Delineating the neurochemical effects of tobacco smoking from alcohol drinking

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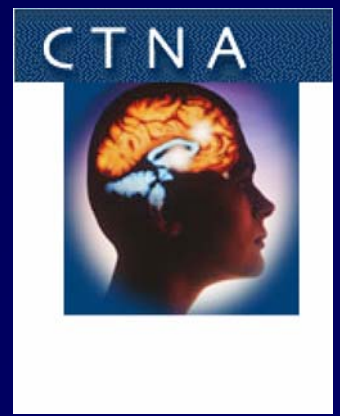


Alcohol & Tobacco Smoking

- **Alcohol drinkers smoke more than nondrinkers &tobacco smokers drink more than nonsmokers**
- **Alcoholic smokers have an earlier age of onset of alcohol dependence and more alcohol related problems**
- **Smokers feel less intoxicated upon alcohol challenge suggesting that smoking enhances tolerance to alcohol**

[Bien et al., 1990; Difranza&Guerrera, 1990; Abrams et al., 1992; Johnson and Jennison, 1992; Gulliver et al., 1995; Deappen et al., 2000]

Tobacco is Like Love

Tobias Humb ***Musicall Humors 1605***

Tobacco, Tobacco, sing sweetly for tobacco, tobacco is like love, O love it For you see I will prove it.

Love maketh leane the fatte mens tumor, so doth tobacco,

Love still dries uppe the wanton humor, so doth tobacco,

Love makes men sayle from shore to shore, so doth tobacco,

Tis fond love often make men poor, so doth tobacco,

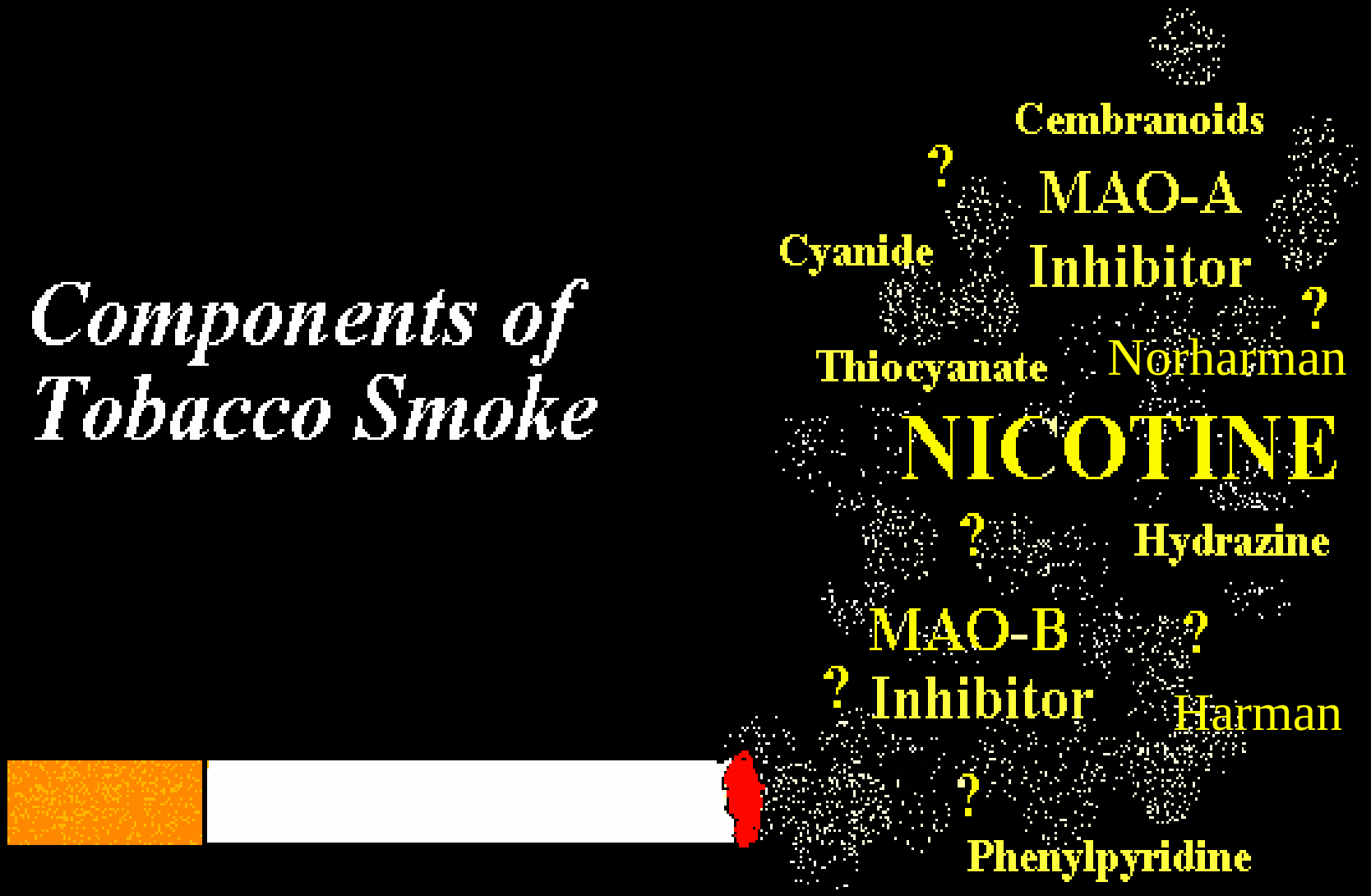
Love makes men scorn al Coward feares, so doth tobacco,

Love often sets men by the eares, so doth tobacco,

Tobaccoe, Tobaccoe, sing sweetly for tobaccoe, Tobaccoe is like Love, O love it, For you see I have provde it.

Anonymous

Components of Tobacco Smoke



Like Alcohol, Tobacco Smoke Facilitates DA Neurotransmission

Via its actions on the cholinergic nicotinic receptor, nicotine indirectly

↓ **DA reuptake** (brain*cells@)

↑ **DA release** (brain#)

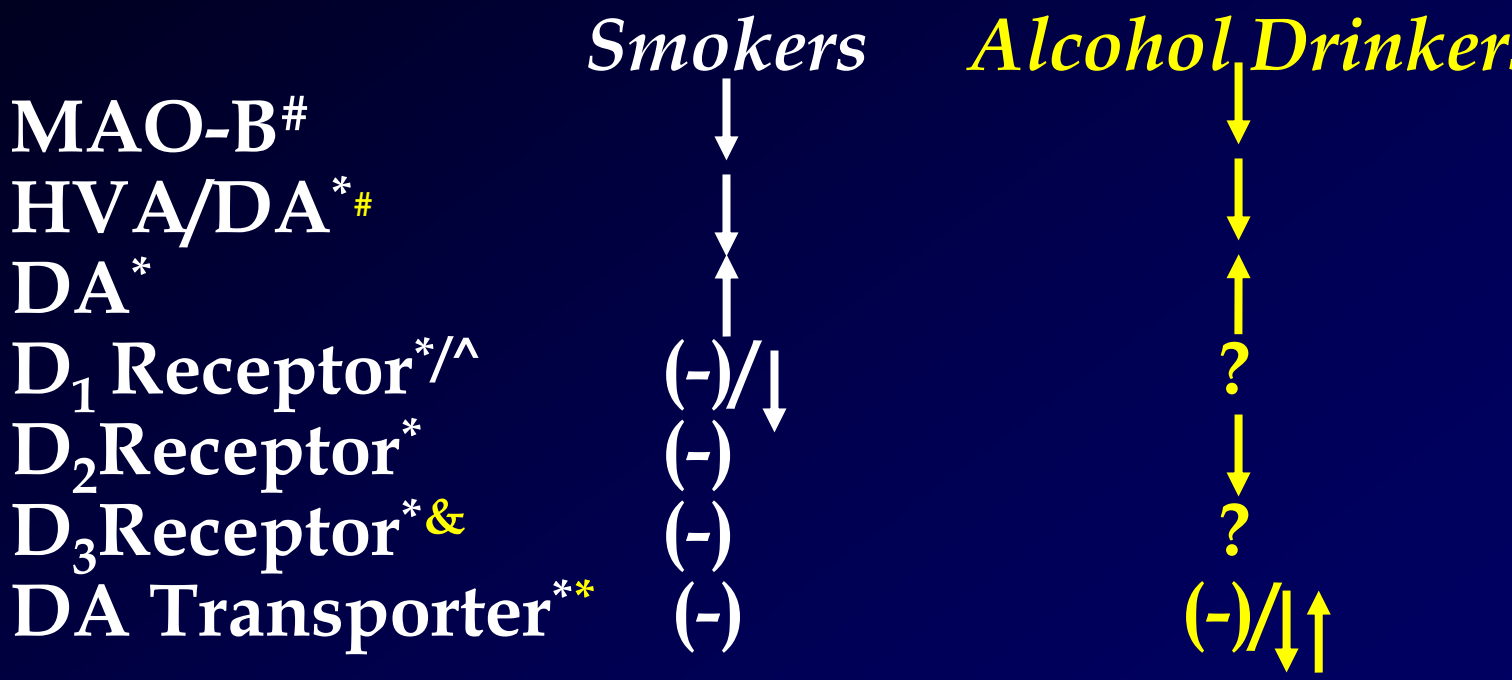
An unknown component of tobacco smoke

↓ **MAO-B activity&**

NET EFFECT ↑ **DA neurotransmission**

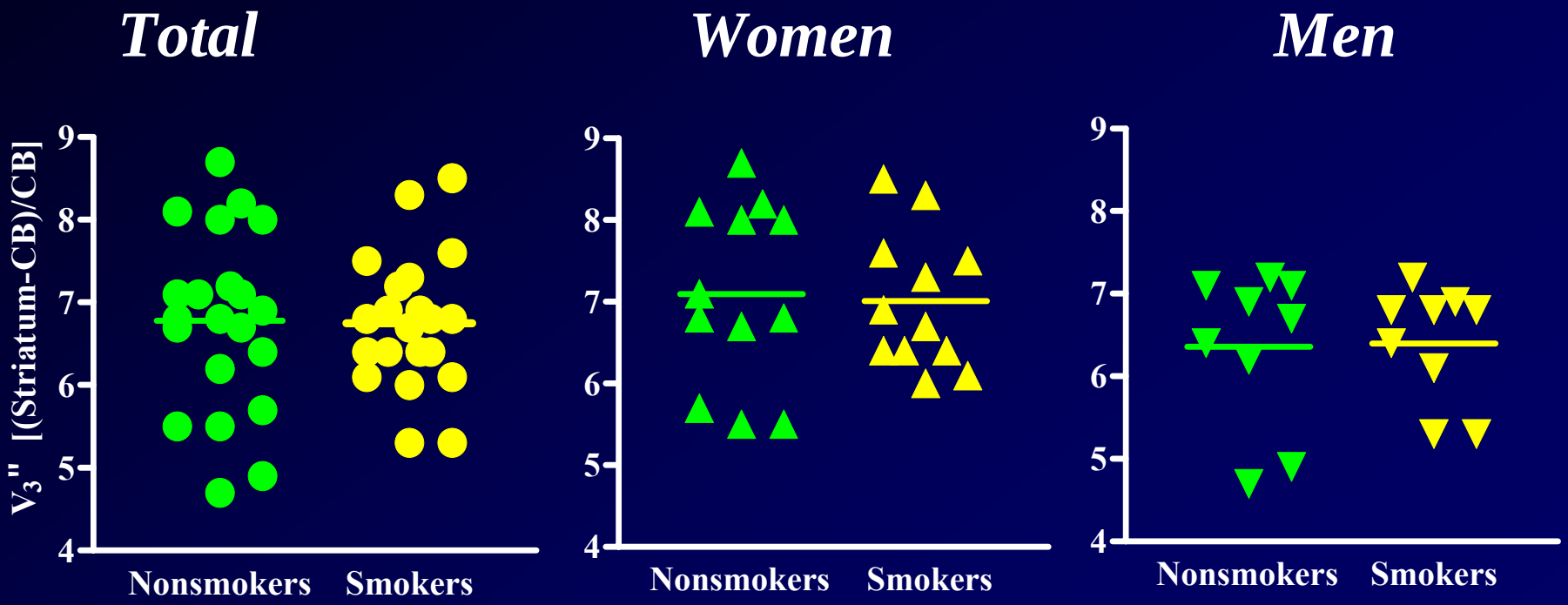
*Izenwasser et al., 1991;@Yamashita et al., 1995;#Westfall et al., 1974; Marien et al., 1983;Rapier et al., 1988;Nisell et al., 1994;Pontieri et al., 1996;&Essman, 1977;Yu and Boulton, 1987

Striatal DA Synapse in Smokers and Alcohol Drinkers

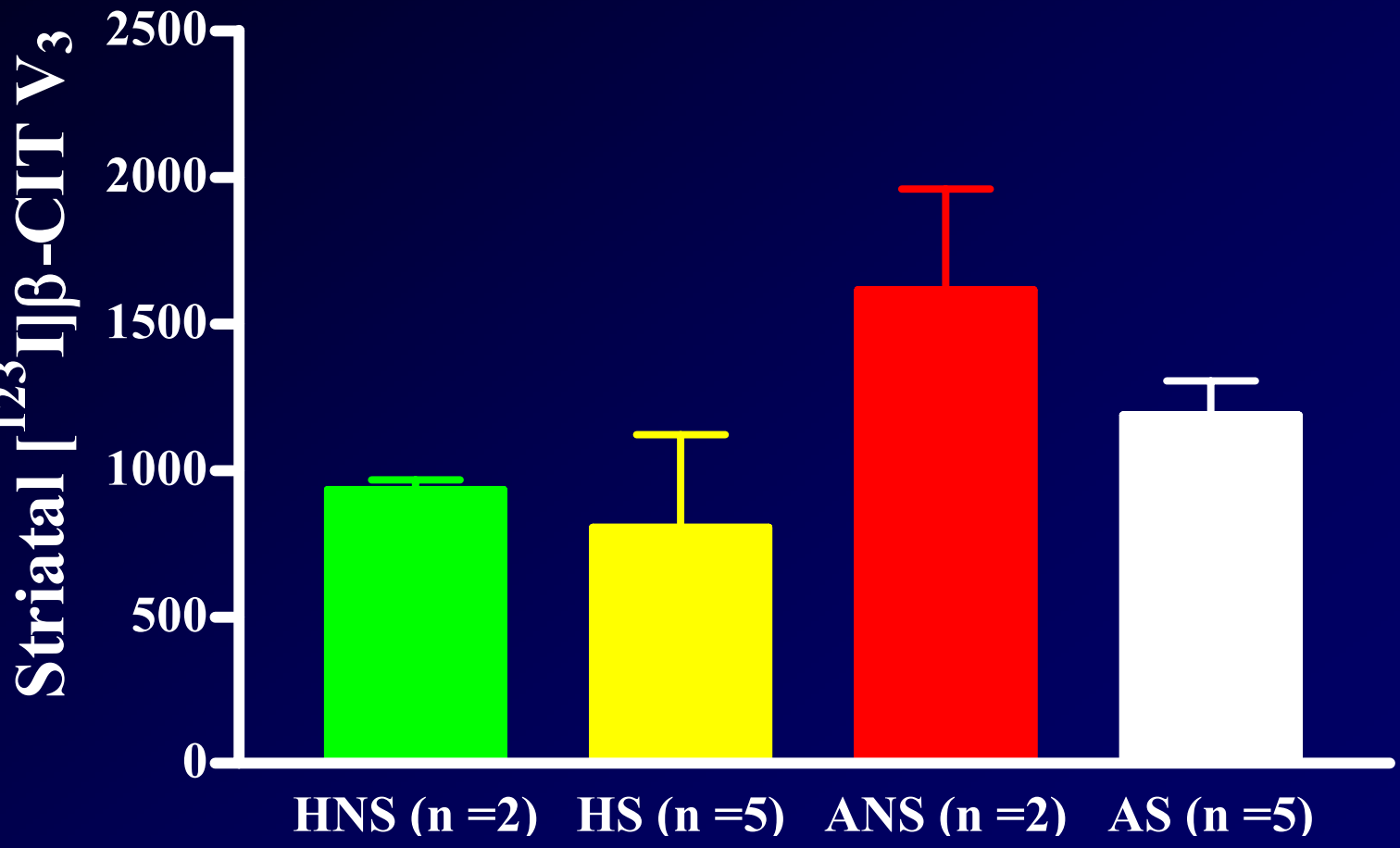


#Fowler et al., 1996;*Court et al., 1998;^ Bliecher et al., 1999;#Fulton et al., 1995; Heinz et al., 1996;*Tiihonen et al., 1995;1998;Volkow et al., 1996; Heinz et al., 1998;Laine et al., 1999; &Hietala et al., 1994

Higher Striatal [^{123}I]β-CIT Uptake in Women vs Men (p = 0.025) No Change in Smokers vs Nonsmokers



Striatal [^{123}I]β-CIT Uptake in Healthy & Alcohol Dependent Smokers & Nonsmokers



Like Alcohol, Tobacco Smoke Facilitates Serotonin Neurotransmission

Via its actions on the cholinergic nicotinic receptor, nicotine indirectly

↓ **5-HT reuptake** (platelet[#*];brain[@])

↑ **5-HT release** (platelet*;brain^)

An unknown component of tobacco smoke

↓ **MAO-A activity**[&]

NET EFFECT ↑ 5-HT neurotransmission

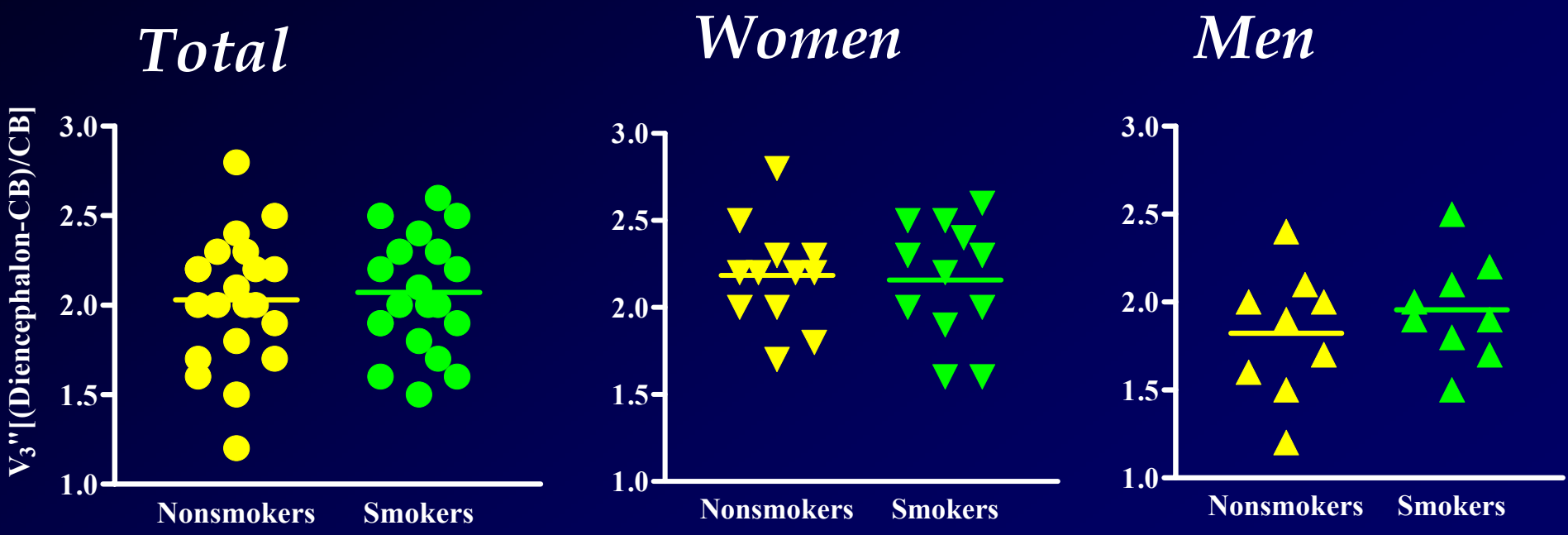
[#]Schievelbein et al., 1967; *Rausch et al., 1989; [@]King et al., 1991; ^Ribeiro et al., 1993;[&]Essman, 1977;Yu and Boulton, 1987

Status of 5-HT Synapse in Smokers & Alcohol Drinkers

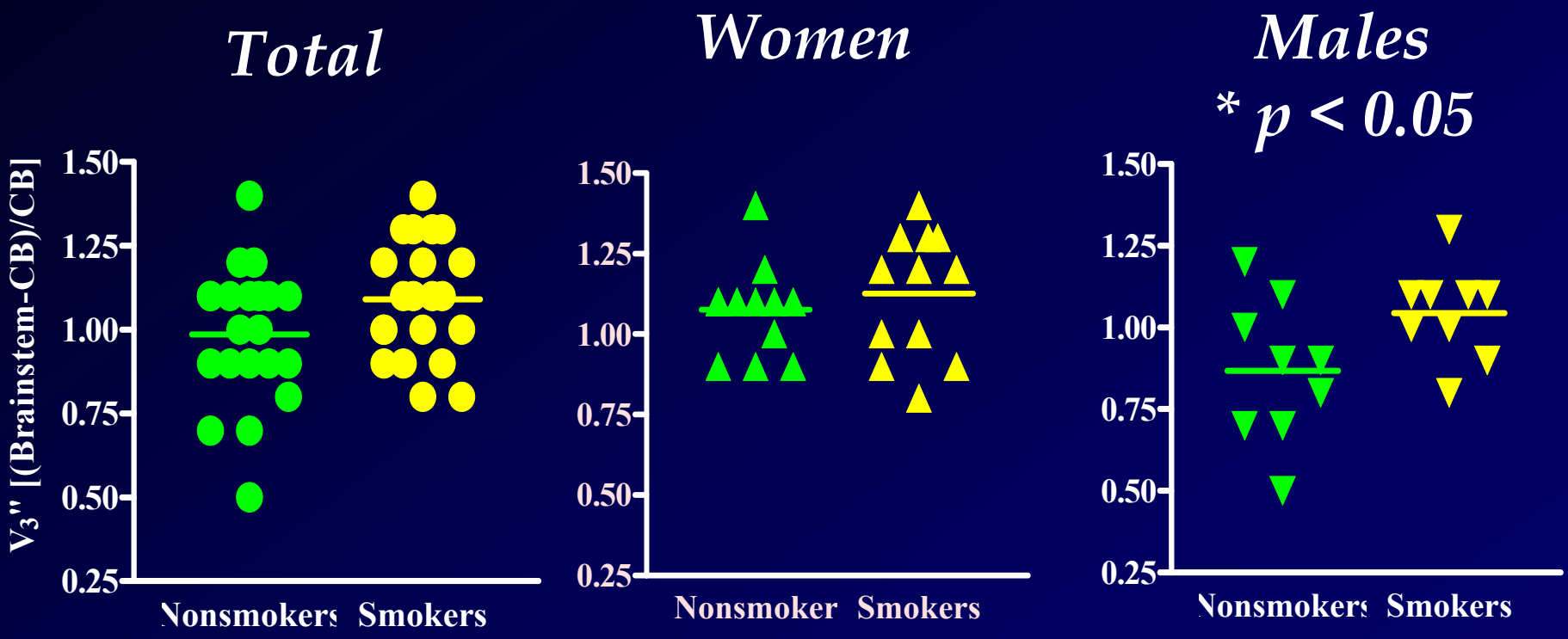
	Smokers	*Alcohol Drinkers*
MAO-A[!]	↓	↓
5-HT (Platelet*Urine[#])	↑	?
5-HIAA (Urine)[#]	↑	↓
5-HT$_{1A}$ Receptor (Brain^)	↑	?
5-HT$_{2A}$ Receptor (Platelet[@]; Brain^)	↑/(-)	(-)
5-HT Transporter	?	↓/(-)

[!]Fowler et al., 1996; *Marasini et al., 1986;Racke et al., 1992; [#]Sparrow et al., 1992; ^Benwell et al., 1990;[@]Markowitz et al., 1999

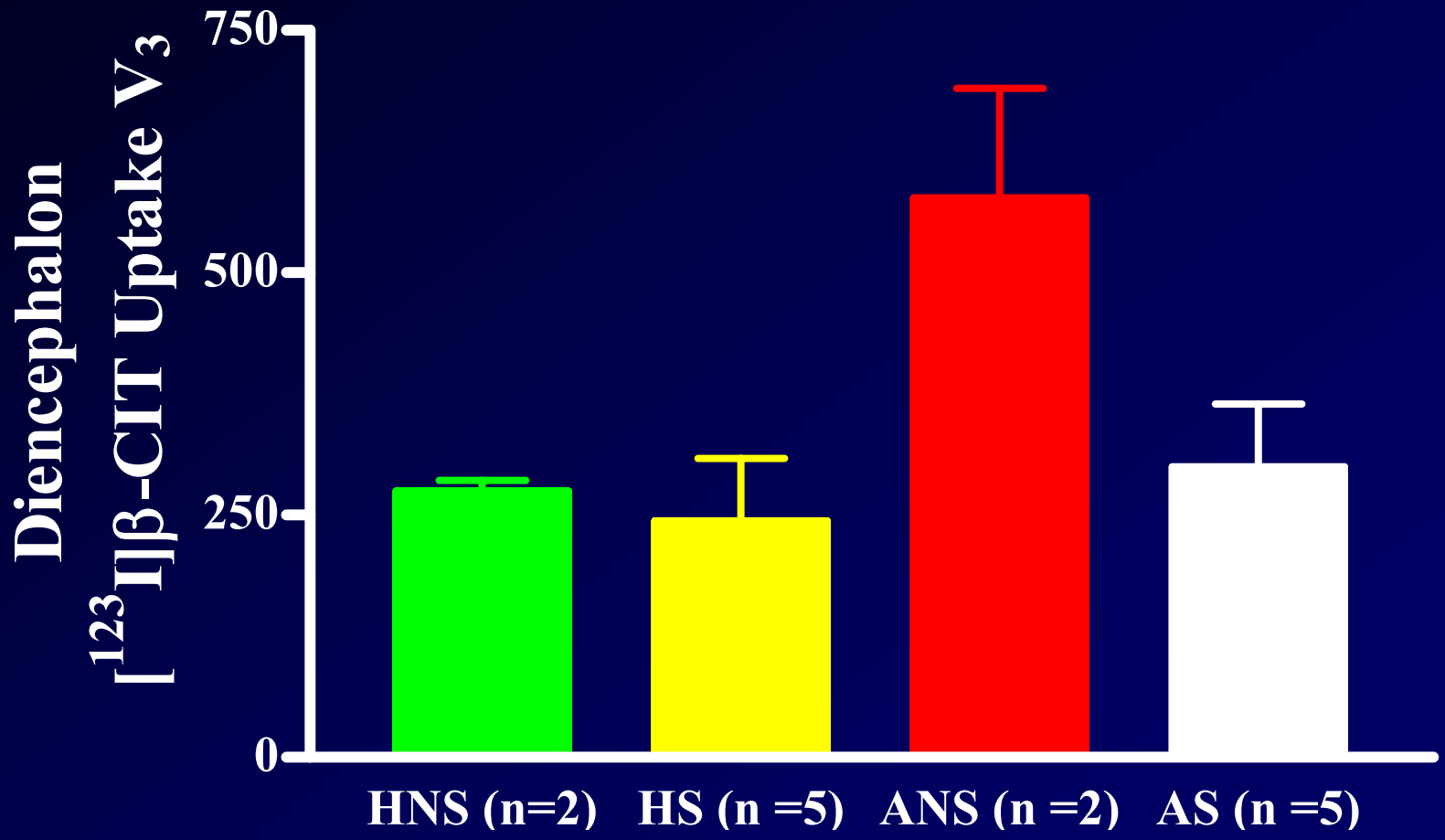
Higher Diencephalon [^{123}I]β-CIT Uptake in Women vs Men (p = 0.008). No Change in Smokers vs Nonsmokers



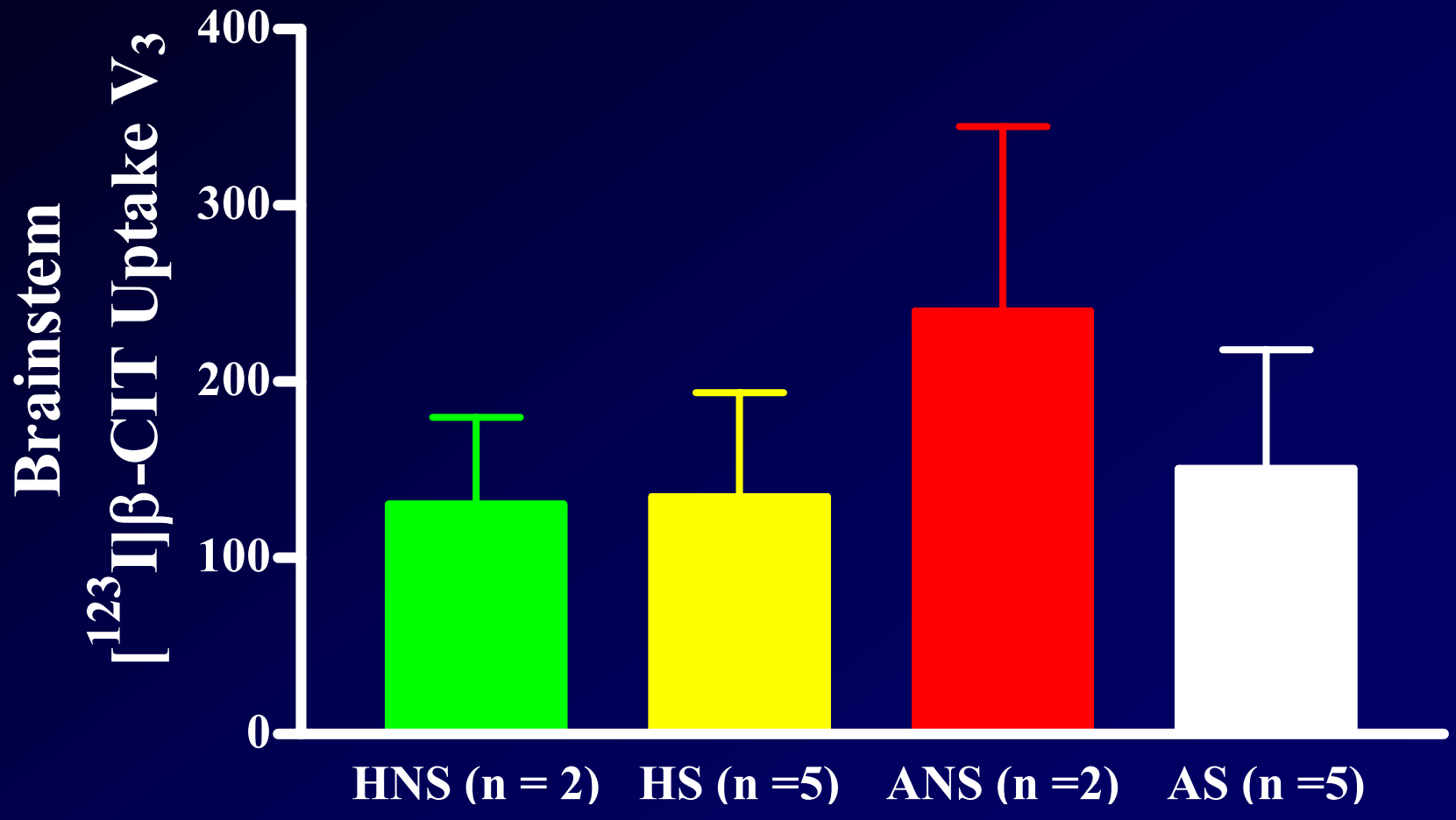
Higher Brainstem [^{123}I]β-CIT Uptake in Women vs Men (p = 0.013) & Men Smokers vs Nonsmokers (p = 0.046)



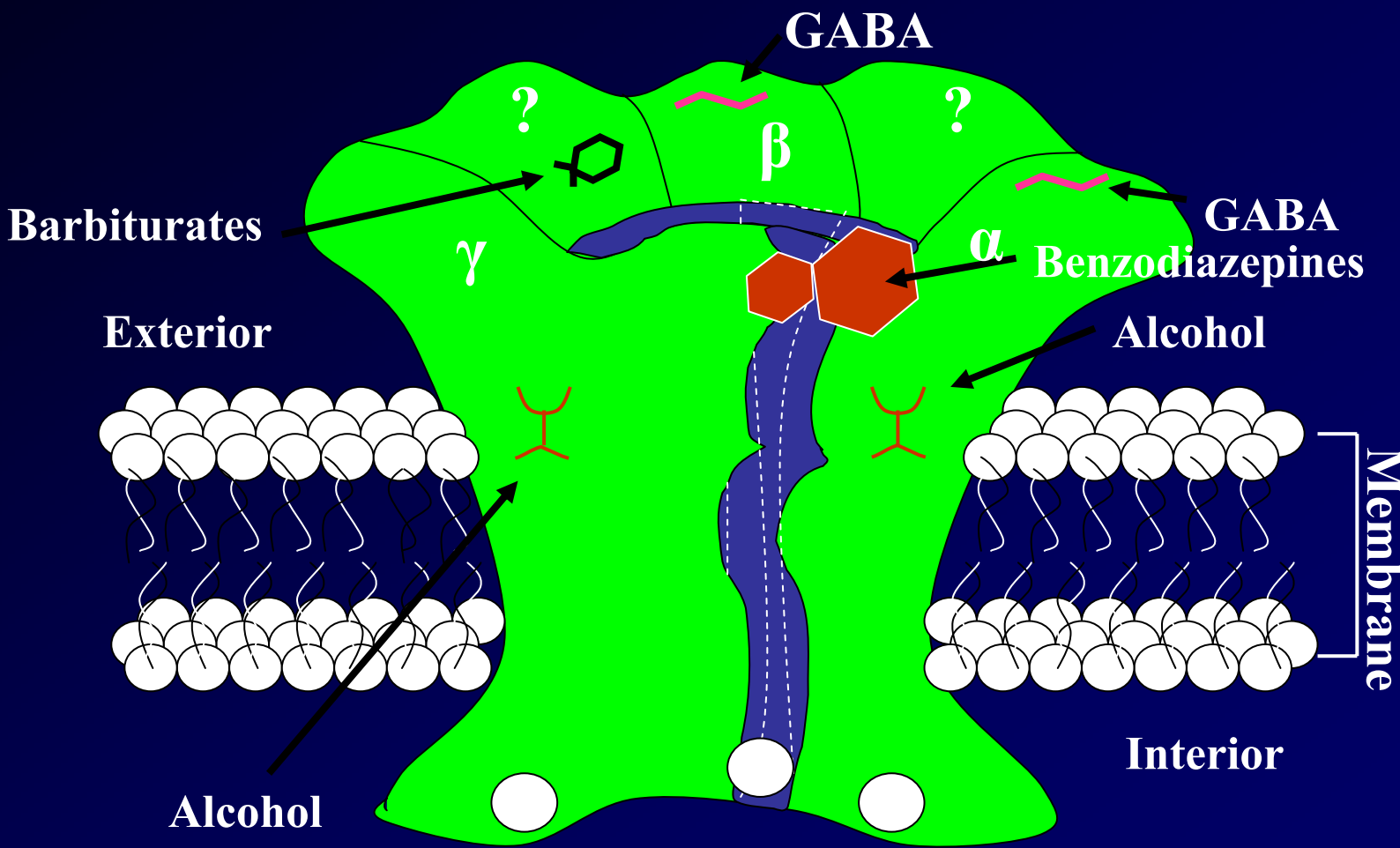
Diencephalon [^{123}I]β-CIT Uptake in Healthy & Alcoholic Smokers & Nonsmokers



Brainstem [^{123}I]β-CIT Uptake in Healthy & Alcoholic Smokers & Nonsmokers



GABA & Ethanol Bind to Distinct but Allosterically Regulated Sites on the $GABA_A$ Receptor



Tobacco Smoke & GABA

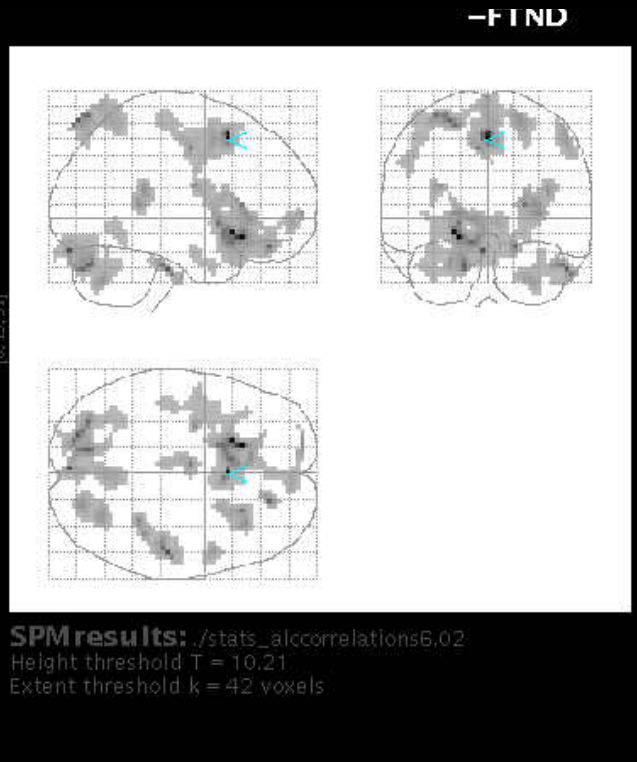
- **Nicotine**
  - **Low doses nicotine enhance GABAergic transmission; higher doses no effect** [Zhu & Chiappinelli, 1999]
  - **Chronic nicotine treatment in mice increase [^{125}I]iomazenil binding sites** [Magata et al., 2000]
- **Beta carbolines**
  - **Competitive antagonists at benzodiazepine receptor** [Totsuka et al., 1999]
  - **Elevated levels of beta carbolines in plasma from healthy and alcoholic smokers** [Breyer-Pfaff et al., 1996]

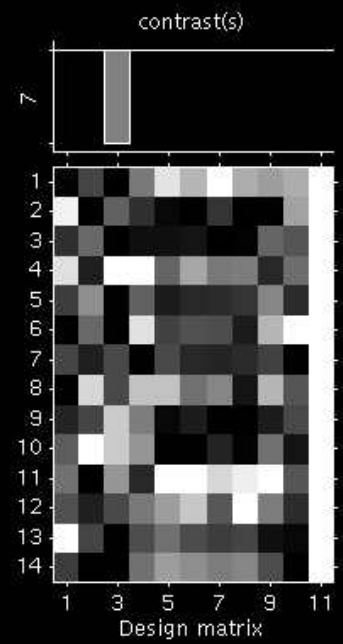
Status of GABA Synapse in Smokers and Alcohol Drinkers

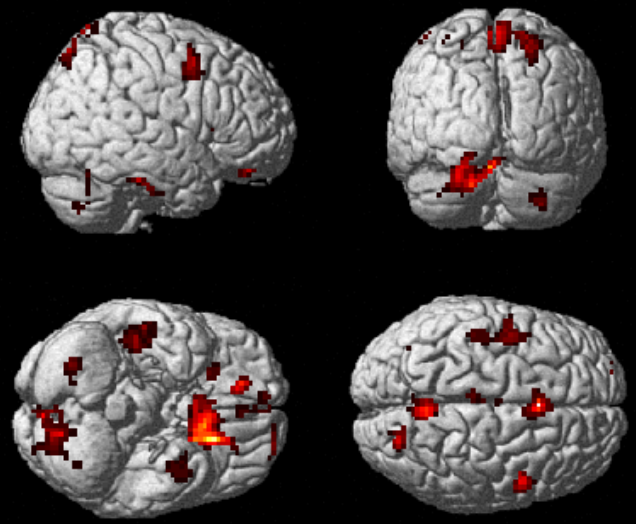
	Smoker	Alcohol Drinker
GABA Plasma/CSF	?	↓
GABA Brain	(-)/↓	↓
$GABA_A$ Receptor (Agonist)	?	↑
$GABA_A$ Receptor (BZ Agonist)	?	(-)/↓↑
$GABA_A$ Receptor (BZ Antagonist)	?	(-)/↓

Tran et al., 1981; Coffman & Petty, 1985; Kril et al, 1988; Freund & Ballinger, 1988; Dodd et al., 1992; Korpi et al., 1992; Petty et al., 1993; Adinoff et al., 1995; Lewohl et al., 1997

Negative Correlation between [^{123}I]Iomazenil Uptake in Alcohol Dependent Subjects Abstinent for < 7 Days and FTND Score for Nicotine Dependence

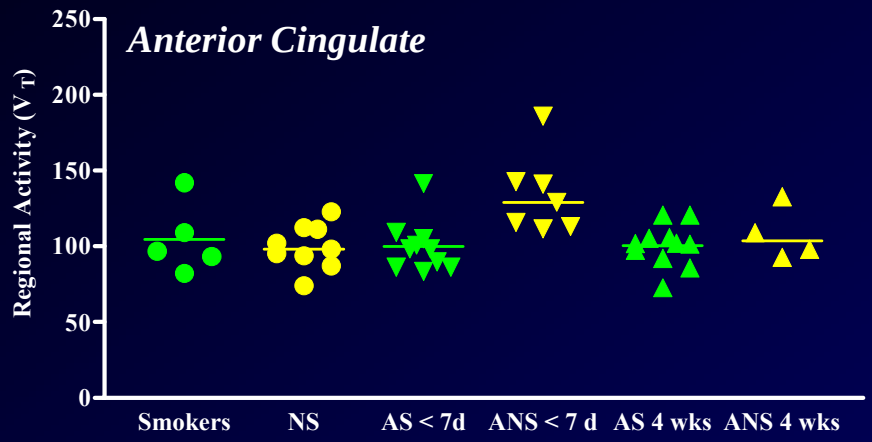


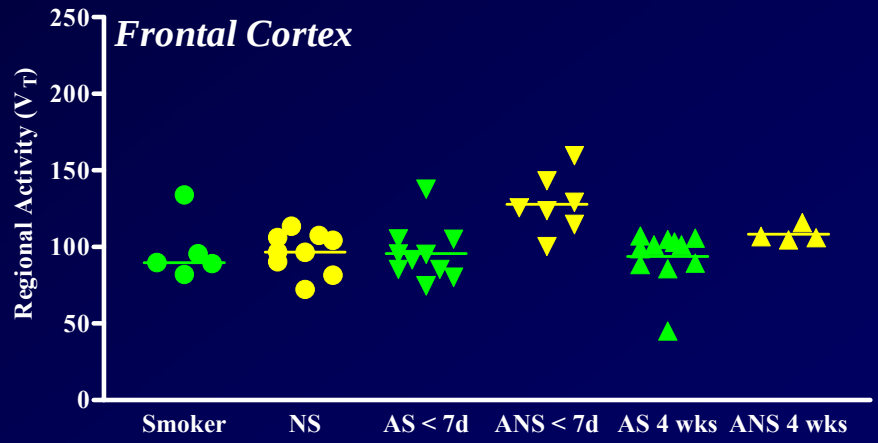


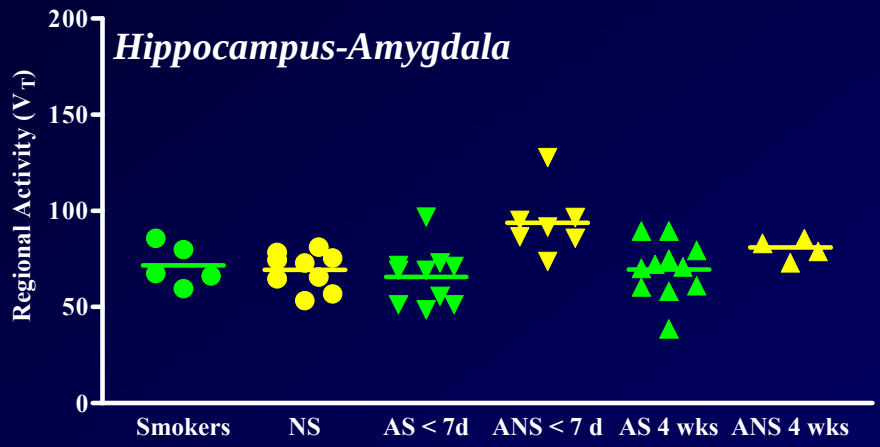


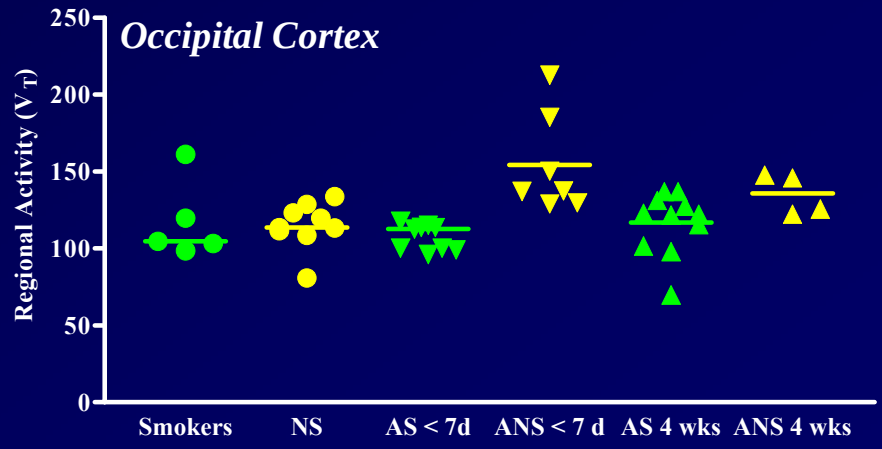
Corrected p values < 0.006 @ cluster level

BDZ-GABA-A Receptor Expression in Healthy & Alcoholic Smokers & Nonsmokers

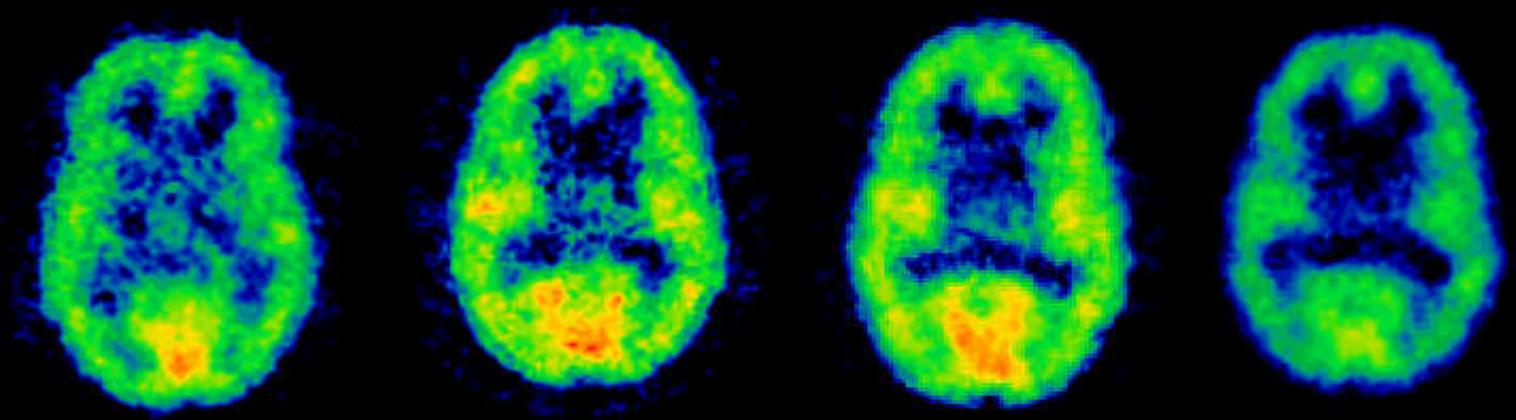








[^{123}I] Iomazenil SPECT Images of GABA-A Receptors



Control

Alcoholic Nonsmoker
5 Days Abstinent

Alcoholic Nonsmoker
25 Days Abstinent

Alcoholic Nonsmoker
157 Days Abstinent

Tobacco Smoke & nAChR

Increased nicotinic agonist binding in

- Peripheral blood cells from tobacco smokers
- Postmortem human brain Benwell et al., 1988; Breese et al; 1997;Court et al., 1998;Perry et al., 1999

Animal studies demonstrate that the upregulation is due to repeated exposure to nicotine

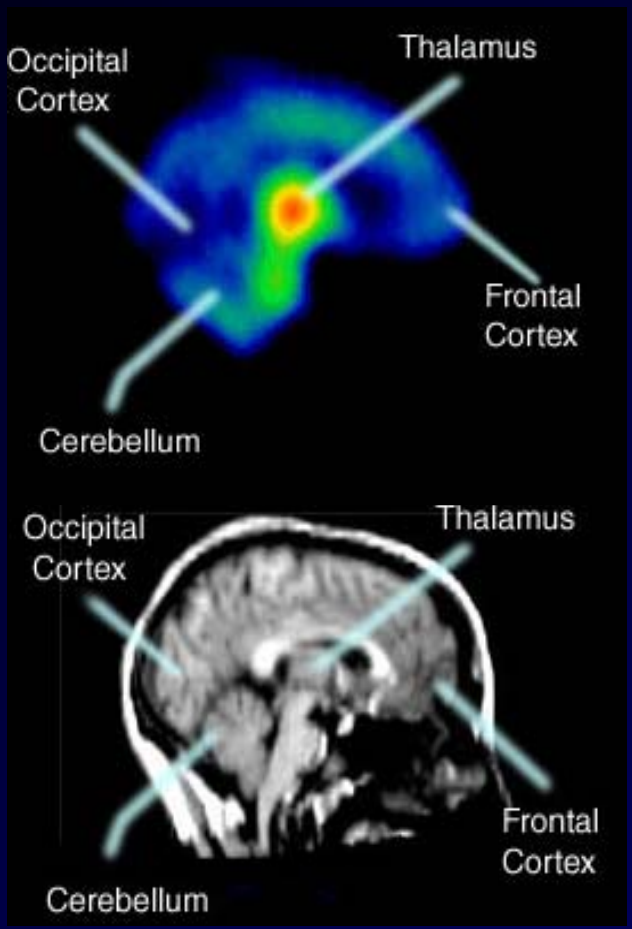
Alcohol & nAChR

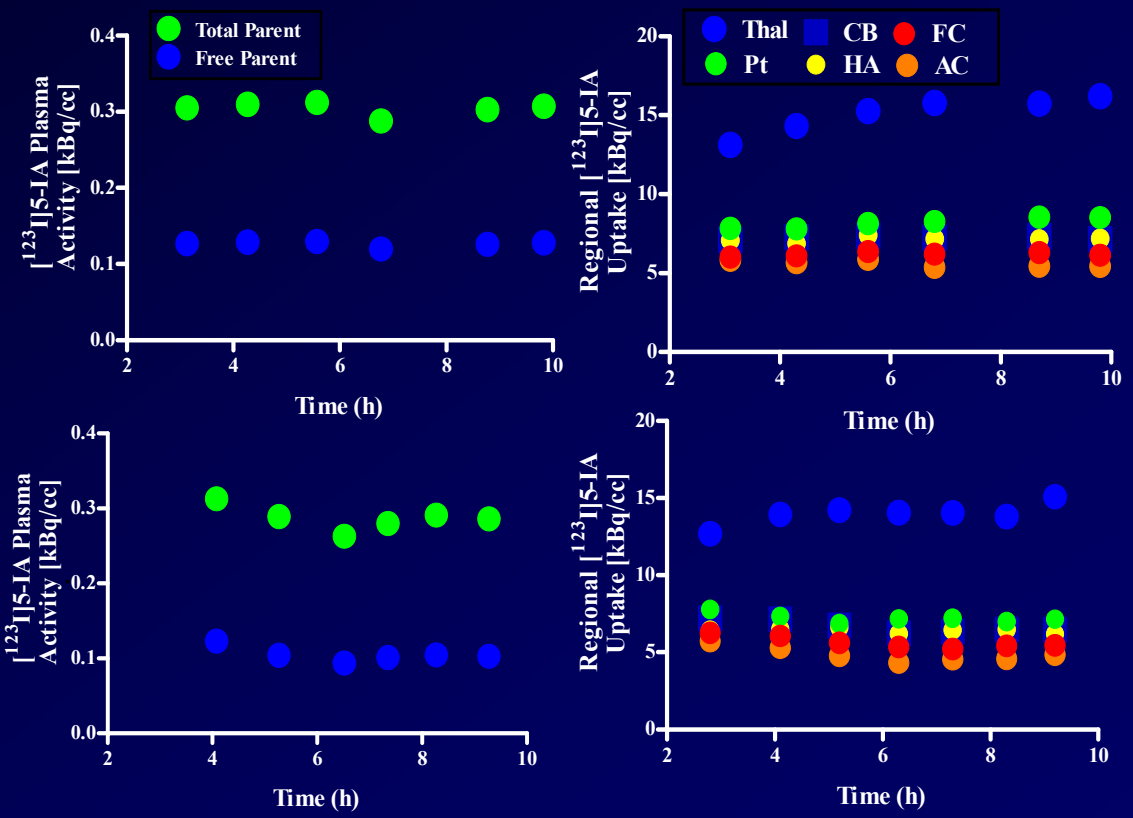
- Low doses of nicotine, decrease or have not effect on ethanol consumption [Gauvin et al., 1993;Katner et al., 1997;Dyr, 1999]
- Nicotine enhances alcohol consumption [Pothoff et al., 1983;Signs et al., 1986; Blomqvist et al; 1996; Gauvin et al., 1993; Le et al., 2000], especially alcohol preferring rats [Gordon et al., 1993]
- Nicotine attenuates ethanol-induced motor impairment [Dar, 1994]

Role of nAChR in Dual Alcohol/Tobacco Smoking: Hypothesis

Tobacco smoking enhances nAChR desensitization. Ethanol may facilitate re-sensitization of β_2-nAChR receptors (and not acute activation or prolonged desensitization) and promote tobacco smoking in alcohol drinkers

Test-Retest Reliability of [^{123}I]5-IA



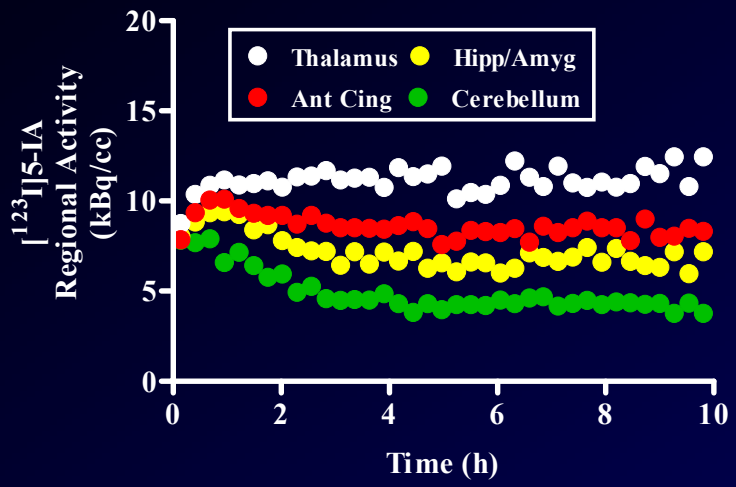


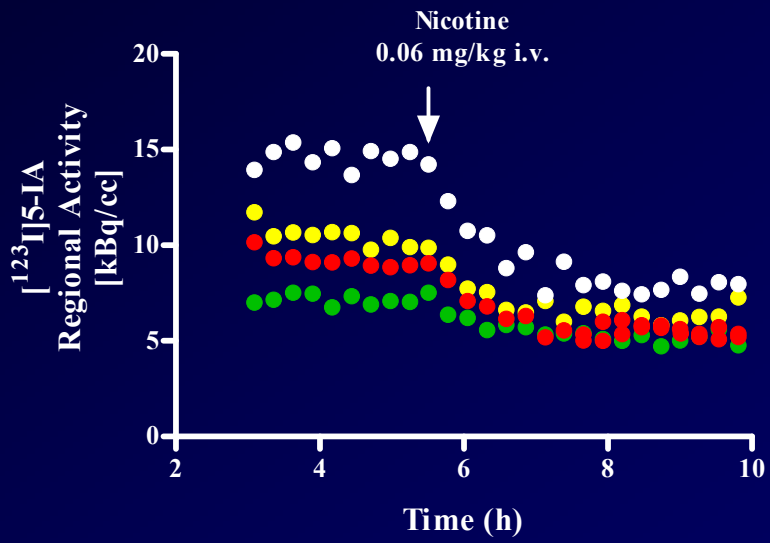
Summary of Test-Retest Reliability for Various Brain Outcome Measures

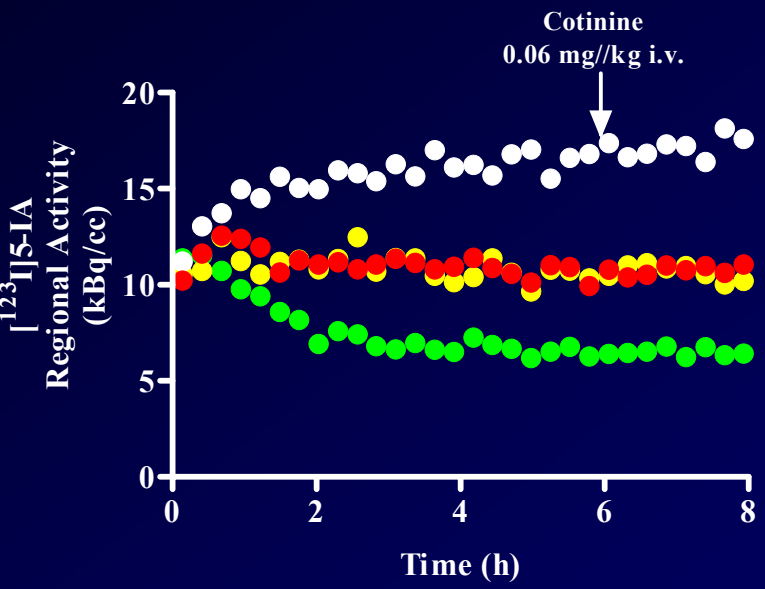
	kBq/cc	%ID/cc	V_T'	V_T
FC	15.2 ± 13.0	13.5 ± 12.6	**5.4± 6.6**	13.4 ± 12.2
AC	15.3 ± 12.3	12.6± 11.5	**5.2 ± 5.3**	13.0 ± 11.8
TC	15.3 ± 12.4	12.3 ± 10.6	**5.6 ± 5.8**	12.1 ± 13.2
OC	17.4 ± 13.4	14.2 ± 12.3	**5.0 ± 5.8**	12.0 ± 12.7
Cd	16.5 ± 13.7	12.0 ± 11.5	**4.8 ± 6.4**	11.3 ± 14.3
Pt	13.1 ± 10.3	11.3 ± 9.4	**7.2 ± 6.9**	12.8 ± 14.0
Thal	12.3 ± 10.1	11.2 ± 9.7	**6.5 ± 4.8**	13.3 ± 12.5
HA	13.7 ± 9.9	11.2 ± 8.4	**5.4 ± 5.7**	12.1 ± 11.7
CB	16.3 ± 13.6	12.8 ± 12.1	**5.9 ± 5.4**	13.8 ± 13.5

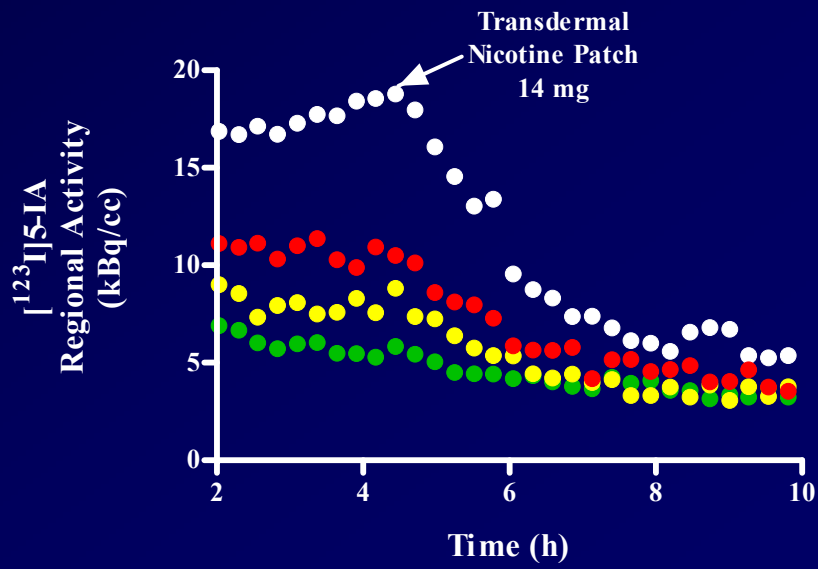
The mean + S.D. % Test-Retest Reliability is shown (n = 10).

Displacement of [^{123}I]5-IA-85830 by Nicotine in Nonhuman Primate Brain

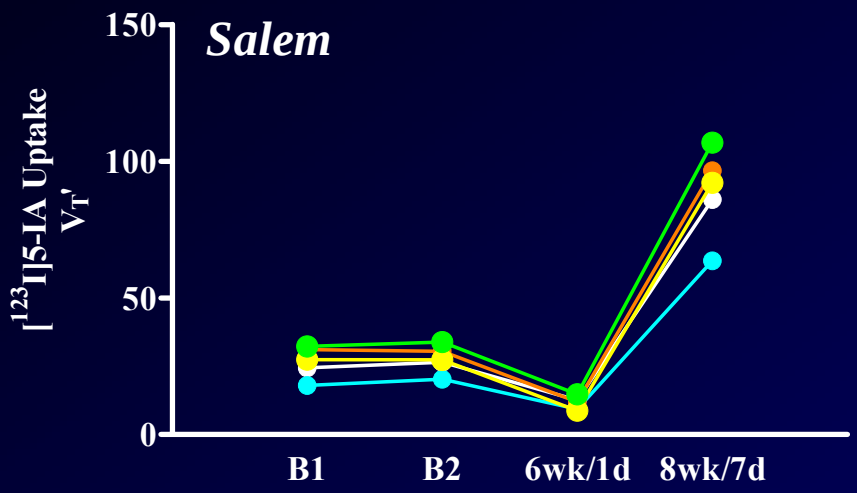


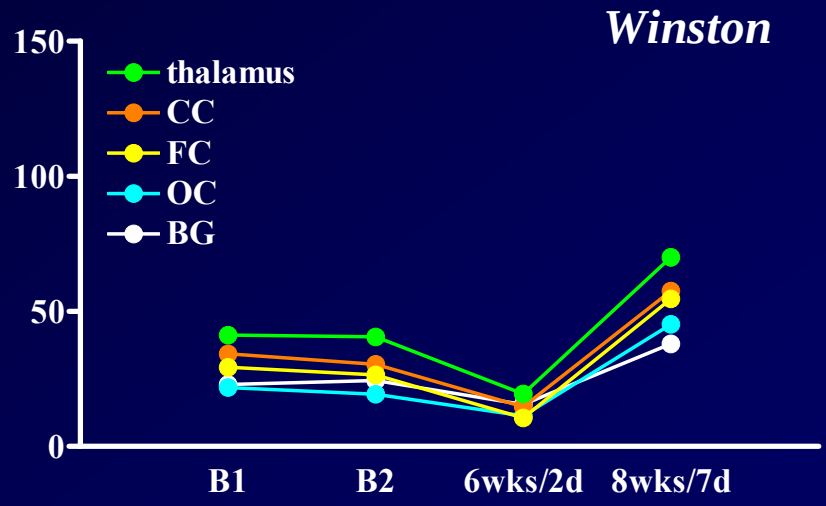


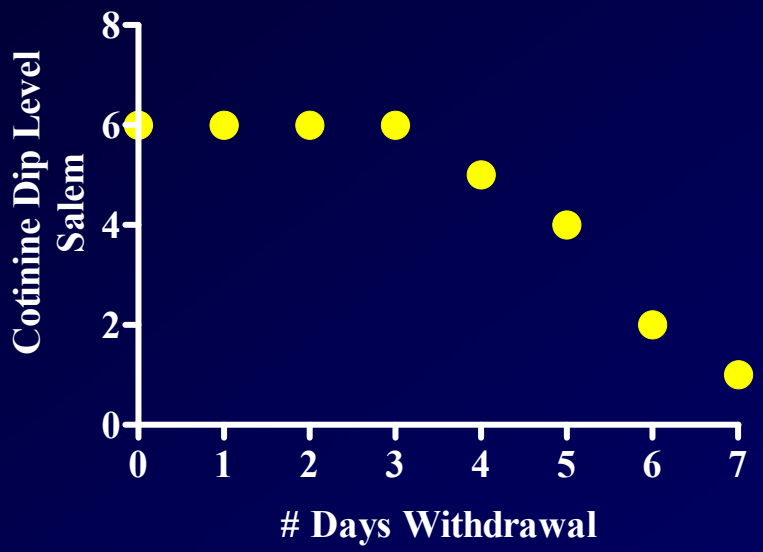


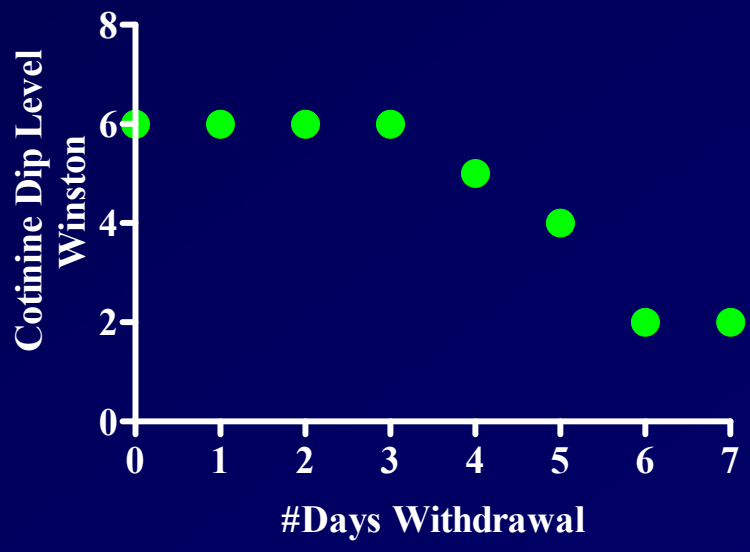


[^{123}I]5IA SPECT Imaging of Nonhuman Primates Administered Oral Nicotine



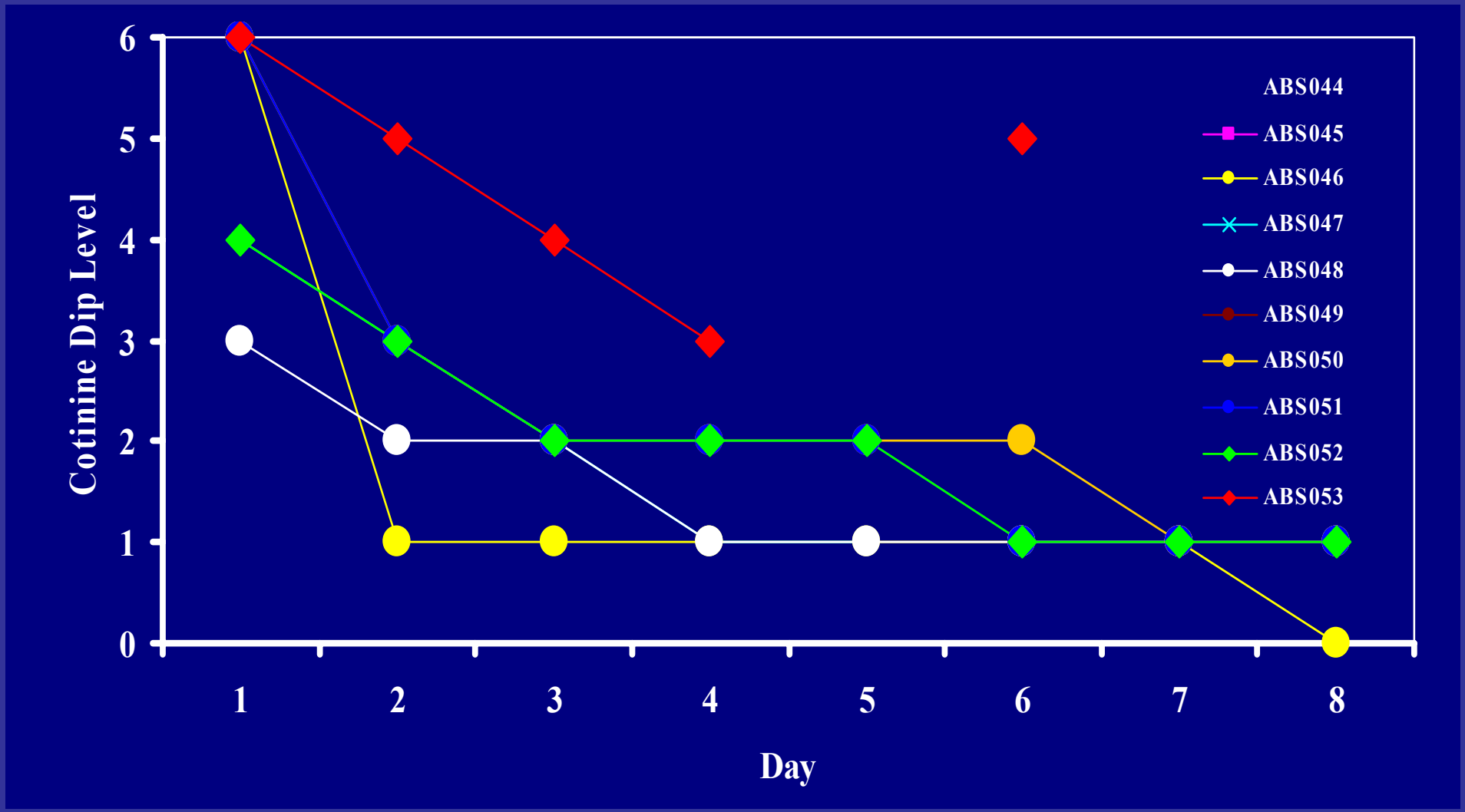




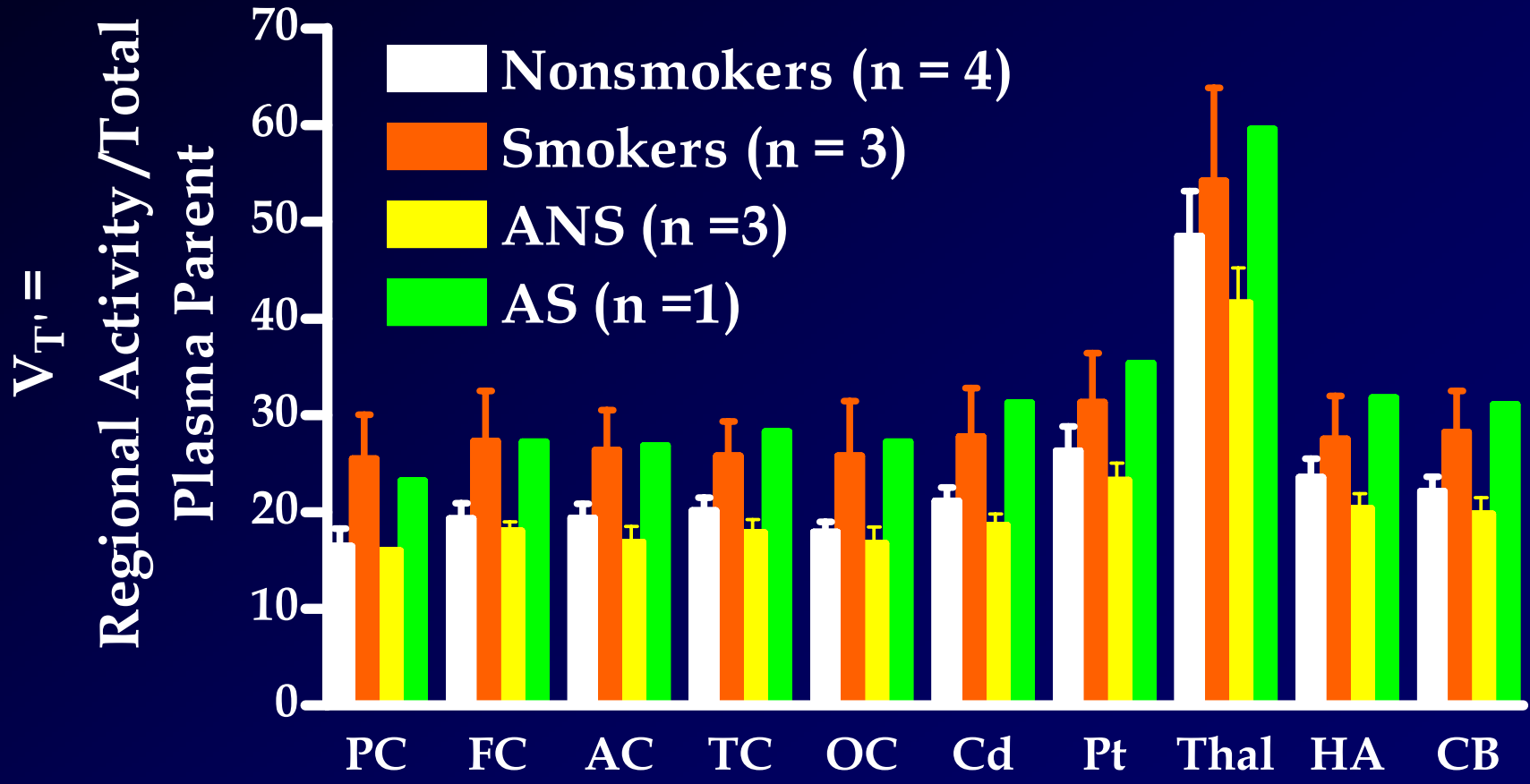


Urinary Cotinine in Human Tobacco Smokers Over the First Week of Abstinence

[Krishnan-Sarin & Colleagues, unpublished data]



[^{123}I]5-IA-85830 Imaging of nAChR in Healthy & Alcohol Dependent Smokers & Nonsmokers



SUMMARY

Critical need to control for possible regulatory effects of tobacco smoke in brain imaging studies of alcoholics

- Alcohol Abstinence*Smoking
- Alcohol Drinking* Smoking Cessation
- Alcohol Abstinence*Smoking Cessation
- All of above*Genotype
- All of above*Personality Traits
- All of above*Sex

- Chronic effects of tobacco smoking on blood flow

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