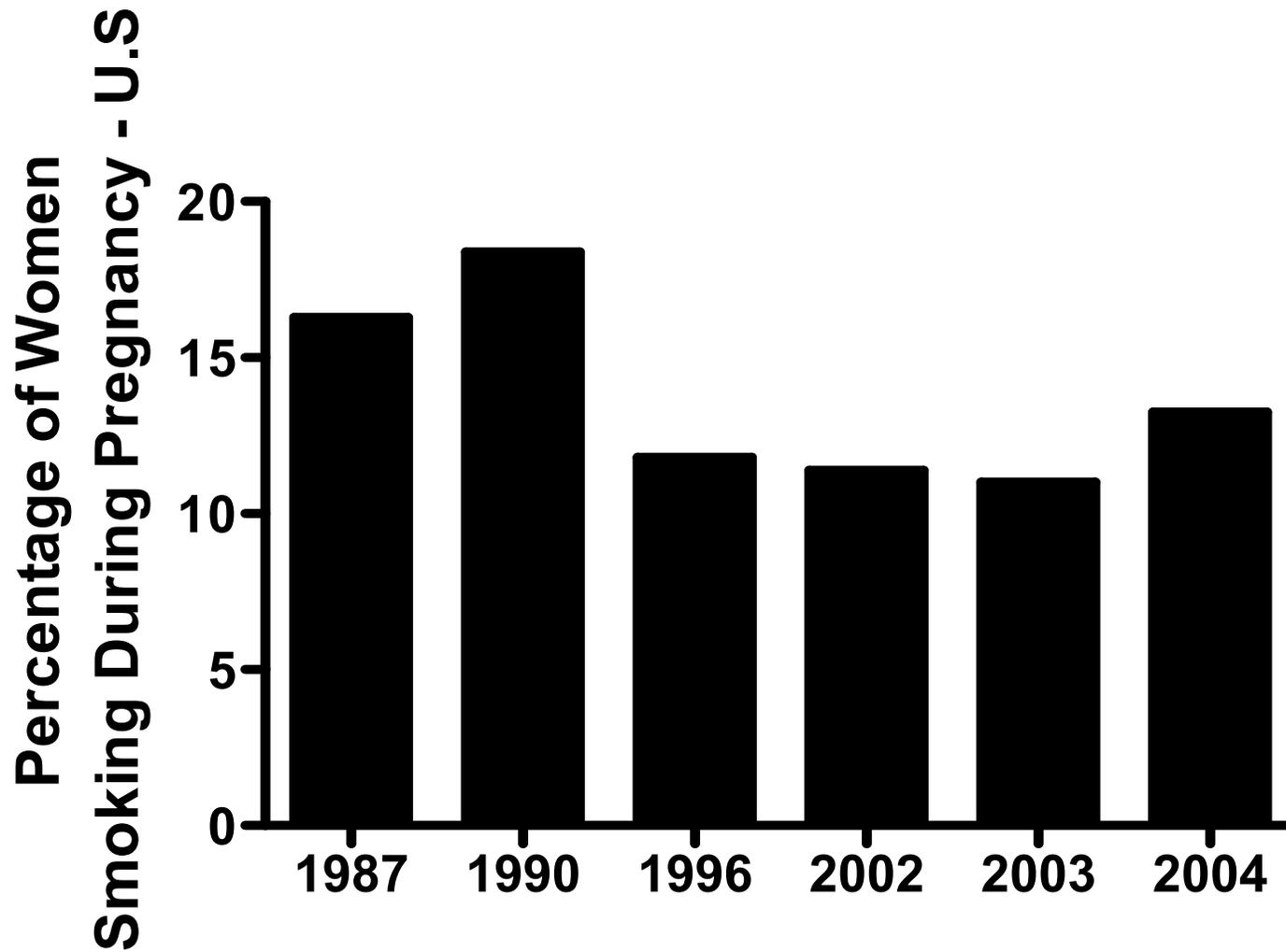


Impact of Prenatal and Adolescent Exposure to Tobacco Smoke on Memory and Attention

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Haskins Laboratories

Tobacco Smoking During Pregnancy



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.

Preclinical Studies of Developmental Exposure to Nicotine

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

Study Design

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

| | Exposed (N=35) | Not Exposed (N=26) | t / X² | p |
|--|---------------------------|-------------------------------|--------------------------|----------|
| Age (years) [range] | 16.9 (1.3) | 16.9 (0.8) | 0.1 | 0.9 |
| Education (years) | 10.0 (1.3) | 10.2 (0.9) | 0.6 | 0.6 |
| IQ (KBIT) | 95.4 (8.3) | 96.0 (7.1) | 0.3 | 0.7 |
| Reading Achievement (WJR) | 99.4 (14.9) | 103.6 (13.4) | 1.2 | 0.2 |
| Alcohol Consumption (drinks per week) | 3.8 (8.0) | 1.3 (2.4) | 1.5 | 0.1 |

Demographic Characteristics of Adolescent Smokers with and without Gestational Exposure

| | Exposed (N=35) | Not Exposed (N=26) | t / X ² | p |
|---|-------------------|-----------------------|--------------------|--------|
| Life Events | 9.8 (4.6) | 8.1 (4.2) | 1.5 | 0.1 |
| Connors | 16.5 (9.6) | 16.6 (9.4) | 0.04 | 1.0 |
| MASC | 33.4 (13.6) | 33.7 (10.0) | 0.1 | 0.9 |
| Beck Depression Score | 5.2 (5.1) | 5.4 (4.5) | 0.2 | 0.8 |
| Rate of Tobacco Smoking (cigs/d) | 13.6 (17.1) | 9.2 (4.9) | 2.7 | < 0.01 |
| FTND | 3.9 (2.2) | 2.2 (1.9) | 3.2 | < 0.01 |

Study Design

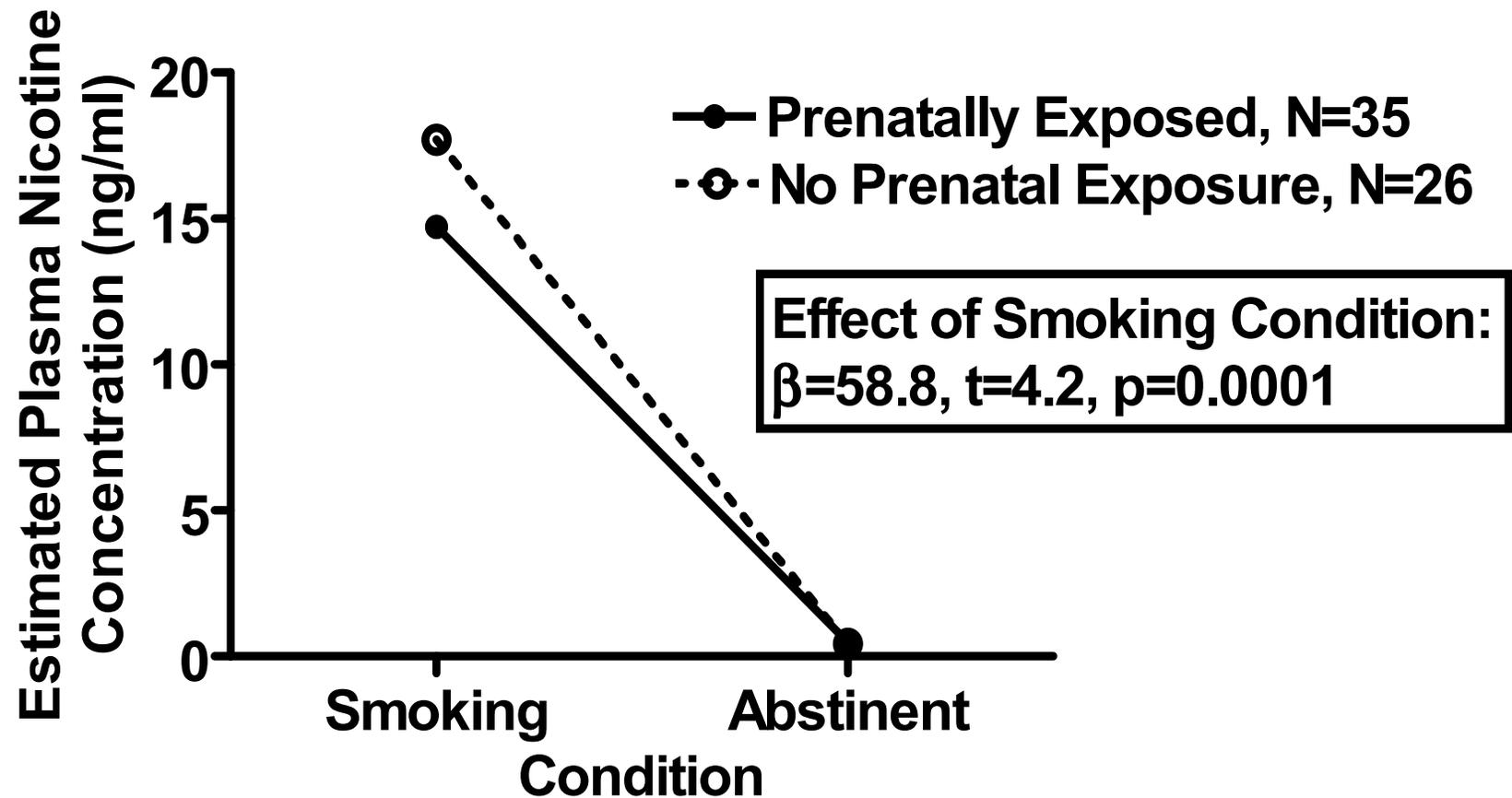
All subjects tested twice

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

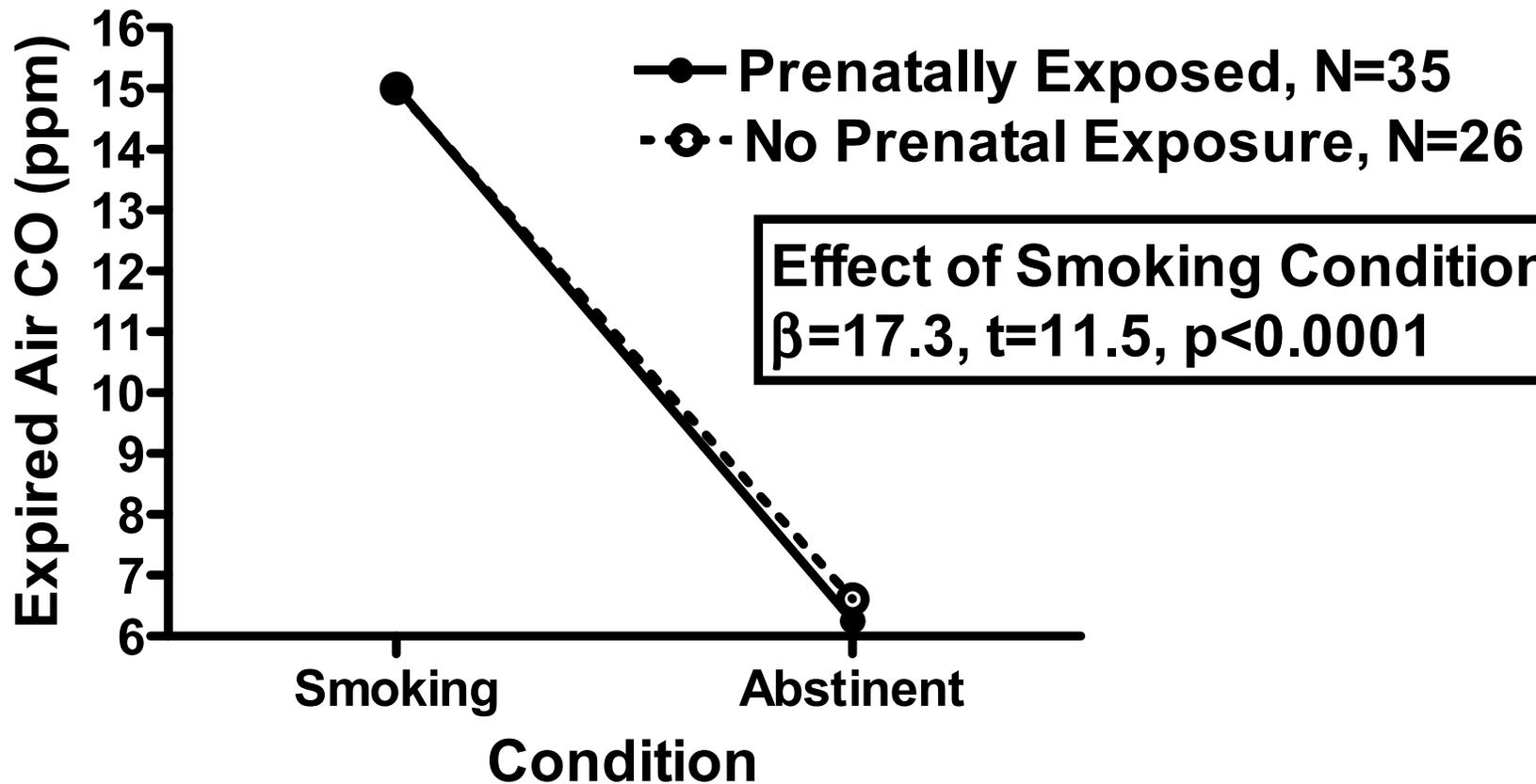
Assessment of Visuospatial and Verbal Memory

- ▶ Brief Visuospatial Memory Test
- ▶ Hopkins Verbal Memory Test
 - Learn 12 figures or 12 words
 - Immediate recall
 - Delayed recall (20 min)

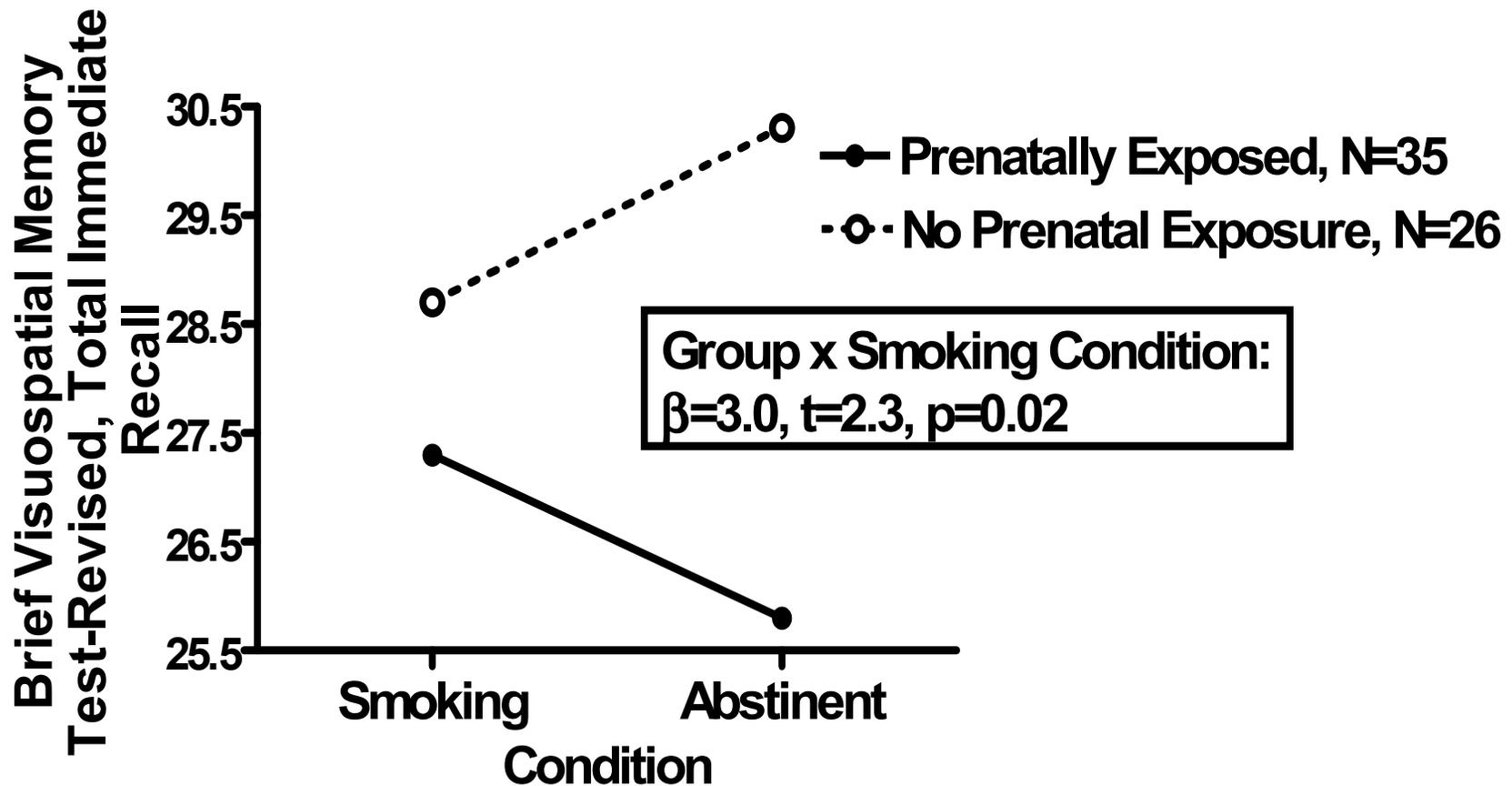
Estimated Plasma Nicotine Concentrations at Assessment



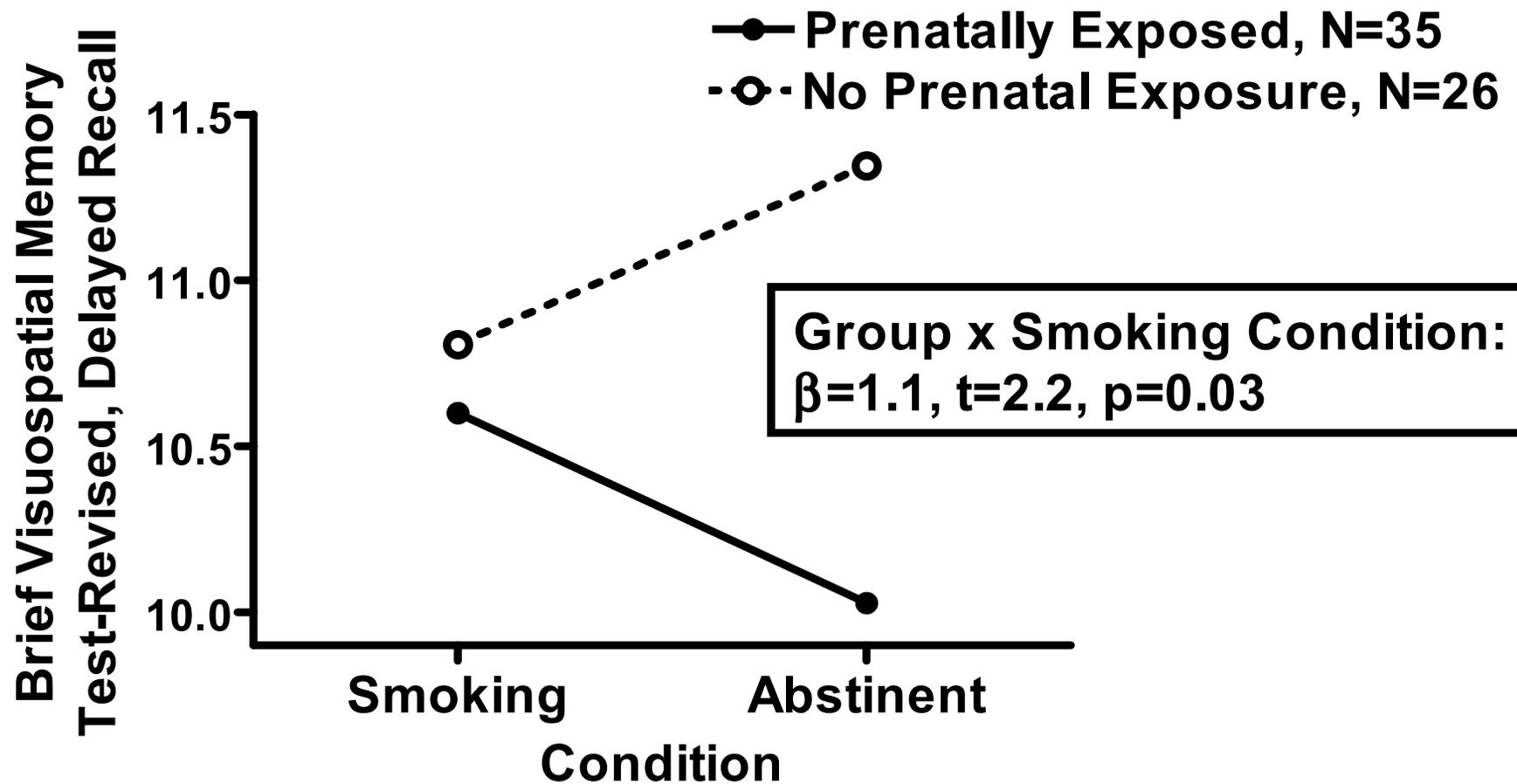
Expired Air CO at Assessment



Impact of Smoking Abstinence on Visuospatial Immediate Recall



Impact of Smoking Abstinence on Visuospatial Delayed Recall



Assessment of Neurocircuitry Supporting Visuospatial Encoding and Retrieval

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

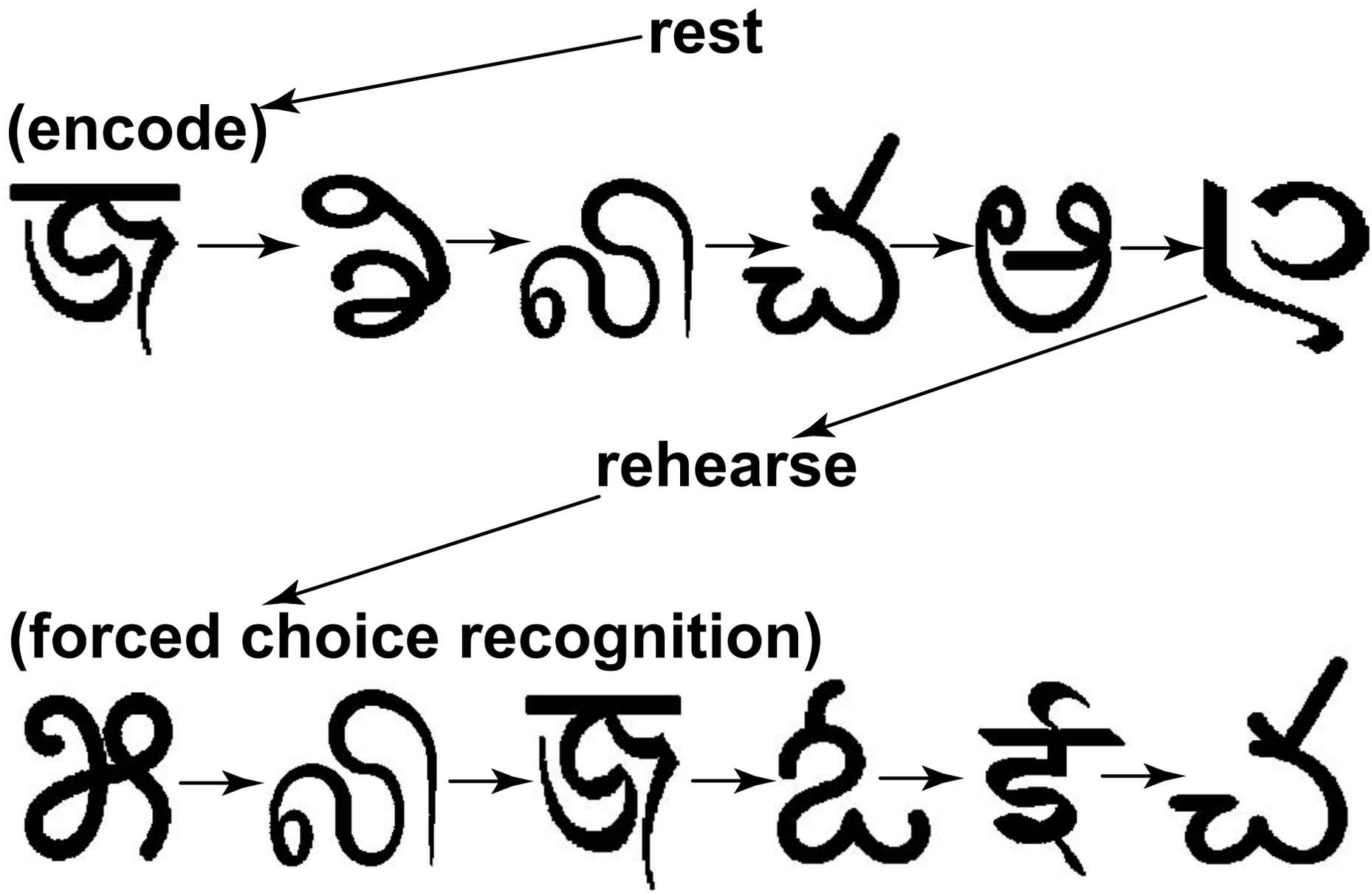
Scanned at 3 T

Axial acquisition (FA 80, TE 30, TR 2, 5mm)

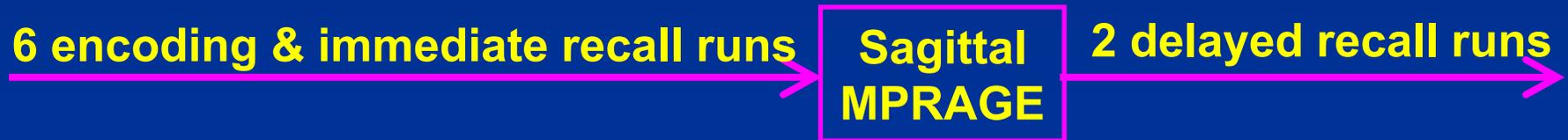
Mixed event-related/block design

Each imaging run = 2 verbal & 2 nonverbal cycles

Nonverbal Cycle



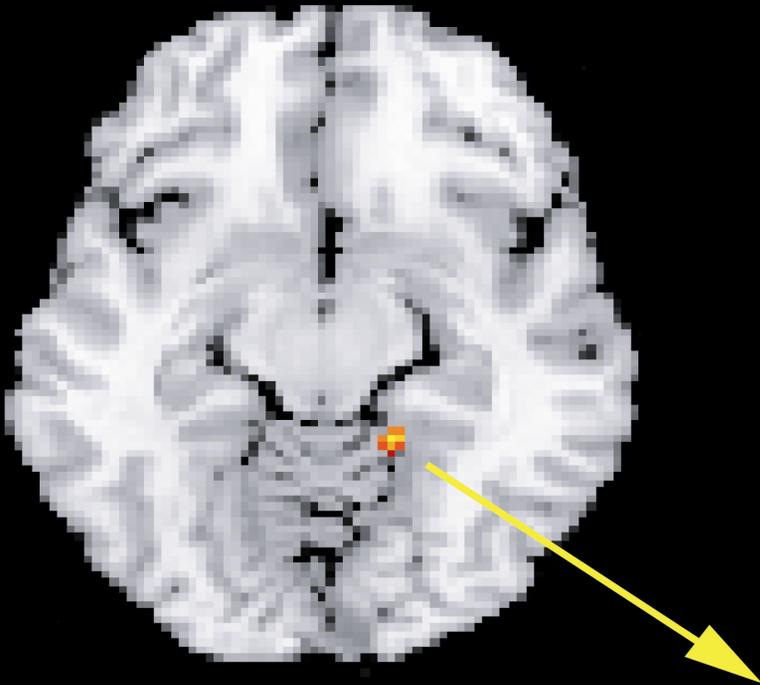
Assessment of Nonverbal Encoding & Retrieval Scan Session Structure



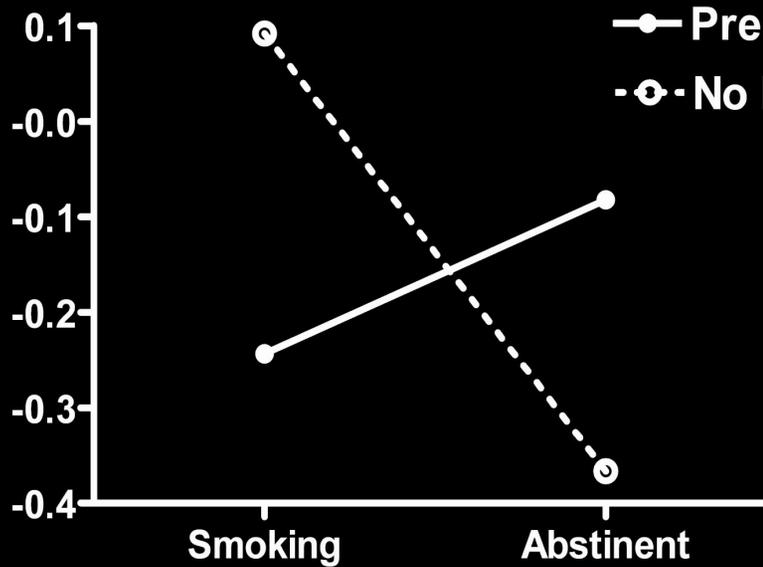
Average duration between end of tested immediate recall runs & start of delayed recall runs was 22 minutes.

voxel $p=0.001$, cluster threshold=8

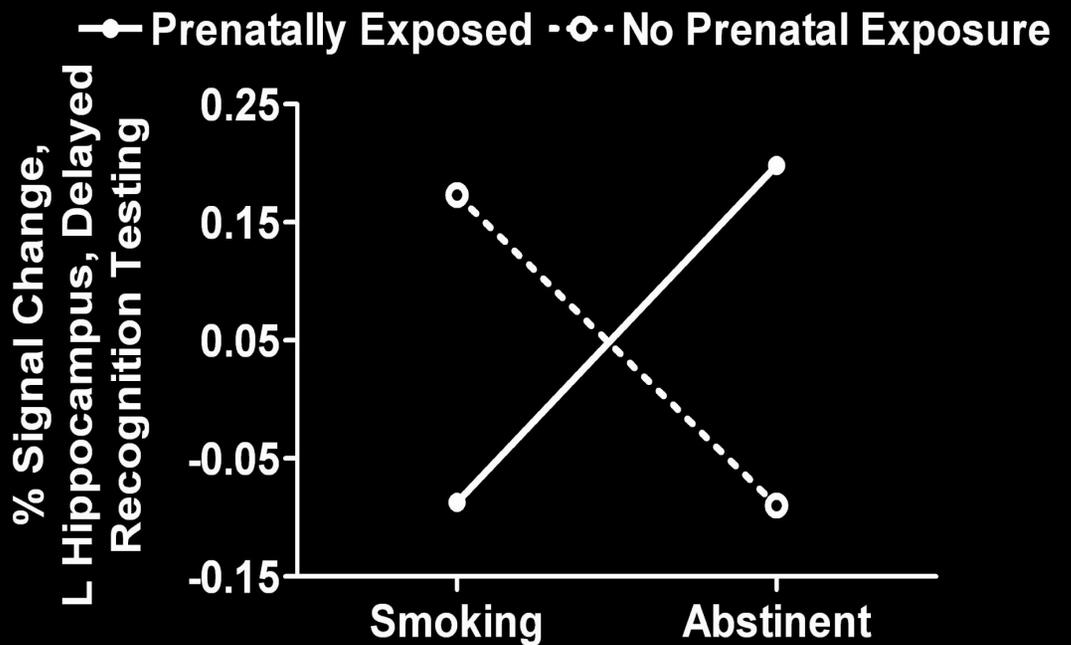
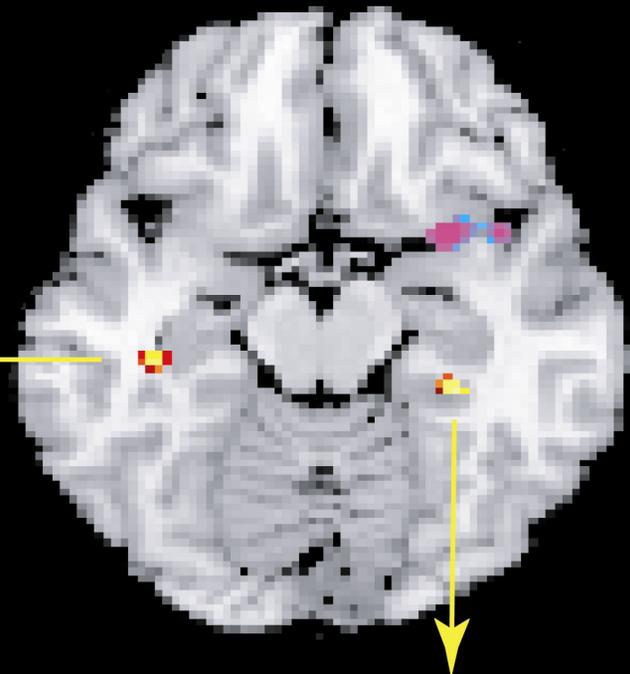
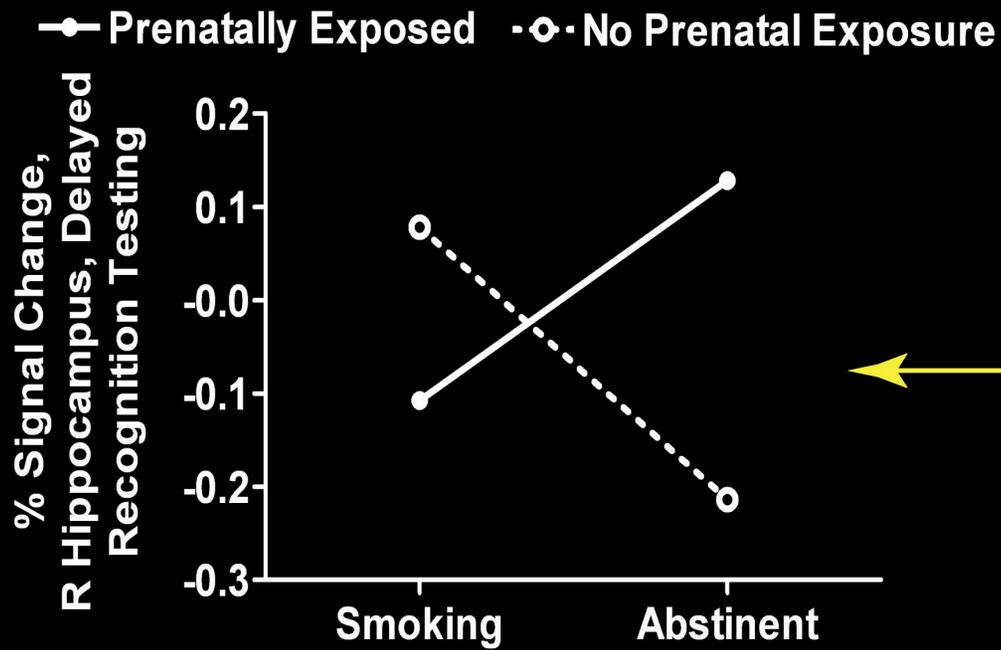
Immediate Recognition Memory



% Signal Change,
Left Parahippocampal Gyrus,
Immediate Recognition Testing



Delayed Recognition Memory



Comment

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

Attention and Cortical Cholinergic Neurotransmission

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.

Study Design

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

| | Exposed Smokers (N=67) | Non-Exposed Smokers (N=44) | Exposed Nonsmokers (N=25) | Non-Exposed Nonsmokers (N=45) |
|-----------------------|------------------------------|----------------------------------|---------------------------------|-------------------------------------|
| Age (years) | 16.6 (1.3) | 16.9 (0.9) | 16.2 (1.2) | 16.6 (1.4) |
| Gender (F/M) | 52 / 15 | 24 / 20 | 15 / 10 | 22 / 23 |
| Education (years) | 9.7 (1.3) | 10.2 (1.0) | 9.6 (1.3) | 10.0 (1.4) |
| Parent Ed. (years) | 14.4 (3.7) | 14.5 (2.8) | 13.7 (2.0) | 15.2 (2.4) |
| Conners | 19.5 (12.3) | 17.2 (9.4) | 15.4 (10.6) | 13.3 (7.3) |
| IQ (K-BIT) | 96.2 (9.1) | 98.6 (9.4) | 101.1 (9.3) | 105.8 (9.4) |

Assessment of Auditory and Visual Selective Attention

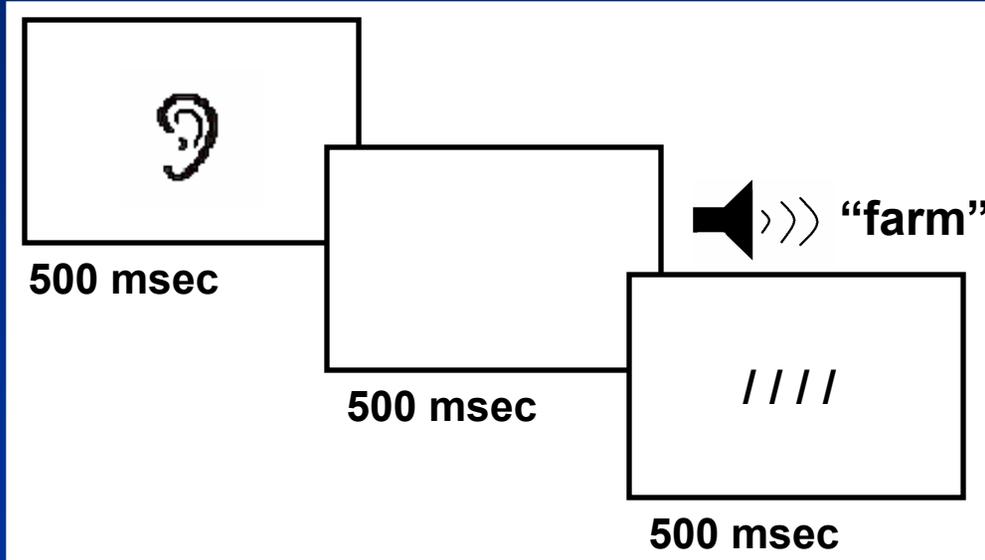
Computerized word recognition task

2 levels of attention load: simple, select
2 Modalities

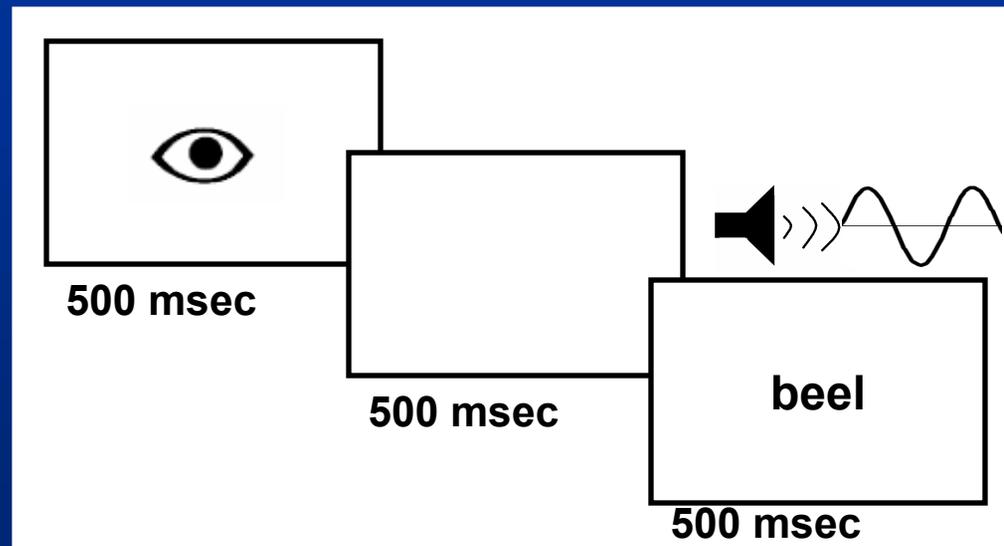
Dependent Measure: speed/accuracy linguistic judgement

Subjects cued to modality before stimulus presentation

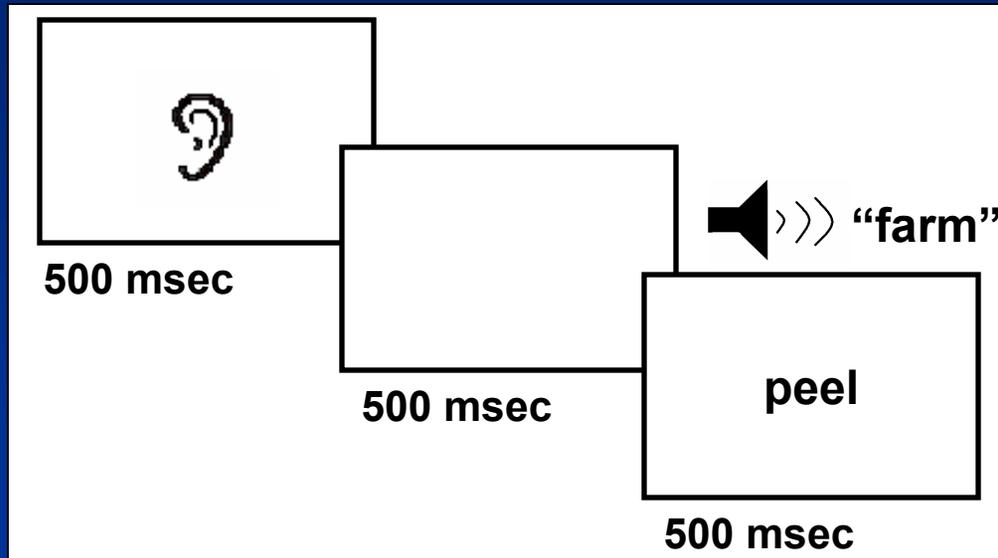
Auditory Simple Condition



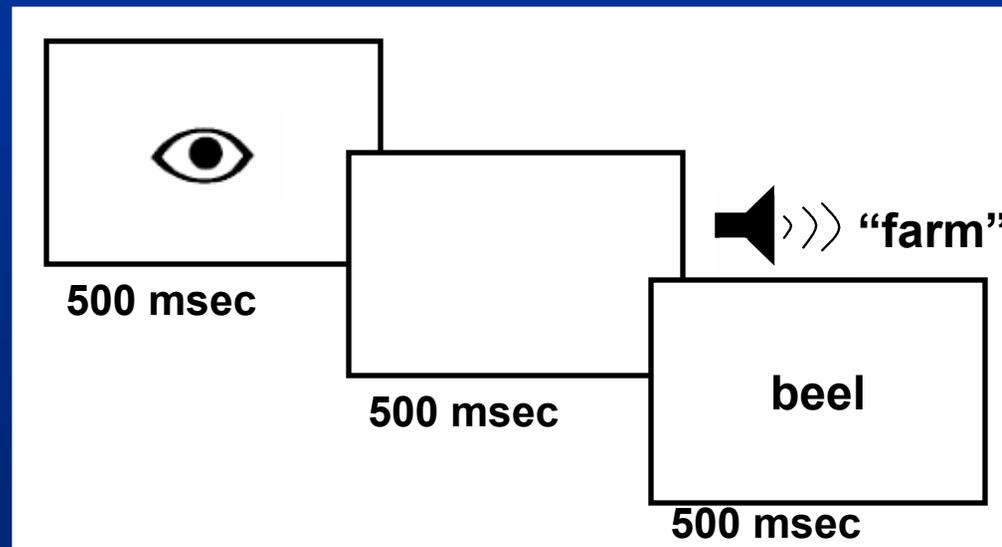
Visual Simple Condition



Auditory Select Condition



Visual Select Condition



Data Analysis

Linear Mixed Effects Regression:

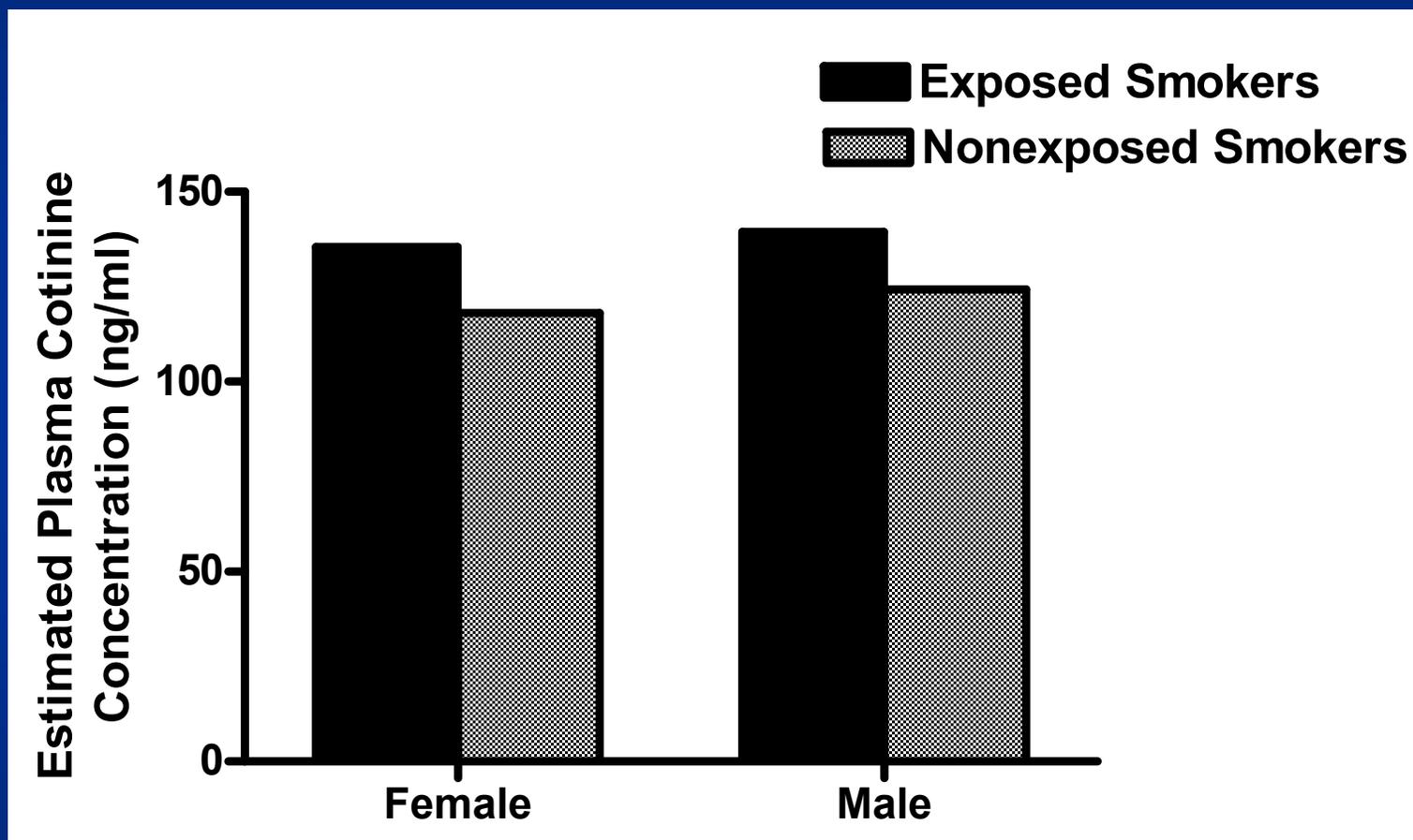
Simple/Select attention RT & accuracy

Fixed Effects: modality, attention load

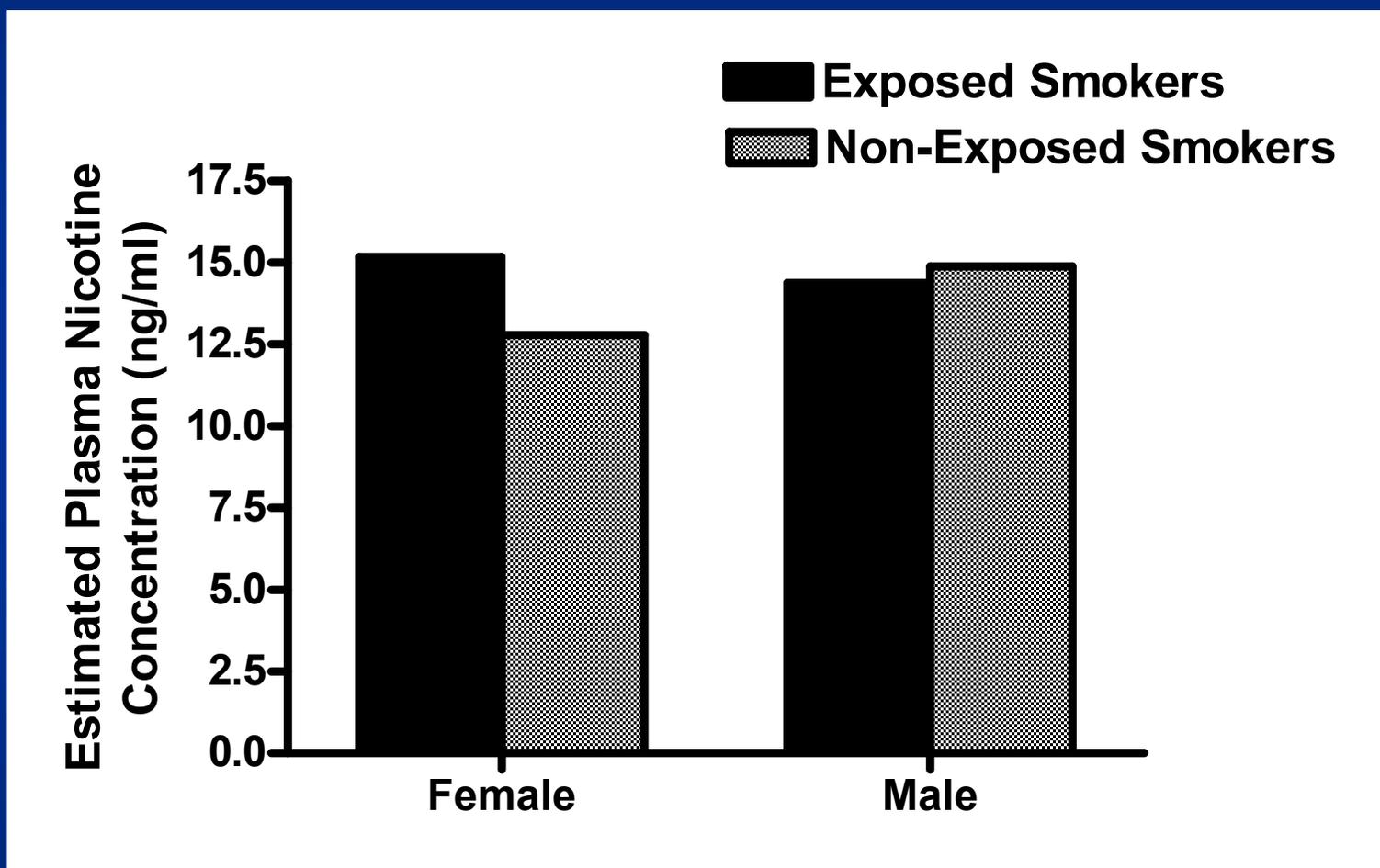
Analyses controlled for:

IQ, reading achievement, Beck scores, alcohol use, cannabis use, gestational exp. to environmental tobacco smoke, maternal alcohol use.

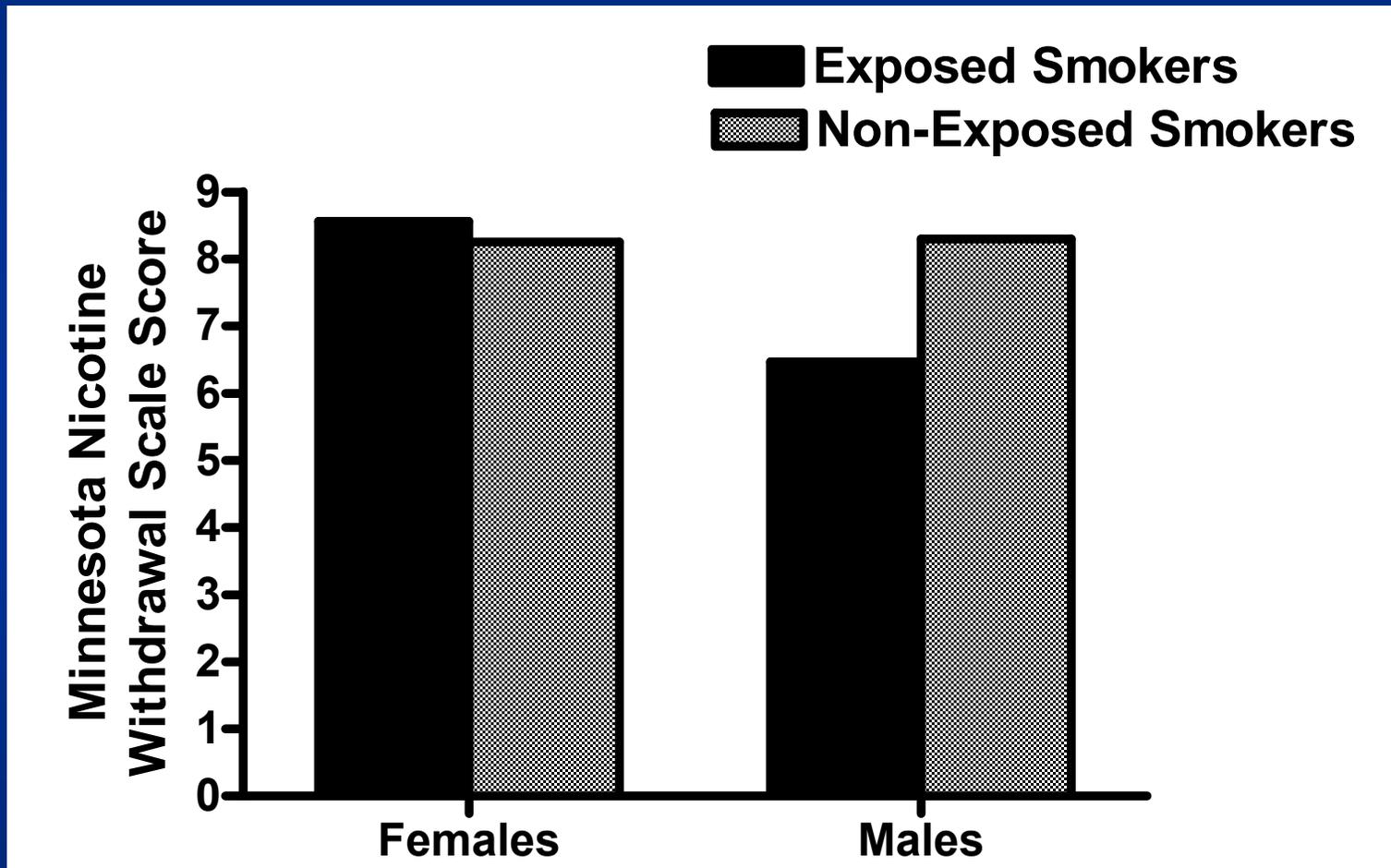
Plasma Cotinine at Assessment



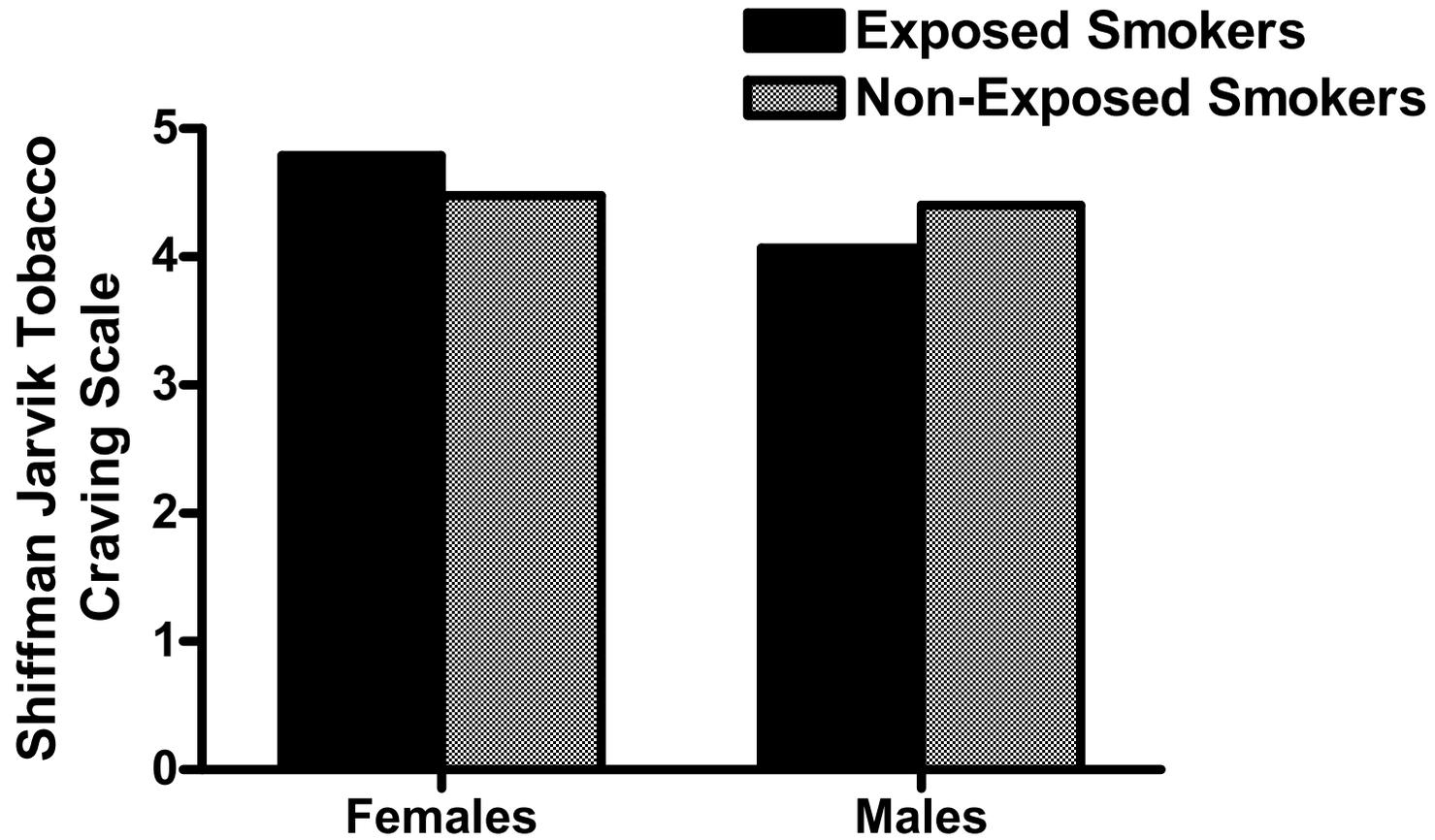
Plasma Nicotine at Assessment



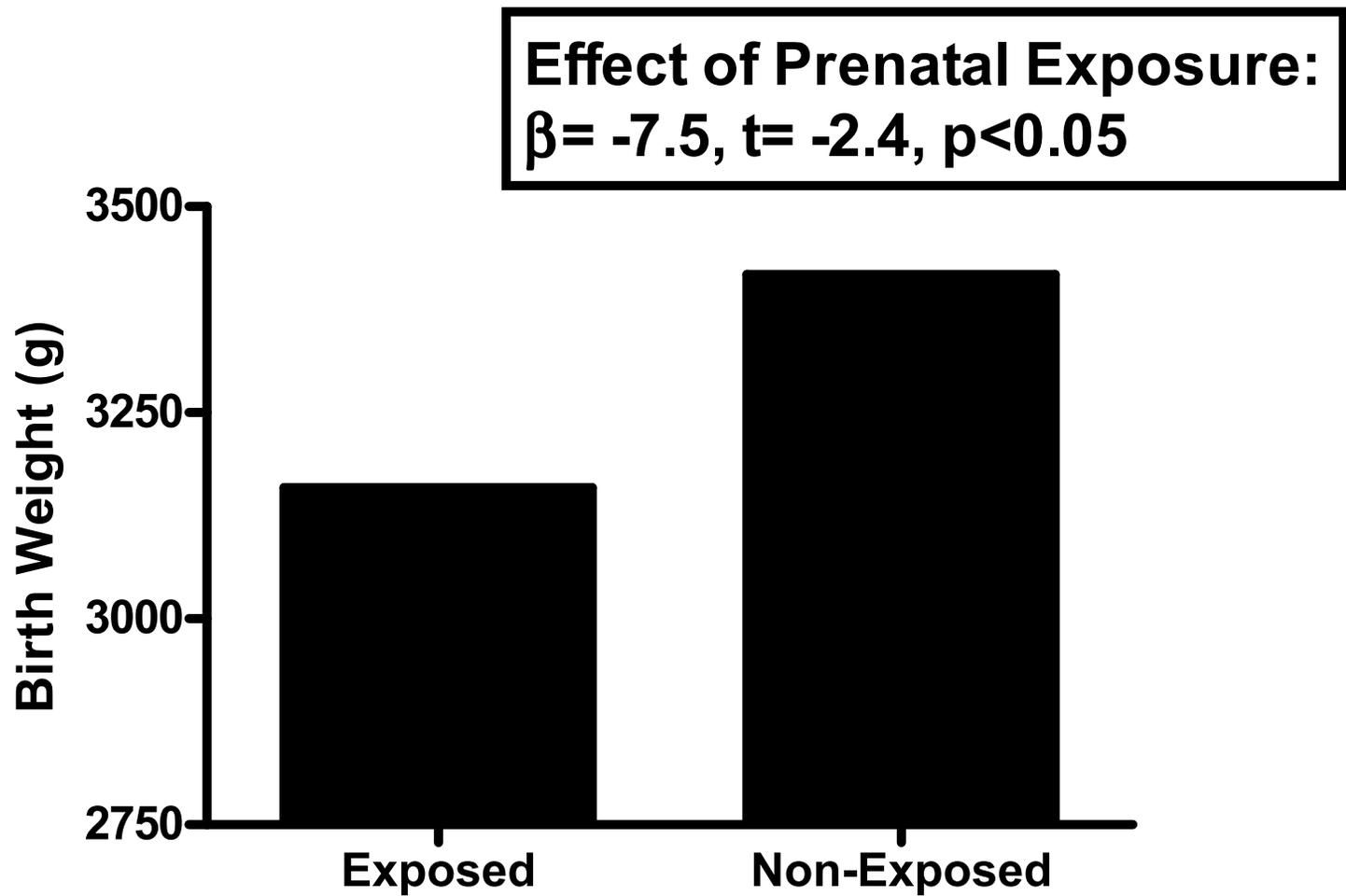
Symptoms of Nicotine Withdrawal



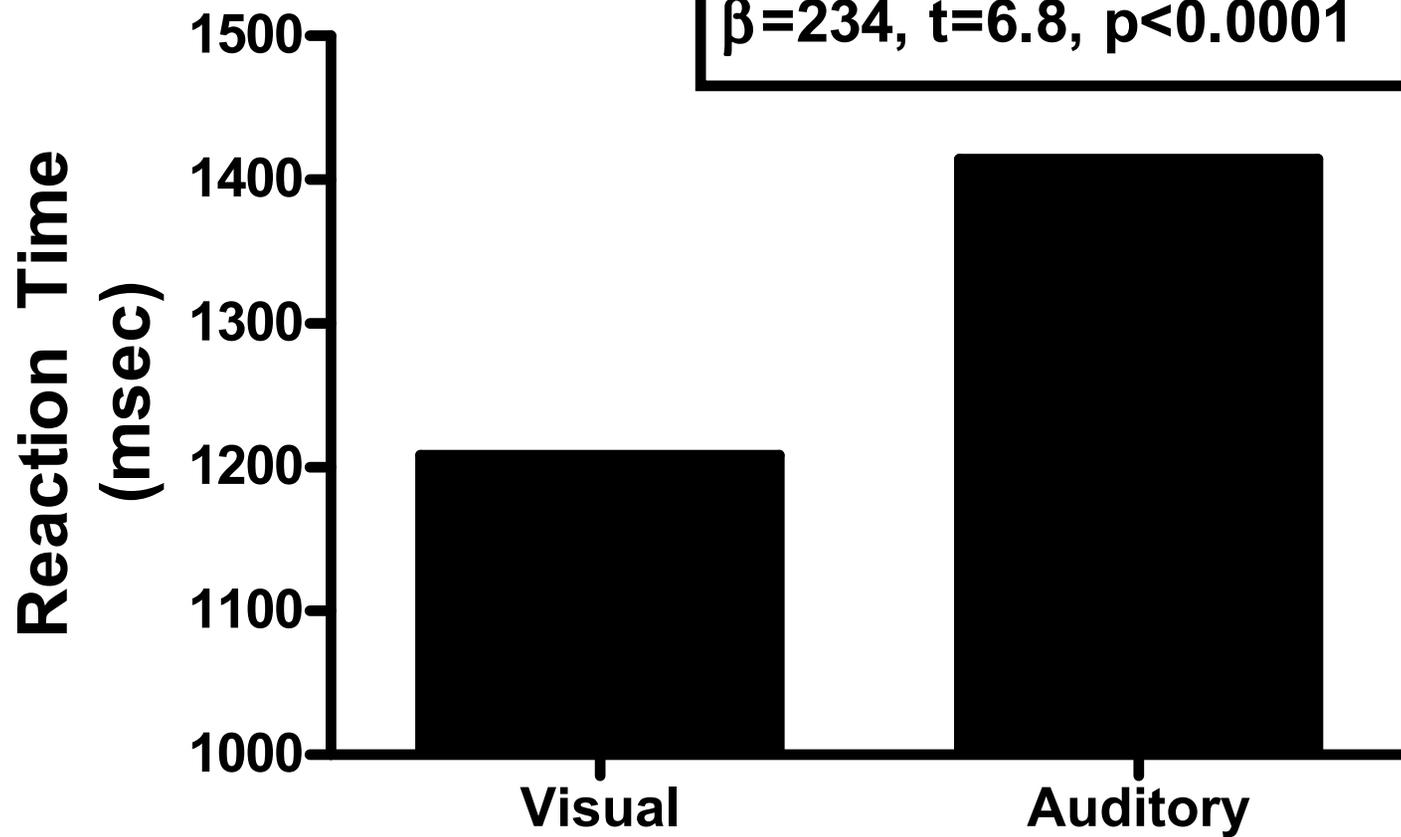
Tobacco Craving



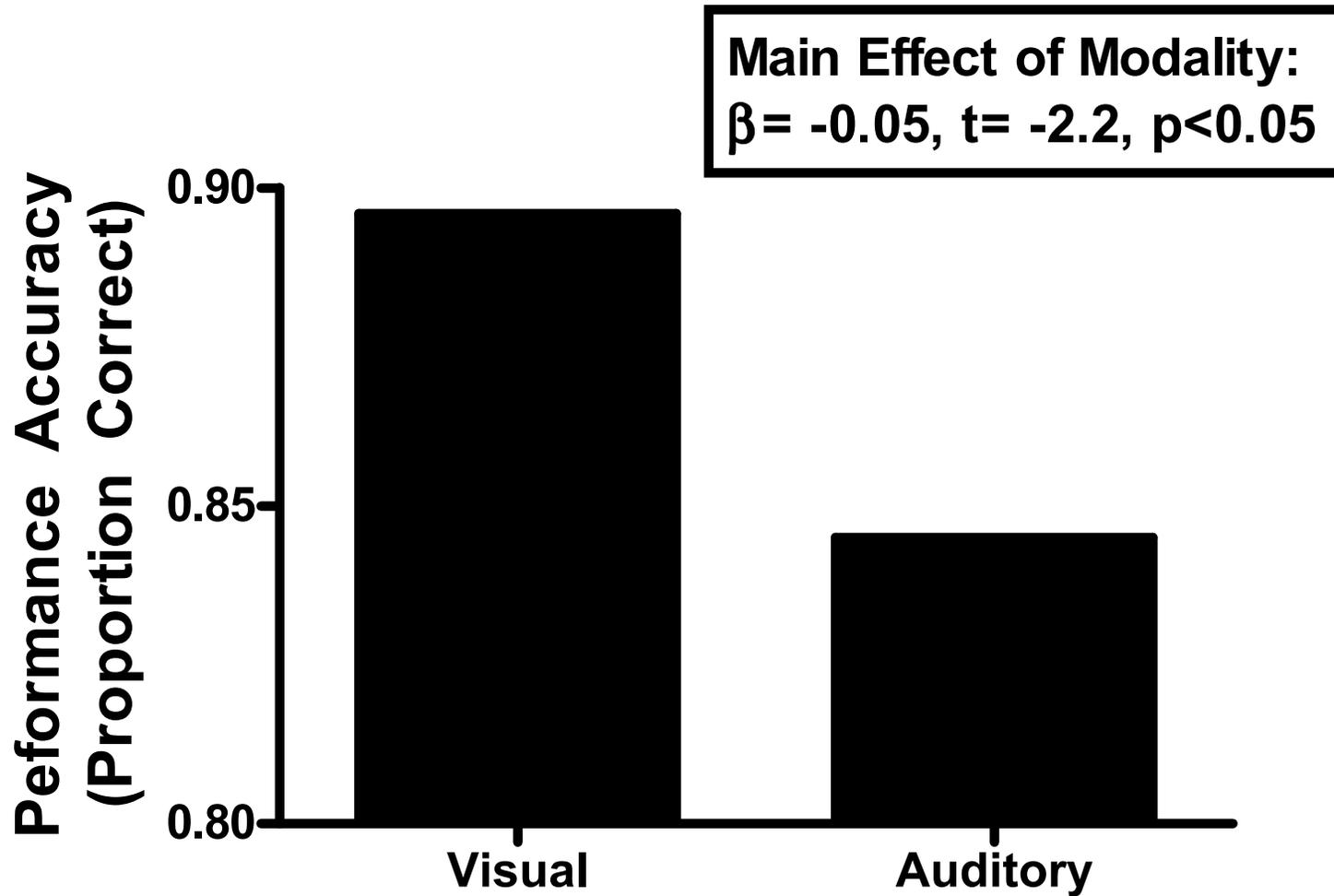
Birth Weight



Simple/Selective Attention

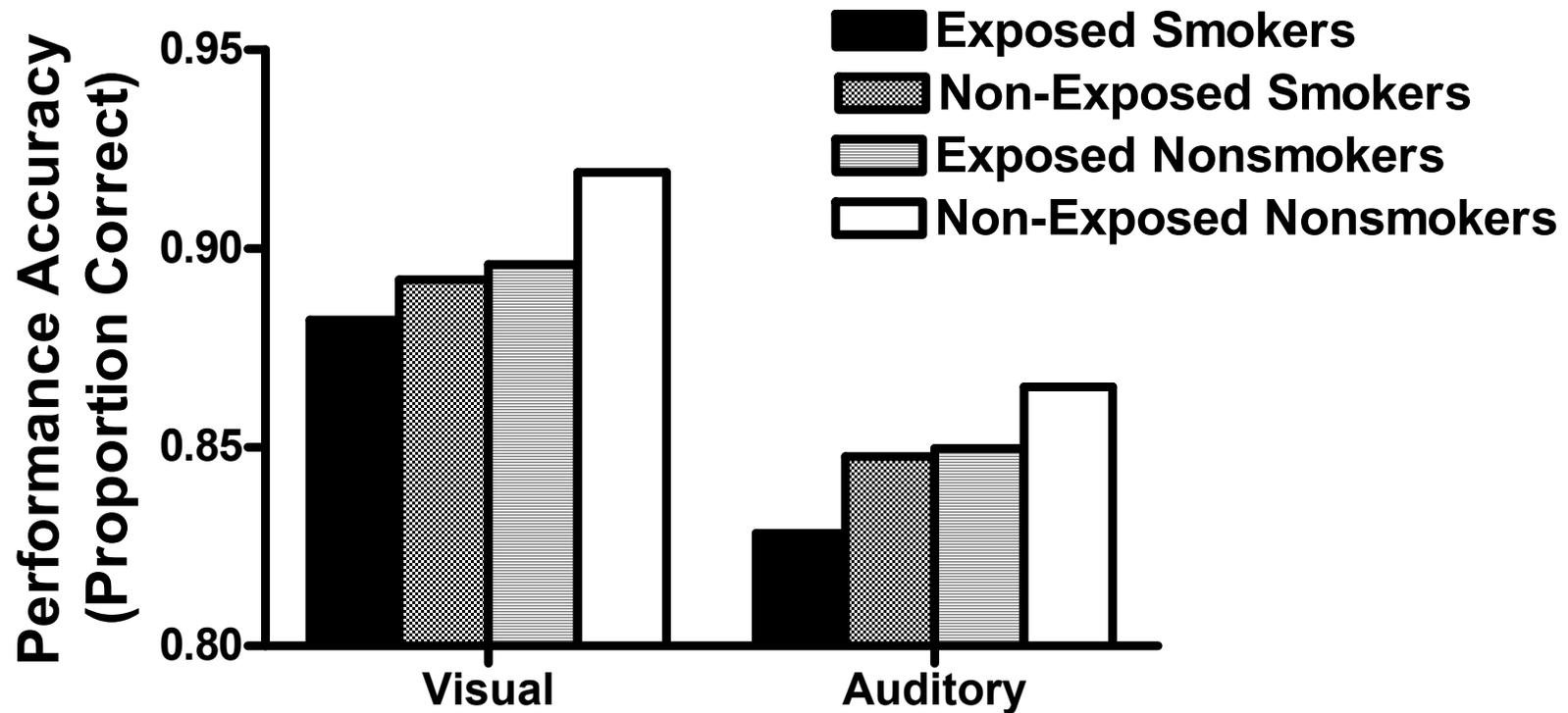


Simple/Selective Attention



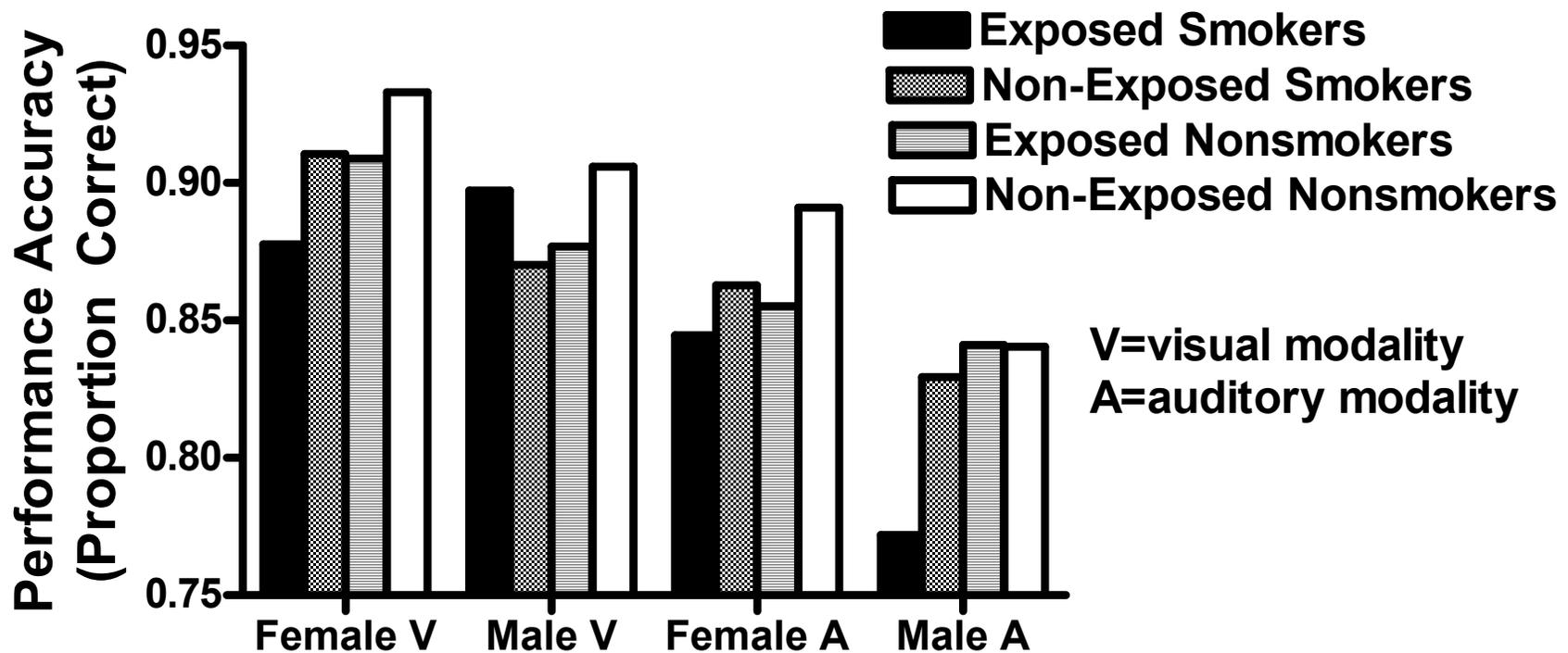
Simple/Selective Attention

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



Simple/Selective Attention

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



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.**

Comment

▶ **Pattern observed in males may reflect greater vulnerability of auditory than visual neurocircuitry to exposure related reductions in cholinergic transmission in males.**

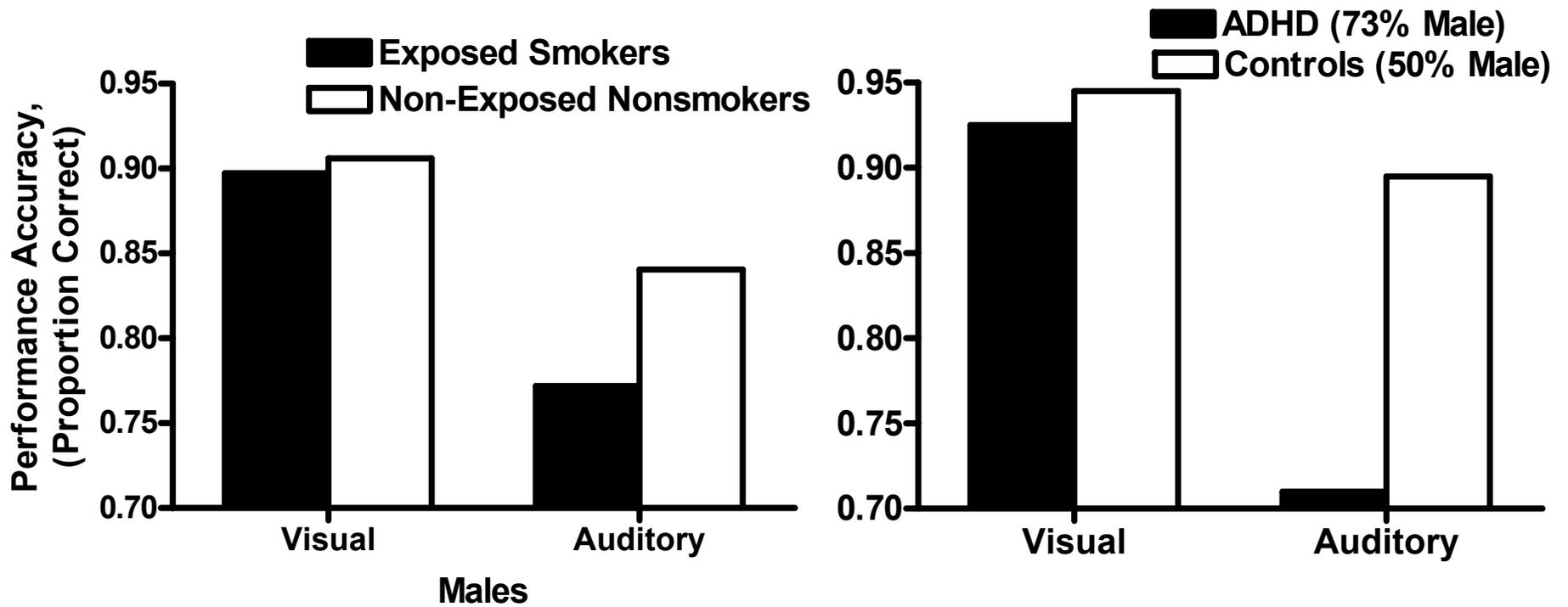
- **No sex difference in cortical nAChR density in unexposed rodents.** (Slotkin et al, 2007)
- **Sex specific effects of developmental exposure to tobacco may stem from sex differences in downstream effects of nAChR activation or in hormonal regulation of these downstream effects.**

Comment

- ▶ **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



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

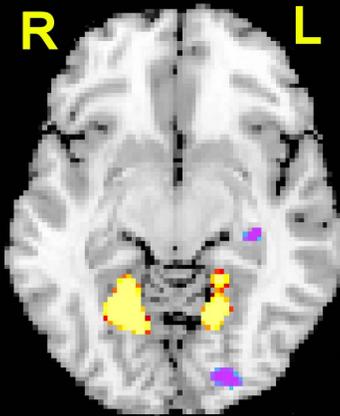
Pixel threshold: $p < 0.0001$, FDR corrected

Cluster threshold: 10 contiguous significant voxels

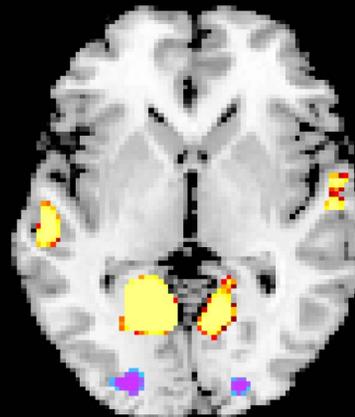
Main Effects of Modality

activated by auditory conditions

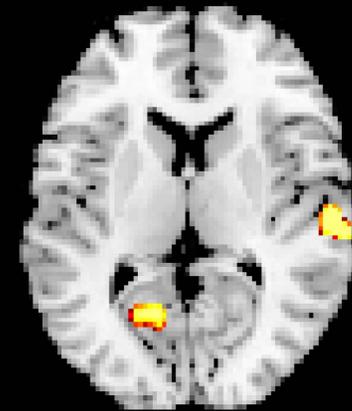
activated by visual conditions



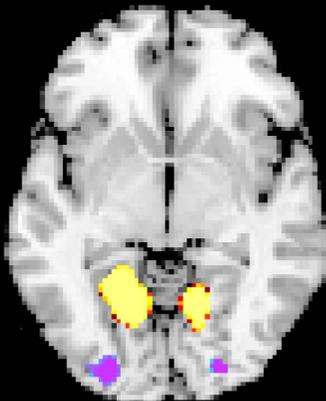
Z = -3



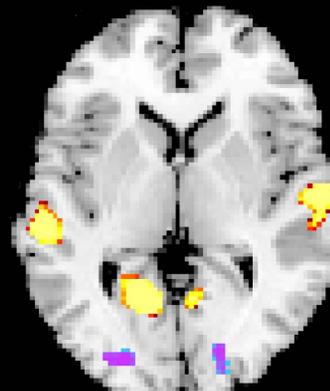
Z = +4



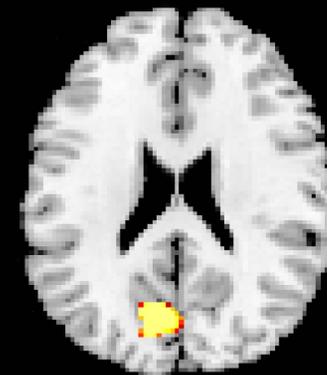
Z = +12



Z = 0

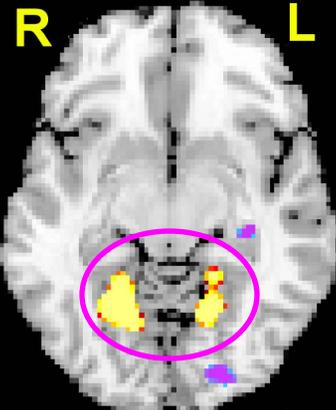


Z = +7

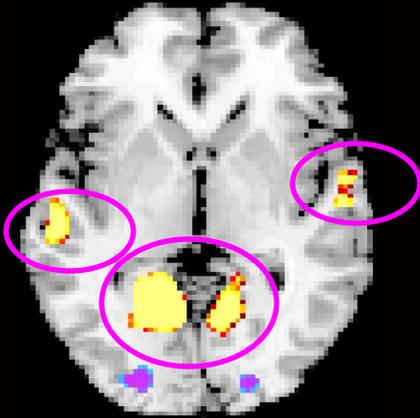


Z = +25

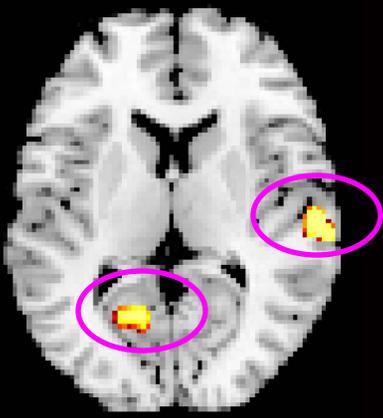
Modality x Prenatal x Adolescent Exposure Effects



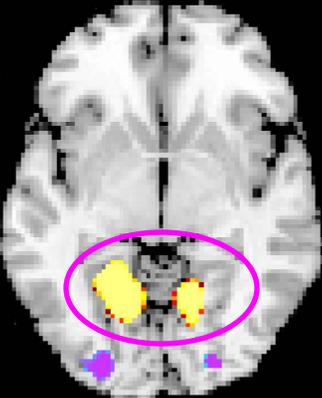
Z = -3



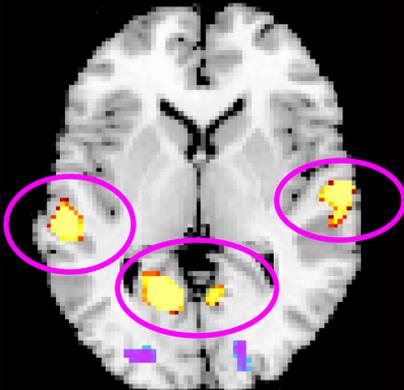
Z = +4



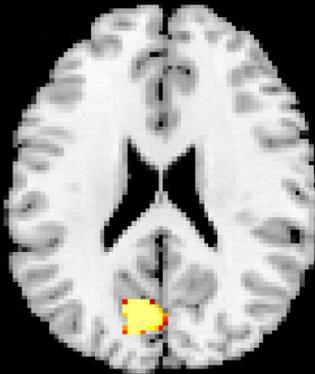
Z = +12



Z = 0



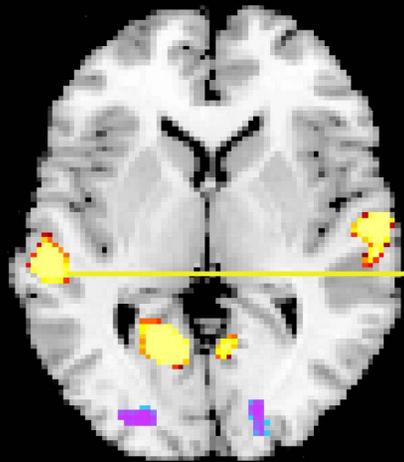
Z = +7



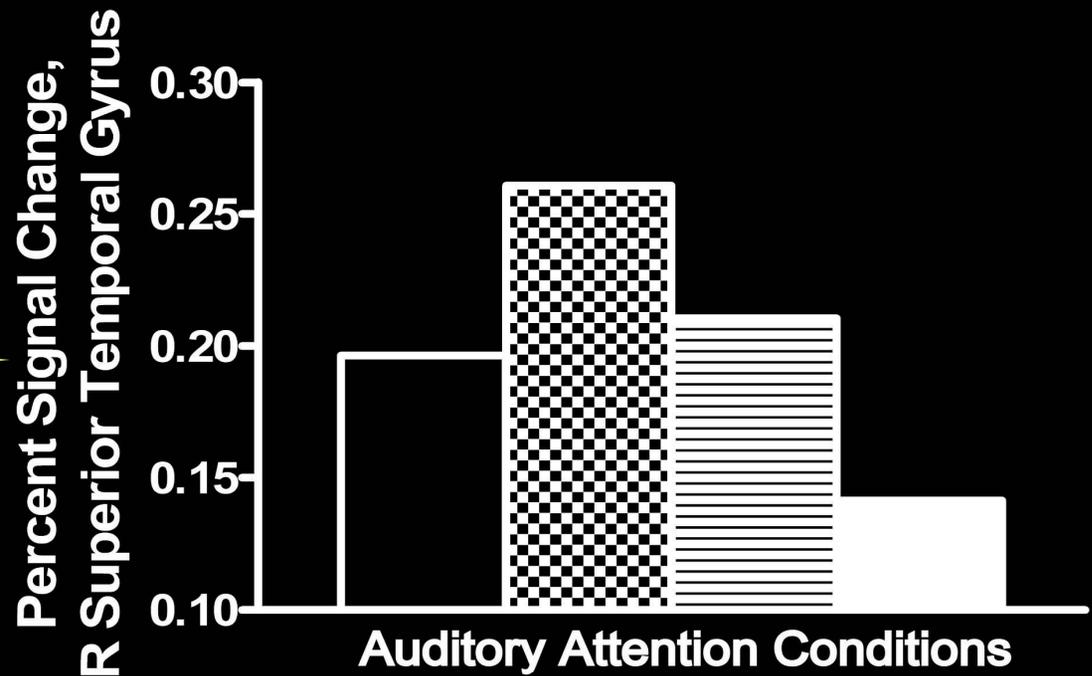
Z = +25

Prenatal x Adolescent Exposure Effects on Neurocircuitry Supporting Auditory Attention

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

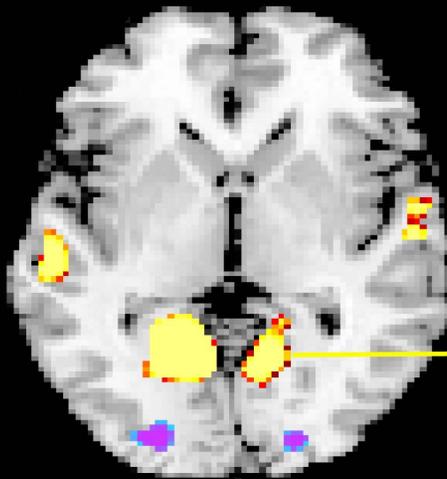


Z = +7



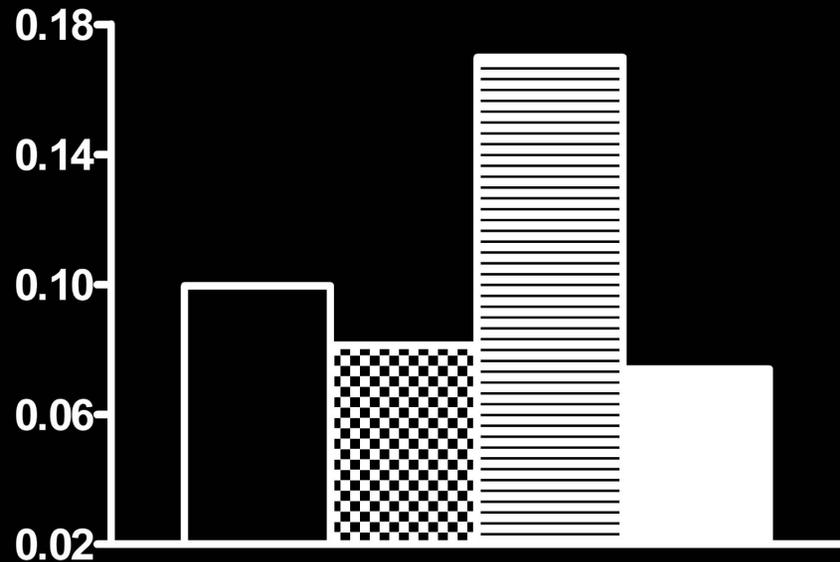
Prenatal x Adolescent Exposure Effects on Neurocircuitry Supporting Auditory Attention

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



Z = +4

Percent Signal Change,
Left Lingual Gyrus



Comment

- ▶ **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.**

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