Despite considerable progress in reducing overall rates of tobacco use during the past few decades, we are currently experiencing dramatic increases in the rates of pediatric and adolescent consumption of nicotine-containing products. These highly concerning trends correspond to the rising popularity of vaping and electronic cigarette (e-cigarette) technologies, a phenomenon that represents a new smoking epidemic among young people. Indeed, despite some jurisdictional attempts to limit youth access to these products, many of these nicotine-delivery devices are now marketed specifically to young people, with the growing popularity of flavored e-cigarette and vaping offerings combined with youth-oriented marketing campaigns. In addition to these market factors, the increasing prevalence of mood and anxiety disorders related to the ongoing impacts of the COVID-19 pandemic has led to a corresponding increase in vaping and e-cigarette consumption, particularly among young people.

Neurodevelopment during the prepubescent and adolescent years involves intricate synaptic pruning and neural reorganization mechanisms concomitant with the maturation of complex neural circuits, cortical and subcortical connectivity patterning, and fine-tuning of critical neural networks essential for healthy cognitive function and emotional regulation. These temporally orchestrated neurodevelopmental events take place in the context of increased risk-taking behaviors and the greater likelihood of drug experimentation, typical of childhood and adolescence. This confluence of neurodevelopmental and behavioral dispositions renders the developing brain exquisitely sensitive to extrinsic chemical insults, particularly in the form of dependence-producing drugs, including nicotine, the primary psychoactive compound in tobacco products. Indeed, the brain’s cholinergic system, which is critically involved in many neurotrophic processes during normal brain maturation, is particularly vulnerable during these neurodevelopmental windows and is the primary target of nicotine. Nicotine acts directly on nicotinic acetylcholine receptors found ubiquitously in the brain, including cortical and subcortical circuits essential for normal cognitive and emotional regulation. Extrinsic nicotine exposure may therefore disrupt acetylcholine’s temporal regulation of various trophic cellular events required for healthy brain development. However, beyond the cholinergic system, neurodevelopmental nicotine exposure has been shown to act as a potent neurotoxin affecting various neural systems. For example, in preclinical animal models, adolescent nicotine exposure has been reported to cause long-term dysregulation of cortical and subcortical affective and cognitive neural networks involving dopamine and glutamate signaling, as well as disruption of molecular signaling pathways associated with cognitive disturbances and mood and anxiety disorders.

Dai and colleagues present compelling and novel clinical data demonstrating some significant and deleterious associations of childhood smoking behaviors and nicotine exposure with neurodevelopmental trajectories and cognitive performance measures. Using an integrative combination of cognitive testing measures, morphometric assays, and structural magnetic resonance imaging, the authors found that exposure to e-cigarettes and/or other tobacco products among a cohort of children aged 9 to 10 years selected from a socioeconomically and ethnographically diverse sample from the US displayed significant and enduring cognitive impairments. Using a battery of cognitive assays, the authors reported significant performance deficits in children exposed to...
nicotine products, including measures of oral reading recognition, pattern comparison processing speed, and picture vocabulary tests.

In terms of neuropathological outcomes, using structural magnetic resonance imaging and morphometric analyses, Dai and colleagues found that several whole-brain measures were significantly lower among participants exposed to tobacco during childhood, including reductions in total cortical area and volume along with significant reductions in cerebral white matter volume. In addition, the authors found additional structural associations, including lower cortical surface areas in the superior frontal, medial orbitofrontal, paracentral, inferior parietal, middle temporal, superior temporal sulcus, and several other neural regions. These neural regions are well-defined for their critical roles in cognition, emotional regulation, and affective processing. Importantly, many of these observed neuropathological outcomes were present 2 years after the initial analyses were performed, suggesting potential long-term associations with even limited childhood nicotine exposures. Such findings are consistent with those of preclinical studies showing that even limited exposure to nicotine during periods of adolescent brain development can lead to long-term deficits in cognition and dysregulation of frontal cortical function.

The risks of childhood nicotine exposure for long-term cognitive outcomes extend beyond self-administration. Indeed, previous evidence has shown that exposure to parental smoking is similarly associated with poorer cognitive outcomes in later life. For example, Rovio et al reported that childhood exposure to parental second-hand smoke was associated with significantly increased risk for deficits in midlife episodic memory function and associative learning, along with impairments in short-term and spatial working memory. In addition, a growing body of research using both clinical and translational animal models are reporting that prenatal nicotine exposure may similarly lead to long-term neuropsychiatric disorders in offspring. Finally, it is well-established that nicotine dependence is highly comorbid with a wide range of neuropsychiatric disorders, including mood and anxiety disorders, schizophrenia, and other substance use disorders such as alcohol and cannabis use, although the mechanistic associations between these comorbidities are poorly understood. Together, this emerging evidence from both preclinical and clinical studies underscores the neurotoxic effects of nicotine exposure during sensitive periods of brain development and highlights the ability of nicotine to pathologically interfere with a host of neurochemical, morphological, and molecular pathways critical to healthy cognitive outcomes and long-term mental health.

The findings reported by Dai and colleagues raise many important questions for future clinical and preclinical investigations. Notably, it will be important to determine how persistent these pathophysiological outcomes remain beyond the windows of prepubertal and adolescent brain maturation. In addition, it will be critical to identify the specific molecular mechanisms and biomarkers underlying these enduring, tobacco-induced pathophysiological outcomes. Characterizing these underlying mechanisms can potentially lead to the identification of more effective intervention and/or reversal strategies for ameliorating neuropsychiatric phenotypes caused by pediatric, adolescent, and perhaps even prenatal nicotine exposure. In addition, advances in genomic and transcriptomic assays may provide improved understanding of the underlying genetic factors that may predispose individuals to a greater risk of accessing nicotine products during critical periods of brain development and of the factors that may render certain individuals at increased risk of severe neuropathological and neurocognitive outcomes after exposure to nicotine during the developmental windows. Finally, given that the observed structural abnormalities reported in this study are critical biomarkers for a host of neuropsychiatric disorders, including schizophrenia, mood and anxiety disorders, and drug dependence, it will be critical to determine precisely how these nicotine-related neurodevelopmental perturbations might increase risk for future neuropsychiatric disorders and/or psychiatric comorbidities with nicotine dependence.
ARTICLE INFORMATION
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