NICOTINE EFFECTS ON WHITE MATTER MICROSTRUCTURE IN MALE AND FEMALE YOUNG ADULTS

by

Megan M. Kangiser

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ABSTRACT

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Under the Supervision of Professor Krista Lisdahl

Nicotine use is still widely prevalent among adolescents and young adults. Nicotine use is associated with white matter microstructural changes as measured by diffusion tensor imaging (DTI), a magnetic resonance imaging technique that measures the diffusion of water in the brain. In adults, nicotine use is generally associated with poorer white matter microstructure, exhibiting lower fractional anisotropy (FA), but in adolescents/young adults, microstructure appears healthier, as indicated by higher FA. No study has examined gender differences in the effects of nicotine on white matter microstructure in young adults. 53 subjects (18 nicotine users [10 female] and 35 controls [17 female]) underwent an MRI scan, neuropsychological battery, toxicology screening, and drug use interview. Nicotine group and gender*nicotine group were used to predict FA and mean diffusivity (MD) in various white matter tracts. In significant tracts, axial (AD) and radial (RD) diffusivity were measured. 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. The gender*nicotine group interaction did not predict any diffusion measures. These results are inconsistent with other adolescent/young adult studies, likely due to methodological differences and a slightly older sample. Further studies should examine the longitudinal effects of nicotine use and gender in a larger sample.

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LIST OF ABBREVIATIONS

ACb	Anterior Cingulate Bundle
AD	Axial Diffusivity
ADHD	Attention-Deficit/Hyperactivity Disorder
ALIC	Anterior Limb of Internal Capsule
ATR	Anterior Thalamic Radiation
Ca^{2+}	Calcium
CCG	Cingulum Cingulate Gyrus
ChAT	Choline Acetyltransferase
CVLT-II	California Verbal Learning Test-2nd Edition
D-KEFS	Delis-Kaplan Executive Functioning System
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
fminor	Forceps Minor
FTND	Fagerström Test for Nicotine Dependence
ILF	Inferior Longitudinal Fasciculus
MD	Mean Diffusivity
MRI	Magnetic Resonance Imaging
nAChR	Nicotinic Acetylcholine Receptor
PASAT	Paced Auditory Serial Attention Test
PCR	Posterior Corona Radiata
PTR	Posterior Thalamic Radiation
RD	Radial Diffusivity

SCR	Superior Corona Radiata
SLF	Superior Longitudinal Fasciculus
SLFp	Superior Longitudinal Fasciculus-Parietal
SLFt	Superior Longitudinal Fasciculus-Temporal
SUD	Substance Use Disorder
TRACULA	Tracts Constrained by Underlying Anatomy
TLFB	Timeline Follow-Back
UNC	Uncinate Fasciculus
WRAT-4	Wide Range Achievement Test-4th Edition

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†AMDG

1. Introduction

1.1 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, despite recent declines in use (Center for Behavioral Health Statistics and Quality, 2017). 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 12^{th} graders and 6.0% of young adults ages 19-29 report use of electronic vaporizers (Schulenberg et al., 2017). The vast majority (98%) of smokers initiate smoking by age 25 (U.S. Department of Health and Human Services, 2014). Thus, characterizing the effects of nicotine use in adolescence and young adulthood on the developing brain is critically important.

1.2 *Psychopharmacology of Nicotine*

Nicotine, the psychoactive component of tobacco, reaches the brain within seconds of inhaling cigarette smoke (Benowitz, 2009). Nicotine activates nicotinic acetylcholine receptors (nAChRs), which are ligand-gated ion channel, pentameric receptors that can be composed of a combination of α (α_2-α_{10}) and β (β_2-β_4) subunits, such as $\alpha_4\beta_2$ and $\alpha_3\beta_4$ receptor subtypes, or may be homomeric, as with the α_7 receptor (Benowitz, 2009). Nicotine causes release of neurotransmitters such as acetylcholine, GABA, serotonin, endorphins, norepinephrine, glutamate, and especially dopamine. Nicotine in part has reinforcing qualities due to dopamine release in the nucleus accumbens after upstream stimulation of nAChRs in the ventral tegmental area (Benowitz, 2009; Blaha et al., 1996; Corrigall, Coen, & Adamson, 1994; Nisell, Nomikos, & Svensson, 1994), although dopamine is also released in other areas, including the frontal

cortex (Benowitz, 2009). nAChRs are found throughout the brain, from highest to lowest density in the thalamus, basal ganglia, cortex, hippocampus, and cerebellum (Brody et al., 2006). Both $\alpha_4\beta_2$ (Levin & Simon, 1998) and α_7 (Levin, Bettegowda, Blosser, & Gordon, 1999; Levin & Simon, 1998) subtypes especially are implicated in learning and memory. 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). However, receptor levels do normalize after at least 2 months of abstinence in humans (Breese et al., 1997).

Cigarette smoke contains a wide variety of potentially cytotoxic chemicals, such as free radicals, carbon monoxide, and nitrosamines (Durazzo, Meyerhoff, & Nixon, 2010), including some compounds associated with brain toxicity (Swan & Lessov-Schlaggar, 2007). The compounds come from both the tobacco plant itself and the cigarette manufacturing process (Swan & Lessov-Schlaggar, 2007). In rats, chronic cigarette smoke exposure can cause neuroinflammation and increased expression of inflammatory marker genes (Khanna, Guo, Mehra, & Royal, 2013). Cigarette smoke is widely known to cause oxidative damage and stress in the brain and body (Durazzo et al., 2010; Khanna et al., 2013; Moriarty et al., 2003; Panda, Chattopadhyay, Chattopadhyay, & Chatterjee, 2000; Panda, Chattopadhyay, Ghosh, Chattopadhyay, & Chatterjee, 1999; Swan & Lessov-Schlaggar, 2007). Also, mouse brain mitochondria are damaged by cigarette smoke extract but *not* by nicotine alone (Yang & Liu, 2003). However, the exact mechanisms by which cigarette smoke damages the brain have yet to be fully elucidated (Durazzo et al., 2010; Khanna et al., 2013).

1.3 Effect of Nicotine on Brain Structure

Evidence suggests that chronic nicotine use may impact brain structure. In adults, smokers generally exhibit lower grey matter volume or density in various parts of the brain (Brody et al., 2004; Fritz et al., 2014; Gallinat et al., 2006; Hanlon et al., 2016; Kuhn et al., 2012; R. Yu, Zhao, & Lu, 2011; Zhang et al., 2011) compared to non-smokers, although exceptions exist (Hanlon et al., 2016; Zhang et al., 2011). Grey matter volume/density is typically negatively correlated with pack-years (Brody, 2006; Fritz et al., 2014; Gallinat et al., 2006; Zhang et al., 2011) or nicotine dependence (Kuhn et al., 2012). While chronic nicotine use not only impacts grey matter, it also causes changes in white matter microstructure.

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). Isotropic diffusion is characterized by fluid movement in all directions equally, while anisotropic diffusion is characterized by fluid movement dependent on direction, as with a barrier such as a neuron (Beaulieu, 2002). The most commonly used measure of the amount of anisotropic diffusion is fractional anisotropy, or FA (Alexander, Lee, Lazar, & Field, 2007; Basser & Pierpaoli, 1996). Mean diffusivity, or MD, measures diffusion in all directions. The diffusion measurement parallel to the fiber is referred to as axial diffusivity, or AD, while diffusion perpendicular to the fiber is called radial diffusivity, or RD (Beaulieu, 2009). FA and MD are commonly used in DTI studies, with AD and RD more recently being used to give specificity about microstructure. Higher FA is usually considered indicative of better white matter health, although the other diffusion measures need to be considered in order to more completely understand white matter microstructure (Alexander et al., 2007). Increased RD without changes in AD is indicative of demyelination, while lower AD with modestly lower RD suggests axonal damage (Song et al., 2005).

White matter microstructure has been fairly well studied in adult smokers, with generally consistent results. Adult smokers demonstrate lower FA in the corpus callosum as a whole (Umene-Nakano et al., 2014) and specifically the genu, left body (Lin, Wu, Zhu, & Lei, 2013), and splenium (Savjani et al., 2014); *left* prefrontal cortex (Zhang et al., 2011); and anterior limb of the internal capsule (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). Findings from Savjani et al. (2014) were in 24-hour abstinent smokers; however, sated smokers in their sample exhibited lower FA in right fronto-motor and –habenular and left fronto-accumbal tracts. In contrast, one study (Paul et al., 2008) found *higher* FA in the body of the corpus callosum in adult smokers, especially in the low-dependence group; additionally, cigarettes per day and FA in the corpus callosum genu were positively correlated. Another study (Hudkins et al., 2012) found increased FA in adult smokers in the corpus callosum genu (in contrast with Lin et al. (2013)), *right* prefrontal areas, and middle cingulum; confusingly, FA was negatively correlated with Fagerström Test for Nicotine Dependence (FTND, described in section 2.3.2) score and cigarettes/day in some areas. However, both of these studies have very small sample sizes, with 10 smokers and 10 non-smokers in Paul et al. (2008), and 18 smokers and 18 non-smokers in Hudkins et al. (2012). 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 increased MD within the corpus callosum and anterior limb of the internal capsule. Savjani et al. (2014) also found decreased AD and increased RD in those areas. Lin et al. (2013) discovered decreased AD and increased RD in the left anterior corpus callosum. Duration of regular smoking positively correlated with MD and RD within this region

(Lin et al., 2013). Generally, studies of white matter microstructure in adults find that smokers exhibit poorer white matter health than controls, but none suggest a specific mechanism for this change; further research is needed in this area. Fortunately, most of these studies contain an even amount 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). However, only one study measured alcohol use (Hudkins et al., 2012), while others 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). See Table 1 for a review of adult studies of nicotine use and white matter integrity.

1.4 *Adolescence*

1.4.1 Brain Development During Adolescence and Young Adulthood

Adolescence is characterized by dynamic brain development, particularly by grey matter pruning (Giedd et al., 1999; Giorgio et al., 2010; Giorgio et al., 2008; Sowell, Thompson, Tessner, & Toga, 2001; Yuan, Cross, Loughlin, & Leslie, 2015) and white matter microstructural improvements (Yuan et al., 2015), typically demonstrated by increases in FA (Ashtari et al., 2007; Barnea-Goraly et al., 2005; Giorgio et al., 2010; Giorgio et al., 2008; 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). FA increases with age (Barnea-Goraly et al., 2005), and decreases in gray matter density are positively correlated with increases in FA (Giorgio et al., 2008).

Many white matter tracts involved in sensorimotor function are already mature in childhood, such as the pontine crossing tract, posterior thalamic radiation, posterior and

retrolenticular portions of the internal capsule, and corona radiata. In adolescence, white matter maturity occurs in areas associated with executive functioning and motor response preparation, including the superior longitudinal fasciculus, cerebellar white matter, cortico-hippocampal limbic tracts (e.g. parts of the cingulum and fornix), and white matter terminations in the thalamus and medial temporal lobes. Growth of white matter terminations in the cortex and basal ganglia continued into adulthood, perhaps suggesting that subcortical networks coalesce cognitive and emotional information (Simmonds, Hallquist, Asato, & Luna, 2014). Of note, some of these areas of development in adolescence and young adulthood overlap with nAChR-rich areas, including the basal ganglia, hippocampus, cortex, and cerebellum (Brody, 2006).

nAChRs play a critical role in prenatal brain development, including regulating neurite growth, gene expression, neurotransmitter release, and GABAergic signaling; for a review, see Dwyer, Broide, and Leslie (2008). nAChRs exhibit unique characteristics in adolescence. In adolescent male rodents, nAChRs display higher functionality (Kota, Martin, Robinson, & Damaj, 2007) and responsiveness (Britton, Vann, & Robinson, 2007) compared to adults. Additionally, in male but not female rats, nAChRs on dopaminergic neurons in early adolescence release greater dopamine upon stimulation than in adulthood (Azam, Chen, & Leslie, 2007).

1.4.2 Effects of Nicotine in the Adolescent Brain

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 such as the nucleus accumbens and ventral tegmental area (Yuan et al., 2015), dopamine turnover in the midbrain and striatum and norepinephrine turnover in the midbrain (Trauth, Seidler, Ali, & Slotkin, 2001), and deficits

in serotonergic receptor activity (Xu, Seidler, Ali, Slikker, & Slotkin, 2001). Chronic nicotine administration also causes reductions in choline acetyltransferase (ChAT) activity—indicative of cholinergic cell damage—and hyperactivity of cholinergic neurons in the midbrain during administration, but a deficit in stimulation after cessation, and depressed activity of hippocampal cholinergic neurons both during and after administration (Trauth, McCook, Seidler, & Slotkin, 2000). Additionally, adolescent female rats chronically exposed to nicotine exhibit persistent behavioral deficits not seen in adults (Trauth, Seidler, & Slotkin, 2000b). nAChR up-regulation in the hippocampus, midbrain, and cortex was equivalent in adolescent rats, while adult rats experienced hierarchical up-regulation; additionally, up-regulation persists longer in adolescents than adults (Trauth, Seidler, McCook, & Slotkin, 1999). Nicotine is more potent in late adolescence than in adulthood (Azam et al., 2007).

Chronic nicotine exposure in adolescence and young adulthood also negatively impacts grey matter structure. Young smokers demonstrate lower grey matter volume in the left amygdala (Hanlon et al., 2016), left thalamus (Hanlon et al., 2016; Y. Liao, Tang, Liu, Chen, & Hao, 2012), left anterior cingulate and left medial frontal cortex (Y. Liao et al., 2012). Li et al. (2015) demonstrated cortical thinning in smokers in the cortex of parts of the frontal, parietal, and temporal lobes, along with larger caudate volumes in smokers. Studies disagree on the impact of chronic smoking on insula thickness in adolescents and young adults (Y. Liao et al., 2012; Morales, Ghahremani, Kohno, Hellemann, & London, 2014). Cortical thickness can be negatively correlated with FTND score and pack-years in young adults (Li et al., 2015). Studies of chronic nicotine exposure on grey matter health in young adults are few, but they consistently demonstrate reductions in cortical volume and thickness.

1.4.3 Nicotine and White Matter Integrity in Adolescence and Young Adulthood

To our knowledge, only 5 studies to date have examined the effects of nicotine on white matter microstructure in adolescents and young adults. All 5 studies examined FA in their sample (Huang et al., 2013; Jacobsen, Picciotto, et al., 2007; Y. Liao et al., 2011; van Ewijk et al., 2015; D. Yu et al., 2016), while 2 measured MD (van Ewijk et al., 2015; D. Yu et al., 2016) and 1 measured AD and RD (D. Yu et al., 2016). Huang et al. (2013) also examined streamline density. In a sample of 67 adolescents aged 13-18, Jacobsen, Picciotto, et al. (2007) found higher FA in smokers in the genu of the corpus callosum, anterior limb of the internal capsule, and the left inferior longitudinal fasciculus (ILF); FA was significantly positively correlated with pack-years in the genu. Y. Liao et al. (2011) demonstrated increased FA in the bilateral superior longitudinal fasciculus (SLF) in 44 smokers compared to 44 controls, ages 19-39. In 11 smokers and 10 nonsmokers ages 18-39, Huang et al. (2013) discovered higher FA in the right anterior cingulate bundle (ACb) and lower streamline density in the anterior and posterior cingulum bundles, middle cingulum, and orbitofrontal region in smokers compared to controls. There was a negative correlation between the Level of Physical Dependence measure (a separate measure from the FTND) and FA in the left ACb (Huang et al., 2013). van Ewijk et al. (2015) studied the effects of smoking in 113 participants with Attention-Deficit/Hyperactivity Disorder (ADHD) and 73 healthy controls, divided into groups of nonsmokers (n=95), irregular smokers (n=41), and regular smokers (n=50), in young adults aged 14-24. Results indicated that compared to nonsmokers and irregular smokers, regular smokers had higher FA and lower MD in the basal ganglia regions, including the right SLF and bilateral corpus callosum, corticospinal tract, internal and external capsules, thalamus, and anterior corona radiata. Lastly, in a male-only sample of 23 smokers and 22 matched controls ages 14-23, D. Yu et al. (2016) elucidated higher FA and lower RD in the left SLF, body and splenium of the corpus callosum, and bilateral

posterior thalamic radiation (PTR), superior corona radiata (SCR), posterior corona radiata (PCR), and internal and external capsules. While no differences in MD were found, they also discovered increased AD in the right external capsule, superior corona radiata, and posterior limb of the internal capsule. FTND was negatively correlated with right SCR; RD and pack-years were negatively correlated in the external capsule, posterior limb of the internal capsule, and right SCR (D. Yu et al., 2016).

Overall, these studies find increased FA in various white matter tracts, particularly in the corpus callosum and SLF, in young adult smokers. One study also found decreased MD in young adult smokers. Of note, this pattern opposes that seen in adults described above, in which adults typically display decreased FA after chronic nicotine use. However, these adolescent and young adult studies, summarized in Table 2, exhibit a variety of methodological differences from adult studies, including a lack of female participants, particularly in smoking groups (Huang et al., 2013; Y. Liao et al., 2011; van Ewijk et al., 2015; D. Yu et al., 2016); no apparent full exclusion of participants with comorbid psychiatric disorders (Huang et al., 2013; van Ewijk et al., 2015; D. Yu et al., 2016); and small sample sizes in comparing smokers to non-smokers (Huang et al., 2013; D. Yu et al., 2016) without prenatal exposure (Jacobsen, Picciotto, 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; Y. Liao et al., 2011; van Ewijk et al., 2015; D. 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 psychiatric disorders excluded. This pattern of higher regional FA in adolescent/young adult smokers is particularly puzzling considering adolescents who use other substances typically exhibit lower FA; for example, lower FA is seen in adolescent and young adult marijuana users (Ashtari et al., 2009),

adolescent binge drinkers (McQueeny et al., 2009) and marijuana and alcohol co-users (Bava et al., 2009). Higher MD is also seen in young adult marijuana users (Arnone et al., 2008; Ashtari et al., 2009). For a review, see Thatcher, Pajtek, Chung, Terwilliger, and Clark (2010).

Multiple hypotheses have been put forth as to why nicotine use appears to be suggestive of better white matter health in young adults. One study that found higher FA in adult smokers (Paul et al., 2008), citing Gazdzinski et al. (2005), proposes that the FA/MD changes seen are not adaptive, and may in fact be due to nicotine-induced vasogenic swelling or cytotoxic cell swelling. Another hypothesis is that the microstructural changes are reflective of nicotine's neurogenic properties (Y. Liao et al., 2011; Paul et al., 2008; van Ewijk et al., 2015). Nicotinic stimulation of spinal cord neurons revealed increased nerve growth factor mRNA and protein expression (Garrido, King-Pospisil, Son, Hennig, & Toborek, 2003), and stimulation of nAChRs in external granular layer neuroblasts produced increased DNA synthesis and content, likely indicating higher cell numbers; this effect appeared to be mediated by α_3 nAChRs (Opanashuk, Pauly, & Hauser, 2001). Additionally, Paul et al. (2008) propose that since nAChRs are found in white matter (Ding et al., 2004) and on oligodendrocyte precursor cells (Rogers, Gregori, Carlson, Gahring, & Noble, 2001), and white matter is still developing in young adulthood (Simmonds et al., 2014), nAChR stimulation may affect glial cells, producing improved microstructural integrity and volume (Paul et al., 2008). Indeed, tobacco smoke has been found to decrease neurogenesis (in contrast to studies described above), but increase gliogenesis (Bruijnzeel et al., 2011). In rat astrocytes, nAChR overactivation leads to increased expression of glial call line-derived neurotrophic factor mRNA and proteins, suggesting neuroprotection is provided by astrocytic nAChRs (Takarada et al., 2012). However, the possibility remains that

higher FA and lower MD may predate smoking initiation, and/or be risk factors for nicotine addiction (van Ewijk et al., 2015).

1.5 Gender

1.5.1 Nicotine and Gender

Nicotine differentially impacts the brain by gender. Women experience greater rewarding and aversive effects of nicotine compared to men, and other factors such as hunger suppression contribute to nicotine use in women (O'Dell & Torres, 2014). Preclinical rodent evidence shows that females experience heightened anxiety with chronic nicotine exposure (Caldarone, King, & Picciotto, 2008), and female rats experience stronger HPA axis responses compared to males (O'Dell & Torres, 2014). Adolescent females experience greater rewarding and fewer aversive withdrawal effects of nicotine compared to adult females (O'Dell & Torres, 2014). In the nAChR up-regulation described above, males in particular exhibit increased nAChR densities (Koylu, Demirgoren, London, & Pogun, 1997; Mochizuki et al., 1998), and levels persist after a month of abstinence in rats (Trauth et al., 1999).

Most studies of nicotine's effects on *cognition* in young adults find that male smokers fare worse than male non-smokers, including in attention (Jacobsen et al., 2005; Jacobsen, Slotkin, Mencl, Frost, & Pugh, 2007), recognition memory after abstinence (Merritt, Cobb, & Cook, 2012), and verbal memory (Kangiser, Lochner, Thomas, & Lisdahl, under review). Cognitive effects of nicotine appear to be less consistent in females, with studies finding poorer performance (Jacobsen, Slotkin, et al., 2007), no effect (Jacobsen et al., 2005; Merritt et al., 2012), or better performance (Kangiser et al., under review) in female smokers compared to female non-smokers. Indeed, FA is generally positively associated with cognition (Bava,

Jacobus, Mahmood, Yang, & Tapert, 2010; Bava, Thayer, et al., 2010; Grieve, Williams, Paul, Clark, & Gordon, 2007).

1.5.2 Gender Differences in White Matter Integrity

In studies of young adolescents (average age 12-13 years), boys frequently exhibit higher FA throughout the brain, in white matter tracts (e.g. arcuate fasciculus) and cortical (e.g. superior temporal gyrus, middle/lateral occipital gyrus) and subcortical (e.g. thalamus, midbrain) structures (Herting, Maxwell, Irvine, & Nagel, 2012; Schmithorst, Holland, & Dardzinski, 2008; Silveri et al., 2006). Some studies disagree, finding that girls display higher FA in the splenium (Schmithorst et al., 2008), right SCR, and bilateral corticospinal tracts (Bava et al., 2011). Adolescent girls typically exhibit higher MD than adolescent boys (Herting et al., 2012; Schmithorst et al., 2008), although one study found no difference (Silveri et al., 2006), and other studies disagree (Bava et al., 2011; Schmithorst et al., 2008). Within Herting et al. (2012), when boys had higher FA, they displayed higher AD and/or lower RD in nearly all higher-FA regions; when girls had higher MD, they also had higher AD in the superior frontal gyrus and higher AD and RD in the superior temporal gyrus. Of note, this pattern is opposite that seen in adults, where adult females can exhibit higher FA than males (Kanaan et al., 2014; Lenroot & Giedd, 2010; Szeszko et al., 2003). A longitudinal study of white matter microstructural development found that adolescent boys had greater white matter increases and prolonged growth compared to females, although both sexes experienced white matter growth in adolescence. Males exhibited higher FA and lower RD compared to females in a variety of brain regions (Simmonds et al., 2014). For a review of sex differences in the adolescent brain, see Lenroot and Giedd (2010).

No studies to date have examined the effects of gender and nicotine use on white matter integrity in young adults. As aforementioned, most of the five studies examining the effects of

nicotine on white matter integrity in young adults have a noticeably low number (Huang et al., 2013; Y. Liao et al., 2011; van Ewijk et al., 2015) or absence (R. Yu et al., 2011) of females in their samples (Gogliettino, Potenza, & Yip, 2016). Thatcher et al. (2010) conducted a study of gender differences in white matter integrity in adolescents in treatment for substance use disorders (SUDs). Adolescents with SUDs had lower FA in the right SLF, with lower AD, higher RD, and no difference in MD within the right SLF. Within the substance users, females trended towards lower FA than males in the SLF. This sample included heavy cigarette use, but the study examined SUDs broadly and nicotine use was not parsed out; also, the smoking group had no exclusion criteria for comorbid psychopathology while some disorders (e.g. ADHD and depression) were excluded in the control group (Thatcher et al., 2010).

1.6 Study Aims

Evidence shows that chronic nicotine use impacts white matter health. While adult studies generally find lower FA in smokers, studies in adolescents and young adults have consistently found higher FA in smokers, especially in the SLF, internal and external capsules, and corona radiata. Many of these studies in adolescents and young adults include few female participants, unmeasured alcohol use, and psychiatric comorbidities. To our knowledge, only one prior study of young adult males (D. Yu et al., 2016) has examined the effect of nicotine use on white matter microstructure in young adults using all four measures of diffusion (FA, MD, AD, and RD); these results need replicated, particularly in a sample that includes females. Further, no study to date has examined the effects of gender and nicotine use together on white matter integrity in young adults.

Therefore, the aims of the present study were to thoroughly characterize white matter microstructure in young adult smokers and non-smokers, and to examine how gender moderates

any relationships. We also examined how white matter changes relate to nicotine dependence. Further, given the differences by gender and nicotine use on long delay free recall of the CVLT-II (Delis, Kramer, Kaplan, & Ober, 2000), a verbal memory task, and marginal differences on the Paced Auditory Serial Attention Test (PASAT) (Gronwall, 1977), a sustained attention and working memory task, in an overlapping sample (Kangiser et al., under review), exploratory correlations were run to examine relationships between FA in the significant tracts in the present study and performance on the CVLT-II and the PASAT.

The present study excludes psychiatric comorbidities, includes a greater number of females in our sample, and measures and controls for alcohol use. Because of these changes, the methodology is more consistent with the adult literature, which typically finds lower FA in smokers. Additionally, our sample of 18-25 year olds is older than some samples in the adolescent/young adult literature. Moreover, young adulthood is a time of brain development characterized by white matter microstructure improvements, indicated by higher FA. Given all of these factors, it is difficult to hypothesize a direction for change in white matter microstructure between nicotine users and controls. Thus, we hypothesized that young adult nicotine users will 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. Additionally, we hypothesized that males would exhibit lower FA and higher MD than females, given that FA is associated with cognition, and cognitive deficits are seen primarily in male smokers. Lastly, we hypothesized that FA wound negatively correlate with FTND and past year cigarettes.

2. Methods

2.1 Participants

Participants include 53 young adults ages 18-25 (27 female) sampled as part of a larger study (PI: Lisdahl NIH R03 DA027457). The University of Cincinnati Institutional Review Board approved all protocols. Inclusion criteria included: right-handedness; age 18-25; for the control group, <5 past year nicotine exposures, no regular exposure to second-hand nicotine smoke, and never having been a regular smoker; for the nicotine group, minimum weekly cigar or twice-weekly nicotine cigarette, smokeless tobacco, and/or nicotine replacement exposure in the past year. Exclusion criteria included: current pregnancy; MRI contraindications (non-removable ferromagnetic metal in/on body); history of special education or a learning disability; history of chronic neurologic or medical illness (brain tumor, traumatic brain injury, >2min loss of consciousness and concussion symptoms, chronic migraines, epilepsy, meningitis, HIV, cerebral palsy, Parkinson's disease, Huntington's disease, stroke, uncontrolled high blood pressure, diabetes); 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 of any of these drug categories: 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 WRAT-4 Reading t-score ≤ 80. Eligible participants were divided into nicotine users (n= 18, 10 female) and controls (n=36, 17 female).

2.2 Procedure

Recruitment was conducted through advertisements in a free local newspaper and through fliers. Interested potential participants completed a phone screen for exclusionary criteria, described in further detail in Lisdahl and Price (2012). 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). Eligible participants with minimal other substance use underwent one 4.5-hour session with a neuropsychological battery, questionnaires, drug use interview, and MRI scan. Participants with moderate other substance use underwent two sessions, 2-3 days apart, with neuropsychological battery, questionnaires, and drug use interview at the first session, and the MRI at the second session. All participants received an image of their brain, local substance abuse treatment resources, and parking reimbursement; participants who completed one session received $110, while those with two sessions received $160.

2.3 Measures

2.3.1. 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 marijuana were excluded.

2.3.2. 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: alcohol in standard drinks; marijuana in joints; nicotine in number of cigarettes and cigars, and number of uses of smokeless tobacco and nicotine replacement; ecstasy in tablets; inhalants (nitrous oxide, paint, gas, cleaners, glue, etc.), hallucinogens (PCP, LSD, acid, peyote), and opioids (opium and heroin) 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 (GHB, ketamine, downers, etc.) in pills or hits.

Additionally, 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 0-10 points. Questions ask about difficulty refraining from smoking, number of cigarettes per day, and other dependence questions (Heatherton et al., 1991). Although there are no standardized cutoff scores (Moolchan et al., 2002), Heatherton et al. (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.

2.4. 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, including measures of working memory (Paced Auditory Serial Attention Test, PASAT (Gronwall, 1977); Wechsler Adult Intelligence Scale-3rd Edition – Letter Number Sequencing subtest (Wechsler, 1997a)), verbal memory (California Verbal Learning Test-2nd edition, CVLT-II (Delis et al., 2000)), facial memory (Wechsler Memory Scales – Faces subtest (Wechsler,

1997b)), attention (Ruff 2 & 7 (Ruff & Allen, 1996)), executive functioning (Wisconsin Card Sorting Task (Kongs, Thompson, Iverson, & Heaton, 2000); Delis-Kaplan Executive Functioning System (D-KEFS) – Trails, Color-Word Interference, Verbal Fluency, and Design Fluency subtests (Delis, Kaplan, & Kramer, 2001)), general intelligence (Wechsler Abbreviated Scale of Intelligence – Vocabulary and Block Design subtests (Wechsler, 1999)), and motor dexterity (Grooved Pegboard Test; Lafayette Instrument Company, Lafayette, IN).

2.5. Neuroimaging

2.5.1. 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 = 13ms, TE = 5.3ms, flip angle = 22°, FOV = 25.6cm, data matrix = 256 x 256 x 192, slice thickness = 1mm, in-plane resolution = 1 x 1mm). 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 = 8000ms, TE = 88.8ms, flip angle = 90°, FOV = 25.6cm, data matrix = 64 x 64 x 30, resolution = 4 x 4 x $3mm^3$).

2.5.2. Processing

Images were processed using FreeSurfer version 5.3 (Dale, Fischl, & Sereno, 1999). Scan images were first subjected to motion correction (Reuter, Rosas, & Fischl, 2010), intensity normalization (Sled, Zijdenbos, & Evans, 1998), conversion to Talairach space (Collins, Neelin, Peters, & Evans, 1994), and skull stripping. Images were then segmented into white matter and grey matter structures (Fischl et al., 2002; Fischl et al., 2004), followed by registration and white matter segmentation. 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 subjects were excluded from the regressions for fminor and left ILF, and right ILF, respectively.

2.6. Data Analysis

SPSS was be used for all analyses. dfBeta weights were examined to remove any outliers. A series of multiple regressions was be conducted to examine whether nicotine group status and an interaction between nicotine group and gender predict FA, MD in the aforementioned tracts after controlling for gender and any demographic or drug use variables that differ between nicotine groups or by gender. In tracts that have significant findings for FA or MD, we examined whether nicotine group status and gender*nicotine group predict AD and RD. For tracts that are predicted by group or gender*nicotine group, follow-up correlations were conducted to examine the relationship between nicotine dependence score and the white matter measure (FA, MD, AD, or RD). Significance was determined if $p<.05$. Post-hoc power analyses were conducted using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007).

3. Results

Demographic and drug use variables were examined using Chi-squares and ANOVAs with Fischer's LSD for post-hoc analyses, after dividing participants into male nicotine users (n=8), male controls (n=18), female nicotine users (n=10), and female controls (n=17).

3.1 Demographic and Mood Information

Demographic and drug use results are summarized in Table 3. Groups did not differ in age (F[3,49]=0.28, p=.84), ethnicity (64.2% Caucasian, $\chi^2(12)=8.24$, $p=.77$), years of education (F[3,49]=0.92, p=.44), WRAT-4 Reading standard score (F[3,49]=1.02, p=.30), or Beck Depression Inventory-II score (F[3,49]=0.18, p=.91).

3.2 Drug Use

Groups significantly differed in past year cigarette use (F[3,49]=21.64, p<.001), cotinine level (F[3,49]=202.39, p<.001), past year hookah use (F[3,49]=2.91, p=.04), and past year alcohol drinks (F[3,49]=3.94, p=.04). Post-hoc analysis revealed that male and female smokers had significantly higher past year cigarette use and higher cotinine levels compared to male and female controls, all ps<.001. Male nicotine users exhibited significantly higher past year hookah puffs compared to male controls (p=.01), female nicotine users (p=.02), and female controls (p=.01). Additionally, female nicotine users consumed significantly more past year alcohol drinks than male and female controls, p=.03. Lastly, female nicotine users consumed marginally significantly more other drugs in the past year (F[3,49]=2.76, p=.052) compared to male and female controls (p=.02), but this marginal effect is driven by one female nicotine user with 13 past year other drug uses. Groups did not differ in past year cigar (F[3,49]=2.57, p=.07), smokeless tobacco (F[3,49]=2.45, p=.08), cannabis (F[3,49]=1.25, p=.30), or ecstasy use (F[3,49]=1.47, p=.23).

3.3 Primary Findings

Results are summarized in Table 4. After controlling for gender and past year alcohol use, nicotine group predicted 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 [$\beta=-.30$, $t(49)=-2.05$, $p<.05$, $f^2=.09$]. Nicotine group predicted marginally lower FA in the

left [β=-.27, t(49)=-1.824, p=.07, f^2=.07] and right SLFp [β=-.29, t(49)=-1.96, p=.06, f^2=.08], but did not predict FA in any other tracts, *p*s>.10. Nicotine group marginally predicted higher MD in the fminor [β=.26, t(48)=1.77, p=.08, f^2=.06], but other tracts were not 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, *p*s>.10. There were no significant nicotine by gender interaction effects.

3.4 Brain-Behavior Relationships

No significant correlations were observed between FTND score and FA in the left ATR (r=-.34, *p*=.16), left ILF (r=-.24, *p*=.34), left SLFt (r=.04, *p*=.89), or left UNC (r=-.34, *p*=.17). Neither were correlations significant between past year cigarette use and FA in the left ATR (r=-.29, p=.10), left ILF (r=-.21, p=.14), left SLFt (r=-.24, p=.08), or the left UNC (r=-.22, p=.12).

PASAT performance positively correlated to FA in the left SLFt (r=.30, p=.03), but not to FA in any of the other tracts (ps>.23). FA did not correlate with CVLT-II performance in the left ATR, left ILF, left SLFt, or left UNC, *p*s>.40. Perhaps no correlations were observed with CVLT-II long delay free recall performance because performance differed by gender in the prior study but gender differences were not seen in the present study.

3.5 Covariate Findings

We did statistically control for past year alcohol use, which actually predicted *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 also predicted marginally 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].

4. Discussion

4.1 Discussion of Findings

The aim of the present study was to examine whether nicotine use predicted white matter microstructural features, as measured by fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), in a young adult sample, and whether gender moderated these relationships. Nicotine group status predicted 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). There were no significant differences in AD or RD in any of those tracts, nor in MD in any tract. Symptoms of nicotine dependence were not correlated with FA in any of the significant tracts. We also found that gender did not moderate these effects. Using the above effect sizes and 3 predictors in the model, we had 56.1% power in detecting the left ATR effect, 59.0% for the left ILF, 69.5% for the left SLFt, and 54.8% for the left UNC. To achieve 80% power for the left UNC analysis, an estimated sample size of 95 participants would have been required.

These results are inconsistent with other adolescent and young adult studies, which typically find *higher* FA in adolescent and young adult smokers, including in the SLF (Y. Liao et al., 2011; van Ewijk et al., 2015; D. Yu et al., 2016) and ILF (Jacobsen, Picciotto, 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 et al., 2012; Jacobus et al., 2009; M. Liao et al., 2014; Ma et al., 2007; McQueeny et al., 2009; Murphy & Frodl, 2011; Schmithorst et al., 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 (Simmonds et al., 2014).

The ILF connects the occipital cortex with the anterior temporal lobes, below the optic pathways (Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007); it may be associated with object recognition in children (Ortibus et al., 2012) and indirectly associated with language function in adults (Mandonnet et al., 2007). The ATR connects the medial dorsal and anterior thalamic nuclei to the prefrontal cortex. It appears to be associated with affect regulation (Coenen, Panksepp, Hurwitz, Urbach, & Madler, 2012) and social responsiveness (Cheon et al., 2011). The SLF is an association fiber connecting the precentral gyrus with the posterior temporoparietal area (Bernal & Altman, 2010); it is likely not indicated in language semantics (Maldonado, Moritz-Gasser, & Duffau, 2011) but the left SLF has been associated with spatial working memory performance in children (Vestergaard et al., 2011). Consistent with this finding, FA in the left SLF positively correlated with performance on a working memory and sustained attention measure in the present study. The UNC is a bidirectional long-range association fiber tract connecting the anterior temporal lobes with the orbitofrontal cortex; Von Der Heide (2013) hypothesize that the UNC allows for the synthesis of mnemonic associations with information regarding reward/punishment. Of note, higher FA and/or lower MD in the UNC is correlated with verbal memory performance (Von Der Heide, 2013) in healthy adults and in adults with TBI (Niogi et al., 2008), and in children and adolescents (Mabbott, Rovet,

Noseworthy, Smith, & Rockel, 2009). However, FA in the left UNC did not correlate with verbal memory performance in the present study.

The fact that the gender by nicotine group interaction did not predict white matter microstructure in any tract is surprising given the differing receptor-level (Koylu et al., 1997; Mochizuki et al., 1998) and cognitive (Jacobsen et al., 2005; Kangiser et al., under review; Merritt et al., 2012) effects of nicotine between the genders. However, this study is the first to examine gender differences in nicotine effects on white matter microstructure and is limited by a very small sample size within the nicotine group—8 males and 10 females. An effect of gender may be seen in larger samples. Additionally, perhaps there are simply no effects on white matter between the genders in chronic smoking; perhaps gender differences exist with functional connectivity, neurotransmitters, or grey matter. Chronic smoking is associated with sex differences in functional connectivity of the default mode network (Beltz, Berenbaum, & Wilson, 2015) and has been shown to differentially impact grey matter volumes by sex and region (Franklin et al., 2014).

4.2 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). While the present study did not replicate these RD findings, RD in the left ILF (p=.07) and left UNC (p=.10) were marginally higher in nicotine users. Effect size calculations determined small effect sizes for the left ILF (f^2=.07) and the left UNC (f^2=.06), indicating 47.2% power for the left ILF and 41.6% power for the left UNC with 3 predictors. To achieve 80% power in detecting these effects, sample sizes of 115 (left ILF) to 133 (left UNC)

would be needed. Thus, it is possible that the lower FA seen in smokers in the present study is due to demyelination, but this is purely speculation with our small sample size and limited power.

Additionally, it is possible that the compounds in cigarette smoke excluding or in addition to nicotine have caused the deterioration in white matter microstructure seen in the present study. Indeed, compounds in 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 neuronal damage or death is caused by calcium (Ca^{2+}) overload (Xiao, Wei, Xia, Rothman, & Yu, 2002) as a result of cigarette smoke exposure (Anbarasi, Vani, Balakrishna, & Devi, 2005). Nicotine's effect in raising Ca^{2+} appears to be mediated by the α7 nAChR (Dajas-Bailador, Soliakov, & Wonnacott, 2002), which is up-regulated with chronic exposure to nicotine (Melroy-Greif, Stitzel, & Ehringer, 2016). Calcium overload not only contributes to neuronal damage and death (Xiao et al., 2002), but is also associated with white matter degradation (Stys, 2004), including degradation of axons (R. M. LoPachin & Lehning, 1997). Cytokine levels, which are involved with inflammation and elevated with cigarette smoke exposure (Khanna et al., 2013), can impact Ca^{2+} signaling in both neurons and glia, inducing elevated Ca^{2+} levels in these cells (Sama & Norris, 2013). Perhaps, then, the neuroinflammation associated with cigarette smoking causes Ca^{2+} overload, and subsequently damage and death, in neurons and glia, thus impacting white matter microstructure. Another possibility is that cigarette smoking causes hypoxia (Jensen, Goodson, Hopf, & Hunt, 1991). Anoxic events cause accumulation of Ca^{2+} in the myelin (R. M. LoPachin, Jr. & Stys, 1995), which, with influx, causes oligodendrocyte damage (Scolding,

Morgan, Campbell, & Compston, 1992). Specifically, it appears that the myelin separates from the axon (Waxman, Black, Ransom, & Stys, 1993), which may explain the higher RD seen in other studies (Lin et al., 2013; Savjani et al., 2014), and marginally in the present study. Mechanisms for injury to white matter are reviewed in Stys (1998) and Stys (2004).

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 predicted *higher* FA in a variety of mostly left-lateralized tracts in our moderate-drinking sample. *Lower* FA is seen in adolescent binge drinkers (McQueeny et al., 2009) (Jacobus et al., 2009). The present study screened out very high drinkers, as well as had an older sample, which may explain the differences in the findings. Additionally, moderate alcohol consumption has some protective cardiovascular effects (Sacco et al., 1999), and thus, perhaps 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 alcohol is active at nAChRs (Tang & Liao, 2013). Tobacco and alcohol use alone appear to influence use of the other substance, and this fact may have genetic underpinnings (Cross, Lotfipour, & Leslie, 2017). While, to our knowledge, no studies have examined the effects of chronic nicotine and alcohol co-use on white matter microstructure, other studies, summarized in Swan and Lessov-Schlaggar (2007), have found lower frontal, temporal, total neocortical (Durazzo, Cardenas, Studholme, Weiner, & Meyerhoff, 2007), and parietal (Durazzo, Cardenas, et al., 2007; Gazdzinski et al., 2005) grey matter volume and higher temporal white matter volume (Gazdzinski et al., 2005) in co-users. For further review, see Durazzo,

Gazdzinski, and Meyerhoff (2007). Future studies should examine the effects of nicotine and both moderate and heavy alcohol co-use on white matter microstructure.

4.3 Limitations

The results of the current study should be viewed in light of several limitations. First, the present study is cross-sectional in nature and thus cannot elucidate causality. It is possible that alterations in white matter microstructure predispose individuals to smoke cigarettes. Additionally, similar to other adolescent/young adult studies of nicotine and white matter microstructure (Huang et al., 2013; Jacobsen, Picciotto, et al., 2007; D. Yu et al., 2016), our sample size is small, particularly of smokers, which made the present study underpowered. Studies such as the Adolescent Brain and Cognitive Development Study, a prospective longitudinal study with a very large sample, could address both of these concerns. Also, this study used a self-report measure of substance use, the Timeline Follow-Back (Sobell et al., 1979). However, the TLFB demonstrates high reliability when compared to cigarette use self-monitoring (Brown et al., 1998). While the present study included a relatively equal number of males and females in the sample, no hormone or menstrual cycle phase data was collected; future studies should examine these variables in nicotine 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); however, a higher number of directions requires longer scan time (Alexander et al., 2007). Lastly, while urine cotinine was measured and all participants were not allowed to smoke one hour before 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.

4.4 Conclusions

In summary, nicotine group status predicted lower FA in the left ATR, ILF, SLFt, and UNC in young adults, while no other diffusion measures exhibited significant differences. Additionally, the gender by nicotine group interaction did not predict any differences in white matter microstructure, which is surprising given the differential effects of nicotine seen between males and females. These results indicate that chronic smoking in young adulthood may disrupt white matter integrity. Future studies should replicate these findings in a larger sample that includes hormone data, as well as elucidate the mechanism by which smoking changes white matter microstructure.

Table 1. Review of Adult Studies

	Zhang et al., 2011	Hudkins et al., 2012	Savjani et al., 2014	Paul et al., 2008	Umene-Nakano et al., 2014	Lin et al., 2013
Smoker Sample (M/F)	48 (24/24)	18 (10/8)	30 (17/13)	10 (4/6)	19 (all male)	34 (27/7)
Control Sample (M/F)	48 (24/24)	18 (9/9)	32 (14/18)	10 (6/4)	18 (all male)	34 (28/6)
Smokers Age M (SD) [Range]	31.4 (8.1)	33.7 (7.9)	39.0 (9.9)	38.5 (14.2)	40.5 (8.6) [27-54]	46.9 (7.3) [33-58]
Control Age M (SD) [Range]	31.1 (8.8)	33.3 (10.1)	36.0 (13.6)	38.6 (12.5)	36.4 (8.0) [30-61]	47.0 (8.9) [33-58]
Age of Onset M (SD)	15.6 (3.4)	Not specified	~ 18.9	Not specified	19.6 (1.4)	21.0 (5.2)
Excl. Psych D/O?	Yes	Yes	Yes, for smokers only	Yes	Yes	Yes
Measure Alcohol Drinks?	No (measured 'social drinkers')	Yes	No	No (AUDIT-type questions)	AUDIT sig. dif., not controlled	No (AUDIT-type questions)
Measure Cannabis?	No	Yes	No	No	No	No
Equal Gender Split?	Yes	Yes	Yes	Yes	No	No
Findings	↓ FA	↑ FA	↓ FA, ↑ MD ↓ AD, ↑ RD	↑ FA, -- MD	↓ FA	↓ FA, -- MD

Table 2. Review of Adolescent/Young Adult Studies

	Jacobsen et al., 2007	van Ewijk et al., 2015	Yu et al., 2016	Huang et al., 2013	Liao et al., 2011
Smoker Sample (M/F)	14 (7/7)	IS = 23 (23/18) RS = 50 (39/11)	23 (all male)	11 (9/2)	44 (36/8)
Control Sample (M/F)	20 (8/12)	95 (59/36)	22 (all male)	10 (6/4)	44 (34/10)
Smokers Age M (SD) [Range]	17.0 (0.7) [13-18]	IS = 19.1 (2.5) RS = 18.8 (2.0) [14-24]	19.6 (1.9) [16-23]	23.7 (2.0) [18-39]	28.0 (5.6) [19-39]
Control Age M (SD) [Range]	16.3 (1.2) [13-18]	16.7 (2.2) [14-24]	19.3 (2.4) [14-23]	22.5 (6.8) [18-39]	26.3 (5.8) [19-39]
Age of Onset M (SD)	13.1 (1.8)	IS = 15.1 (1.6) RS = 13.5 (2.1)	15.4 (1.9)	Not specified	17.9 (4.3)
Excl. Psych D/O?	Yes	No	No (psych meds excluded)	No (excl. "mental illness req. meds")	Yes
Measure Alcohol Drinks?	Yes	No	No (abuse excluded)	No	No (AUDIT-type questions)
Measure Cannabis?	Yes	No	No	No	No
Equal Gender Split?	Yes	No	No (all male)	No	No
Findings	↑ FA	↑ FA, ↓ MD	↑ FA, -- MD ↑ AD, ↓ RD	↑ FA	↑ FA

Table 3. Demographic and Drug Use Information
*p<.05, **p<.001

M (SD) [Range]	Male Nicotine Users (n=8)	Male Controls (n=18)	Female Nicotine Users (n=10)	Female Controls (n=17)	p
Age	21.88 (2.75) [18-25	21.22 (2.18) [18-25]	20.90 (3.00) [18-25]	21.06 (2.14) [19-25]	.84
Ethnicity (% Caucasian)	62.50%	61.11%	90%	52.94%	.77
Years of Education	13.63 (2.77) [12-19]	14.28 (1.93) [12-18]	13.10 (1.29) [12-16]	13.88 (1.45) [11-17]	.44
WRAT-4 Reading Score	102.75 (12.65) [93-133]	103.94 (10.36) [85-120]	103.20 (10.75) [82-117]	98.18 (9.2) [81-120]	.39
BDI-II Score	3.88 (3.48) [1-11]	4.78 (5.07) [0-17]	3.80 (3.39) [0-11]	4.18 (2.63) [0-9]	.91
Past Year Cigarettes	**3671.13 (3192.50) [260-7300]****	0 (0) [0]	**3793.00 (2452.86) [1806-9109]****	0.06 (0.24) [0-1]	<.001
Past Year Cigars	42.38 (105.01) [0-302]	0 (0) [0]	0.10 (0.32) [0-1]	0.24 (0.75) [0-3]	.07
Past Year Smokeless Tobacco (# uses)	13.50 (21.70) [0-49]	0 (0) [0]	15.00 (38.08) [0-120]	0 (0) [0]	.08
Past Year Hookah Puffs	**176.25 (410.22) [0-1170]***	0.44 (1.29) [0-4]	1.00 (3.16) [0-10]	0.18 (0.73) [0-3]	.04
Past Year Nicotine Replacement Therapy (# Uses)	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	---
Cotinine Level	**5.38 (1.06) [3-6]****	0.33 (0.59) [0-2]	**5.80 (0.42) [5-6]****	0.59 (0.80) [0-2]	<.001
Past Year Alcohol Use† (drinks)	205.88 (251.24) [0-687]	73.39 (76.83) [0-250]	**227.00 (273.55) [14-878]***	70.59 (110.81) [1-459]	.04
Past Year Marijuana Use (joints)	13.50 (20.20) [0-59]	4.83 (10.43) [0-34]	3.60 (8.38) [0-27]	3.47 (13.29) [0-55]	.30
Past Year Ecstasy Use (tablets)	0 (0) [0]	0 (0) [0]	0.20 (0.63) [0-2]	0 (0) [0]	.23
Past Year Other Drug Use	1.25 (3.15) [0-9]	0.11 (0.32) [0-1]	2.30 (4.24) [0-13]	0.12 (0.49) [0-2]	.052

Table 4. Primary Findings

	FA		MD		AD		RD	
	β	*p*	β	*p*	β	*p*	β	*p*
Fminor								
Nicotine group	-.16	.29	.26	.08	--	--	--	--
Nicotine group * Gender	-.11	.41	.03	.84	--	--	--	--
L ATR								
Nicotine group	-.30	**.04**	.11	.49	.02	.88	.15	.33
Nicotine group * Gender	-.13	.32	.15	.30	--	--	--	--
R ATR								
Nicotine group	-.22	.16	.01	.97	--	--	--	--
Nicotine group * Gender	-.18	.20	.09	.52	--	--	--	--
L CCG								
Nicotine group	-.23	.14	.11	.46	--	--	--	--
Nicotine group * Gender	-.14	.31	.03	.85	--	--	--	--
R CCG								
Nicotine group	-.23	.13	.11	.49	--	--	--	--
Nicotine group * Gender	-.09	.52	.04	.81	--	--	--	--
L ILF								
Nicotine group	-.31	**.04**	.20	.19	.05	.74	.27	.07
Nicotine group * Gender	-.13	.33	.15	.29	--	--	--	--
R ILF								
Nicotine group	-.18	.25	.22	.16	--	--	--	--
Nicotine group * Gender	-.19	.19	.15	.29	--	--	--	--
L SLFp								
Nicotine group	-.27	.07	.05	.75	--	--	--	--
Nicotine group * Gender	-.10	.47	.07	.61	--	--	--	--
R SLFp								
Nicotine group	-.29	.06	.13	.41	--	--	--	--
Nicotine group * Gender	-.12	.39	.05	.73	--	--	--	--
L SLFt								
Nicotine group	-.35	**.02**	.11	.48	-.35	.73	.20	.18
Nicotine group * Gender	-.17	.20	.12	.41	--	--	--	--
R SLFt								
Nicotine group	-.22	.14	.04	.77	--	--	--	--
Nicotine group * Gender	-.01	.92	-.03	.80	--	--	--	--
L UNC								
Nicotine group	-.30	**.05**	.22	.14	.13	.39	.24	.10
Nicotine group * Gender	-.03	.84	-.05	.74	--	--	--	--
R UNC								
Nicotine group	-.07	.64	.13	.37	--	--	--	--
Nicotine group * Gender	-.04	.78	-.01	.96	--	--	--	--

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