclude participants with psychiatric comorbidities (Lin et al., 2013; Paul et al., 2008; Umene-Nakano et al., 2014; Zhang et al., 2011). While one study measured alcohol use (Hudkins et al., 2012), which may impact white matter microstructure (Jacobus et al. 2009; McQueeny et al. 2009), other studies only measured problematic drinking behavior or alcohol abuse without measuring alcohol drinks (Lin et al., 2013; Paul et al., 2008; Umene-Nakano et al., 2014; Zhang et al., 2011).

Adolescence

Nicotine effects during adolescence. Adolescence, which takes place roughly from 12 to 18 years of age (Yuan, Cross, Loughlin, & Leslie, 2015), is characterized by dynamic brain development, particularly by gray matter pruning (Giedd et al., 1999; Giorgio et al., 2008, 2010; Sowell, Thompson, Tessner, & Toga, 2001; Yuan et al., 2015) and white matter microstructural improvements (Yuan et al., 2015), typically demonstrated by increased FA (Ashtari et al., 2007; Barnea-Goraly et al., 2005; Giorgio et al., 2008, 2010; Schmithorst, Wilke, Dardzinski, & Holland, 2002; Yuan et al., 2015). Decreased MD (Schmithorst et al., 2002), increased AD, and minimally increased RD are also seen (Ashtari et al., 2007). In adolescence, white matter maturity occurs in areas associated with executive functioning and motor response preparation (Simmonds, Hallquist, Asato, & Luna, 2014). Development of some tracts continues into young adulthood, including the superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), superior and inferior fronto-occipital fasciculi (Lebel & Beaulieu, 2011), and white matter terminations in the cortex and basal ganglia (Simmonds et al., 2014). Of note, some of these areas of development overlap with nAChR-rich areas (Brody, 2006).

Given the many developmental changes just described, the adolescent brain is especially sensitive to nicotine (Slotkin, 2002; Yuan et al., 2015). When chronically administered in adolescence, nicotine causes neural cell death, changes in gene expression (Trauth, Seidler, & Slotkin, 2000a), greater neuronal activity in reward-related areas (Yuan et al., 2015), dopamine and norepinephrine turnover (Trauth, Seidler, Ali, & Slotkin, 2001), behavioral deficits (Trauth, Seidler, & Slotkin, 2000b), and activity deficits in serotonergic receptors (Xu, Seidler, Ali, Slikker, & Slotkin, 2001) and cholinergic neurons (Trauth, McCook, Seidler, & Slotkin, 2000). Nicotine is more potent in late adolescence than in adulthood (Azam, Chen, & Leslie, 2007), and nAChR up-regulation is more persistent and severe in adolescence (Trauth, Seidler, McCook, & Slotkin, 1999).

Nicotine and white matter microstructure in adolescence and young adulthood. To our knowledge, only five studies to date have examined the effects of nicotine on white matter microstructure in adolescents and young adults (average age ≤30 years; Gogliettino, Potenza, & Yip, 2016). These studies find *higher* FA in smokers, particularly in the corpus callosum (Jacobsen et al., 2007; van Ewijk et al., 2015; Yu et al., 2016), SLF (Liao et al., 2011; van Ewijk et al., 2015; Yu et al., 2016), ILF (Jacobsen et al., 2007), internal capsule (Jacobsen et al., 2007; van Ewijk et al., 2015; Yu et al., 2016), corona radiata (van Ewijk et al., 2015; Yu et al., 2016), cingulum (Huang et al., 2013), thalamus (van Ewijk et al., 2015), and posterior thalamic radiation (Yu et al., 2016). Lower MD (van Ewijk et al., 2015), higher AD, and lower RD (Yu et al., 2016) are also seen in some regions. Of note, while higher FA is typically seen in adolescents/young adult smokers, this pattern opposes that of lower FA seen in adults, described above. This is particularly true in the corpus callosum and parts of the internal capsule. It is possible that the relationship between nicotine use and white matter microstructure changes throughout development (Gogliettino et al., 2016). However, these adolescent and young adult studies exhibit a variety of methodological differences from adult studies, including a lack of female participants (Huang et al., 2013; Liao et al., 2011; van Ewijk et al., 2015; Yu et al., 2016), no apparent full exclusion of participants with comorbid psychiatric disorders (Huang et al., 2013; van Ewijk et al., 2015; Yu et al., 2016), and small sample sizes in comparing smokers to non-smokers (Huang et al., 2013; Yu et al., 2016) without prenatal exposure (Jacobsen et al., 2007) or psychiatric comorbidity (van Ewijk et al., 2015). Further, most of these studies did not measure alcohol use (Huang et al., 2013; Liao et al., 2011; van Ewijk et al., 2015; Yu et al., 2016). Given these limitations, it is difficult to know whether these results would replicate in a sample with an equal gender distribution, alcohol measured and controlled, and excluding for psychiatric disorders.

Study Aims

The aims of the present study were to characterize white matter microstructure in young adult smokers and non-smokers and examine how white matter microstructure related to nicotine dependence. Further, given that cognitive differences were seen between male and female nicotine users versus controls in an overlapping sample (Kangiser, Lochner, Thomas, & Lisdahl, Under review), exploratory correlations were run to examine relationships between white matter quality and performance on the California Verbal Learning Test, 2nd Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000), a verbal memory task, and the Paced Auditory and Serial Attention Test (PASAT; Gronwall, 1977), a sustained attention and working memory task. We hypothesized that young adult nicotine users would exhibit different FA and MD compared to controls, and that within tracts of differing FA and/or MD, AD/RD would exhibit a significant difference from controls. We also hypothesized that FA would negatively correlate with nicotine dependence score and past year cigarettes.

Methods

Participants

Participants include 53 young adults ages 18–25 (27 female) sampled as part of a larger study conducted from 2008 to 2011. The University of Cincinnati Institutional Review Board approved all protocols. Inclusion criteria included: right-handedness; age 18–25; for the control group, <5 uses of nicotine in the past year (including cigarettes, cigars, hookah, smokeless tobacco, and nicotine replacement therapy), no regular exposure to second-hand nicotine smoke, and never having been a regular smoker; for the nicotine group, minimum 5 times weekly cigarette use in the past year. Exclusion criteria included: current pregnancy; MRI contraindications; history of special education or learning disability; history of chronic neurologic or medical illness; current psychoactive medication use; DSM-IV Axis I disorders independent of substance use; prenatal exposure to nicotine (cigarette use daily for more than 1 month), alcohol (>4 drinks/day or >7 drinks/week), or illicit drugs (>10 uses); >9 lifetime uses of ecstasy; >20 lifetime uses each of opiates, inhalants, stimulants, sedatives, or hallucinogens; >60 cannabis joints past year; refusal to maintain abstinence from drugs and alcohol for 7 days before testing; and Wide Range Achievement Test, 4th Edition (WRAT-4) Reading standard score ≤80. Eligible participants were divided into nicotine users (n = 18, 10 female) and controls (n = 35, 17 female).

Procedure

Recruitment was conducted through advertisements in a free local newspaper and fliers. Interested potential participants completed a phone screen for exclusionary criteria, described in further detail in Price and colleagues (2015). In short, a semi-structured interview was administered for Axis I anxiety, mood, and psychotic disorders based on DSM-IV-TR criteria (First,

Spitzer, Gibbon, & Williams, 2001). After completing informed consent, eligible participants underwent one or two sessions with a neuropsychological battery, questionnaires, drug use interview, and MRI scan. For the participants who completed two sessions, the sessions were separated by 2–3 days, with all measures but the MRI at the first session, and MRI at the second session. All participants received an image of their brain, local substance abuse treatment resources, and parking reimbursement; participants received $110 or $160 for one or two sessions, respectively.

Measures

Toxicology and pregnancy testing. Participants provided a urine sample and were tested for recent drug use with the One Step Drug Screen Test (Dip Card Panel; Innovacon, Inc., San Diego, CA). Levels of cotinine, a nicotine metabolite that measures recent nicotine exposure or use, were also tested (NicAlert strips; Nymox Pharmaceutical Corporation, Hasbrouck Heights, NJ). Pregnancy tests were administered to female participants (HGC Pregnancy Test Card; DrugTestStrips, Greenville, SC). Urine was examined for adulterants (Specimen Validity Test; DrugTestStrips, Greenville, SC). Recent alcohol use was assessed with a breath alcohol test (Alco-Sensor IV; Intoximeters, Inc. St. Louis, MO). Participants testing positive for any substance other than nicotine or cannabis were excluded.

Drug use. The Timeline Follow Back (TLFB; Sobell, Maisto, Sobell, & Cooper, 1979) was used to measure past year drug use. In this semi-structured measure, participants are asked to recall their use of substances for the past year using a calendar. They may consult their personal calendar or social media for reminders of important milestones or events. Substances were measured as follows: nicotine in number of cigarettes and cigars, number of uses of smokeless tobacco and nicotine replacement, and number of hookah hits; alcohol in standard drinks; cannabis in joints; ecstasy in tablets; inhalants, hallucinogens, and opioids in number of hits; stimulants such as cocaine, crack cocaine, and methamphetamine in milligrams; stimulants such as amphetamine, Ritalin, Adderall, and ephedrine in pills; and sedatives in pills or hits.

Nicotine dependence was assessed using the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). The FTND is a 6-item questionnaire and scores range from 0 to 10. Questions ask about difficulty refraining from smoking, number of cigarettes per day, and others (Heatherton et al., 1991). Although there are no standardized cutoff scores (Moolchan et al., 2002), Heatherton and colleagues (1991) propose the following criteria: 1–2 = very low dependence; 3–4 = low dependence; 5 = medium dependence; 6–7 = high dependence; 8–10 = very high dependence.

Neuropsychological assessments

Quality of education and verbal intelligence were estimated using the Wide Range Achievement Test-4th Edition (WRAT-4) Reading subtest (Wilkinson, 2006) for group comparison purposes; the Reading total score variable was used. As part of the larger study, participants underwent a neuropsychological battery, described in Kangiser and colleagues (under review) and Price and colleagues (2015).

Neuroimaging

Acquisition parameters. 3D SPGR, T-1 weighted images were acquired on a 4T Varian Unity MR scanner, using a modified driven equilibrium Fourier transform (MDEFT) sequence (TR = 13 ms, TE = 5.3 ms, flip angle = 22°, FOV = 25.6 cm, data matrix = 256 × 256 × 192, slice thickness = 1 mm, in-plane resolution = 1 × 1 mm). Anatomical scans were reviewed by a neuroradiologist, and participants with abnormalities were excluded. Diffusion tensor imaging data was collected with 12 diffusion directions, $b \approx 600$ s/mm^2 (TR = 8000 ms, TE = 88.8 ms, flip angle = 90°, FOV = 25.6 cm, data matrix = 64 × 64 × 30, resolution = 4 × 4 × 3 mm^3).

Processing. Images were processed using FreeSurfer version 5.3 (Dale, Fischl, & Sereno, 1999), and FreeSurfer's Tracts Constrained by Underlying Anatomy (TRACULA) software (Yendiki et al., 2011) was used to extract the diffusion variables (average weighted FA, MD, AD, and RD) in MNI space for the following tracts: forceps minor (fminor), and bilateral anterior thalamic radiation (ATR), cingulum cingulate gyrus (CCG), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus—parietal (SLFp), superior longitudinal fasciculus—temporal (SLFt), and uncinate fasciculus (UNC). The fminor and left ILF could not be constructed on one subject, and the right ILF on another. These participants were excluded from the regressions for fminor and left ILF, and right ILF, respectively.

Data Analysis

SPSS (IBM; version 24) was used for all analyses. dfBetas were examined to remove any outliers; none required removal. A series of multiple regressions was conducted to examine whether nicotine group status was associated with FA and MD in the aforementioned tracts after controlling for gender and demographic or drug use variables that differed between groups. We examined whether nicotine group status was associated with AD and RD only in tracts that were significantly different by FA or MD in order to reduce the number of comparisons. Tracts significantly different by group were subjected to a Principal Components Analysis (PCA); one factor reflecting white matter quality emerged. Follow-up correlations were conducted to examine the relationship between nicotine dependence (FTND) score and past year cigarettes and white matter quality. Significance was determined if $p < .05$. Post-hoc power analyses were conducted using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007).

Results

Demographic and Mood Information

Participants into were divided into nicotine users ($n = 18$, 10 female) and controls ($n = 35$, 17 female). Demographic and drug use results are summarized in Table 1. Groups did not differ in age ($F[1,51] = 0.08$, $p = .78$), ethnicity (64.2% Caucasian, $\chi^2(4) = 2.80$, $p = .59$), years of education ($F[1,51] = 2.03$, $p = .16$), WRAT-4 Reading standard score ($F[1,51] = 0.37$, $p = .55$), or Beck Depression Inventory-II score ($F[1,51] = 0.35$, $p = .56$).

Drug Use

Nicotine users had greater cotinine level ($F[1,51] = 597.23$, $p < .001$) and past year cigarette ($F[1,51] = 67.49$, $p < .001$), smokeless tobacco ($F[1,51] = 7.62$, $p = .01$), and alcohol use ($F[1,51] = 9.09$, $p < .01$). Groups did not differ in past year cigar ($F[1,51] = 2.51$, $p = .12$), hookah ($F[1,51] = 2.85$, $p = .10$), cannabis ($F[1,51] = 1.03$, $p = .30$), or ecstasy use ($F[1,51] = 1.98$, $p = .17$).

Primary Findings

Results are summarized in Table 2. After controlling for gender and past year alcohol use, nicotine group status was associated with lower FA in the left ATR [$\beta = -.30$, $t(49) = -2.07$, $p = .04$, $F^2 = .09$], left ILF [$\beta = -.31$, $t(48) = -2.12$, $p = .04$, $f^2 = .09$], left SLFt [$\beta = -.35$, $t(49) = -2.43$, $p = .02$. $f^2 = .12$], and left UNC [$\beta = -.30$, $t(49) = -2.05$, $p < .05$, $f^2 = .09$]. The nicotine group demonstrated marginally lower FA in the left [$\beta = -.27$, $t(49) = -1.824$, $p = .07$, $f^2 = .07$] and right SLFp [$\beta = -.29$,

Table 1. Demographic, mood, and drug use information

M (*SD*) [Range]	Nicotine users ($n = 18$)	Controls ($n = 35$)	*p*
Age	21.33 (2.85) [18–25]	21.12 (2.12) [18–25]	.78
Gender (% Female)	55.56%	48.57%	.63
Ethnicity (% Caucasian)	77.78%	57.14%	.59
Years of Education	13.33 (2.03) [12–19]	14.09 (1.70) [11–18]	.16
Wide Range Achievement Test-4 Reading Scores	103.00 (11.27) [82–133]	101.14 (10.10) [81–120]	.55
Beck Depression Inventory-II Score	4.49 (4.02) [0–17]	3.83 (3.33) [0–11]	.56
Past Year Cigarettes	3738.83 (2717.69) [260–9109]	0.03 (0.17) [0–1]	**<.001***
Past Year Cigars	18.89 (70.79) [0–302]	0.11 (0.53) [0–3]	.12
Past Year Smokeless Tobacco (# uses)	14.33 (31.02) [0–120]	0 (0) [0]	**.01***
Past Year Hookah Puffs	78.89 (278.08) [0–1170]	0.31 (1.05) [0–4]	.10
Past Year Nicotine Replacement Therapy (# uses)	0 (0) [0]	0 (0) [0]	—
Cotinine Level	5.61 (0.78) [3–6]	0.46 (0.70) [0–2]	**<.001***
Fagerström Test for Nicotine Dependence Score	2.83 (2.26) [0–6]	—	—
Past Year Alcohol Use (drinks)	217.61 (256.37) [0–878]	72.03 (93.44) [0–459]	**<.01***
Past Year Cannabis Use (joints)	8.00 (15.19) [0–59]	4.17 (11.75) [0–55]	.32
Past Year Ecstasy Use (tablets)	0.11 (0.47) [0–2]	0 (0) [0]	.17

*$p < .05$.

Table 2. Primary findings

	FA		MD		AD		RD	
	β	*p*	β	*p*	β	*p*	β	*p*
Fminor	–.16	.29	.26	.08	—	—	—	—
L ATR	–.30	**.04***	.11	.49	.02	.88	.15	.33
R ATR	–.22	.16	.01	.97	—	—	—	—
L CCG	–.23	.14	.11	.46	—	—	—	—
R CCG	–.23	.13	.11	.49	—	—	—	—
L ILF	–.31	**.04***	.20	.19	.05	.74	.27	.07
R ILF	–.18	.25	.22	.16	—	—	—	—
L SLFp	–.27	.07	.05	.75	—	—	—	—
R SLFp	–.29	.06	.13	.41	—	—	—	—
L SLFt	–.35	**.02***	.11	.48	–.35	.73	.20	.18
R SLFt	–.22	.14	.04	.77	—	—	—	—
L UNC	–.30	**.05***	.22	.14	.13	.39	.24	.10
R UNC	–.07	.64	.13	.37	—	—	—	—

*$p < .05$.

$t(49)=-1.96$, $p = .06$, $f^2 = .08$], but ps > .10 in all other tracts. MD in the fminor was marginally higher in the nicotine group [β = .26, $t(48) = 1.77$, $p = .08$, $f^2 = .06$], but no other tracts were significant or marginally significant, ps > .10. Further examination of the left ATR, ILF, SLFt, and UNC revealed marginally higher RD in the left ILF [β = .27, $t(48) = 1.83$, $p = .07$, $f^2 = .07$] and left UNC [β = .24, $t(49) = 1.70$, $p < .10$, $f^2 = .06$] in nicotine users, but no differences in AD, ps > .10.

Brain-Behavior Relationships

In order to reduce the number of correlations conducted, the four significant tracts (FA in the left ATR, ILF, SLFt, and UNC) were subjected to a Principal Components Anaylsis (PCA) which revealed one factor reflecting white matter quality across these regions. This factor was then correlated with FTND score, past year cigarettes, CVLT-II Long Delay Free Recall (LDFR) raw score, and PASAT total correct score in the nicotine group. The DTI factor was positively correlated with PASAT performance ($r = .57$, $p = .02$). No significant correlations were observed between the white matter quality factor and FTND score ($r = -.25$, $p = .32$), past year cigarettes ($r = -.19$, $p = .44$), or CVLT-II LDFR score ($r = .02$, $p = .94$).

Covariate Findings

We statistically controlled for past year alcohol use in the primary analysis, which correlated with *higher* FA in the fminor [β = .31, $t(49) = 2.10$, $p < .05$], left ATR [β = .33, $t(49) = 2.30$, $p = .03$], left CCG [β = .30, $t(49) = 2.05$, $p < .05$], left ILF [β = .34, $t(49) = 2.33$, $p = .02$], left SLFp [β = .31, $t(49) = 2.11$, $p = .04$], left SLFt [β = .33, $t(49) = 2.27$, $p = .03$], right SLFt [β = .35, $t(49) = 2.38$, $p = .02$], and left UNC [β = .31, $t(49) = 2.16$, $p = .04$]. Past year alcohol use was marginally associated with lower RD in the left ILF [β = −.29, $t(48) = -1.97$, $p = .06$] and left UNC [β = −.26, $t(49) = -1.86$, $p = .07$].

Discussion

Discussion of Findings

The aim of the present study was to examine whether nicotine use was associated with white matter microstructural features, as measured by FA, MD, AD, and RD, in a young adult sample. Nicotine group status was associated with lower FA in the left anterior thalamic radiation (ATR), left inferior longitudinal fasciculus (ILF), left superior longitudinal fasciculus-temporal (SLFt), and left uncinate fasciculus (UNC), with small ($f^2 = .09$; left ATR, left ILF, & left UNC) to medium ($f^2 = .12$; left SLFt) effect sizes. There were no significant differences in AD or RD in any of those tracts, nor in MD in any tract. Neither symptoms of nicotine dependence nor total past year cigarettes were correlated with FA in any of the significant tracts.

Possible Mechanisms

Of the adult studies that find lower FA in smokers (Lin et al., 2013; Savjani et al., 2014; Umene-Nakano et al., 2014; Zhang et al., 2011), two found higher RD in their samples, likely indicating that the lower FA seen in smokers was likely due to demyelination (Lin et al., 2013; Savjani et al., 2014; Song et al., 2005). While the present study did not replicate these RD findings, RD in the left ILF ($p = .07$, $f^2 = .07$) and left UNC ($p = .10$, $f^2 = .06$) were marginally higher in nicotine users. It is possible that the lower FA seen in smokers in the present study is due to demyelination, but the findings were not significant due to sample size and limited power.

These results are consistent with studies of adults, which generally find lower FA in smokers, and are inconsistent with other adolescent and young adult studies, which typically find higher FA in adolescent and young adult smokers, including in the SLF (Liao et al., 2011; van Ewijk et al., 2015; Yu et al., 2016) and ILF (Jacobsen et al., 2007). The inconsistency may be due to methodological and sample differences from other adolescent/young adult studies, such as exclusion of Axis I disorders, inclusion of participants of both genders, and measuring alcohol and cannabis use, all of which may influence white matter microstructure (Bava et al., 2011; Bessette, Nave, Caprihan, & Stevens, 2014; Gruber, Dahlgren, Sagar, Gonenc, & Lukas, 2014; Herting, Maxwell, Irvine, & Nagel, 2012; Jacobus et al., 2009; Liao et al., 2014; Ma et al., 2007; McQueeny et al., 2009; Murphy & Frodl, 2011; Schmithorst, Holland, & Dardzinski, 2008). Additionally, compared to the adolescent and young adult studies, the sample of the present study is slightly older, with an average age of 21.2 years; perhaps our results differ partially because different white matter tracts finish development in adolescence versus young adulthood (Lebel & Beaulieu, 2011; Simmonds et al., 2014).

Compounds in nicotine cigarette smoke excluding or in addition to nicotine may have caused the deterioration in white matter microstructure seen in the present study. Indeed, compounds in nicotine cigarette smoke cause neuroinflammation and oxidative stress (Durazzo et al., 2010; Khanna et al., 2013), and cigarette smoke extract may cause damage separate from nicotine itself (Yang & Liu, 2003). While the exact mechanism by which cigarette smoke injures neurons is not yet clear, one possibility (Durazzo et al., 2010) is that white matter degradation (Stys, 2004), including degradation of axons (LoPachin & Lehning, 1997) or neuronal damage or death is caused by calcium (Ca^{2+}) overload (Xiao, Wei, Xia, Rothman, & Yu, 2002) as a result of nicotine cigarette smoke exposure (Anbarasi, Vani, Balakrishna, & Devi, 2005). The α7 nAChR mediates the raising of Ca^{2+} levels (Dajas-Bailador, Soliakov, & Wonnacott, 2002), and this receptor subtype is up-regulated with chronic exposure to nicotine (Melroy-Greif, Stitzel, & Ehringer, 2016). Another possibility is that cigarette smoking causes hypoxia (Jensen, Goodson, Hopf, & Hunt, 1991). Anoxic events cause accumulation of Ca^{2+} in the myelin (LoPachin & Stys, 1995), which, with influx, causes oligodendrocyte damage (Scolding, Morgan, Campbell, & Compston, 1992).

It is also possible that lower FA seen in the nicotine group can be attributed to an interaction of nicotine and alcohol use. While 94.4% of each group (17 nicotine users, 34 controls) consumed alcohol in the past year, the nicotine group (4.16 drinks/week) consumed significantly more alcohol drinks in the past year compared to controls (1.38 drinks/week). Unexpectedly, past year alcohol use was associated with *higher* FA in a variety of tracts in our moderate-drinking sample. Since moderate alcohol consumption has some protective cardiovascular effects (Sacco et al., 1999), perhaps it has neuroprotective qualities. Nevertheless, nicotine and alcohol are known to interact. Alcohol and nicotine are often used at the same time (Piasecki et al., 2011), and both are active at nAChRs (Tang & Liao, 2013). Future studies should examine the effects of nicotine and alcohol co-use on white matter microstructure.

Nicotine users exhibited lower FA in the left ILF, left ATR, left SLFt, and left UNC; potential downstream behavioral effects of these tracts will be discussed. The ILF connects the occipital cortex with the anterior temporal lobes (Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007) and may be associated with object recognition in children (Ortibus et al., 2012) and indirectly with language function in adults (Mandonnet et al., 2007). The ATR connects the medial dorsal and anterior thalamic nuclei to the prefrontal cortex and is associated with affect regulation (Coenen, Panksepp, Hurwitz, Urbach, & Madler, 2012) and social responsiveness (Cheon et al., 2011). Future studies should examine the relationship between affective processing and white matter microstructure in smokers. The SLF is an association fiber tract connecting the precentral gyrus with the posterior temporoparietal area (Bernal & Altman, 2010) and has been associated with spatial working memory performance in children (Vestergaard et al., 2011). Interestingly, white matter quality positively correlated with performance on a working memory and sustained attention measure in the present study, although individual tracts were not analyzed. Nicotine use has been associated with poorer working memory and sustained attention (Chamberlain, Odlaug, Schreiber, & Grant, 2012; Jacobsen et al., 2005). The UNC is a bidirectional long-range association fiber tract connecting the anterior temporal lobes with the orbitofrontal cortex and may facilitate the synthesis of mnemonic associations with information regarding reward/punishment (Von Der Heide, Skipper, Klobusicky, & Olson, 2013). Of note, higher FA and/or lower MD in the UNC is correlated with verbal memory performance (Von Der Heide *et al.* 2013), but this was not replicated in the present study.

Of note, significant tracts were lateralized to the left hemisphere, consistent with Lin and colleagues (2013) and Savjani and colleagues (2014). Savjani and colleagues (2014) propose that this may be due to left lateralization of dopamine systems. At high concentrations, nicotine primarily activates nAChRs at D1 receptors (Hamada, Higashi, Nairn, Greengard, & Nishi, 2004), which are primarily left lateralized (Franco et al., 2016), in the striatum (Hamada et al., 2004).

Limitations

The current study has several limitations. The present study is cross-sectional in nature and thus cannot elucidate causality. Risk for nicotine dependence is a heritable trait (Benowitz, 2009; Ho & Tyndale, 2007; Lessov-Schlaggar, Pergadia, Khroyan, & Swan, 2008; Uhl et al., 2007) and even gene variants for nAChR subunits appear to be associated with nicotine dependence (Bierut et al., 2007; Saccone et al., 2007). nAChRs are present in white matter (Ding et al., 2004) and on oligodendrocyte precursor cells (Rogers, Gregori, Carlson, Gahring, & Noble, 2001); thus, perhaps genetic influences explain the present findings, although further research is needed in this area. Additionally, similar to other adolescent/young adult studies of nicotine and white matter microstructure (Huang et al., 2013; Jacobsen et al., 2007; Yu et al., 2016), our sample size is small, particularly of smokers. Another potential weakness of the study was that we did not correct for multiple comparisons after running 7 regressions for both FA and MD outcomes; however, due to relatively low power to detect the smaller effect size (f^2 = .09; power = 57%), we were more concerned with Type II error. Future studies with larger sample sizes will be needed to replicate these findings. Additionally, the effect sizes of the significant findings of the present study were small to medium; unfortunately, it is difficult to judge the clinical significance of these findings without normative data. Studies such as the Adolescent Brain and Cognitive Development Study, a prospective longitudinal study of 10,000 youth, could address these concerns of design, genetics, sample size, and clinical significance. Also, this study used a self-report measure of substance use, the TLFB (Sobell et al., 1979). However, the TLFB demonstrates high reliability when compared to cigarette use self-monitoring (Brown et al., 1998). Nicotine users smoked an average of 10.24 cigarettes/day; findings may not generalize to lighter, heavier, or e-cigarette users. Additionally, the present study used only 12 diffusion directions. DTI measures may have been more accurate with a higher number of directions (Alexander et al., 2007; Jones, 2004; Ni, Kavcic, Zhu, Ekholm, & Zhong, 2006). Lastly, while urine cotinine was measured and no participants were allowed to smoke one hour before cognitive testing, the present study did not account for acute withdrawal effects. However, participants were not forced into withdrawal as in other studies, and the one-hour abstinence period was intended to prevent the cognitive boost (Warburton, 1992) and changes in FA (Kochunov et al., 2013) seen with acute nicotine exposure.

Conclusions

In summary, nicotine group status was associated with lower FA in the left fronto-, parieto-, and occipito-temporal white matter tracts in young adults, while no other diffusion measures exhibited significant differences. These results indicate that chronic smoking in young adulthood may disrupt white matter microstructure. Future studies should replicate these findings in a larger sample that examines gender differences in the effects of nicotine on white matter microstructure, as well as elucidate the mechanism by which smoking changes white matter microstructure.

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Conflict of Interest

None declared.

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