

# **NICOTINE DELIVERY-ISSUES AND TECHNOLOGY**

**Jed E. Rose, Ph.D.**

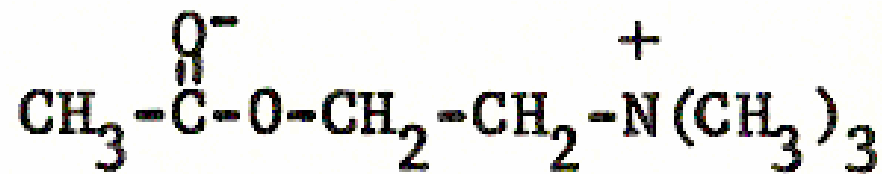
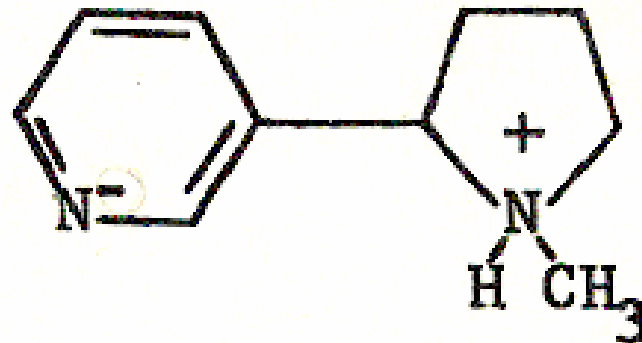
**Center for Nicotine and Smoking  
Cessation Research  
Duke University Medical Center**

**1. “To what degree is habit maintenance reinforced by the nicotine content and delivery itself and/or by factors other than nicotine?”**

**2. “What predictors of quitting and relapse exist, how strong are they and how might these interact with the existence of potential reduced risk tobacco products?”**

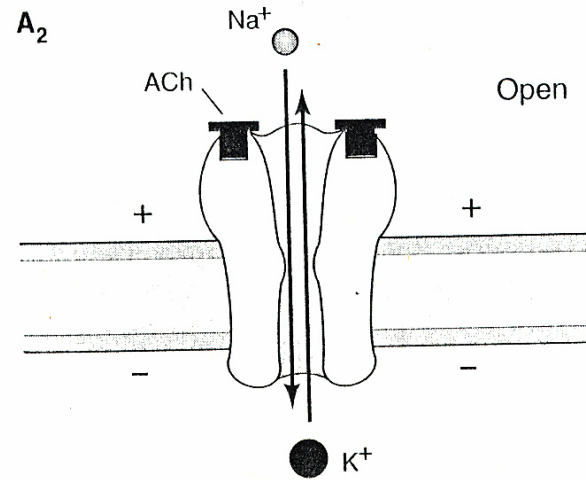
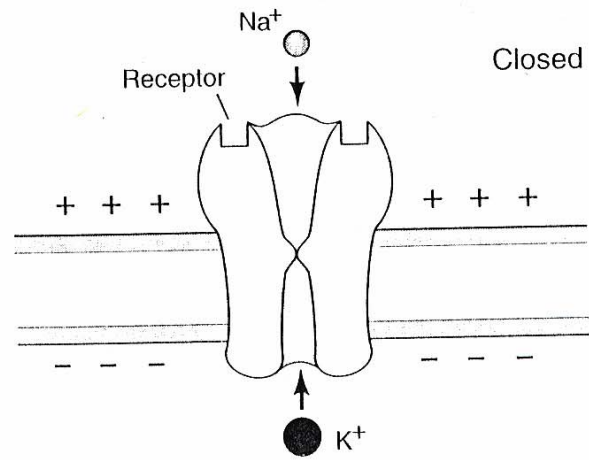
- 1. PHARMACOLOGY AND  
PHARMACOKINETICS OF NICOTINE**
- 2. SENSORY/HABIT FACTORS IN  
TOBACCO ADDICTION**
- 3. IMPLICATIONS FOR SMOKING  
CESSATION AND REDUCED RISK  
PRODUCTS**

# NICOTINE

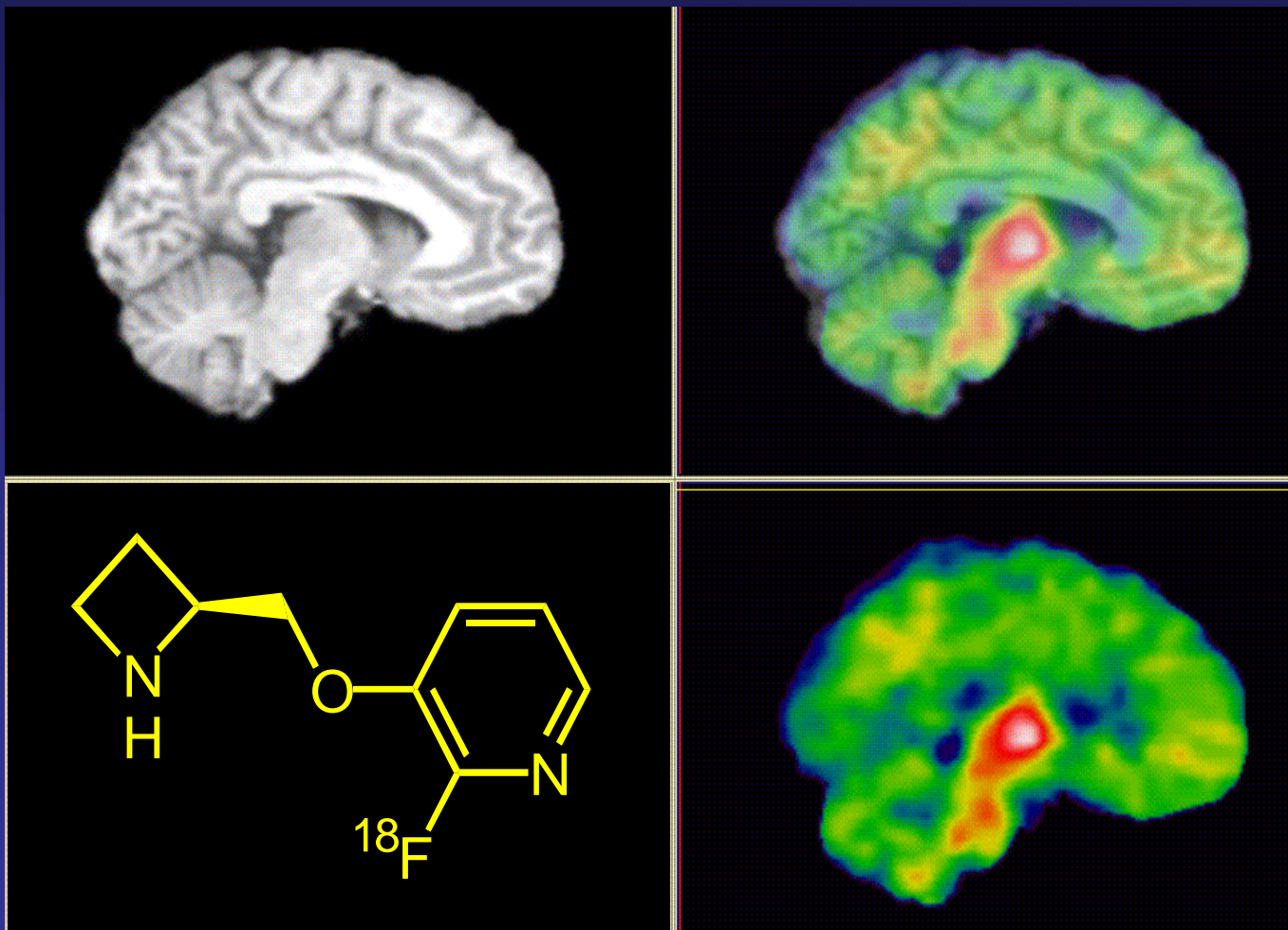


# ACETYLCHOLINE

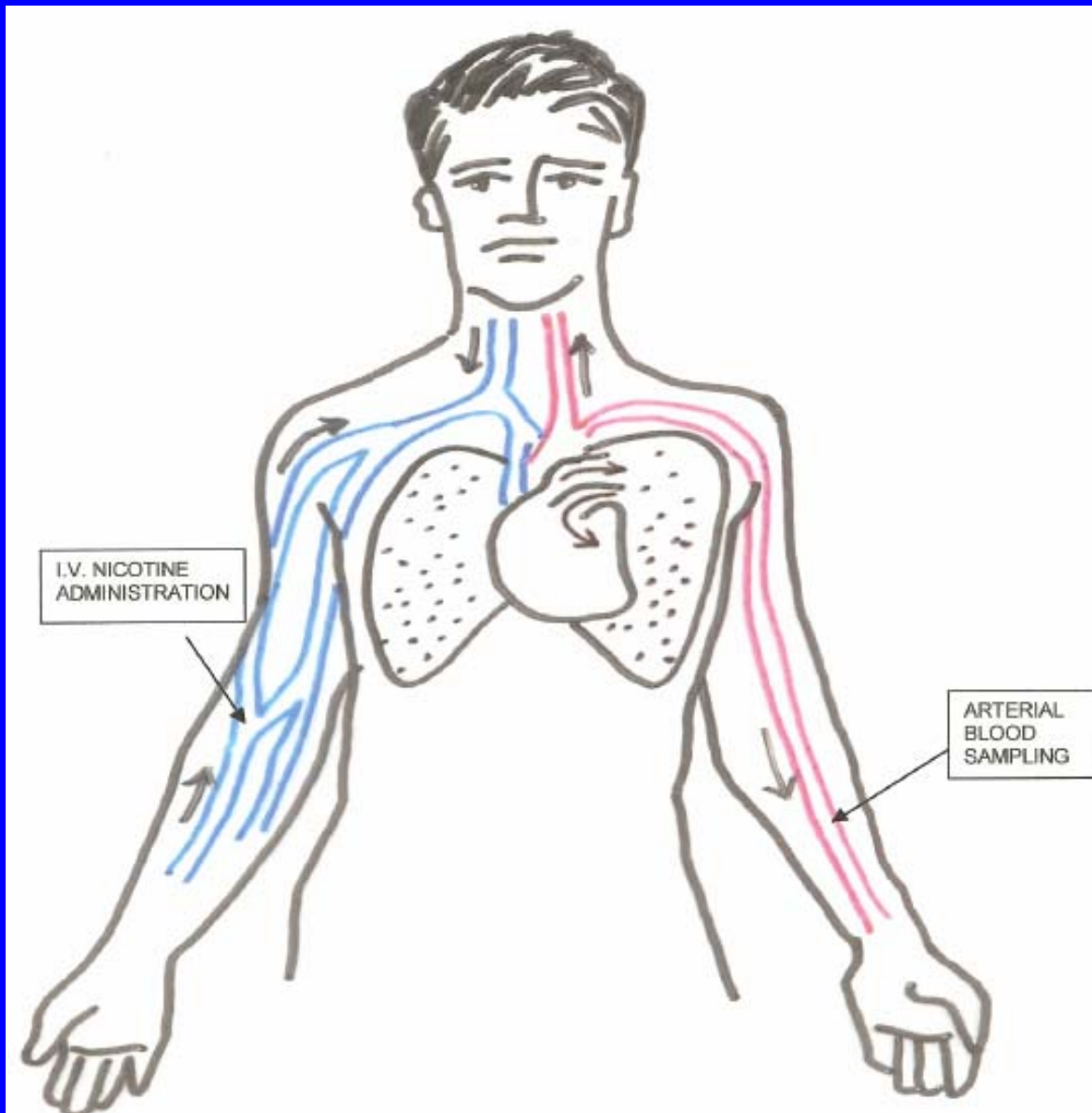
A<sub>1</sub> Excitation by transmitter due to opening an ion channel



# PET Image of Human Brain with 2-<sup>[18F]</sup>Fluoro-A-85380



# PHARMACOKINETICS OF INHALED NICOTINE



I.V. NICOTINE  
ADMINISTRATION

ARTERIAL  
BLOOD  
SAMPLING

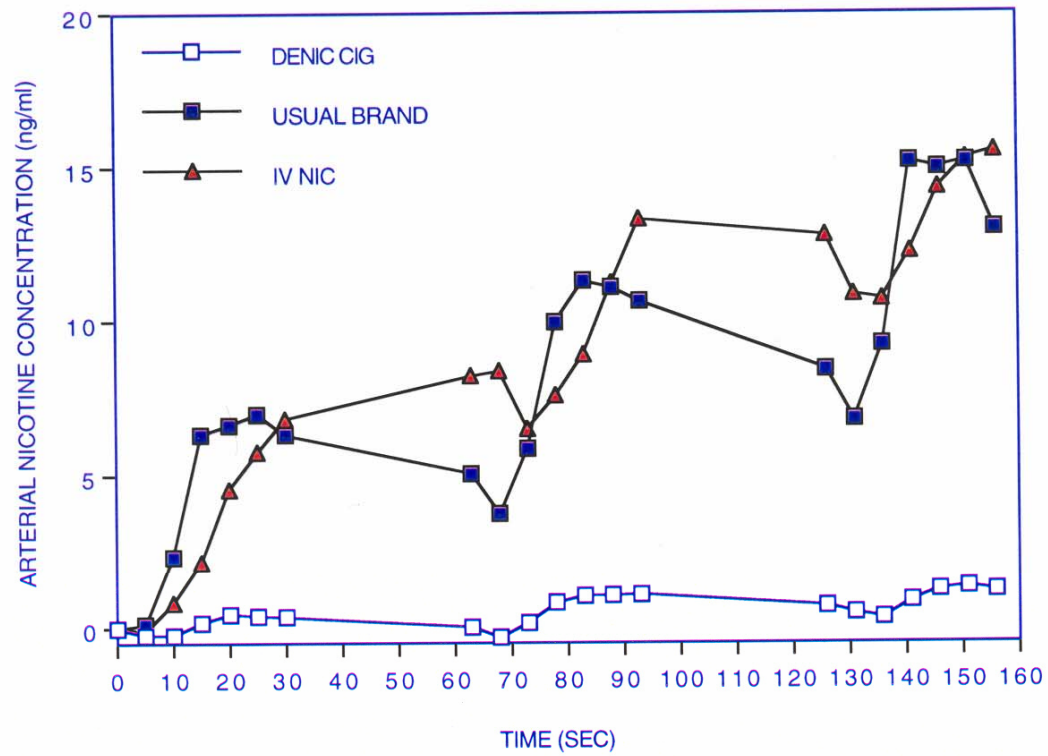


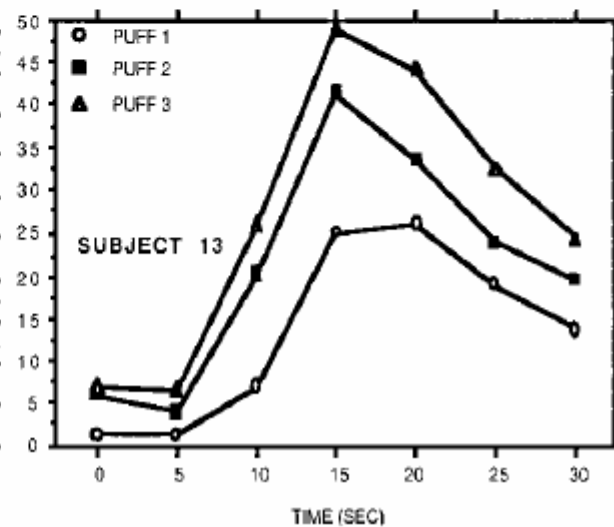
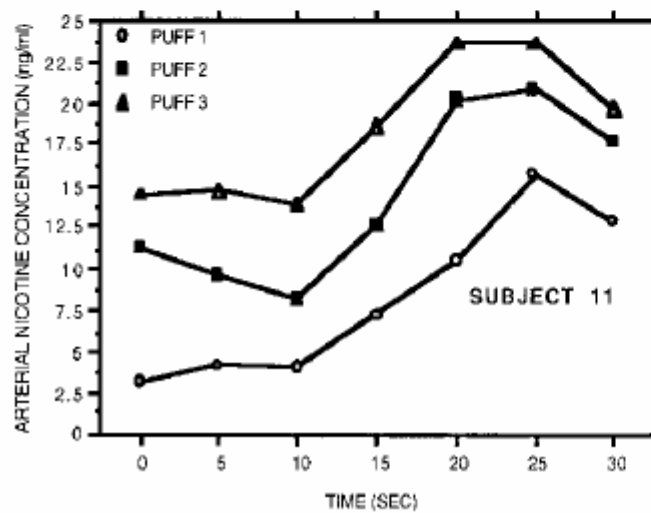
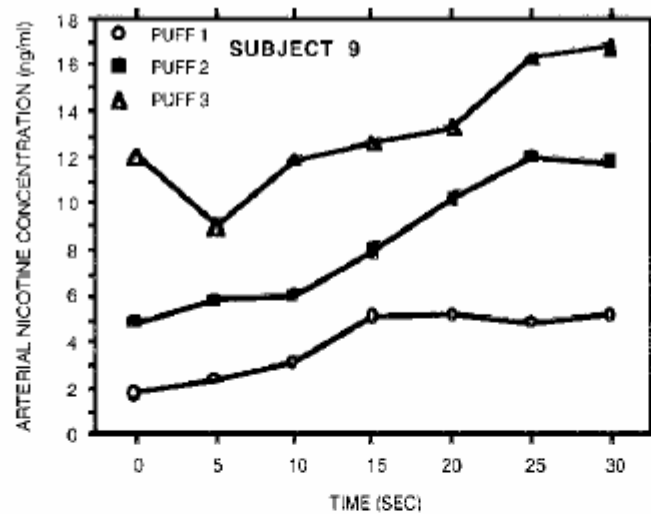
# Measurement of arterial blood nicotine concentrations every 5 s during cigarette smoking vs. IV nicotine administration

**Sample:**

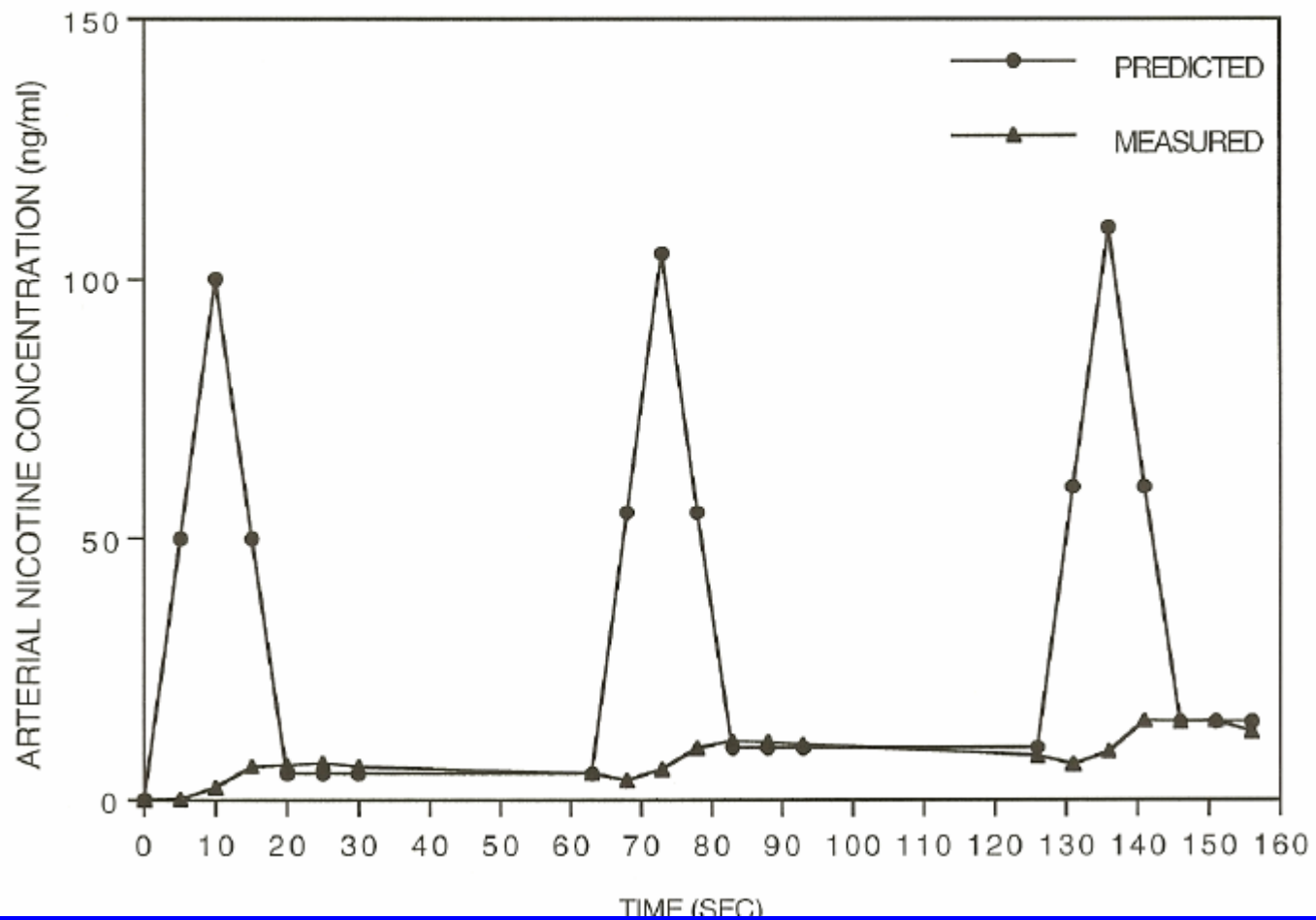
**13 smokers (10 males, 3 females)**

<u>Characteristics</u>	<u>mean (SD)</u>
Age (yr.)	38 (7.9)
Cigs/day	28 (11)
FTND score	7.0 (1.6)
FTC nicotine	0.7 (.34)
Puff vol. (ml)	48 (28)
Dose/puff (mg)	.12 (.04)
# puffs	6.2 (1.9)
Interpuff interval (s)	66 (31)

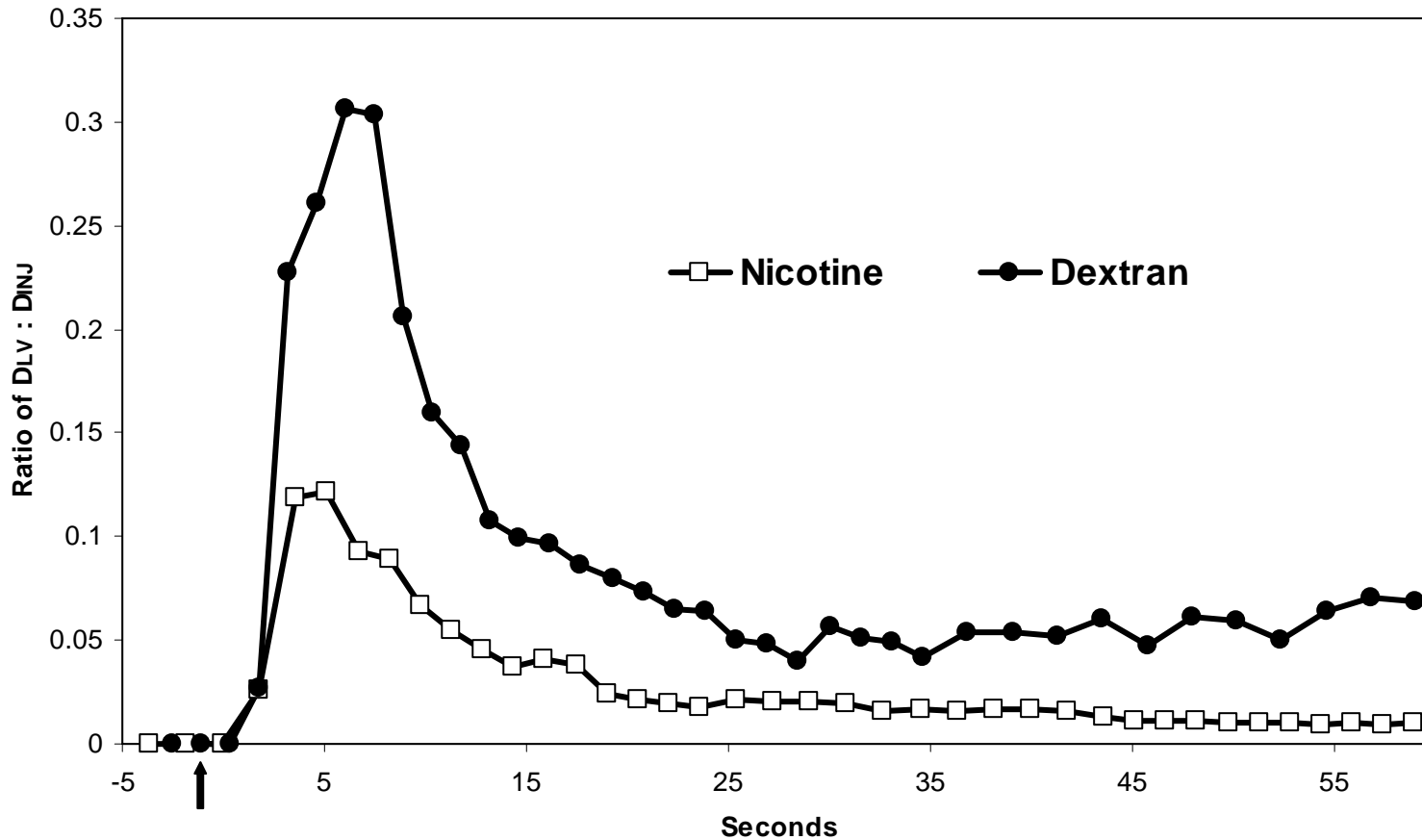


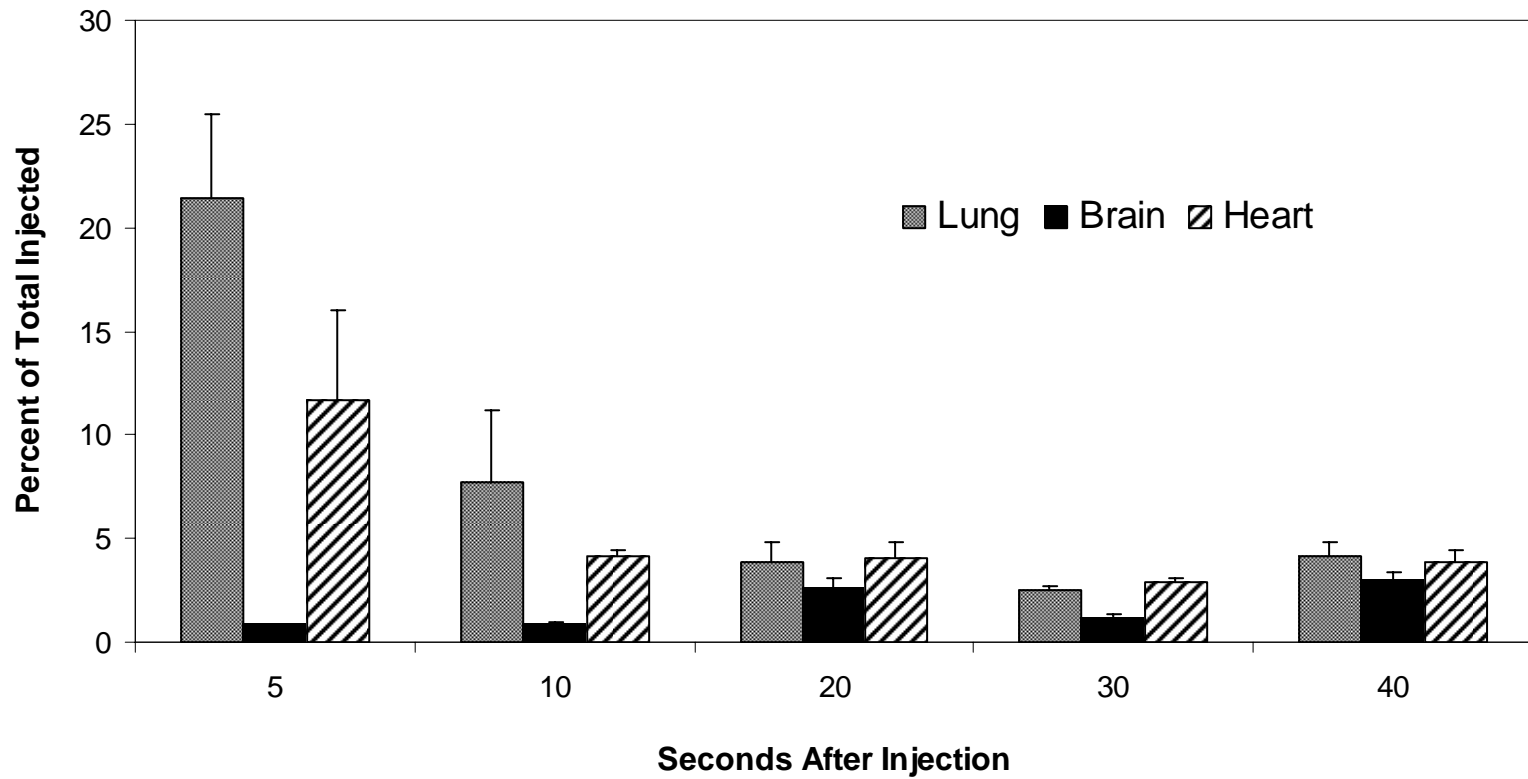


## TEMPORAL PATTERN OF ARTERIAL NICOTINE CONCENTRATION: PREDICTED VS. MEASURED



# Short-term distribution of nicotine in the rat lung (courtesy of Peter P. Rowell, Ph.D.)

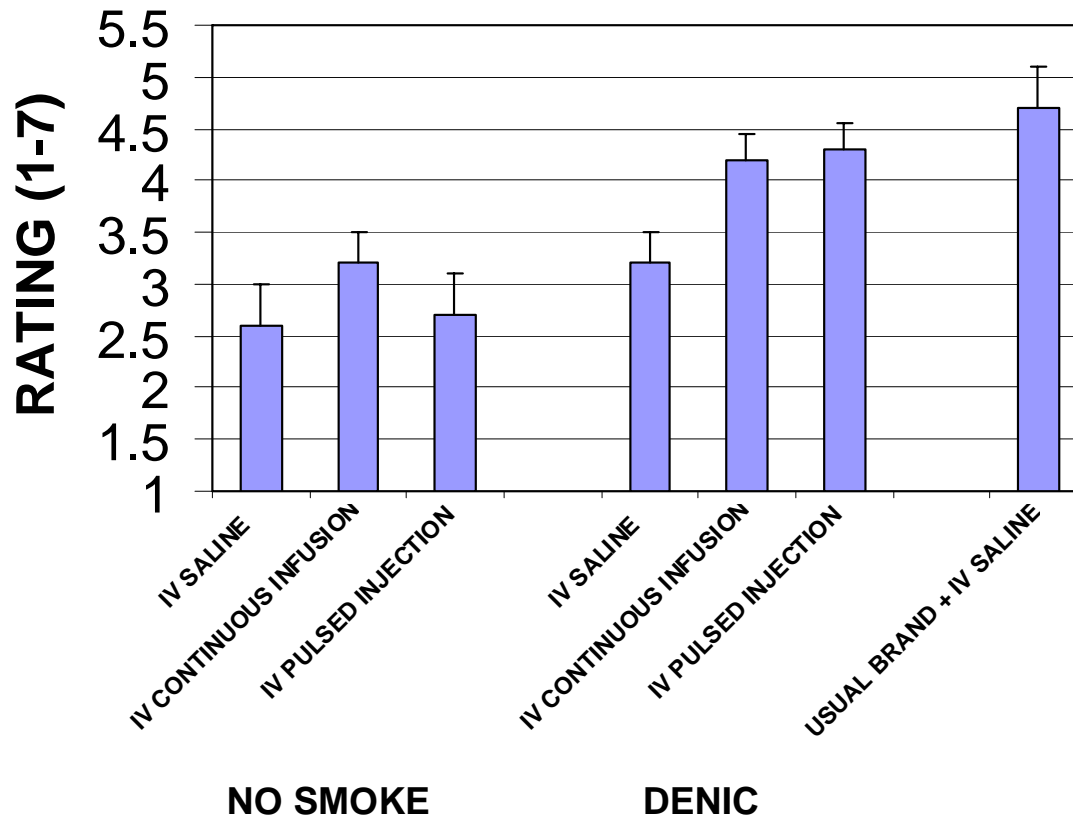




**Rose et al. Pharmacology Biochemistry and Behavior  
67 (2000) 71-81.**

<b>GROUP</b>	<b>CIGARETTE</b>	<b>I.V. CONDITION</b>
1	DENIC (or no smoking)	Continuous Nicotine
2	DENIC (or no smoking)	Pulsed Nicotine
3	DENIC (or no smoking)	Saline
4	USUAL BRAND (or no smoking)	Saline

# CRAVING REDUCTION



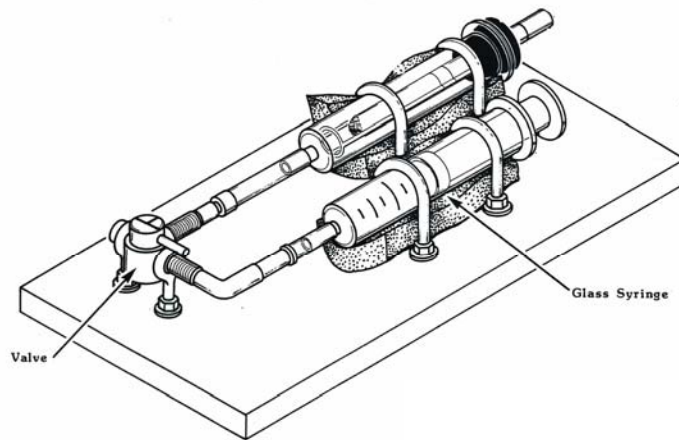


# EFFECTS ON AD LIB SMOKING BEHAVIOR OF CONTROLLED PRESENTATIONS OF SMOKE COMPONENTS VS. IV NICOTINE

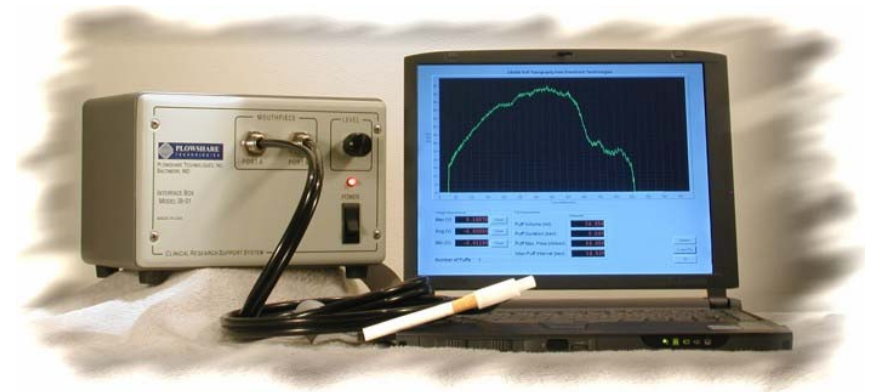
## EXPERIMENTAL CONDITIONS

CONDITION	CONTROLLED SMOKE	IV
A	USUAL BRAND	SALINE
B	DENICOTINIZED	SALINE
C	DENICOTINIZED	NICOTINE (pulsed)
D	NO SMOKE	NICOTINE (pulsed)
E	NO SMOKE	NICOTINE (slow infusion)
F	NO SMOKE	SALINE

# Apparatus for delivering smoke doses and for assessing *ad lib* smoking

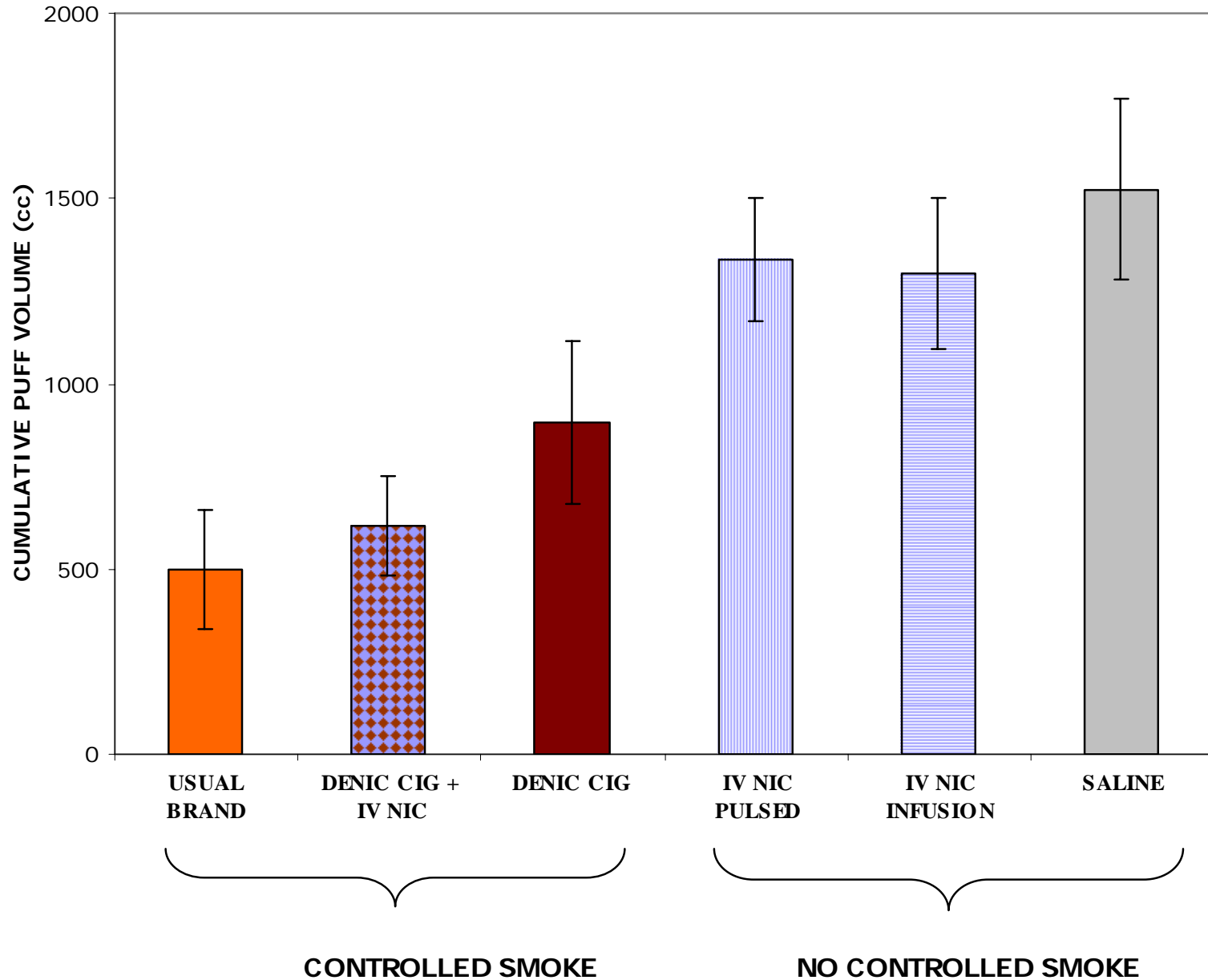


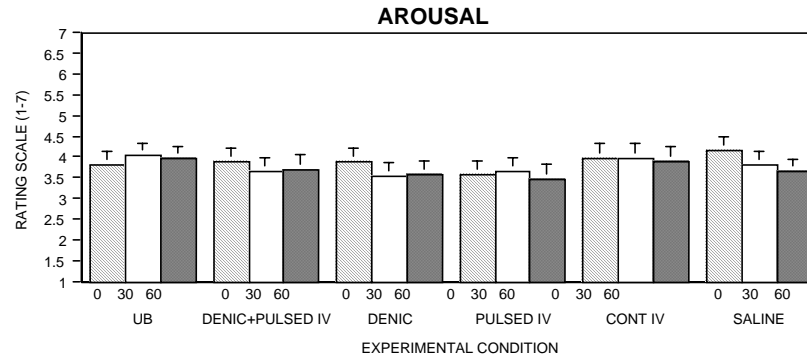
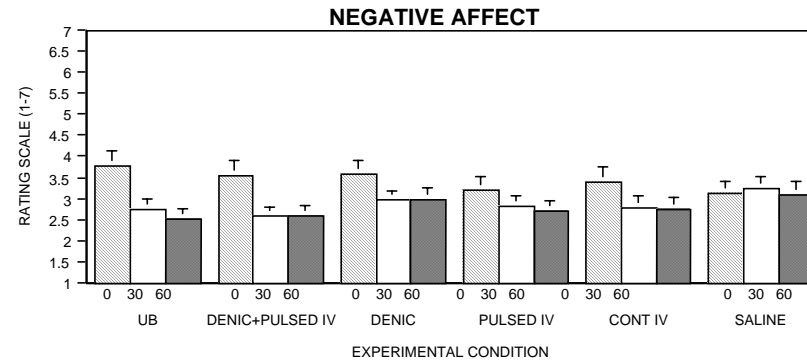
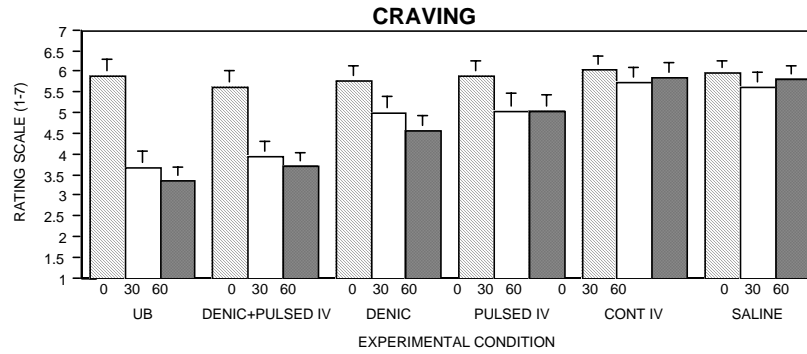
**Controlled Puff Apparatus**



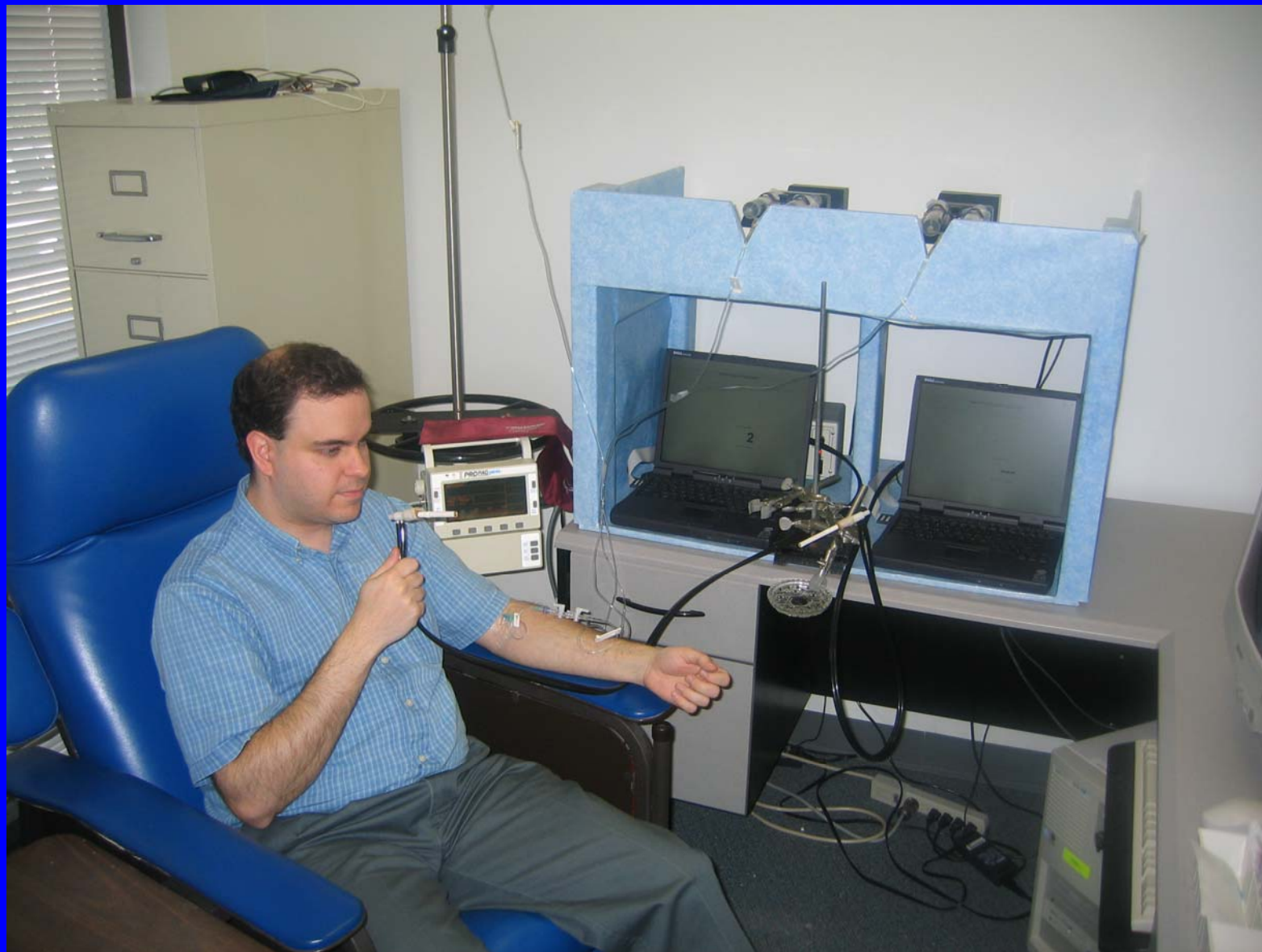
**CReSS Smoking  
Topography Monitor (*ad lib* smoking)**

# AD LIB SMOKING

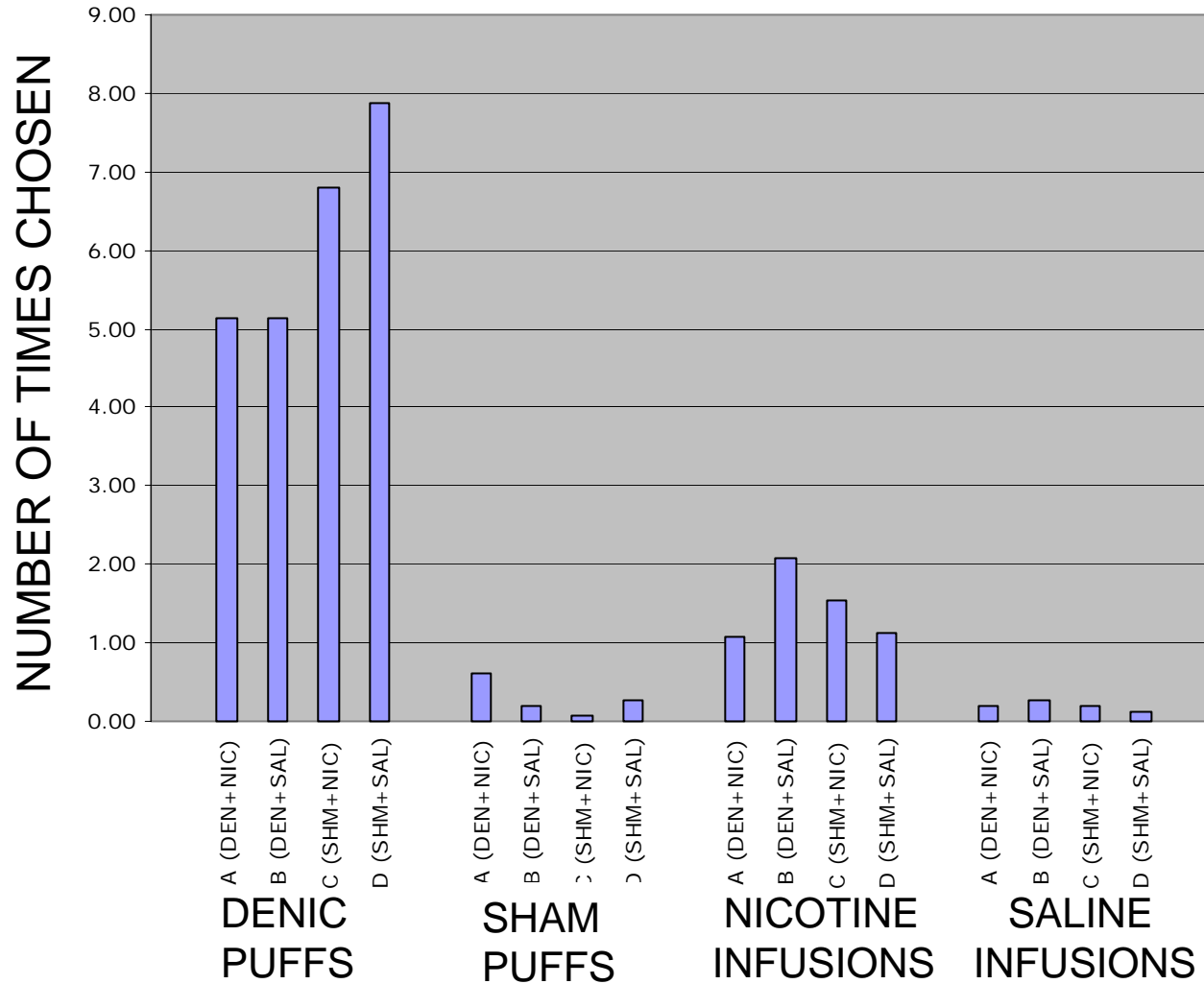




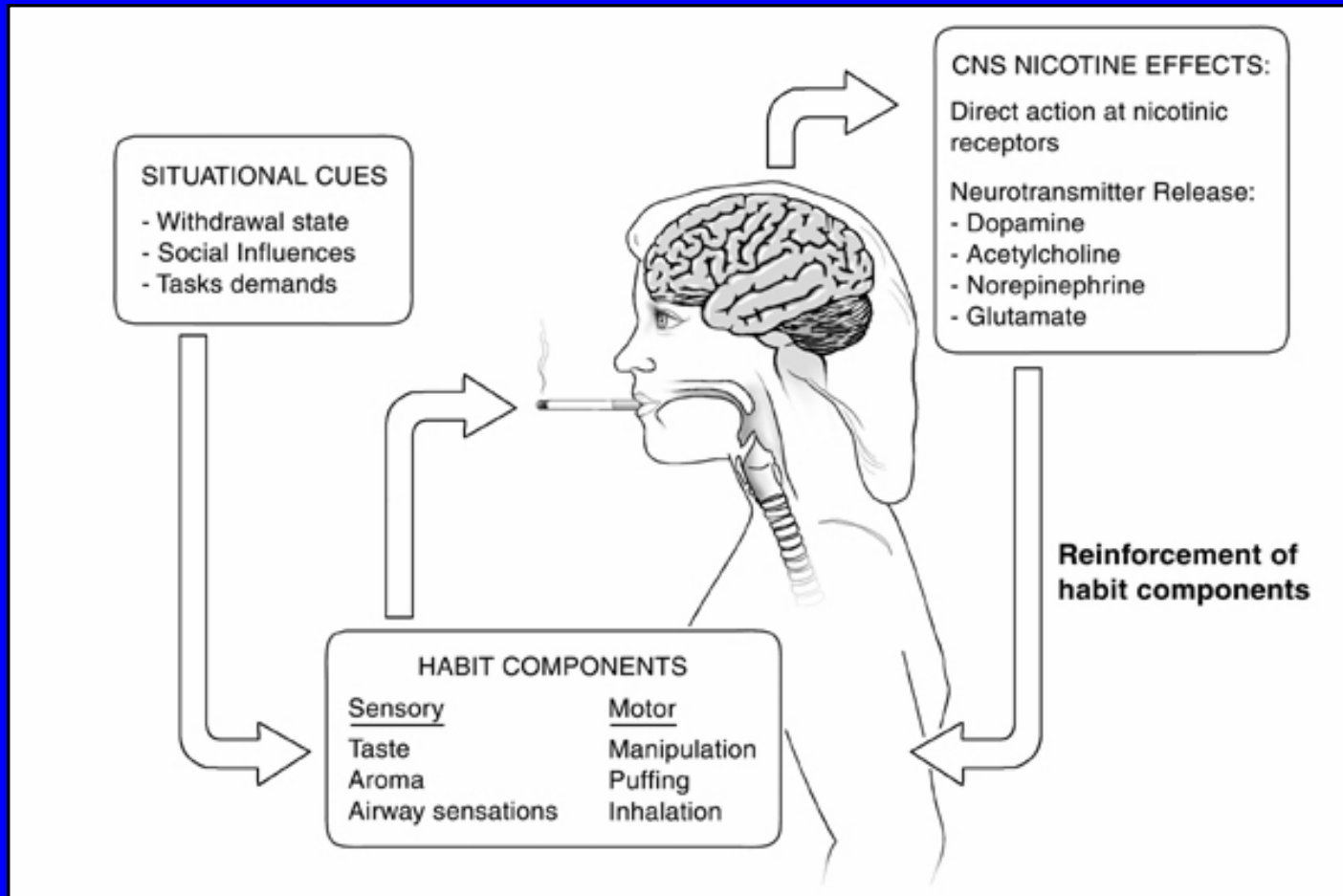
# SMOKE/IV NICOTINE PREFERENCE TEST APPARATUS



# PREFERENCE TEST RESULTS



# PHARMACOLOGIC AND HABIT/SENSORY COMPONENTS OF CIGARETTE SMOKING



# Stimuli

Male

Female

Control

Control



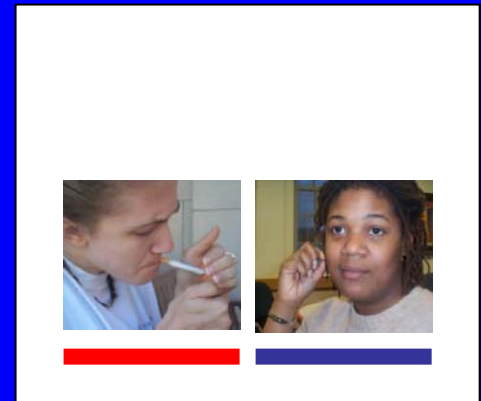
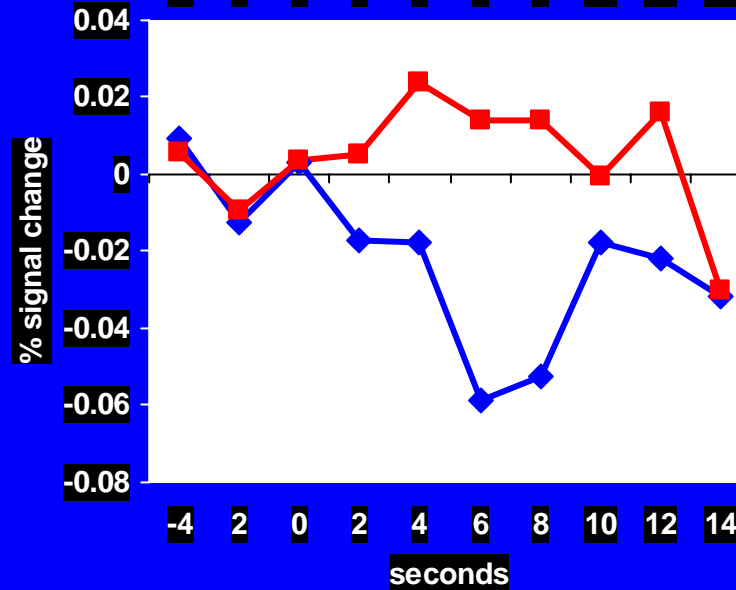
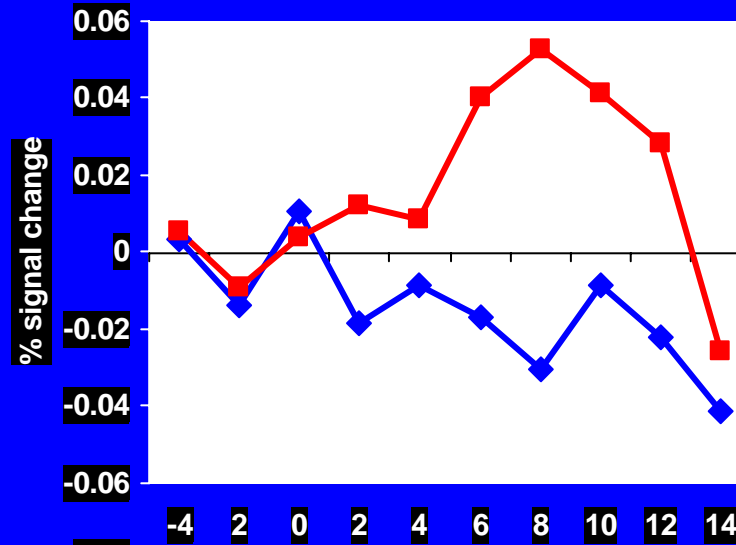
Smoking





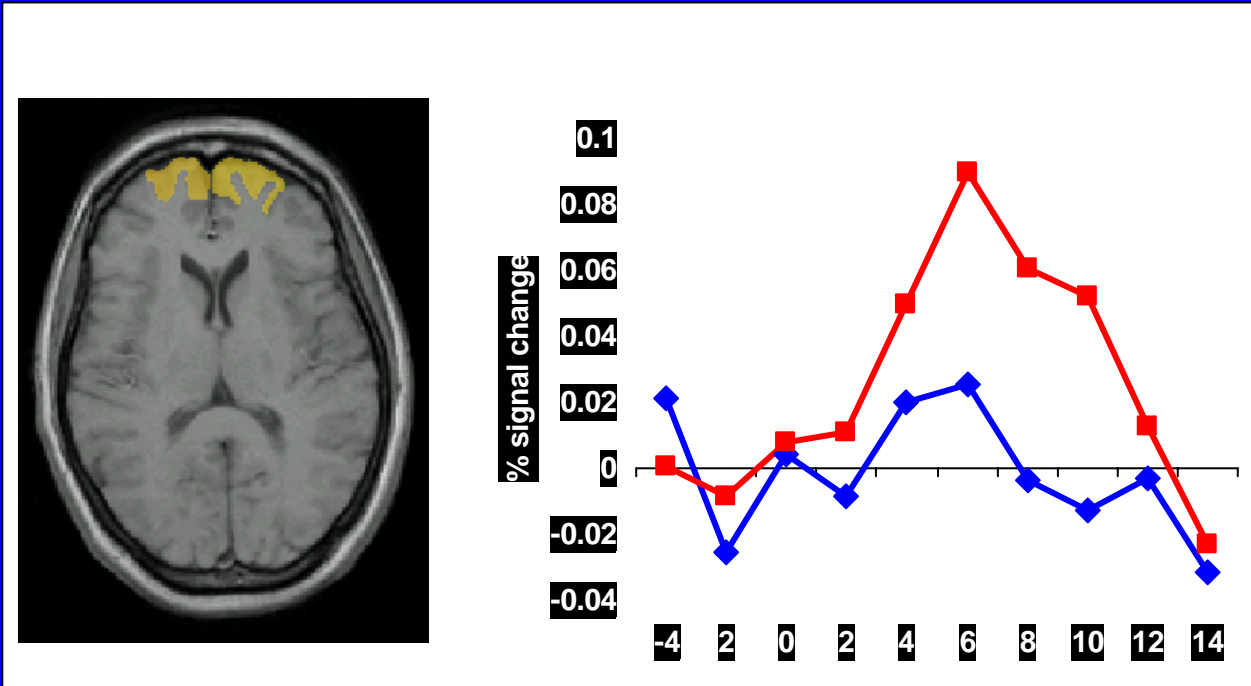
# Cue-Induced Responses (Across smoking conditions)

## Ventral Striatum/Ventral ACC



# Cue-induced effects (Across smoking conditions)

Superior Frontal Gyrus



Stimulus,  $p = .009$

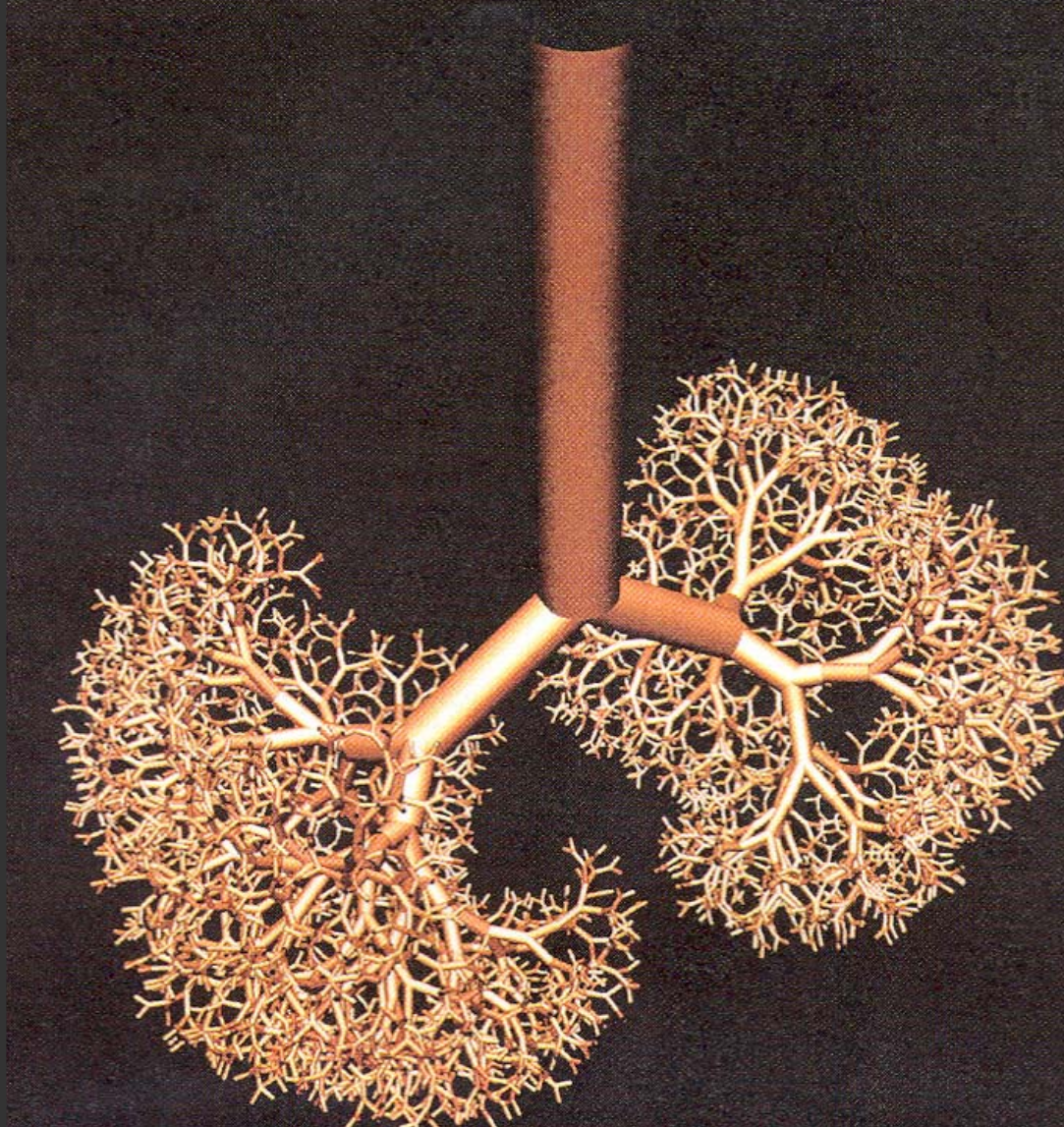


**Abstinence-induced changes in self-report craving correlate with event-related fMRI responses to smoking cues.**

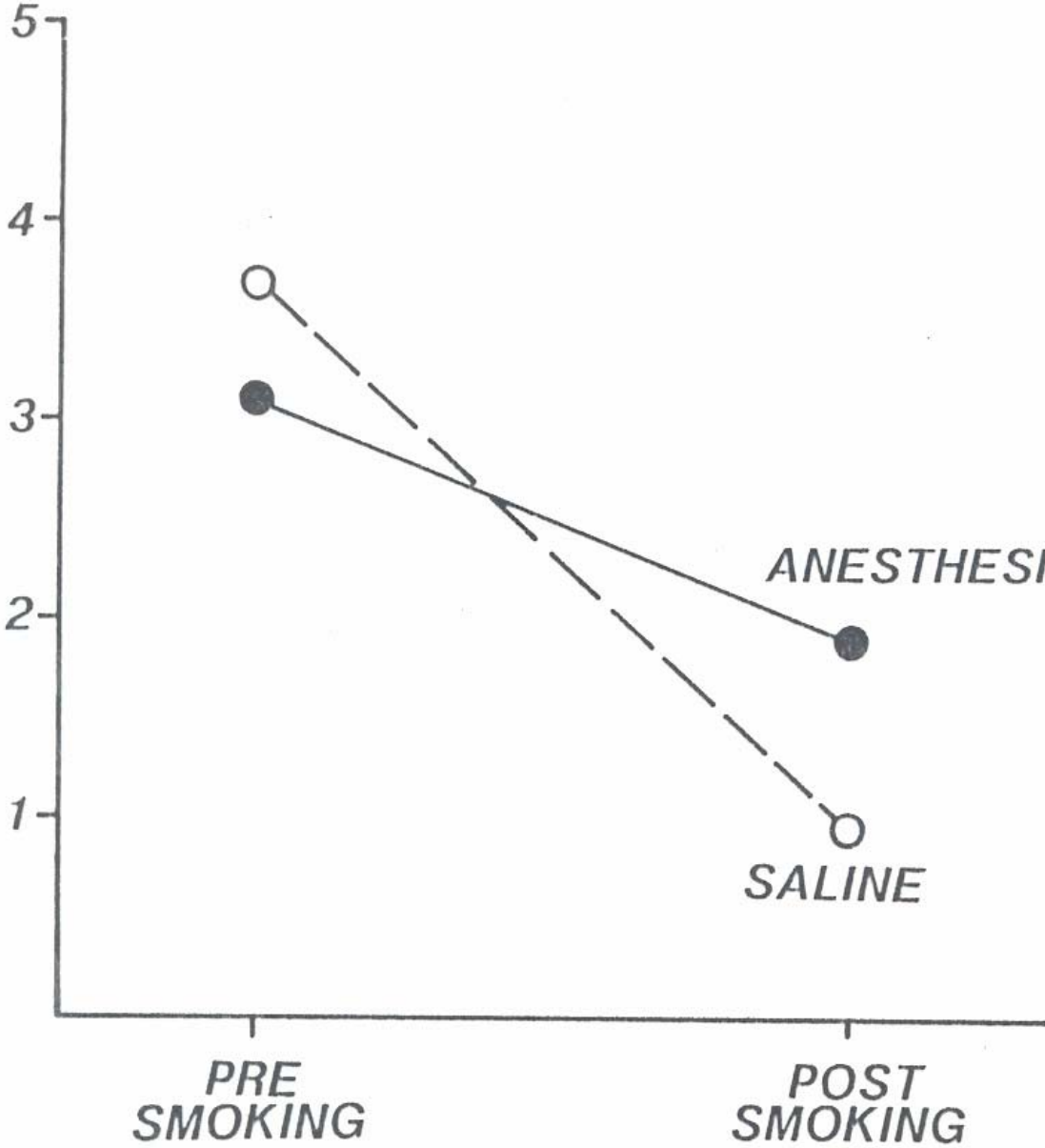
**McClernon FJ, Hiott FB, Huettel SA, Rose JE**

***Neuropsychopharmacology, in press, 2005***

Katz IM et al. (2001) Diabetes Technology & Therapeutics 3:387-397.



MEAN CIGARETTE CRAVING



# **Citric acid aerosol as a potential smoking cessation aid**

**JE Rose and CS Hickman**

**Chest, Vol 92, 1005-1008**

# **Development of a citric acid aerosol as a smoking cessation aid**

**Levin ED, Rose JE, Behm F.**

**Drug Alcohol Depend 1990 Jun;25(3):273-9.**

# **Clinical evaluation of a citric acid inhaler for smoking cessation**

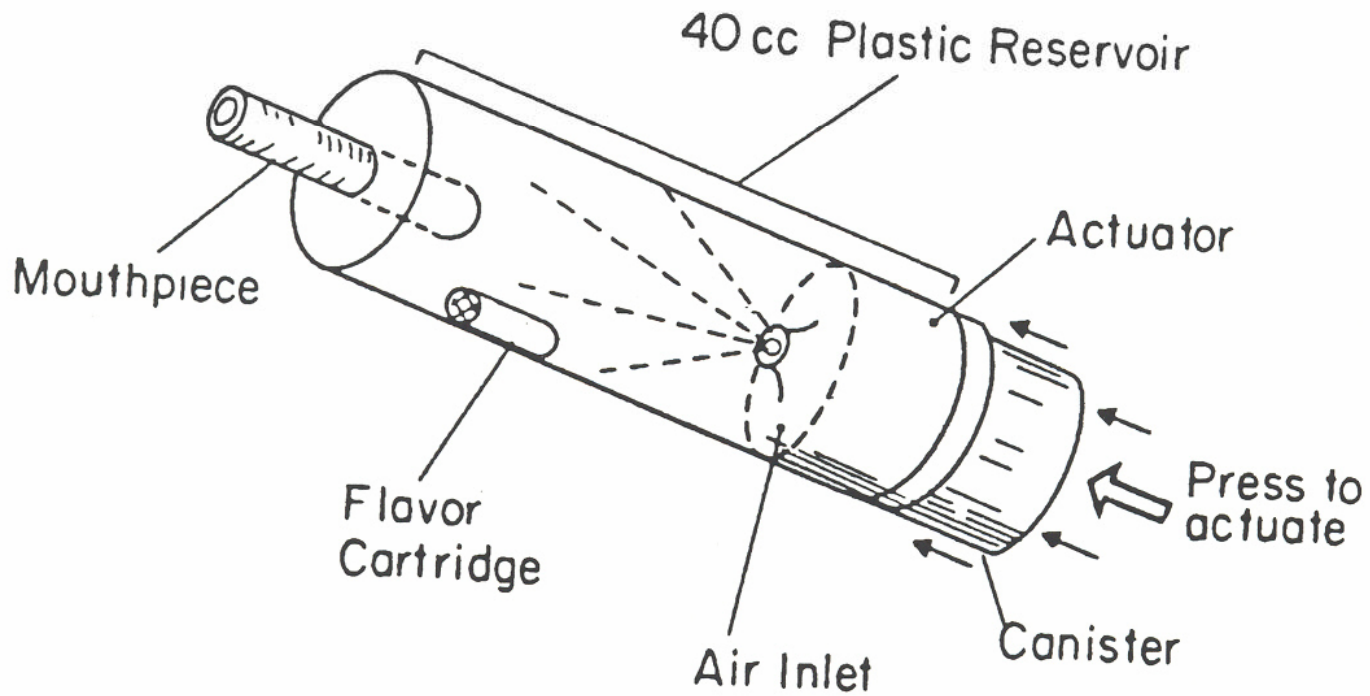
**Behm FM, Schur C, Levin ED, Tashkin DP, Rose JE**

**Drug Alcohol Depend 1993**

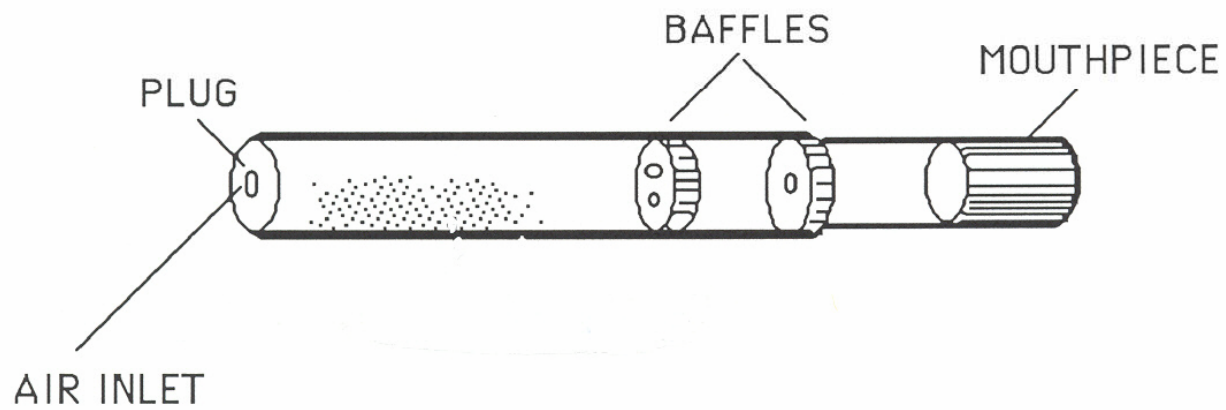
**Jan;31(2):131-8.**



# HAND - HELD AEROSOL DELIVERY SYSTEM



## DELIVERY SYSTEM



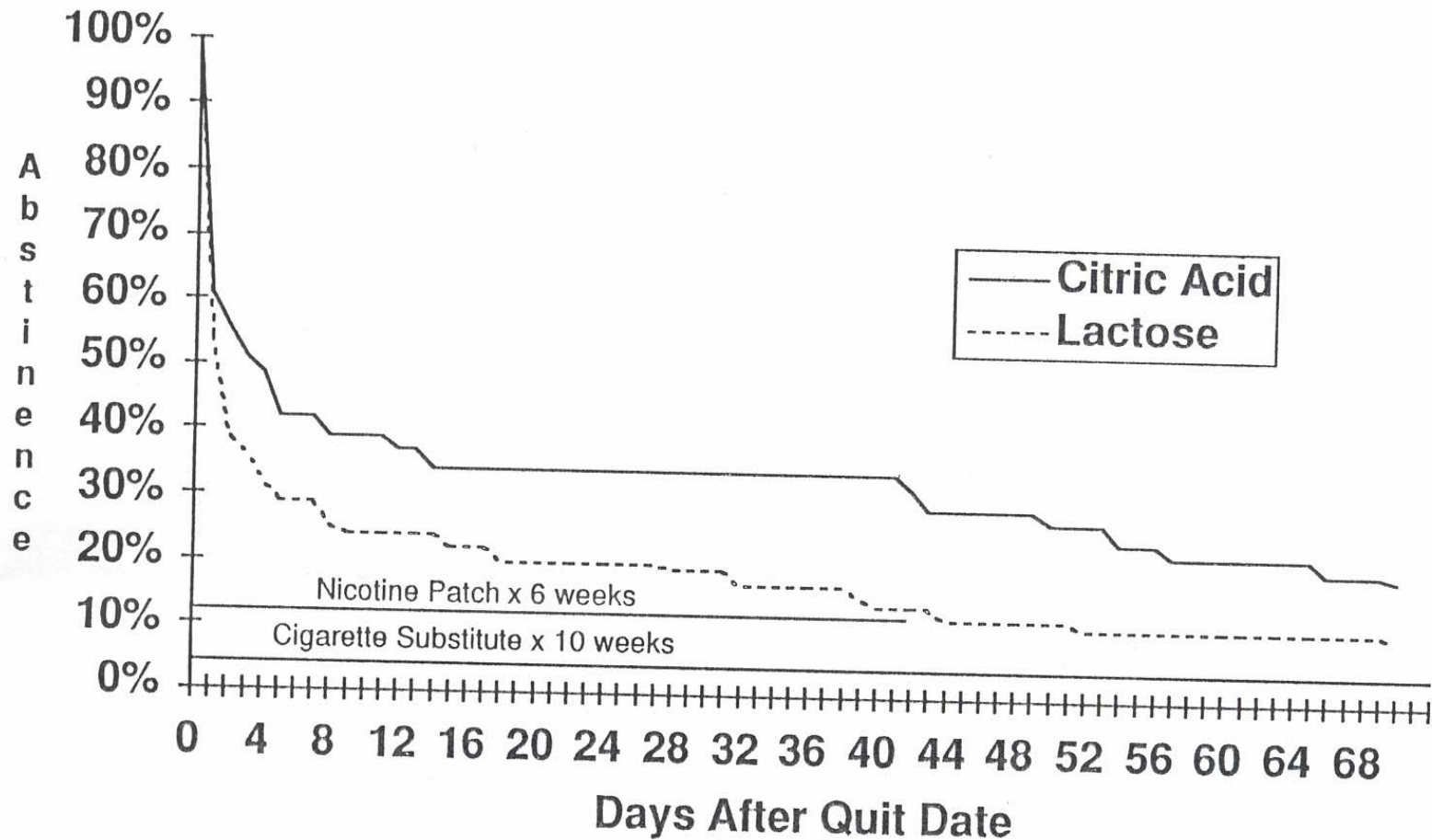


**Airway sensory replacement combined with nicotine replacement for smoking cessation. A randomized, placebo-controlled trial using a citric acid inhaler**

**EC Westman, FM Behm and JE Rose**

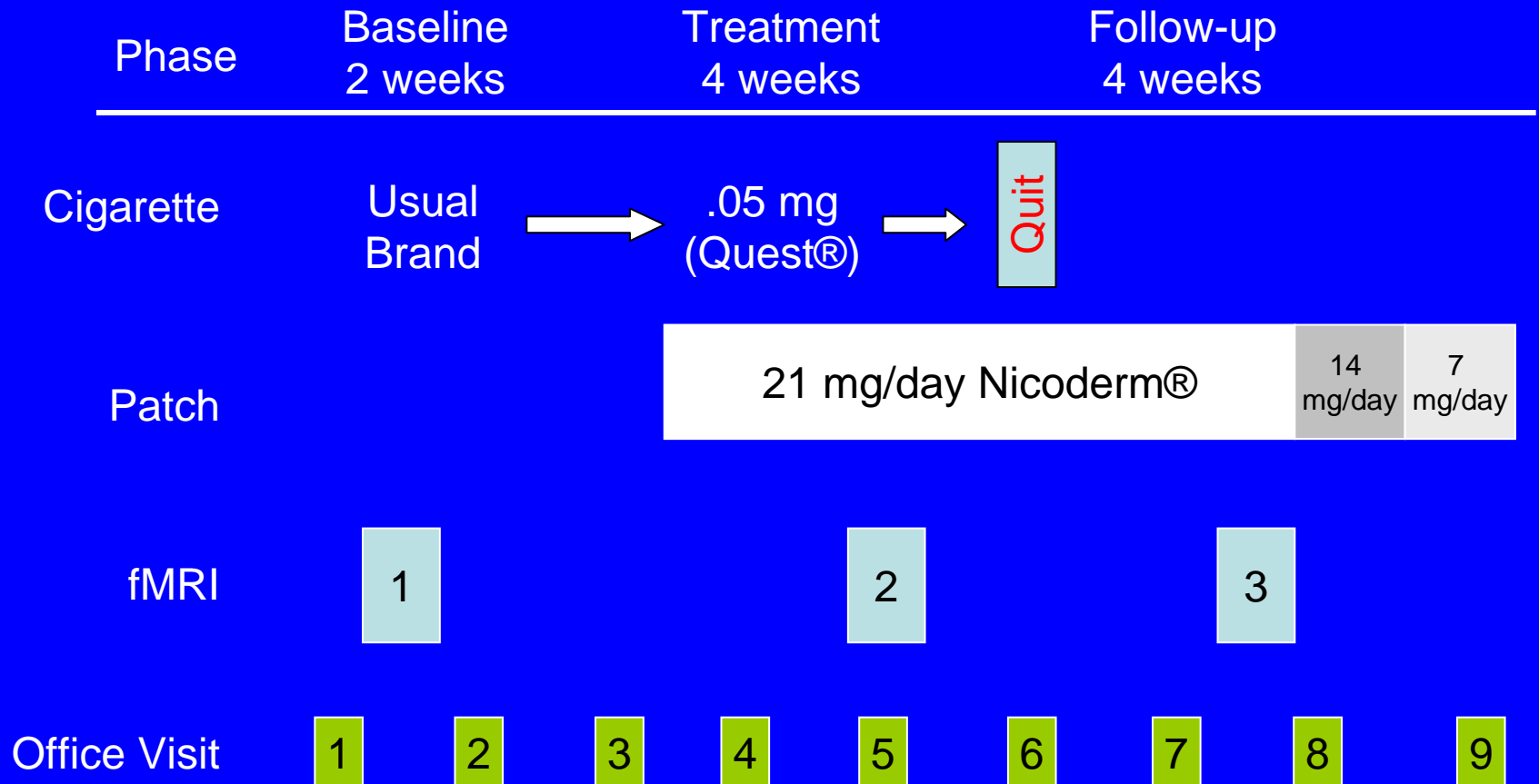
**Chest, Vol 107, 1358-1364, 1995**

# Continuous Smoking Abstinence Citric Acid Inhaler and Nicotine Patch vs. Lactose Inhaler and Nicotine Patch



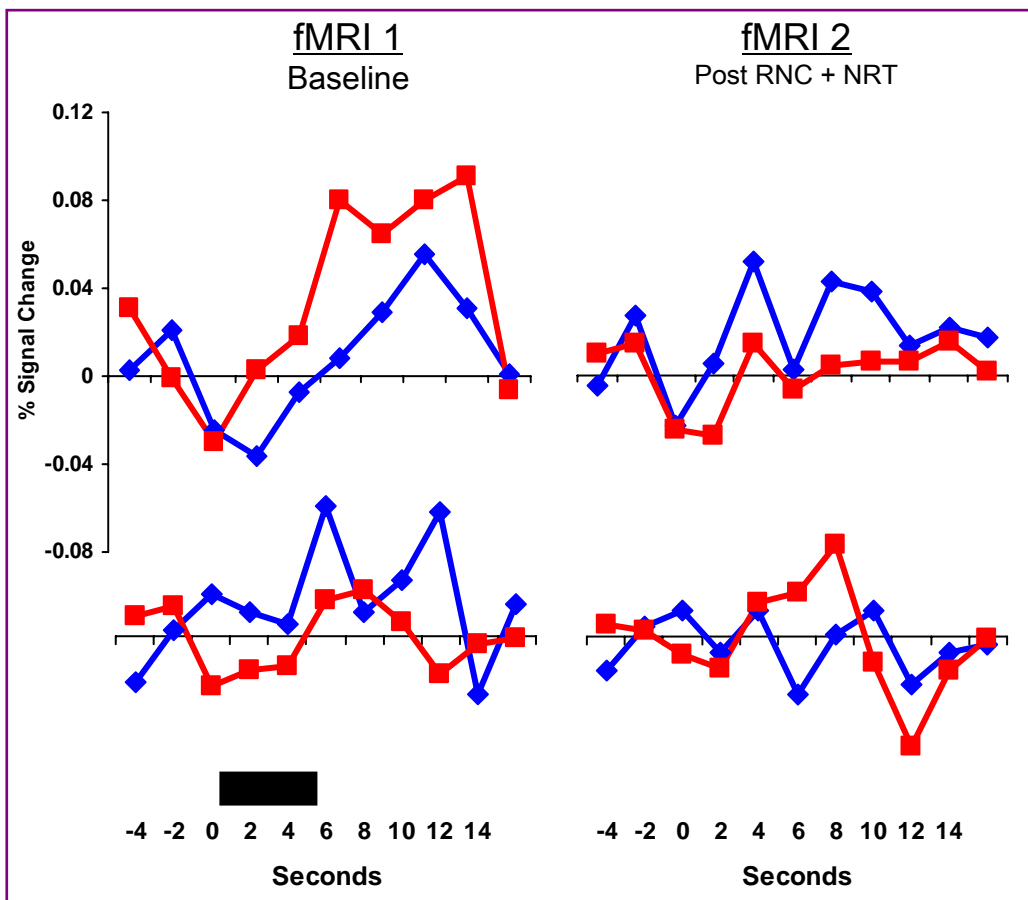
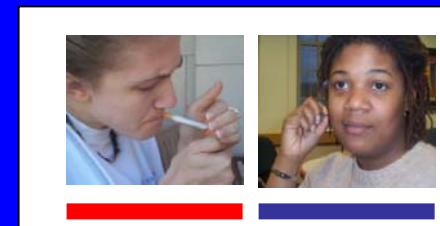
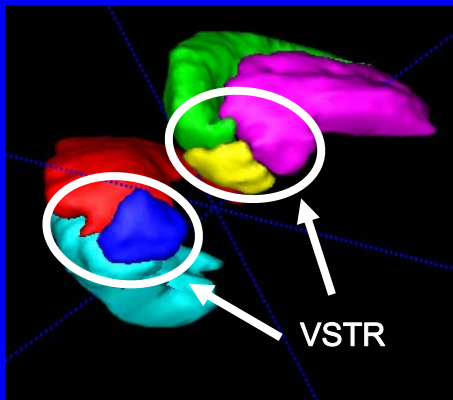
**USE OF LOW NICOTINE CONTENT  
TOBACCO CIGARETTES IN  
SMOKING CESSATION  
TREATMENT**

# Research Design



# Event-related fMRI results

Ventral Striatum: Stimulus x Scan x Group\*,  $p = .041$





# CONCLUSIONS

- 1. Nicotine plays a major role in tobacco addiction; nicotine absorption from cigarette smoking is fast, but not substantially more rapid than IV administration or nasal spray administration. 5-10 min bolus may be as effective as 5-10 s bolus.**
- 2. Rapid nicotine administration (e.g. 5 min) appears to relieve craving for cigarettes more effectively than slow (e.g. 40 min) nicotine administration.**

- 3. Sensory cues, both exteroceptive and interoceptive, also play a major role in tobacco addiction.**
- 4. Therapeutic strategies that entail substituting for these cues, or, alternatively, attenuating their potency (e.g. extinction therapy), may be promising avenues for new smoking cessation treatments.**