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Review

White matter development and tobacco smoking in young adults: A systematic review with recommendations for future research

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ABSTRACT

Background: Adolescence and young adulthood are critical vulnerability periods for initiation of tobacco smoking. White matter development is ongoing during this time and may be influenced by exposure to nicotine. Synthesis of findings from diffusion tensor imaging (DTI) studies of adolescent and young adult smokers may be helpful in understanding the relationship between neurodevelopment and initiation and progression of tobacco-use behaviors and in guiding further research.
Methods: A systematic literature review was conducted to identify DTI studies comparing adolescent and young adult (mean age <30 years) smokers versus nonsmokers. A total of 5 studies meeting inclusion criteria were identified. Primary study findings are reviewed and discussed within the context of neurodevelopment and in relation to findings from adult studies. Directions for further research are also discussed.
Results: All identified studies reported increases in fractional anisotropy (FA) among adolescent/young adult smokers in comparison to non-smokers. Increased FA was most frequently reported in regions of the corpus callosum (genu, body and spenium), internal capsule and superior longitudinal fasciculus.
Conclusions: Findings of increased FA among adolescent/young adult smokers are contrary to those from most adult studies and thus raise the possibility of differential effects of nicotine on white matter across the lifespan. Further research including multiple time points is needed to test this hypothesis. Other areas warranting further research include DTI studies of e-cigarette use and studies incorporating measures of pubertal stage.

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1. Introduction

1.1. Tobacco smoking and adolescence

Tobacco smoking is addictive and associated with negative health effects including lung cancer, emphysema, and type-II diabetes (Adcock et al., 2011; Caramori et al., 2011; Tuesta et al., 2011; USDHHS, 2014). Despite significant advancements in treatments for smoking cessation (Cahill et al., 2013; Morean et al., 2015; Pbert et al., 2015), tobacco smoking remains a significant public health concern, with the prevalence of past-year tobacco use among US citizens over the age of 12 estimated at 25.5%, equating to 66.9 million individuals (SAMHSA, 2014).

Adolescence is a critical vulnerability period for the initiation of tobacco smoking, with earlier ages of initiation associated with greater severity of nicotine dependence (Riggs et al., 2007; Behrendt et al., 2009; Klein et al., 2013; Lanza and Vasilenko, 2015). In the United States, more than 85% of adult smokers report initiation of cigarette smoking prior to the age of 18 and essentially all adult smokers (i.e., 99.9%) report initiation by the age of 30 (USDHHS, 2014). For most individuals, tobacco-use disorder may therefore be considered an adolescent-onset disorder.

Neural development of both grey- and white-matter tissue structures is ongoing throughout childhood and adolescence and into adulthood (Giedd et al., 1999; Giedd, 2004; Lebel and Beaulieu, 2011; Raznahan et al., 2014). Within the brain, nicotine binds to nicotinic acetylcholine receptors (nAChRs) and influences neurotransmission and neuronal growth (Rüdiger and Bolz, 2008). Stimulation of nicotinic receptors with nAChR agonists (such as nicotine) results in decreased axonal surface areas, whereas nAChR antagonists increase axonal surface areas (Nordman and Kabbani, 2012). Chronic exposure to nicotine is associated with upregulation of nAChRs (Sallette et al., 2005), and preclinical data indicate that the adolescent brain may be more susceptible than the adult brain to nicotine-associated increases in nAChR expression (Goriounova and Mansvelder, 2012). Thus, relationships between neural structural characteristics and nicotine exposure may vary across developmental epochs.

1.2. Diffusion-weighted imaging

Diffusion-weighted magnetic resonance imaging (dMRI) is a widely used method for *in vivo* quantification of white-matter microstructures at high spatial resolution and is commonly analyzed using an approach referred to as diffusion tensor imaging (DTI; Basser, 1995; Soares et al., 2013). During dMRI, the MR signal is sensitized to the diffusion of water molecules in multiple directions. Due to the presence of physical boundaries such as those imposed by cell membranes or myelin in the axon sheath, diffusion within organized white matter is orientation-dependent, or anisotropic (DaSilva et al., 2003; Hagmann et al., 2006). By contrast, when unrestricted, diffusion of water molecules will be random and non-directional, or isotropic (Hagmann et al., 2006). Using the resultant data, it is possible to quantify diffusion within a given voxel in the brain, and this has been used to infer white-matter microstructural characteristics (Basser, 1995; Basser and Pierpaoli, 1996); for reviews see (Sullivan et al., 2010; Jones et al., 2013; Soares et al., 2013). One of the most widely used methods for quantifying diffusion within a given voxel is DTI.

Using DTI, it is possible to calculate a number of scalar indices. The most widely used index is fractional anisotropy (FA), a scalar measure ranging between 0 (isotropic diffusion) and 1 (anisotropic diffusion), based on the ratio of parallel to perpendicular diffusion within a given voxel (Pierpaoli and Basser, 1996). Another frequently used index is mean diffusivity (MD) which corresponds to the overall magnitude of diffusion, irrespective of direction; reviewed in (Sullivan et al., 2010). Broadly speaking, FA increases and MD decreases during typical development, although these changes are increasingly recognized to be both non-linear and tract-specific and vary across individuals (e.g., Barnea-Goraly et al., 2005; Lebel et al., 2008; Hasan et al., 2009; Lebel and Beaulieu, 2011; Lebel et al., 2012). While individual variability in FA values within the genu during adolescence has been associated with measures of impulsivity and risk-taking, the direction of these associations has not always been consistent across studies (e.g., Berns et al., 2009; Olson et al., 2009). Thus, further research is needed to determine the specific behavioral significance of altered white matter development in relation to substance-use behaviors amongst adolescents.

DTI studies have demonstrated alterations in white-matter tissue structures (including regions of the corpus callosum and cingulum) among adult smokers (Paul et al., 2008; Hudkins et al., 2012; Lin et al., 2012; Savjani et al., 2014; Umene-Nakano et al., 2014). Increases in FA within the genu of the corpus callosum have also been reported following acute nicotine administration in human adults (Kochunov et al., 2013). While several recent studies indicate white-matter alterations among adolescent and young adult tobacco-users, the relationship between tobacco smoking and neural development during adolescence and young adulthood is not yet well understood.

To synthesize existing findings related to tobacco smoking and white-matter development during adolescence and young adulthood, and to identify directions for further research, we here systematically review findings from published DTI studies conducted in adolescents and young adults. We aimed to identify areas requiring further study to guide future research endeavors in this

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