Impact of Prenatal and Adolescent Exposure to Tobacco Smoke on Memory and Attention


Yale University School of Medicine
Haskins Laboratories
Gestational Exposure to Maternal Smoking

Elevates risk in offspring for:

- Cognitive deficits
- Deficits in auditory processing
- Tobacco smoking and nicotine dependence
  - Relationships remain significant after controlling for confounds
  - Risk is greater with increasing magnitude of exposure
Preclinical Studies of Developmental Exposure to Nicotine

**Prenatal exposure:** 6 mg/kg/day nicotine, GD 4-21.

**Adolescent exposure:** 6 mg/kg/day nicotine, PND 30-47.

Effects of gestational exposure to tobacco smoke are mediated by disruptive effects of nicotine on brain development.

Period of vulnerability to disruptive effects of nicotine extends into adolescence.
Disruptive effects of prenatal and adolescent exposure to nicotine are additive:

- greater alterations in neural cell number, size
- blunted upregulation of nAChRs in response to nicotine
- cholinergic hypoactivity during nicotine withdrawal
Assessment of Behavioral Effects

Test effect of nicotine withdrawal on verbal and visuospatial memory in N=61 adolescent daily tobacco smokers with and without prenatal exposure to maternal smoking.

Prenatal exposure assessed by parent interview:

- Tobacco/ETOH/drug use during gestation
- Family history of Tobacco/ETOH/drug use
### Demographic Characteristics of Adolescent Smokers with and without Gestational Exposure

<table>
<thead>
<tr>
<th></th>
<th>Exposed (N=35)</th>
<th>Not Exposed (N=26)</th>
<th>t / (X^2)</th>
<th>p</th>
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<tbody>
<tr>
<td>Age (years) [range]</td>
<td>16.9 (1.3)</td>
<td>16.9 (0.8)</td>
<td>0.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Education (years)</td>
<td>10.0 (1.3)</td>
<td>10.2 (0.9)</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>IQ (KBIT)</td>
<td>95.4 (8.3)</td>
<td>96.0 (7.1)</td>
<td>0.3</td>
<td>0.7</td>
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<tr>
<td>Reading Achievement (WJR)</td>
<td>99.4 (14.9)</td>
<td>103.6 (13.4)</td>
<td>1.2</td>
<td>0.2</td>
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<tr>
<td>Alcohol Consumption</td>
<td>3.8 (8.0)</td>
<td>1.3 (2.4)</td>
<td>1.5</td>
<td>0.1</td>
</tr>
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</table>
# Demographic Characteristics of Adolescent Smokers with and without Gestational Exposure

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<th>Not Exposed (N=26)</th>
<th>t / X²</th>
<th>p</th>
</tr>
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<tr>
<td>Life Events</td>
<td>9.8 (4.6)</td>
<td>8.1 (4.2)</td>
<td>1.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Connors</td>
<td>16.5 (9.6)</td>
<td>16.6 (9.4)</td>
<td>0.04</td>
<td>1.0</td>
</tr>
<tr>
<td>MASC</td>
<td>33.4 (13.6)</td>
<td>33.7 (10.0)</td>
<td>0.1</td>
<td>0.9</td>
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<tr>
<td>Beck Depression Score</td>
<td>5.2 (5.1)</td>
<td>5.4 (4.5)</td>
<td>0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Rate of Tobacco Smoking (cigs/d)</td>
<td>13.6 (17.1)</td>
<td>9.2 (4.9)</td>
<td>2.7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>FTND</td>
<td>3.9 (2.2)</td>
<td>2.2 (1.9)</td>
<td>3.2</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
All subjects tested twice

► during ad libitum smoking,
► after 24 hours of abstinence from smoking.

Assessment of Visuospatial and Verbal Memory

► Brief Visuospatial Memory Test
► Hopkins Verbal Memory Test

- Learn 12 figures or 12 words
- Immediate recall
- Delayed recall (20 min)
Estimated Plasma Nicotine Concentrations at Assessment

Effect of Smoking Condition: \( \beta = 58.8, t = 4.2, p = 0.0001 \)
Expired Air CO at Assessment

Effect of Smoking Condition:
\[ \beta = 17.3, \ t = 11.5, \ p < 0.0001 \]
Impact of Smoking Abstinence on Visuospatial Immediate Recall

Group x Smoking Condition: \( \beta=3.0, t=2.3, p=0.02 \)

- Prenatally Exposed, \( N=35 \)
- No Prenatal Exposure, \( N=26 \)
Impact of Smoking Abstinence on Visuospatial Delayed Recall

Group x Smoking Condition: $\beta=1.1$, $t=2.2$, $p=0.03$
Assessment of Neurocircuitry Supporting Visuospatial Encoding and Retrieval

7 subjects with and 6 subjects without gestational exposure to maternal smoking.

Scanned at 3 T
Axial acquisition (FA 80, TE 30, TR 2, 5mm)

Mixed event-related/block design

Each imaging run = 2 verbal & 2 nonverbal cycles
Nonverbal Cycle

(rest)

(encode)

(rehearse)

(forced choice recognition)
Assessment of Nonverbal Encoding & Retrieval
Scan Session Structure

6 encoding & immediate recall runs → Sagittal MPRAGE → 2 delayed recall runs

Average duration between end of tested immediate recall runs & start of delayed recall runs was 22 minutes.

voxel p=0.001, cluster threshold=8
Immediate Recognition Memory
Delayed Recognition Memory
Comment

► In rats, prenatal + adolescent nicotine exposure –
  - blunts ability of nicotine to upregulate nAChR.
  - nicotine withdrawal induced cholinergic hypoactivty.

► In humans, reduction of cholinergic neurotransmission –
  - disrupts memory, particularly encoding
  - reduces efficiency of brain regions supporting non-sensory processing during cognitive tasks.
Comment

- Nicotine withdrawal induced memory deficits observed in gestationally exposed adolescents:
  - reductions in cholinergic neurotransmission.

- Nicotine withdrawal related increases in hippocampal activation during recognition memory testing:
  - reduced efficiency of neurocircuits supporting memory.
Comment

- Increased risk of progression to regular tobacco smoking in gestationally exposed offspring:
  - self-medication of brain functional deficits stemming from cholinergic hypoactivity.

- Improved memory performance and more efficient hippocampal processing observed in adolescents with no gestational exposure:
  - normal upregulation of nAChRs in response to nicotine.
Preclinical Studies of Developmental Exposure to Nicotine

**Prenatal exposure:** 6 mg/kg/day nicotine, GD 4-21.

**Adolescent exposure:** 6 mg/kg/day nicotine, PND 30-47.
Normal attentional performance requires intact cortical cholinergic neurotransmission (Sarter et al, 2005).

Cortical cholinergic deafferentation –
- impairs responding to signal trials
- intact responding to nonsignal trials

► impairs signal detection, leaving primary sensory representation intact.
Assessment of Behavioral Effects

Test for effects of prenatal and adolescent exposure to tobacco smoke, and for modifying effects of gender, on auditory and visual attention in N=181 adolescents.

Prenatal exposure assessed by parent interview:

- Tobacco/ETOH/drug use during gestation
- Family history of Tobacco/ETOH/drug use

Subjects tested during ad libitum smoking.
## Demographic Characteristics: Behavioral Sample

<table>
<thead>
<tr>
<th></th>
<th>Exposed Smokers (N=67)</th>
<th>Non-Exposed Smokers (N=44)</th>
<th>Exposed Nonsmokers (N=25)</th>
<th>Non-Exposed Nonsmokers (N=45)</th>
</tr>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>16.6 (1.3)</td>
<td>16.9 (0.9)</td>
<td>16.2 (1.2)</td>
<td>16.6 (1.4)</td>
</tr>
<tr>
<td><strong>Gender (F/M)</strong></td>
<td>52 / 15</td>
<td>24 / 20</td>
<td>15 / 10</td>
<td>22 / 23</td>
</tr>
<tr>
<td><strong>Education (years)</strong></td>
<td>9.7 (1.3)</td>
<td>10.2 (1.0)</td>
<td>9.6 (1.3)</td>
<td>10.0 (1.4)</td>
</tr>
<tr>
<td><strong>Parent Ed. (years)</strong></td>
<td>14.4 (3.7)</td>
<td>14.5 (2.8)</td>
<td>13.7 (2.0)</td>
<td>15.2 (2.4)</td>
</tr>
<tr>
<td><strong>Conners</strong></td>
<td>19.5 (12.3)</td>
<td>17.2 (9.4)</td>
<td>15.4 (10.6)</td>
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<td>96.2 (9.1)</td>
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<td>105.8 (9.4)</td>
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Assessment of Auditory and Visual Selective Attention

Computerized word recognition task

2 levels of attention load: simple, select
2 Modalities

**Dependent Measure:** speed/accuracy linguistic judgement

Subjects cued to modality **before** stimulus presentation
**Auditory Simple Condition**

- Ear icon
- 500 msec
- 500 msec
- “farm”
- 500 msec

**Visual Simple Condition**

- Eye icon
- 500 msec
- 500 msec
- Beel
- 500 msec
Auditory Select Condition

Visual Select Condition
Data Analysis

Linear Mixed Effects Regression:
- Simple/Select attention RT & accuracy
- Fixed Effects: modality, attention load

Analyses controlled for:
- IQ, reading achievement, Beck scores, alcohol use, cannabis use, gestational exp. to environmental tobacco smoke, maternal alcohol use.
Plasma Cotinine at Assessment

Estimated Plasma Cotinine Concentration (ng/ml)
Plasma Nicotine at Assessment

Estimated Plasma Nicotine Concentration (ng/ml)

- Exposed Smokers
- Non-Exposed Smokers

Female
Male
Symptoms of Nicotine Withdrawal

Exposed Smokers
Non-Exposed Smokers

Minnesota Nicotine Withdrawal Scale Score

Females
Males
Birth Weight

Effect of Prenatal Exposure:
\( \beta = -7.5, \ t = -2.4, \ p < 0.05 \)
Main Effect of Modality:
$\beta = 234$, $t = 6.8$, $p < 0.0001$
Main Effect of Modality: 
$\beta = -0.05, t = -2.2, p < 0.05$
Simple/Selective Attention

Adolescent Smoking x Prenatal Exp. x Modality:
\[ \beta = -0.1, \quad t = -1.98, \quad p < 0.05 \]

- Exposed Smokers
- Non-Exposed Smokers
- Exposed Nonsmokers
- Non-Exposed Nonsmokers

Performance Accuracy (Proportion Correct)
Simple/Selective Attention

Adolescent Smoking x Prenatal Exposure x Gender x Modality:
$\beta = 0.12$, $t=2.35$, $p<0.02$

![Graph showing performance accuracy (proportion correct) for different groups: Exposed Smokers, Non-Exposed Smokers, Exposed Nonsmokers, and Non-Exposed Nonsmokers. The graph differentiates between visual (V) and auditory (A) modalities for females and males.]

V=visual modality
A=auditory modality
Comment

- Reduced cholinergic neurotransmission impairs signal detection while leaving sensory perception intact.

- Dose dependent impairment in visual and auditory attention in females is consistent with rodent data showing dose dependent reduction in cholinergic markers in females.

- Effects of exposure in females do not appear to be modality specific.
Pattern observed in males may reflect greater vulnerability of auditory than visual neurocircuitry to exposure related reductions in cholinergic transmission in males.

- No sex difference in cortical nAChR density in unexposed rodents. (Slotkin et al, 2007)

- Sex specific effects of developmental exposure to tobacco may stem from sex differences in downstream effects of nAChR activation or in hormonal regulation of these downstream effects.
Longitudinal studies have linked gestational exposure to tobacco to -

- Deficits in auditory processing.  
  (Fried et al, 1997; 2003; McCartney et al, 1994)

- ADHD  (Linnet et al, 2003; Romano et al 2006; Williams et al 1998)

ADHD symptoms are linearly associated with risk for smoking.  
  (Kollins et al, 2005)

Male gender is an independent risk factor for ADHD.  
  (Romano et al, 2006)
Comment

Simple/Selective Attention

Jacobsen et al, 2007

Shafritz et al, 2004
Assessing the Impact of Prenatal and Adolescent Exposure to Tobacco Smoke on Neurocircuitry Supporting Visual and Auditory Attention

N=63 scanned at 3T (Siemens Trio)

Simple/Selective attention task

  block design
  modified to include button press control

Data analyzed using voxelwise ANOVA

  Pixel threshold: $p < 0.0001$, FDR corrected
  Cluster threshold: 10 contiguous significant voxels
Main Effects of Modality

- Yellow: activated by auditory conditions
- Purple: activated by visual conditions

Z = -3

Z = +4

Z = +12

Z = 0

Z = +7

Z = +25
Modality x Prenatal x Adolescent Exposure Effects
Prenatal x Adolescent Exposure Effects on Neurocircuitry Supporting Auditory Attention

- Exposed Smokers
- Non-Exposed Smokers
- Exposed Nonsmokers
- Non-Exposed Nonsmokers

Z = +7

Percent Signal Change, R Superior Temporal Gyrus

Auditory Attention Conditions

0.30
0.25
0.20
0.15
0.10
0.05
0.00
Prenatal x Adolescent Exposure Effects on Neurocircuitry Supporting Auditory Attention

- Exposed Smokers
- Non-Exposed Smokers
- Exposed Nonsmokers
- Non-Exposed Nonsmokers

\[ Z = +4 \]

Percent Signal Change, Left Lingual Gyrus

0.02
0.06
0.10
0.14
0.18
Imaging data showed increases in activation of regions supporting auditory processing in exposed subjects.

- Possibly reflecting reduced efficiency stemming from exposure related reduction in cholinergic neurotransmission.

- Reduced cholinergic neurotransmission reduces selectivity of perceptual processing increases activation of circuits that support higher order processing. (Furey et al, 2000)
Comment

- Consistent with preclinical evidence that neonatal nicotine exposure impairs central auditory processing. (Liang et al, 2006)

- Consistent with behavioral evidence that auditory circuits may be more vulnerable to effects of developmental exposure to nicotine than visual circuits.
# Acknowledgements

<table>
<thead>
<tr>
<th>Haskins Laboratory &amp; Pediatrics</th>
<th>Psychiatry</th>
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<tbody>
<tr>
<td>Ken Pugh, PhD</td>
<td>Kristen Tsou</td>
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<tr>
<td>Einar Mencl, PhD</td>
<td>Rita Dwan</td>
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<td>Michael Westerveld, PhD</td>
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