

## TOBACCO AND PREGNANCY

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# Association Between Prenatal Exposure to Maternal Cigarette Smoking and the Brain and Behaviour of Adolescent Offspring

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August 2023, Éd. rév.

### Introduction

Approximately 10-15% of mothers smoke during pregnancy in Canada and the United States.<sup>1,2</sup> Given the high prevalence of maternal cigarette smoking, our group has initiated one of the largest studies to date evaluating the effects of developmental exposure to cigarettes on adolescent offspring brain and behaviour.<sup>3</sup> This review discusses a subset of the findings of our study and provides preclinical evidence for the hypothesized cause-and-effect relationships reported.

### Subject

Maternal cigarette smoking can have significant impacts on the offspring. During the period of pregnancy or shortly after birth, reported consequences include smaller birth weight, sudden infant death syndrome and *placenta previa*.<sup>4-6</sup> In late childhood and early adolescence, subjects exposed to maternal cigarette smoking have higher incidents of attention deficit hyperactivity disorder,<sup>7</sup> substance use,<sup>8</sup> and intra-abdominal<sup>9</sup> and overall obesity.<sup>4,10</sup> In the current review, we focus on whether in utero exposure to cigarettes increases substance use behaviour in an adolescent population (12-18 years of age), and describe whether selective brain regions and/or genetic underpinnings could act as mediating factors influencing these associations.

## Problems

In human studies, the causal relationship between maternal cigarette smoking and brain and behaviour is difficult to determine. Confounding factors include parental education, family income, stressful life events, peer influence and genetic predispositions, to name a few. Research using animal models, which does not have the same limitations, has assisted in elucidating the causality vis-à-vis these relationships as well as the mechanisms underlying the early and late-onset deficits seen in the human population.<sup>11-13</sup> In particular, animal models have demonstrated that developmental exposure to nicotine, believed to be the major psychoactive constituent in tobacco smoke, mediates many of the same associations seen in humans, including modifications in the reinforcing properties of nicotine<sup>14</sup> and cocaine,<sup>15</sup> as well as increased locomotor hyperactivity and changes in *cholinergic* and *catecholaminergic* neurotransmitter systems.<sup>11,12,16</sup> These results have provided supportive evidence that gestational nicotine exposure can be harmful to the developing fetus.<sup>11,12</sup>

## Research Context

Based on clinical and preclinical evidence, we have set out to evaluate the consequences of maternal cigarette smoking in the adolescent brain and behaviour. The study encapsulates a population of nearly 800 adolescents (12-18 years of age), with a projected total population of 1,000 participants, half of whom have been exposed to maternal cigarette smoking; exposed adolescents were matched to the non-exposed by maternal education and the school attended.<sup>3</sup>

## Key Research Question

Does prenatal exposure to maternal cigarette smoking influence adolescent brain and behaviour associations through underlying genetic factors, particularly associated with cognition and

substance use?

## Recent Research Results

Our study on the effects of maternal cigarette smoking on the brain and behaviour of adolescent offspring was first published in 2007.<sup>3</sup> We demonstrated that in utero cigarette exposure influenced the cortical thickness of adolescent offspring,<sup>17</sup> a finding also observed in animal models evaluating the consequences of gestational nicotine exposure.<sup>18</sup> In our human adolescent population, the region of the brain most influenced was the orbitofrontal cortex (OFC), a structure that regulates emotion and reward processing.<sup>8</sup> Given the importance of emotional regulation and reward processing in the adolescent brain, our subsequent studies tested whether modifications in this region of the brain could influence substance-use behaviour.<sup>8</sup> Our results illustrated that the thinning of the OFC significantly correlated with lifetime history of experimenting (at least once) with cigarettes, alcohol and other illicit substances in exposed adolescents, while a thicker OFC is associated with greater lifetime history of such experimentation in non-exposed adolescents, suggesting an experience-induced plasticity. For exposed adolescents, we hypothesized that prenatal cigarette smoking induced an insult in the OFC, thus leading to thinning in the structure and thereby predisposing adolescents to substance-use behaviour. These findings are in line with preclinical studies that demonstrate gestational nicotine influences substance use behaviour<sup>14,15</sup> and cortical thinning.<sup>18</sup> For non-exposed adolescents, we hypothesized that experience-induced plasticity may influence the structure of the OFC through drug-taking behaviour. We provided evidence for this hypothesis by demonstrating that a *single nucleotide polymorphism* in the brain-derived neurotrophic factor (BDNF) gene, an important regulator of brain plasticity, could modify the OFC thickness based on lifetime history of drug experimentation in the non-exposed population.<sup>8</sup> In the exposed adolescents, BDNF polymorphisms had no effect on brain structure, which suggested that the BDNF gene has an absent function in this population. In support of this speculation, we demonstrated that maternal cigarette smoking increased *epigenetic* modifications of the BDNF gene, namely enhanced methylation of *cytosine-guanosine* repeats found in the DNA of the blood of the exposed adolescents.<sup>19</sup> These findings are consistent with data from an earlier study demonstrating that maternal cigarette smoking is associated with global increases in DNA methylation in exposed subjects.<sup>20</sup> Such mechanisms have been shown to influence BDNF expression,<sup>21</sup> thereby having potentially critical consequences on the structure of the brain.<sup>22,23</sup> Taken together, the results suggest that the OFC is susceptible to modifications by maternal cigarette smoking and is associated with changes in substance use behaviour; significant effects

which are modified by the BDNF genotype.

Our most recent studies have started to evaluate sub-cortical effects induced by maternal cigarette smoking. We have been particularly interested in *striatal regions* of the brain, which receive rich *dopamine* projections that are quite likely important for mediating reward and addiction.<sup>24</sup> It is well known that nicotine, binding to nicotinic receptors, can induce dopamine release in striatal regions, a hallmark of drug reward.<sup>25</sup> Prenatal exposure to nicotine can reduce dopamine levels in striatal regions<sup>16</sup> and nicotine-induced dopamine release.<sup>26</sup> In humans, reductions in dopamine levels in striatal regions have been proposed to result in a larger striatal size.<sup>27</sup> In animal models, an attenuated dopaminergic system could influence reward-related behaviour, including increased cocaine self-administration observed at higher doses<sup>15</sup> and nicotine self-administration after withdrawal.<sup>14</sup> Such effects may be due to an overcompensation<sup>26</sup> and mediated through a nicotinic-receptor system.<sup>11,12,24</sup> We tested this hypothesis using a polymorphism in the alpha6 nicotinic receptor subunit, recently shown to be critical in the modulation of (i) nicotine-induced dopamine release in the *striatum*<sup>28,29</sup> and (ii) quit attempts in smokers.<sup>30</sup> Our results demonstrated that increased substance-use behaviour and larger striatal size was only present in a subset of adolescents who were exposed to maternal cigarette smoking and had a particular version of the alpha6 gene.<sup>24</sup> Overall, the findings demonstrate long-term consequences of maternal cigarette smoking on a reward-related brain region and substance-use behaviour, with the variant of a nicotinic-receptor gene playing a significant role.

The above effects are present despite the fact that maternal cigarette smoking does not influence how our adolescent population performs on cognitive tasks.<sup>31</sup> Accessing 33 different measures of cognitive function, related to verbal, visual-spatial memory, processing speed, resistance to interference and motor dexterity, no differences were observed between adolescence that were exposed versus those non-exposed to maternal cigarette smoking. These findings suggest that maternal cigarette smoking is associated with selective brain-behaviour modifications in adolescent populations, particularly related to reward-seeking behaviour, but not with global cognitive modifications. It is also possible that subtle cognitive “deficits” are present at an early stage<sup>32</sup> but may diminish through subsequent (beneficial) effects of education.

## Research Gaps

1. Which nicotinic receptor subunits are critical for mediating the consequences of prenatal cigarette exposure?

2. Which stages during pregnancy (or post pregnancy) are most critical for the consequences of maternal cigarette smoking?
3. Do similar effects occur through second hand-smoke exposure or through nicotine replacement therapies?
4. What strategies can be used to prevent emergence of delayed consequences of maternal smoking during pregnancy on the offspring behaviour?

## **Conclusions**

Our findings demonstrate that prenatal exposure to maternal cigarette smoking can have long-lasting consequences on the brain and behaviour of adolescent offspring. While our results do not suggest cognitive differences between the exposed and non-exposed offspring, significant associations are observed for reward related behaviour. Genetic factors appear to be critical players in mediating this behavioural phenotype and its underlying neural mechanisms. In particular, striatal and frontal cortical regions are sensitive to the influences of maternal cigarette smoking. Furthermore, maternal cigarette smoking has significant associations with modifications in the methylation of genes important for brain development, such as BDNF. These findings need to be taken in parallel with animal models that demonstrates prenatal nicotine exposure can have developmental consequences on the brain and behaviour of offspring, also with important changes on BDNF expression in the brain.<sup>33</sup>

## **Implications for Parents, Services and Policy**

The implications of our findings are important to pregnant mothers who smoke or live in an environment where they are continuously exposed to cigarette smoke. On the positive side, not all children of women who smoked during pregnancy differ from those who were not exposed; thus, robust mechanisms must exist that protect the fetus from this adverse intra-uterine environment. On the other hand, data from both clinical and preclinical studies suggest that maternal cigarette smoking could have long-lasting consequences on the brain and behaviour of offspring. Impacts that may influence critical genes involved in brain development and brain structures related to reward related behaviour. Renewed services need to be provided for women who smoke and are planning on becoming pregnant. Further research is needed in order to determine the best smoking cessation therapies for pregnant mothers who are smoking. Given the preclinical evidence, further consideration is needed as to whether nicotine replacement therapies are the

best smoking cessation medication available. Policies need to be developed to promote smoke-free mothers and further assist in reducing second hand cigarette smoke exposure in work and home environments.

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