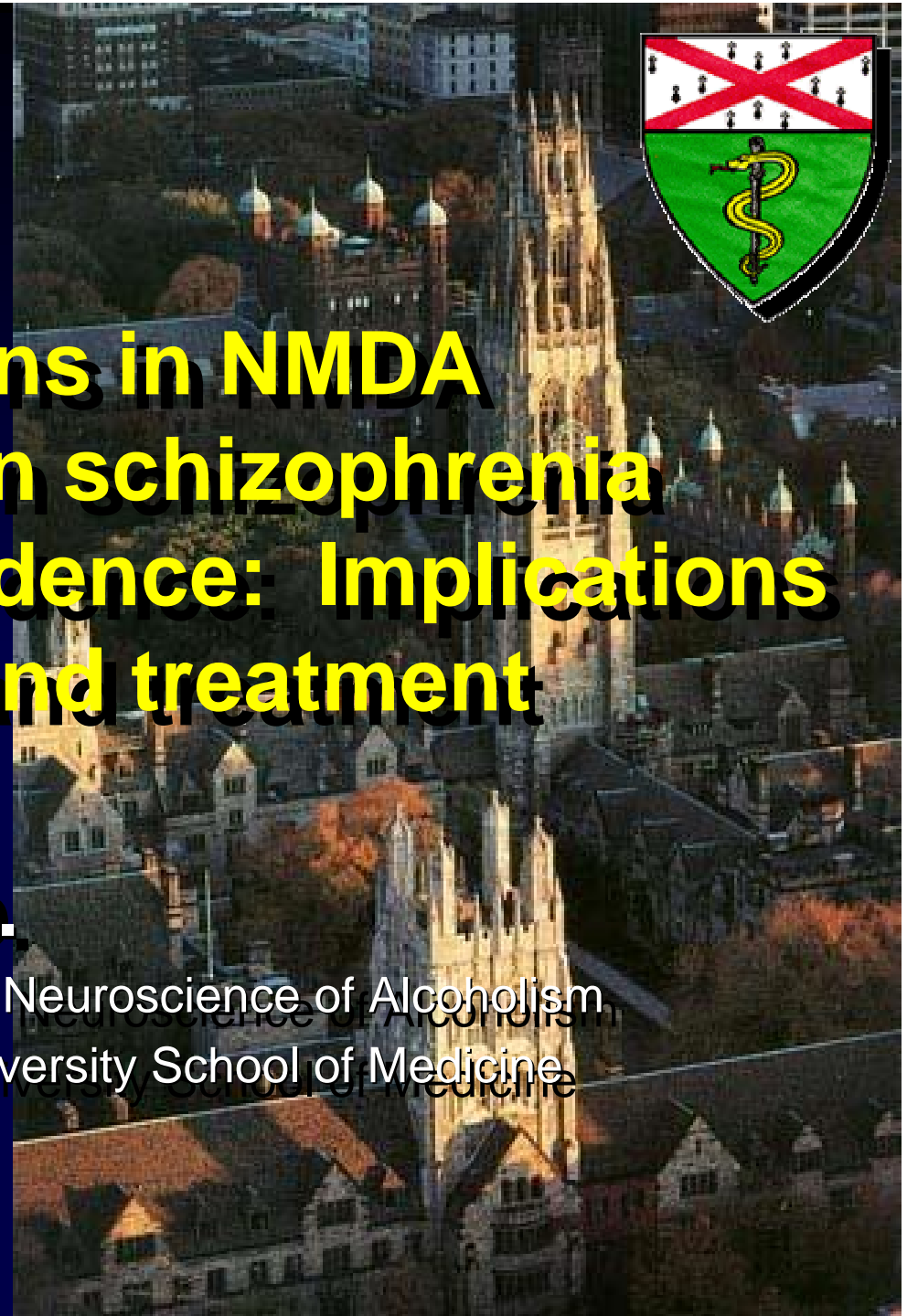


Opposing alterations in NMDA receptor function in schizophrenia and alcohol dependence: Implications for addiction risk and treatment

John H. Krystal, M.D.

NIAAA Center for the Translational Neuroscience of Alcoholism
Department of Psychiatry, Yale University School of Medicine



Ketamine response as an indirect measurement of NMDA receptor function

- **Reduced ketamine response is associated with increases in NMDA receptor function:**
 - Tolerance or cross-tolerance to NMDA receptor antagonists is associated with upregulation of NMDA receptor ligand binding and mRNA (Newell et al. J Neural Trans 2007; Oh et al. Neurochem Res 2001)
- **Increased ketamine response is associated with decreased NMDA receptor function:**
 - mGluR5 antagonists decrease NMDA receptor function and increase reactivity to NMDA receptor antagonists (Homayoun et al. NPP 2004)

Outline

- **Enhanced NMDA receptor function in alcoholism:** Reduced experience of “intoxication” and motivation/reward dysregulation may promote heavy drinking
- **Reduced NMDA receptor function in schizophrenia:** Dysregulation of reward circuitry may promote substance abuse, but increased sensitivity to NMDA receptor antagonist effects may limit intensity of alcohol consumption

Intoxication Cues Prevent Heavy Drinking: From Caroline Knapp (who died of alcoholism complications)

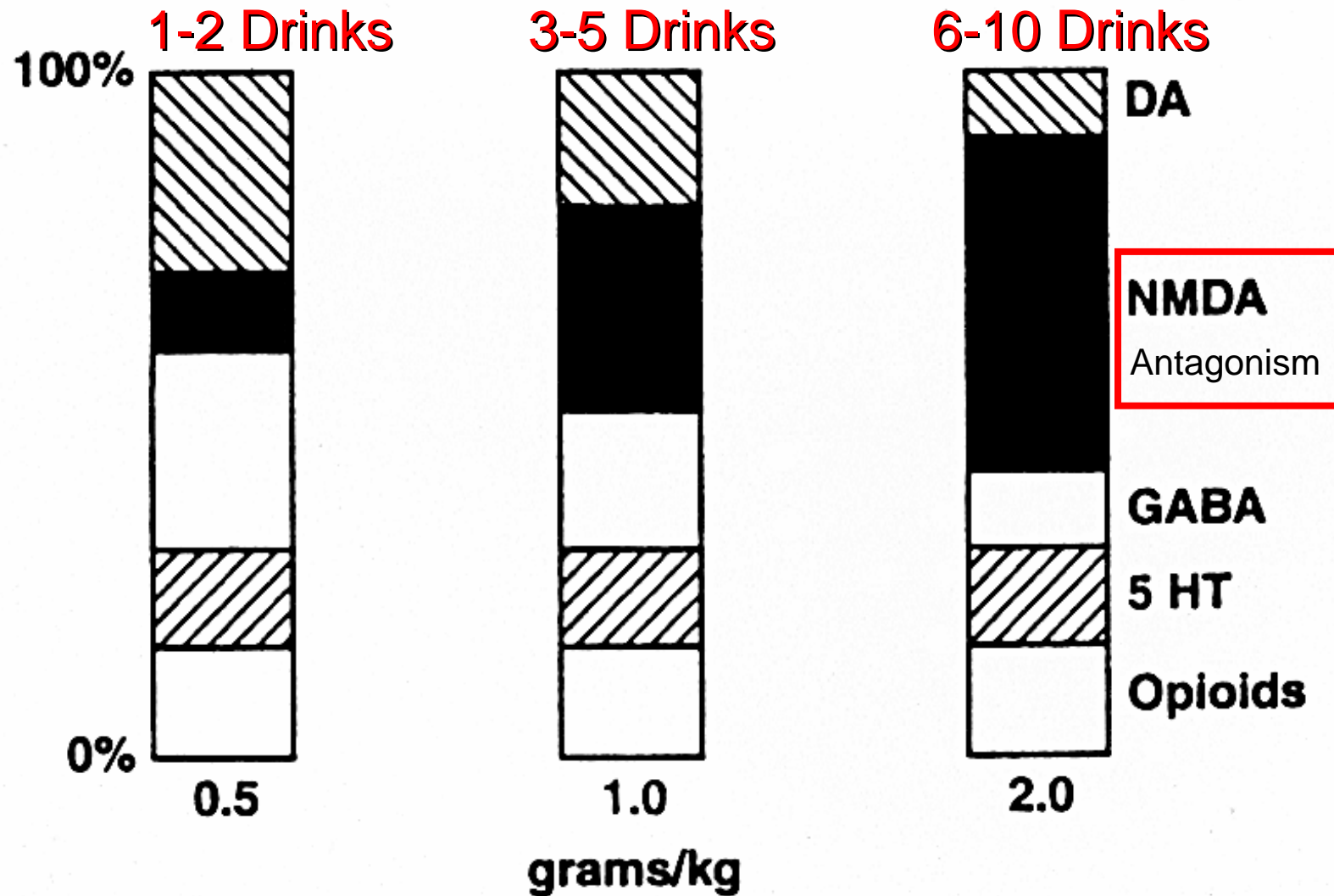
Normal drinkers seem to have a kind of built-in alarm system that tells them...to stop drinking...that elusive internal alarm goes off and says, *No More...Not mine.*

From: *Drinking: A Love Story*

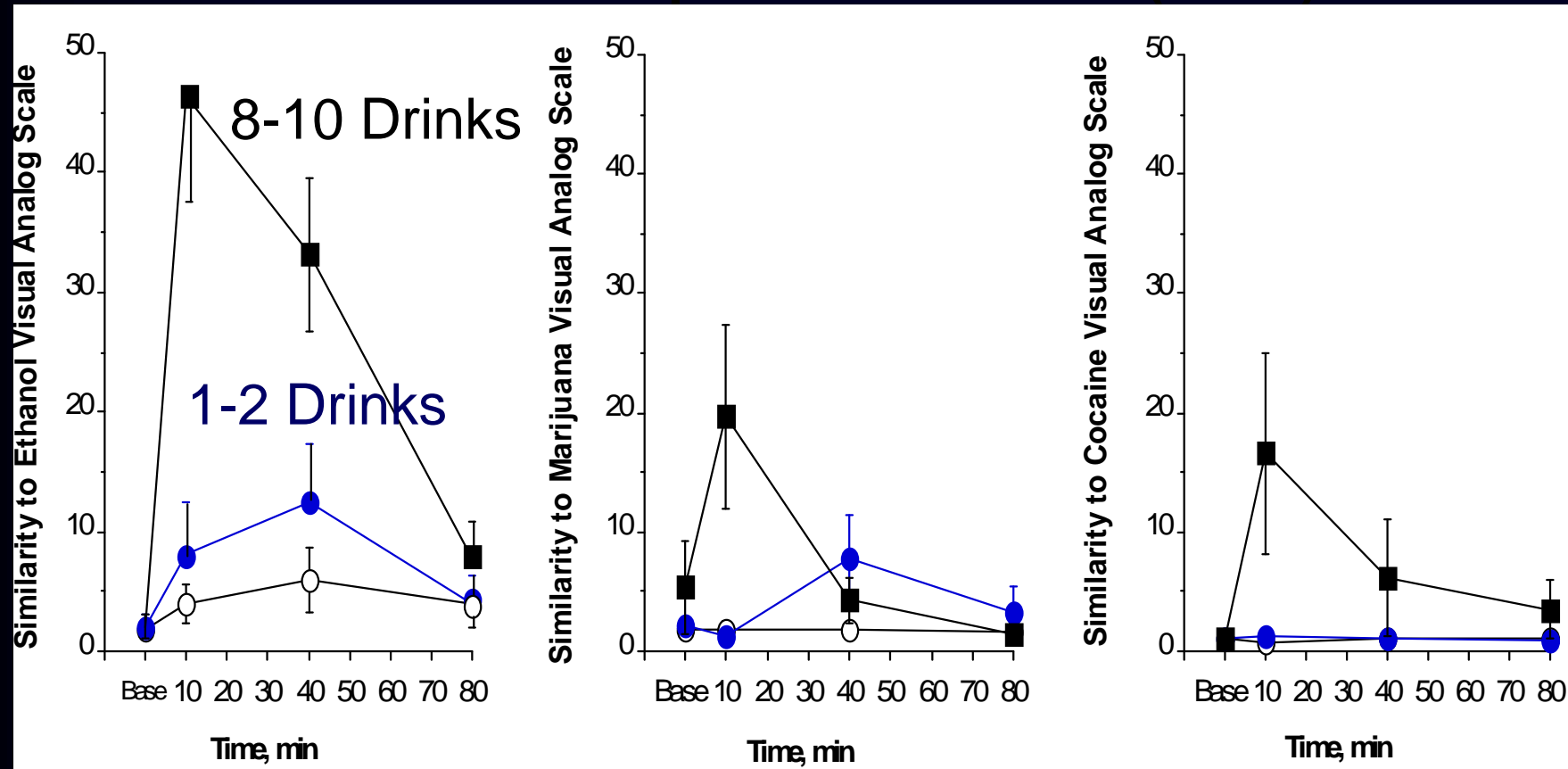
P125-126

Neuropharmacology of Ethanol Reinforcement

(K. Grant)



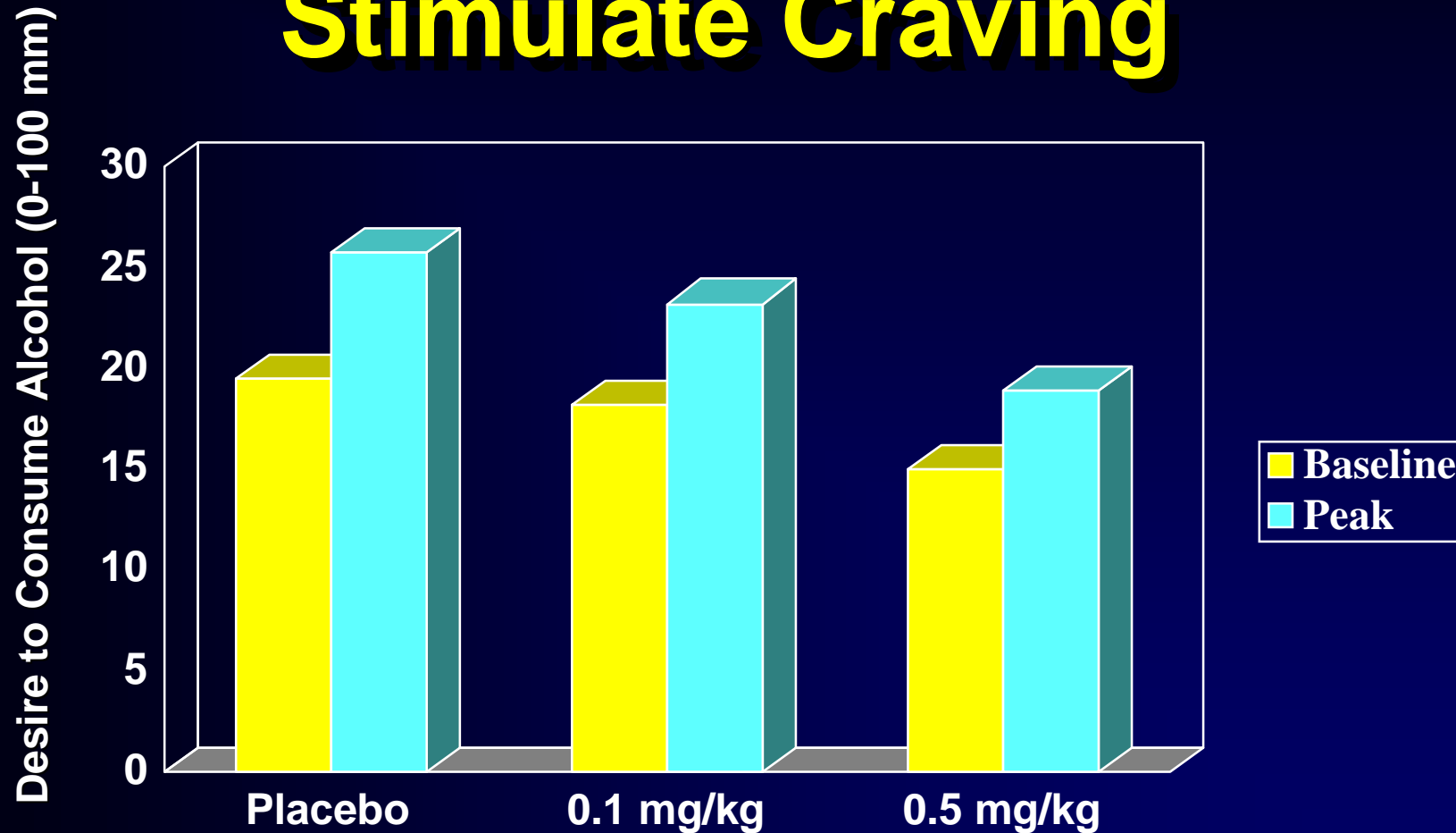
Ketamine Effects are Preferentially Similar to Ethanol Relative to Marijuana and Cocaine in Ethanol Dependent Patients (N=20)



Similarity of ketamine effects, from left to right, to ethanol, marijuana, and cocaine. Symbols: open circle: placebo; filled circle: 0.1 mg/kg; filled square: 0.5 mg/kg
Similarity to ethanol vs. marijuana and cocaine by contrast: $F[1]=6.7$, $p=.02$

Krystal et al. Arch Gen Psychiatry 1998

But Ketamine Does NOT Stimulate Craving

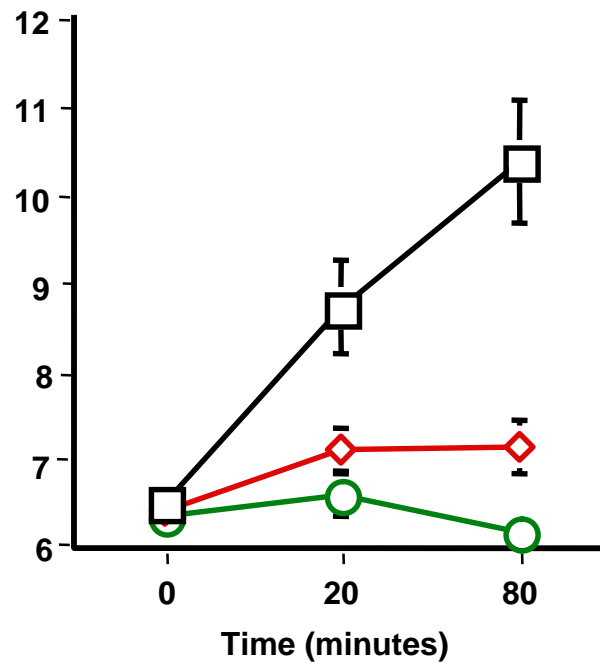


P=NS

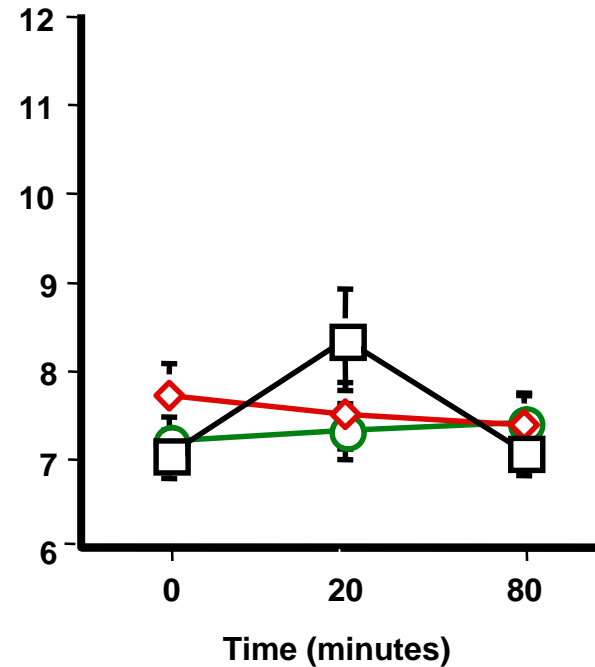
Alcohol Dependence: Blunted Dysphoric Response to Ketamine

BPRS Anxious-Depression Factor Scores

Healthy Human Subjects N=26



Ethanol Dependent Patients N=34



Krystal et al. *NPP* 2003



Saline

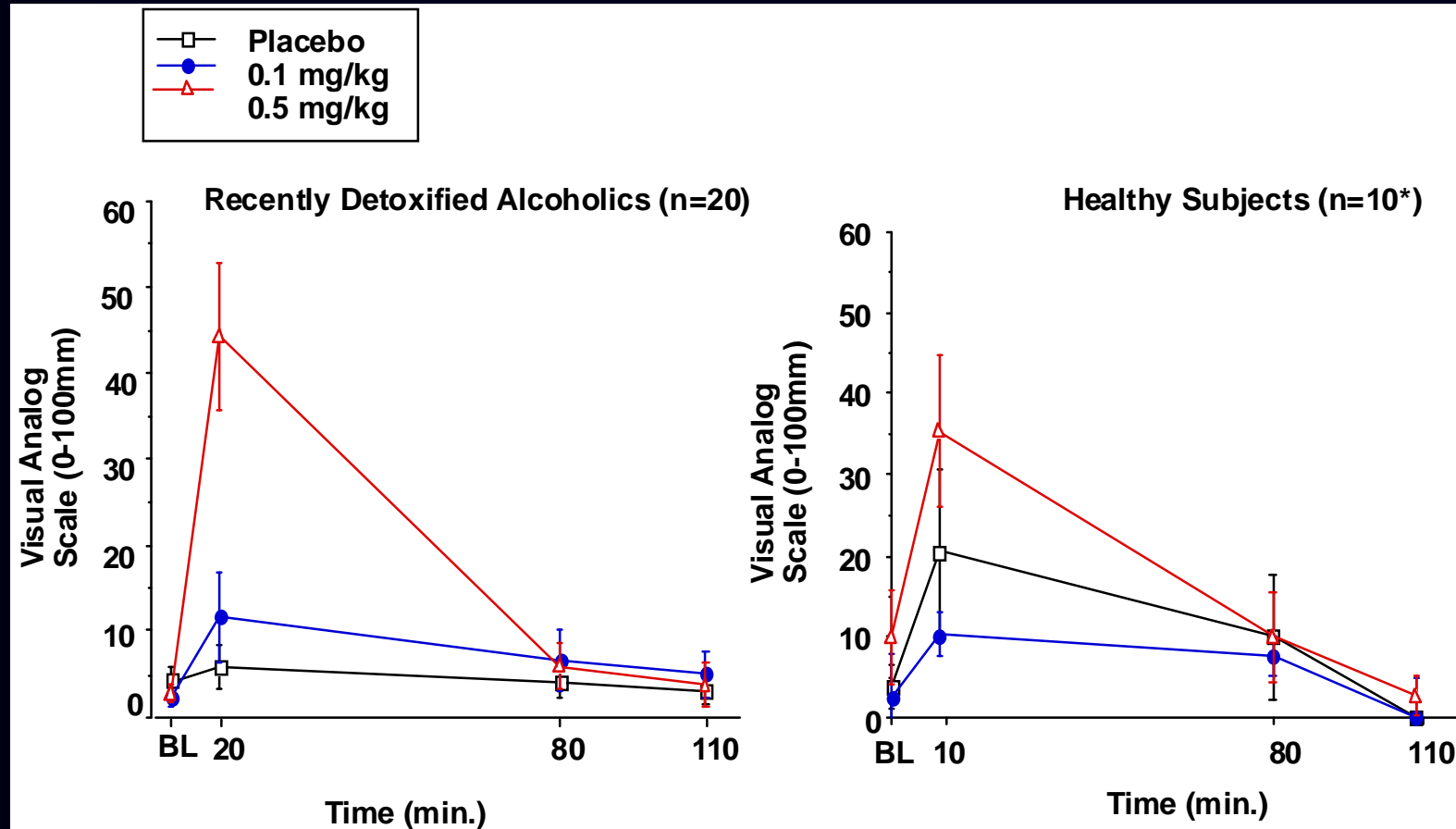


0.1 mg/kg



0.5 mg/kg

Preserved Ketamine "High" in Patients?



ANOVA:

Ketamine Dose by Time: $F= 8.3$; $df=6,168$, $p=.0001$

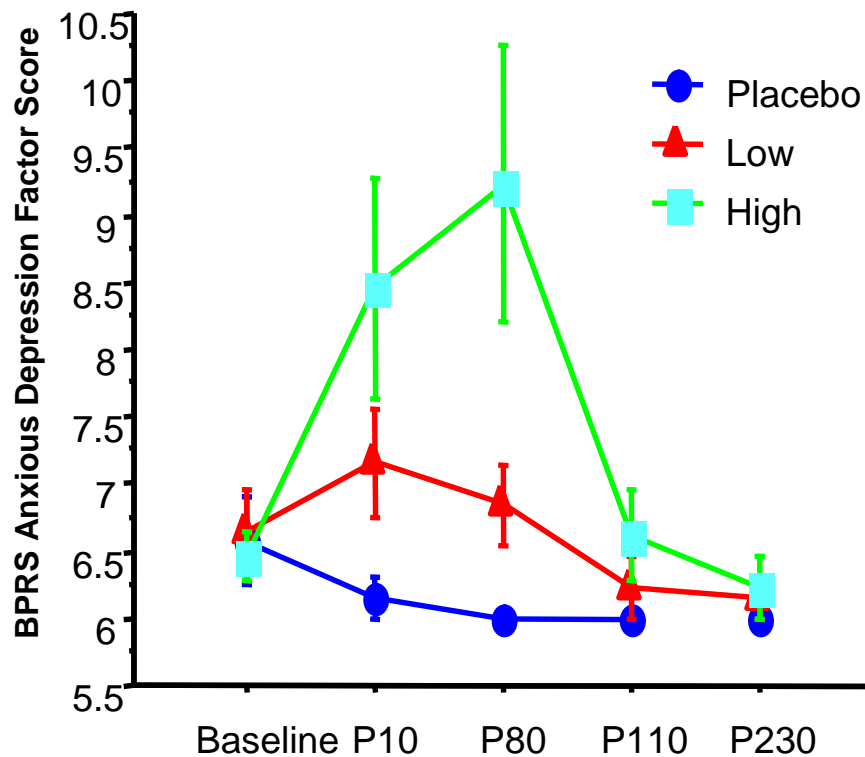
Ketamine Dose by Time by Diagnosis: $F=1.8$;

$df=6;168$; $p=.08$

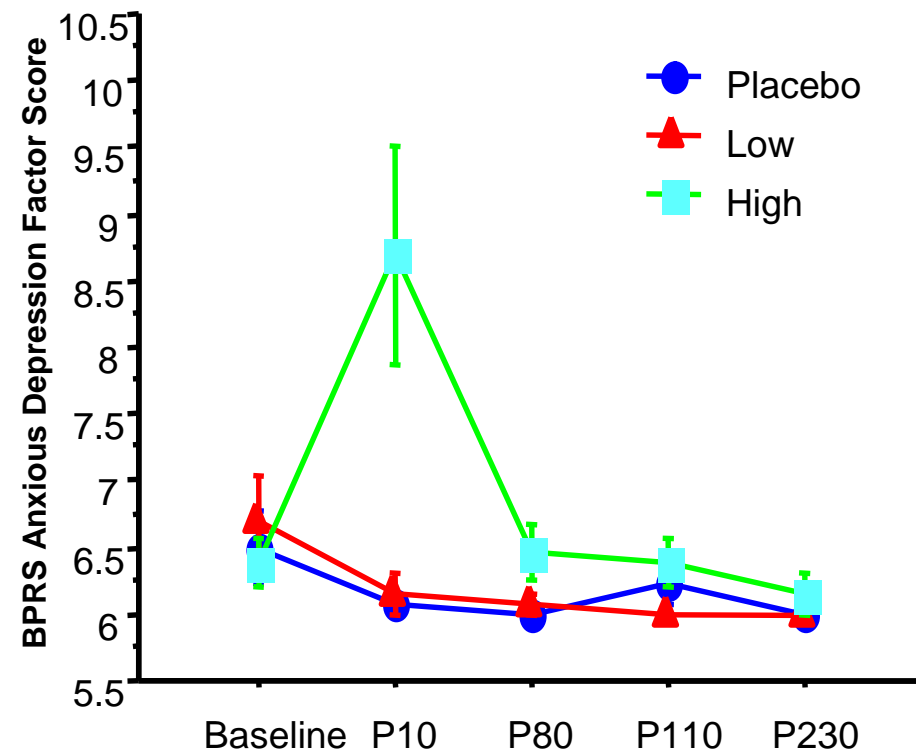
*Analysis of complete sample pending

“ Family History Positive” (FHP) Subjects had Blunted Anxious Dysphoric Mood Compared to FHN Subjects (I. Petrakis et al. *AJP* 2004)

**BPRS Anxious Depression – FHN
by Dosage**



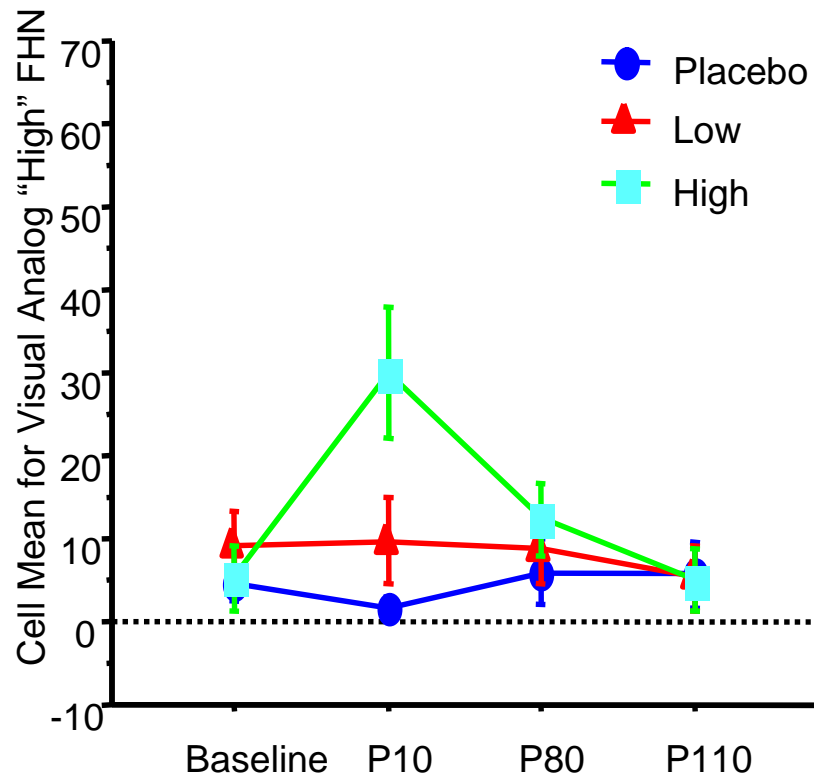
**BPRS Anxious Depression – FHP
by Dosage**



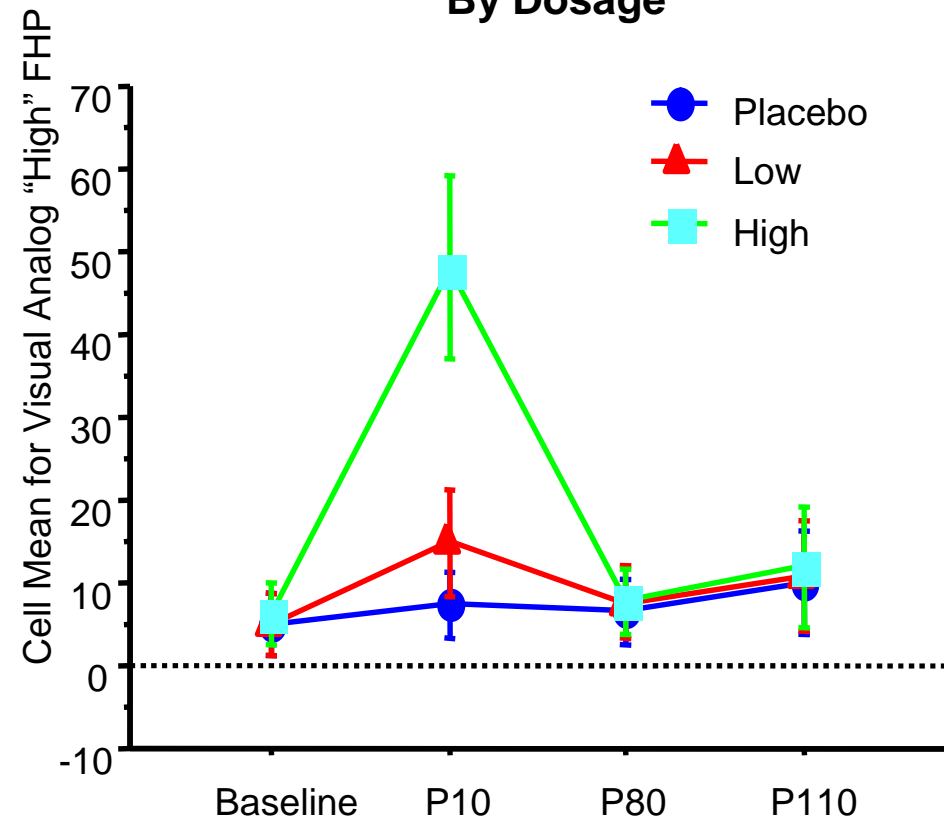
ANOVA: Ketamine Dose by Time by Diagnosis: $F(8,360)=2.19, p=.03$

Ketamine-Induced "High" on Visual Analog Analog in FHP vs. FHN subjects

Visual Analog "High" – FHN
By Dosage



Visual Analog "High" – FHP
By Dosage



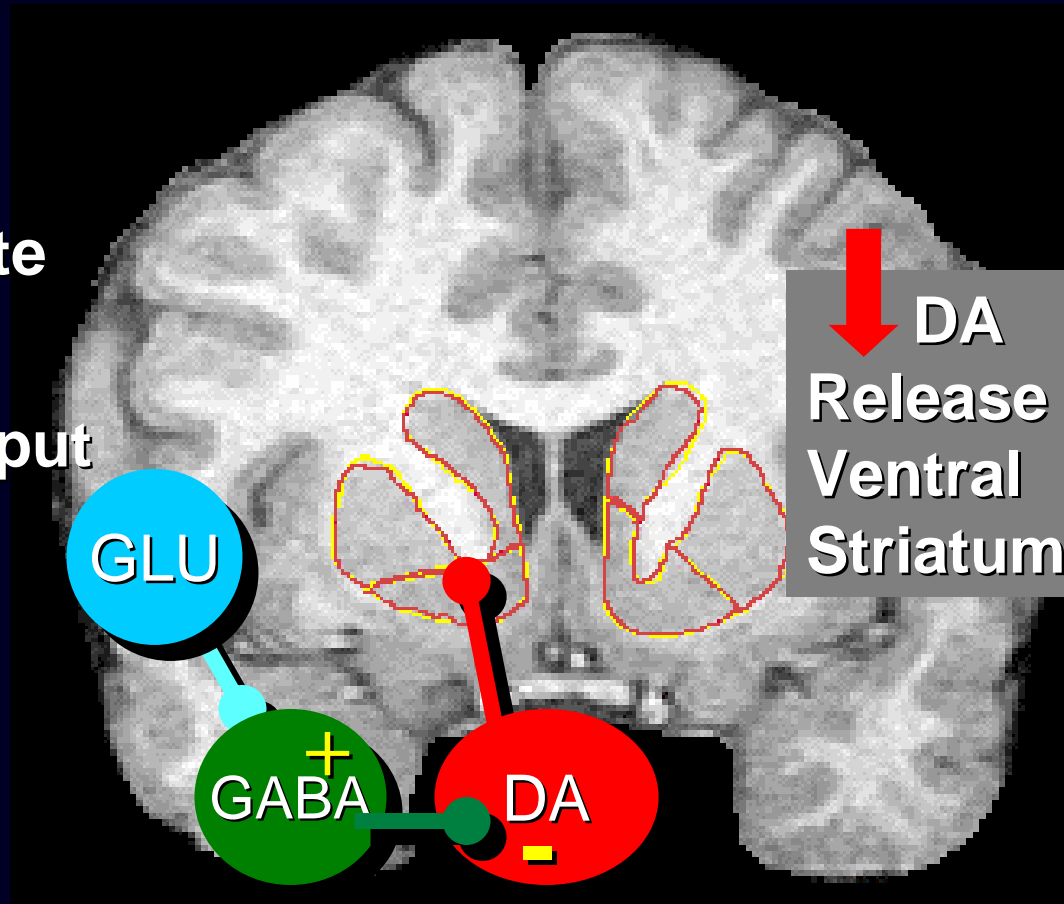
Summary: Enhanced NMDA receptor function reduces intoxication signal?

- Blockade of NMDA receptors generates an “intoxication signal” that may be a negative feedback on drinking and may suppress heavy drinking
- Reduced sensitivity to **DYSPHORIC** effects of ketamine in groups at risk for heavy drinking may reflect **reduced negative feedback** on drinking
- Preserved **REWARDING** effects of ketamine in the “at risk” group may signal a shift in the **REWARD VALENCE** of NMDA antagonists toward reward

Would enhanced NMDA receptor function also alter reward/motivation via regulation of dopamine?

↑ NMDA -
Glutamate
Cortico-
limbic Input

↑ GABA
Tone in
VTA

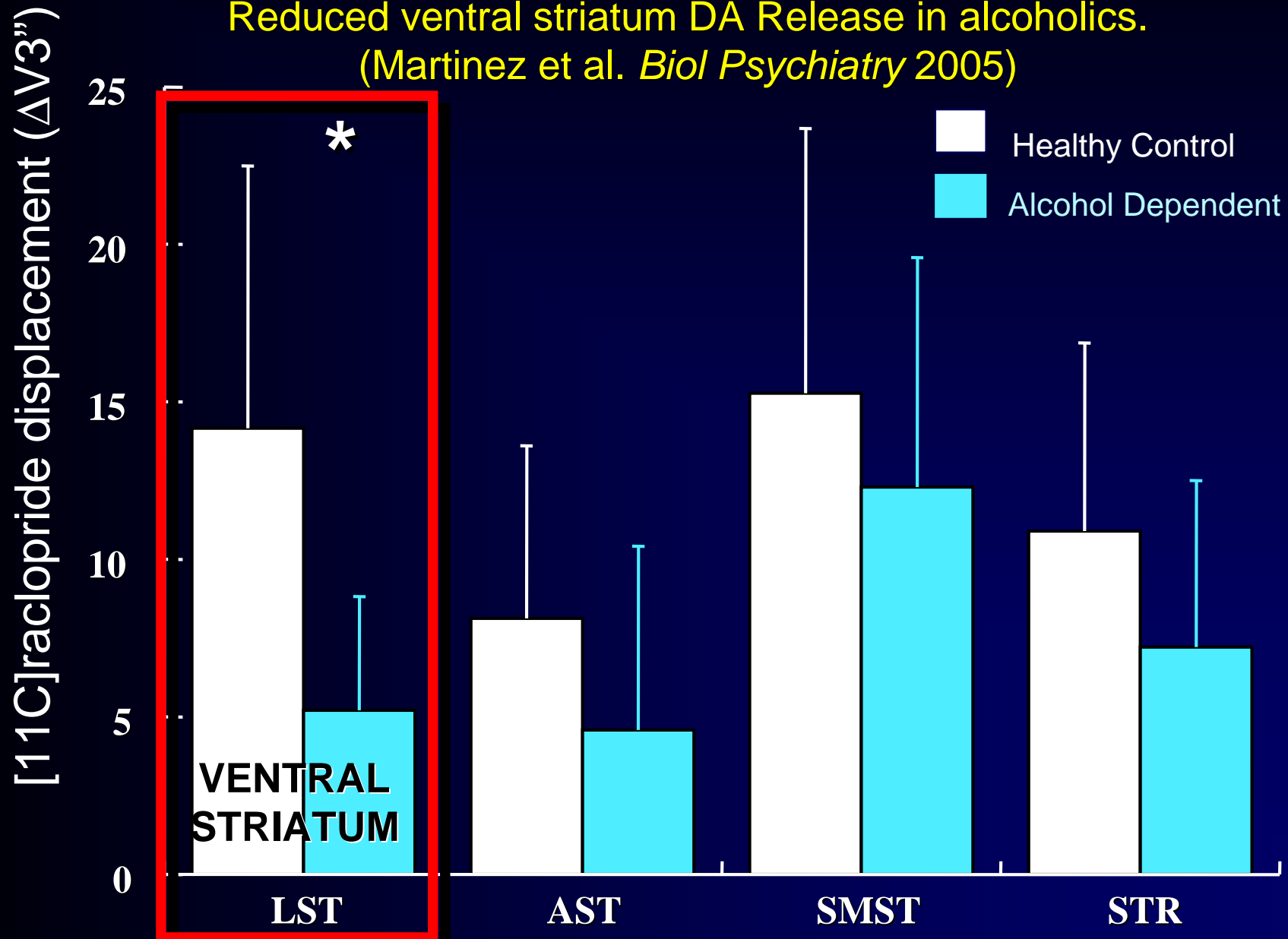


Modified from D. Martinez

Do Ventral Striatal Dopamine Deficits Distort Reward Processing and Motivation?

Reduced ventral striatum DA Release in alcoholics.

(Martinez et al. *Biol Psychiatry* 2005)

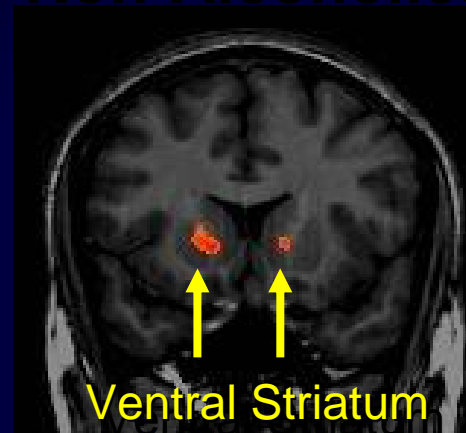


Alcohol Dependence: Deficits in ventral striatal activation during the anticipation of reward

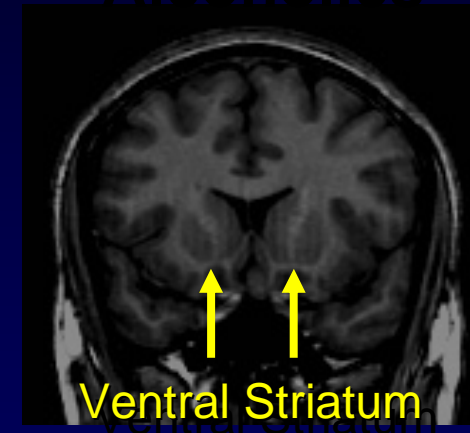
Anticipation:

Alcoholics have less activation in Ventral Striatum while waiting to work for reward. Dysfunctional brain motivation circuits?

Non-Alcoholics

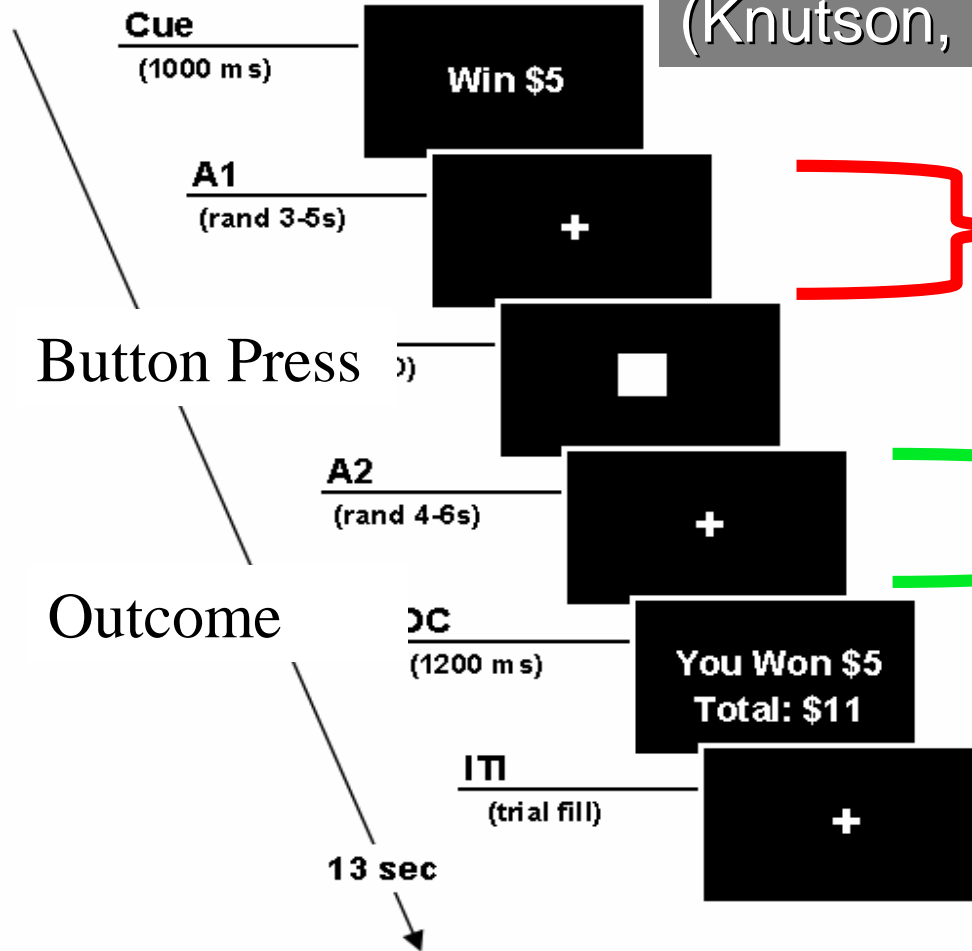


Alcoholics



M I 3

Modified Monetary Incentive Delay Task (Knutson, Bjork, Hommer/Pearlson)



“Prospect”
for Reward
Punishment

“Anticipation”

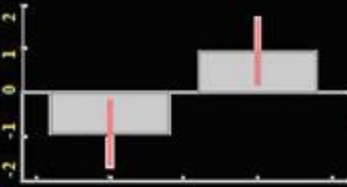
“Receipt”

- Performance-based reward
- Longer trial and anticipation durations
- Anticipation durations optimized and fixed
- Target hit rate 67%
- 11 x 5 Conditions (W/L \$5, \$1; W/L\$0)

a) **FHP > FHN**

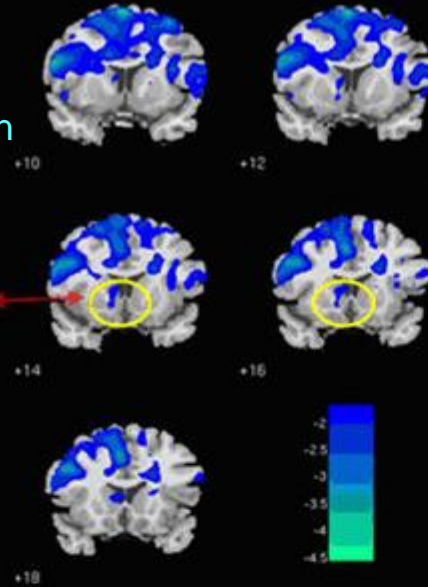
V. Striatal Activation

AVERAGE SIGNAL RESPONSE



FHN FHP

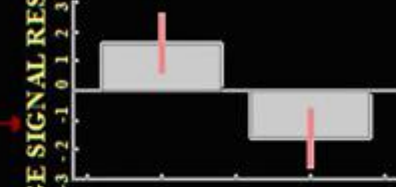
PROSPECT OF
REWARD
(A1)



b) **FHN > FHP**

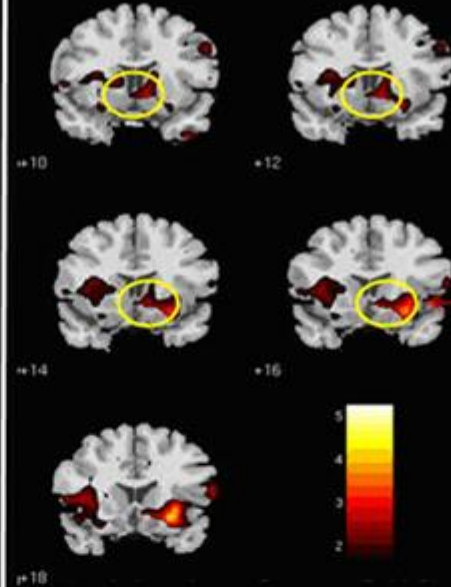
V. Striatal Activation

AVERAGE SIGNAL RESPONSE



FHN FHP

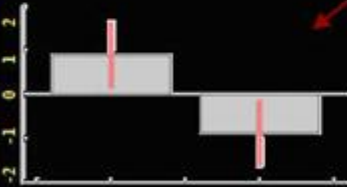
ANTICIPATION OF
REWARD
(A2)



c) **FHN > FHP**

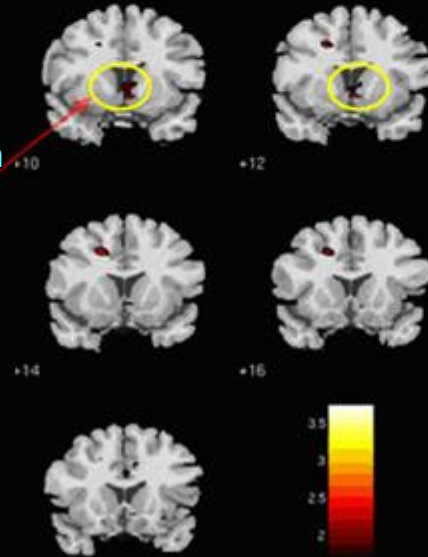
V. Striatal Activation

AVERAGE SIGNAL RESPONSE



FHN FHP

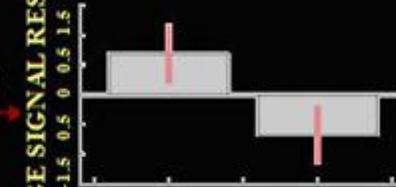
OUTCOME OF
LOSS



d) **FHN > FHP**

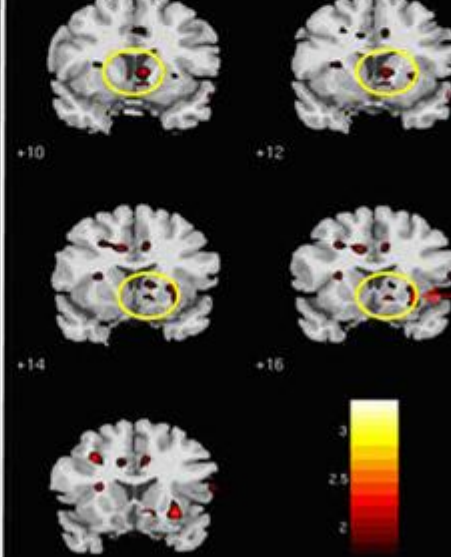
V. Striatal Activation

AVERAGE SIGNAL RESPONSE



FHN FHP

OUTCOME OF
REWARD



Decreased V. Striatal Activation During Anticipation (A2) Associated with Trait Impulsivity

Rotated Component Matrix(a)

	Component			
	1	2	3	4
BIS11_Att_impulsiveness	.438	.142	.689	-.002
BIS11_Motor_impulsiveness_2	.510	.269	.469	-.294
BIS11_Nonplanning_impulsiveness	.138	-.108	.807	-.010
ZSS5_tot	-.046	.032	.714	-.014
SPSRQ_Sum_Punishment	.818	-.161	-.037	.189
SPSRQ_Sum_Reward	.898	.170	.230	-.342
BASDriveScore	.049	.833	-.031	-.046
BASFunScore	.004	.847	.228	-.029
BASRewardScore	-.182	.769	-.134	.314
BISScore	.081	.317	-.155	.763
SUM_PADUA	.786	-.104	.130	.048
EDT_Total_AUC	-.036	-.079	.088	.767

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.

Final factor structure(s):

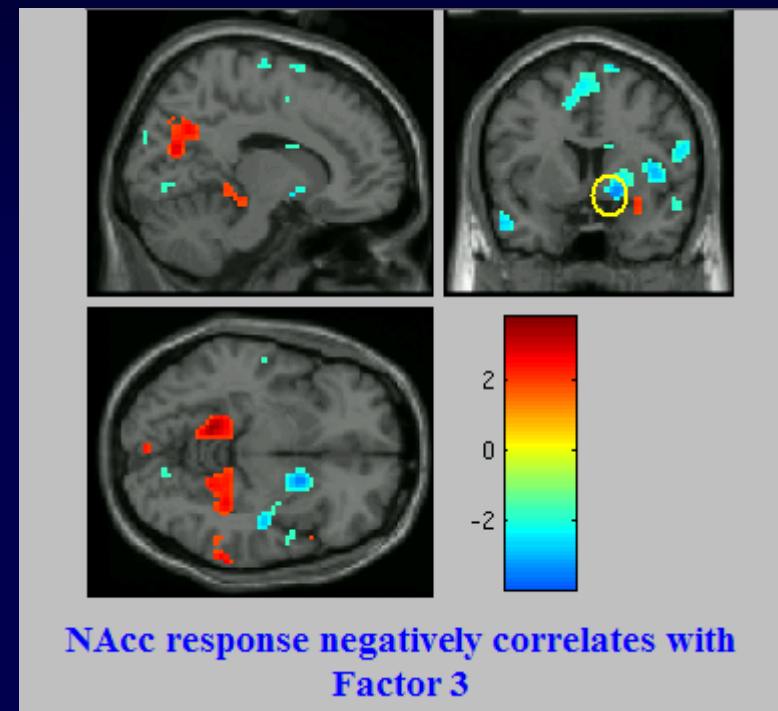
Factor 1: BIS11_Motor, PADUA, SPSRQ

Factor 2: BAS

Factor 3: ZSSS, BIS11_Nonplanning, BIS11_Attention

Factor 4: EDT, BIS

- F1- Control Seeking
- F2- Rash pursuit of rewards
- F3- Reckless**
- F4- Cautious/Tentative**

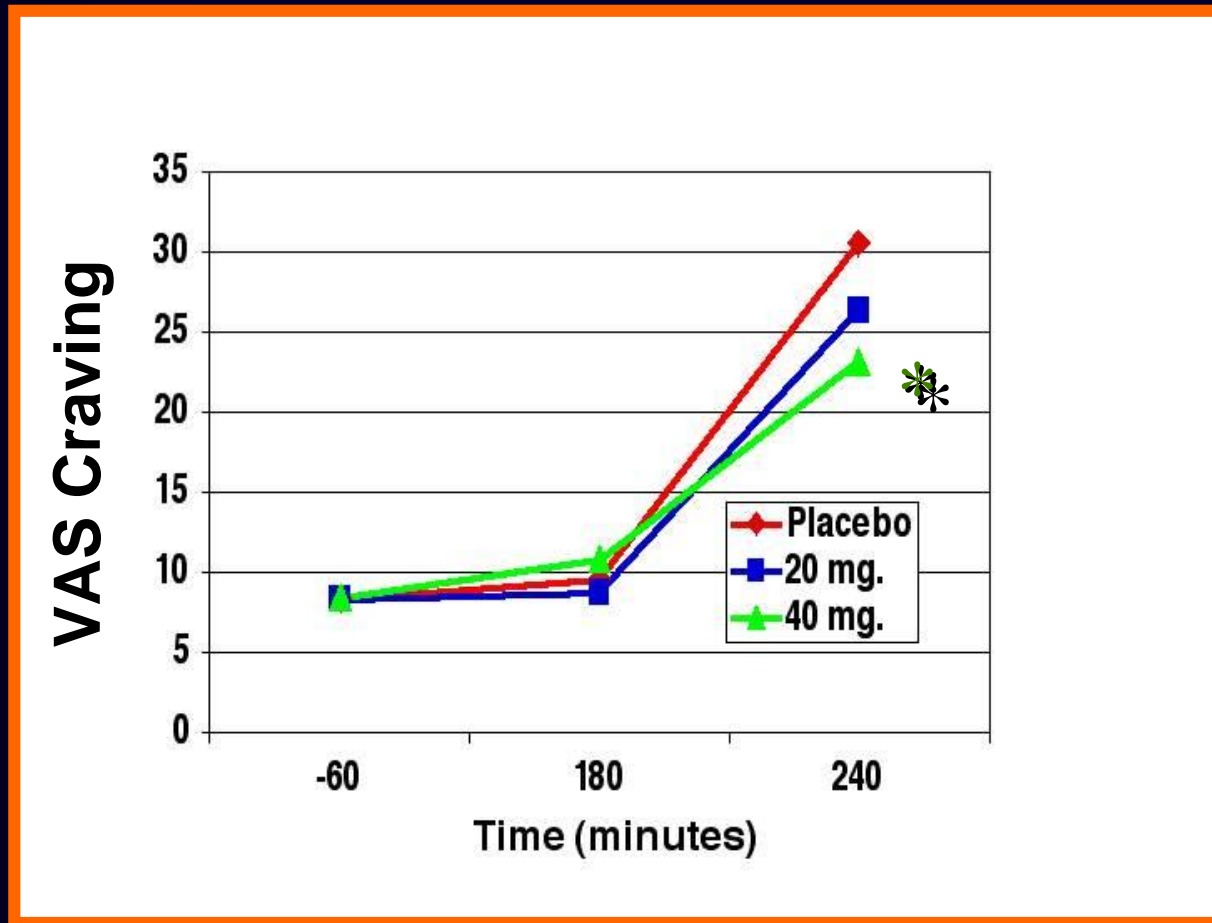


A2 and NAcc BOLD correlations
Factor 4 pos, p=0.003; Factor 3 neg, p=0.001
BART (5th factor) neg p=0.002

A summary hypothesis

- Alcoholism risk is associated with a motivational bias toward immediate drug-like rewards (“opportunity”) and away from delayed “natural” rewards (“anticipation”).
- This pattern of NAc dysregulation is associated with impulsivity
- This devaluation of delayed natural rewards and punishments may reflect increased NMDA receptor function attenuating ventral striatal dopamine release.

**Treatment implication:
NMDA-R antagonists may help to normalize reward:
Memantine Reduces Cue-Induced Alcohol Craving
(Krupitsky et al. AJP 2001)**



Outline

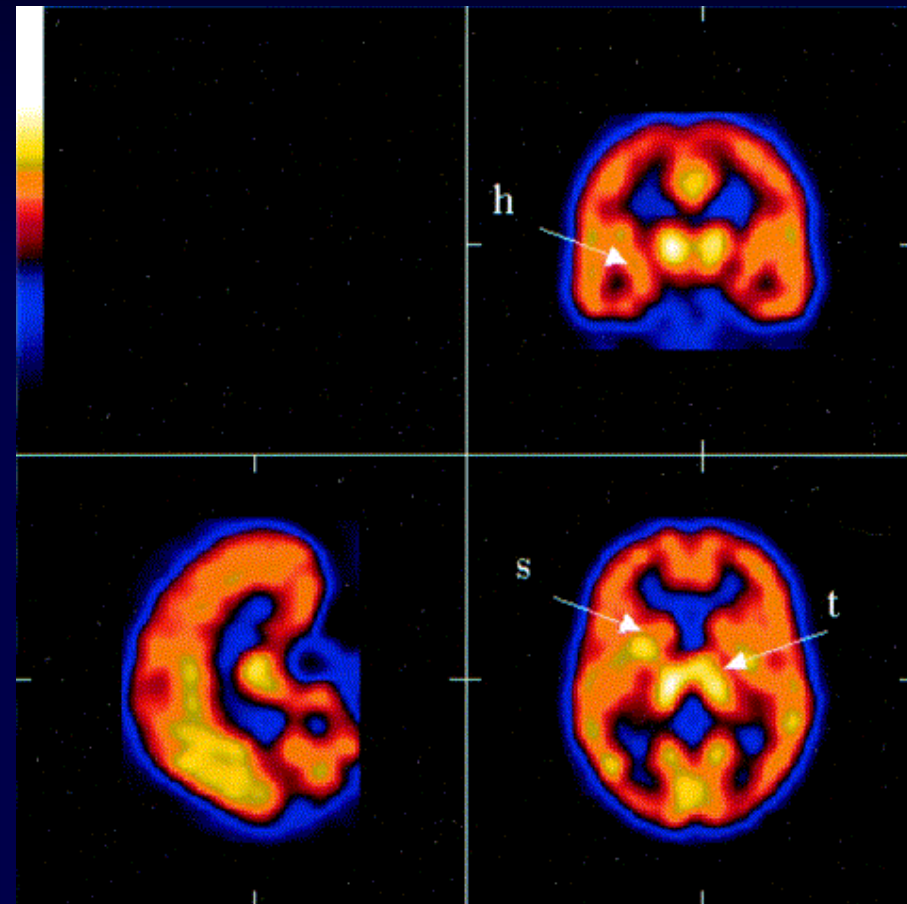
- Enhanced NMDA receptor function in alcoholism: Reduced experience of “intoxication” and reward dysregulation may promote drinking
- **Reduced NMDA receptor function in schizophrenia:** Dysregulation of reward circuitry may promote substance abuse, but increased sensitivity to NMDA receptor antagonist effects may limit intensity of alcohol consumption

Schizophrenia Mini-Outline

- Reduced NMDA receptor function in schizophrenia?
- Increased alcoholism risk but reduced drinking intensity in schizophrenia?
- Mechanisms of reward-related impulsivity in schizophrenia

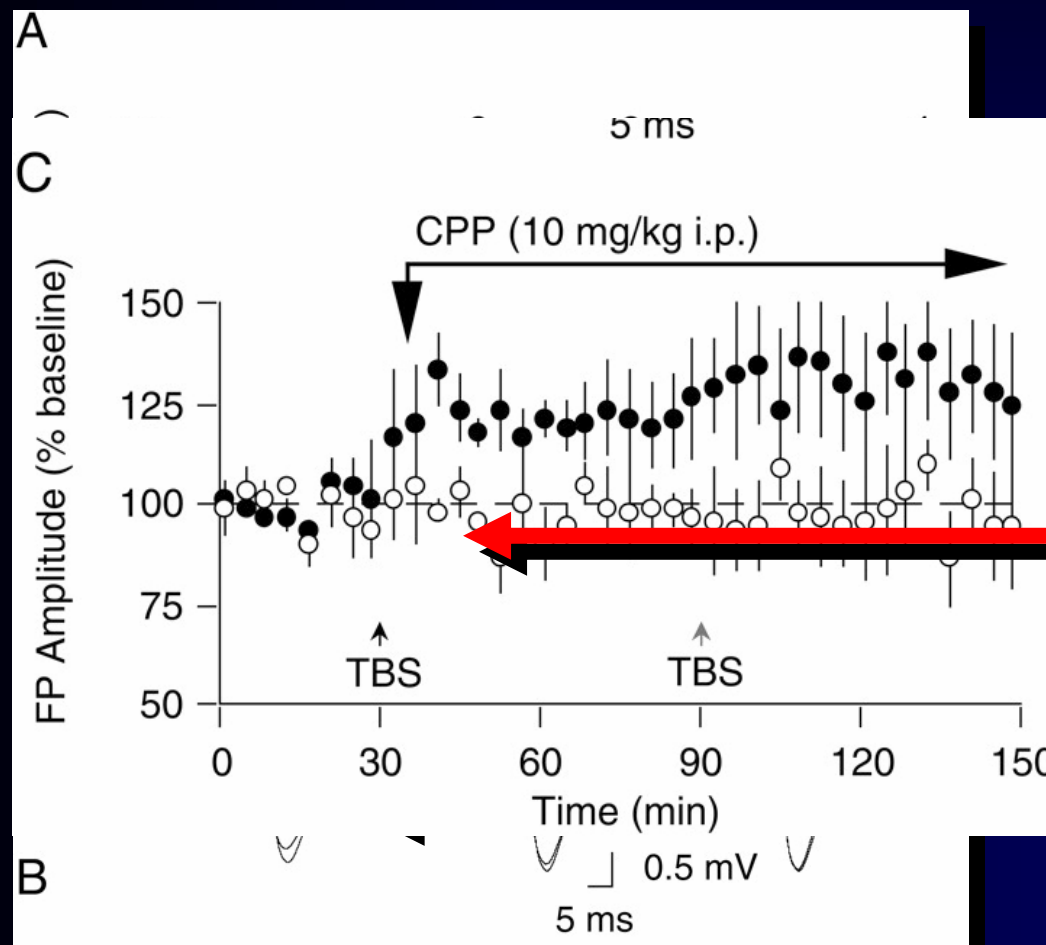
Clinical Evidence Supporting NMDA receptor-related deficits?

- Reduced density of NMDA receptor availability in unmedicated schizophrenic patients *in vivo* using SPECT and [¹²³I]CNS-1261 (Pilowsky et al. *Mol Psychiatry* 2006)



Vt of [¹²³I]CNS1261

Visual Cortex LTP as a “functional assay” for NMDA receptor function in animals (Heynan and Bear *J Neurosci* 2001)

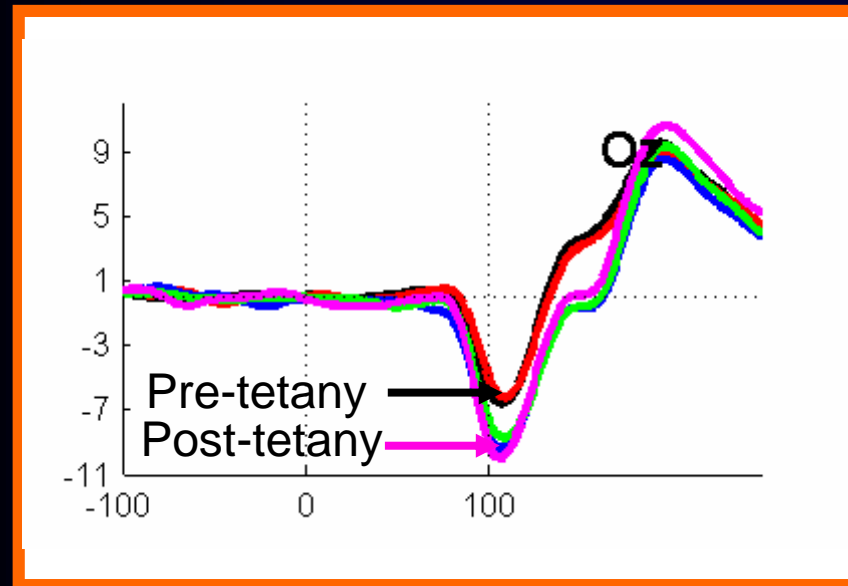


Tetanic (theta) burst stimulation of geniculate increases amplitude of electrically-evoked potentials. LTP is prevented by NMDA-R antagonist (CPP) pretreatment

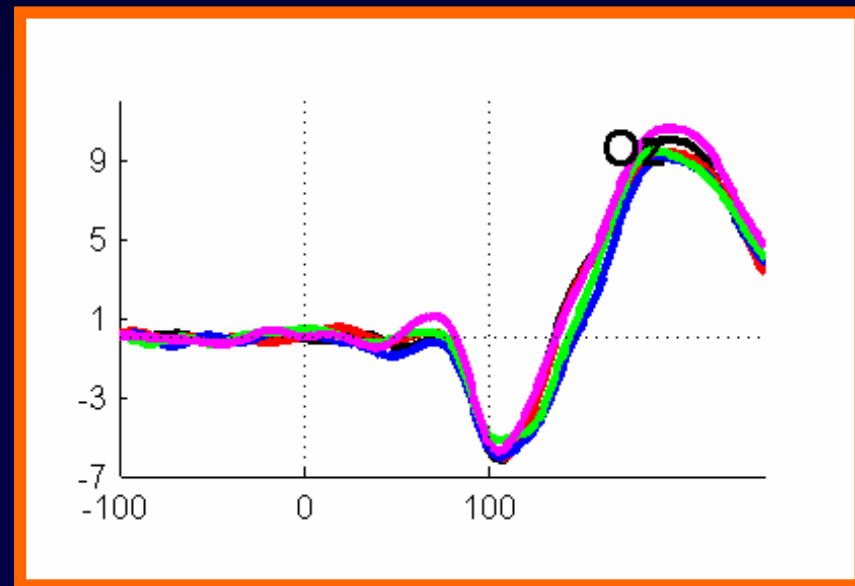
And visually-evoked potentials (equivalent of N100)

NMDA-R functional deficiency in schizophrenia is
consistent with reduced visual LTP
Baseline 0.8 Hz; Tetany 9.0 Hz; N1b

Healthy (N=20)

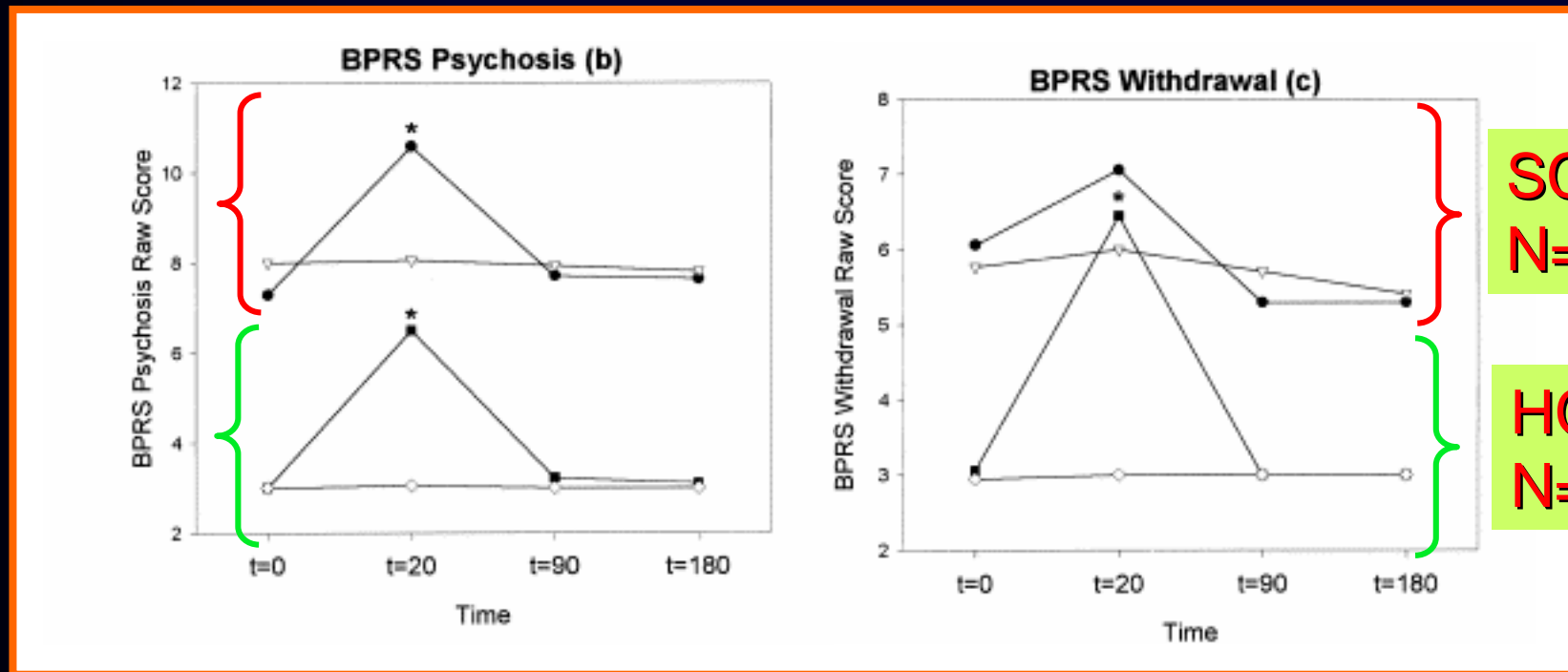


Medicated, Schizophrenia (N=19)



Cavus, Teylor, Kirk, Clapp, Ford, Krystal, Mathalon unpublished

More severe positive symptoms in schizophrenic patients administered ketamine (Lahti et al. NPP 2001)



Schizophrenia Mini-Outline

- Reduced NMDA receptor function in schizophrenia?
- Increased alcoholism risk but reduced drinking intensity in schizophrenia?
- Mechanisms of reward-related impulsivity in schizophrenia

Increased Risk for Alcohol and Substance Abuse with Schizophrenia

(Epidemiologic Catchment Area Study; Regier et al. 1990)

- Any Substance Abuse (excluding nicotine): 4.6-fold greater risk
- Alcohol Abuse or Dependence: 3.3-fold greater risk

Do Alcohol-Dependent Schizophrenic Veterans Drink Less Frequently Than Other Alcohol Dependent Veterans?

Group	% Days Drinking
-------	-----------------

Schizophrenic (n=31)	39.0 ± 28.0%
----------------------	--------------

Other (n=627)	66.6 ± 29.0%
---------------	--------------

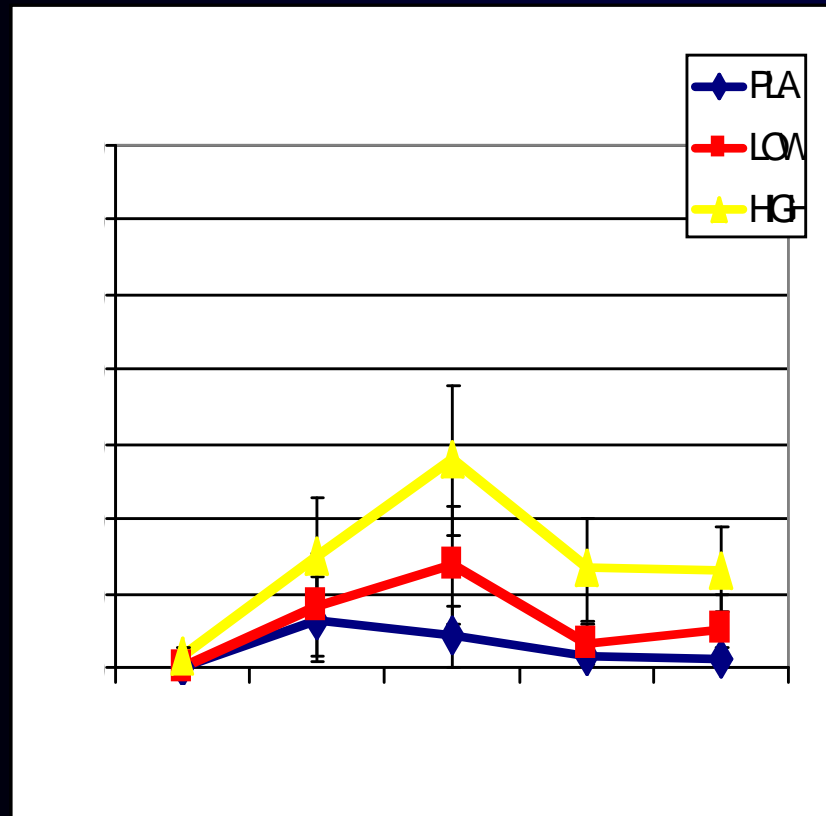
Petrakis et al. *Psychopharmacology* 2004; Krystal et al. *NEJM* 2001

Possible Dualing Mechanisms

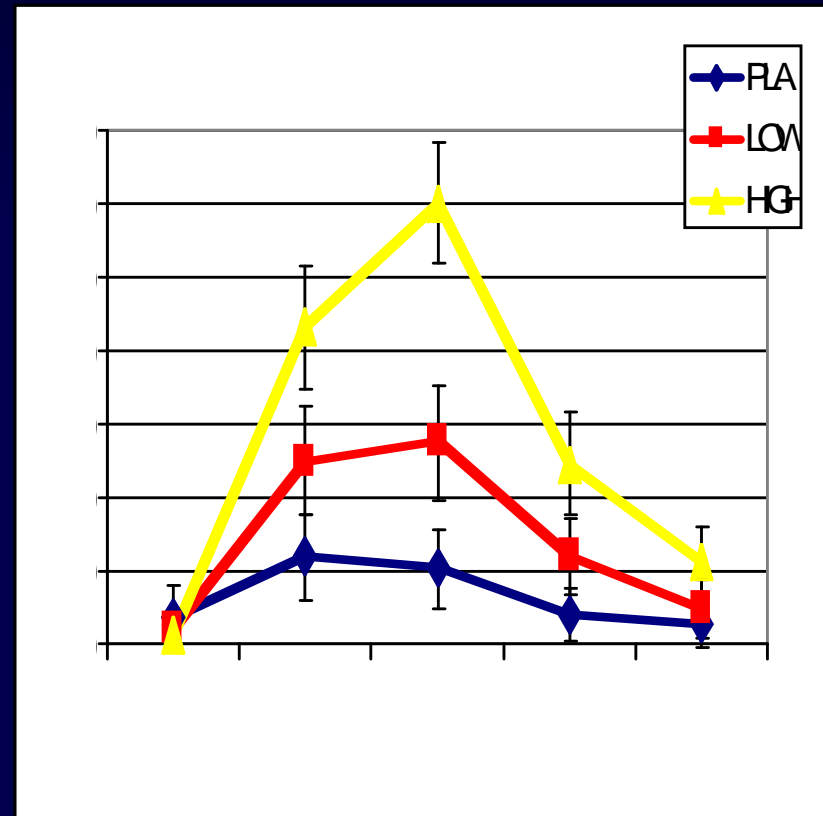
- Promotion of Heavy Drinking:
 - Enhanced positive response to GABA receptor-facilitating effects of ethanol
- Attenuation of Heavy Drinking:
 - Enhanced response to NMDA receptor antagonist effects of ethanol

Ethanol Produces Greater Dose-Related Euphoria in Schizophrenic Patients (D'Souza et al. *Neuropsychopharm* 2006)

Healthy Subjects



Schizophrenic Patients



Schizophrenia Mini-Outline

- Reduced NMDA receptor function in schizophrenia?
- Increased alcoholism risk but reduced drinking intensity in schizophrenia?
- Mechanisms of reward-related impulsivity in schizophrenia

Characteristics Associated with Substance Abuse by Schizophrenic Patients

- Sociopathy/ASPD
 - 10x risk for cocaine use by schizophrenics
- Sensation-seeking
- Impulsive

Meuser et al. 1997, 1999; Galen et al. 2000;
Deriveaux et al. 2001, 2004

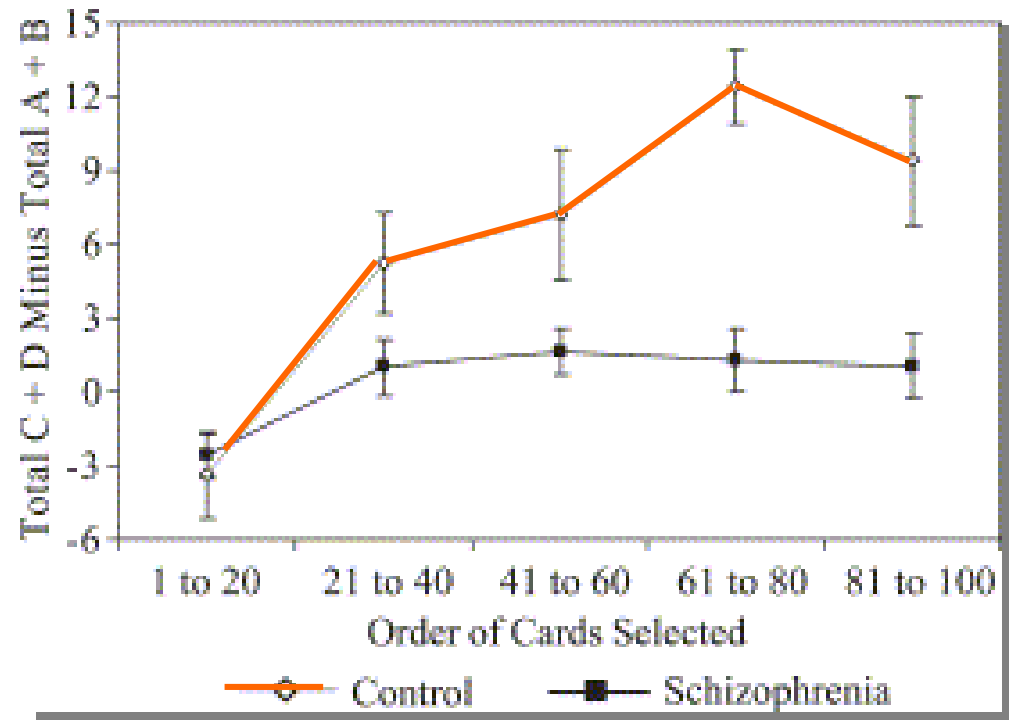
Schizophrenia: Risky Reward/Punishment Decisions

Shurman et al. *Schiz Res* 2005

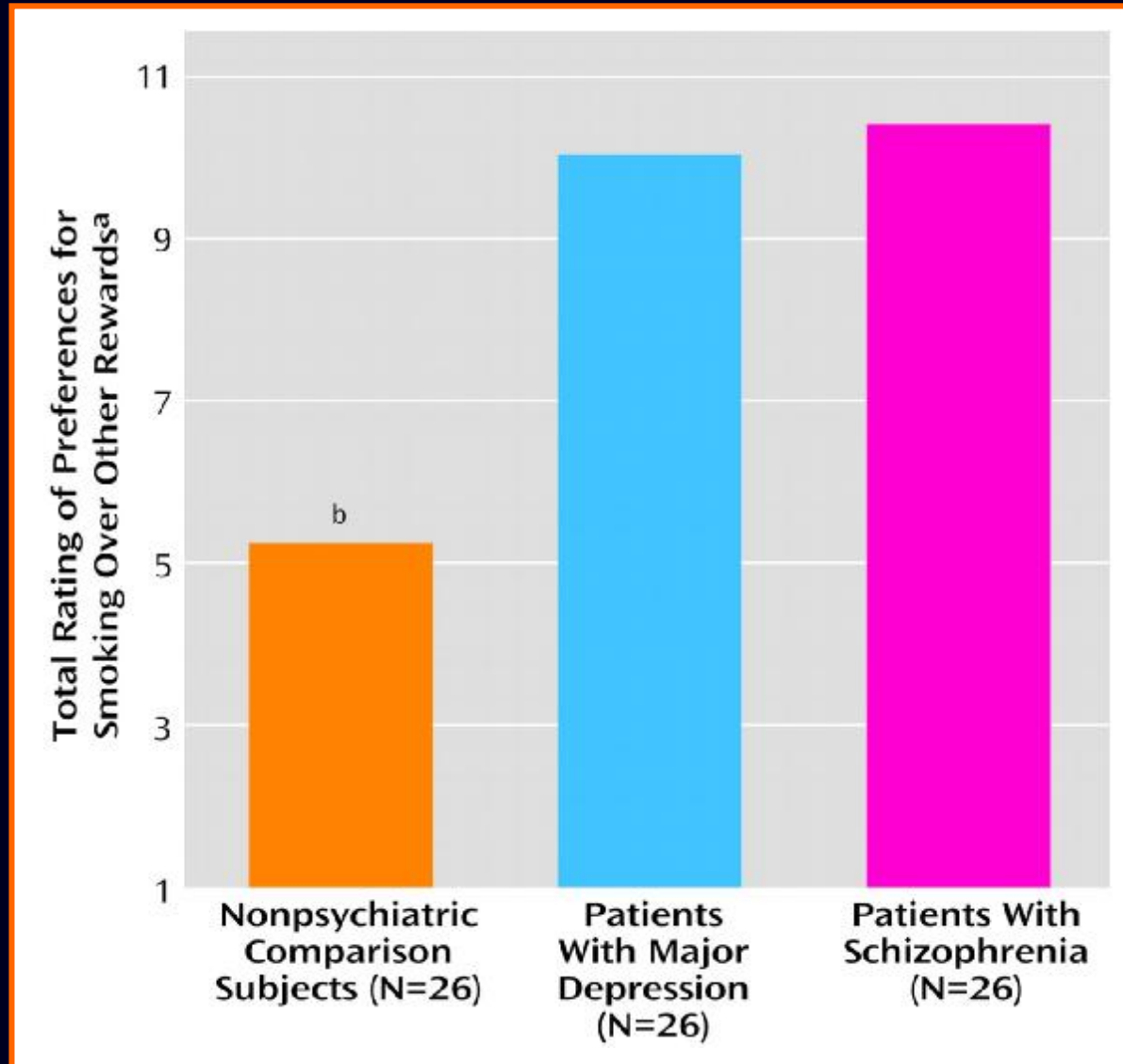
Less Immediate Reward
But Advantageous
“Low Risk”



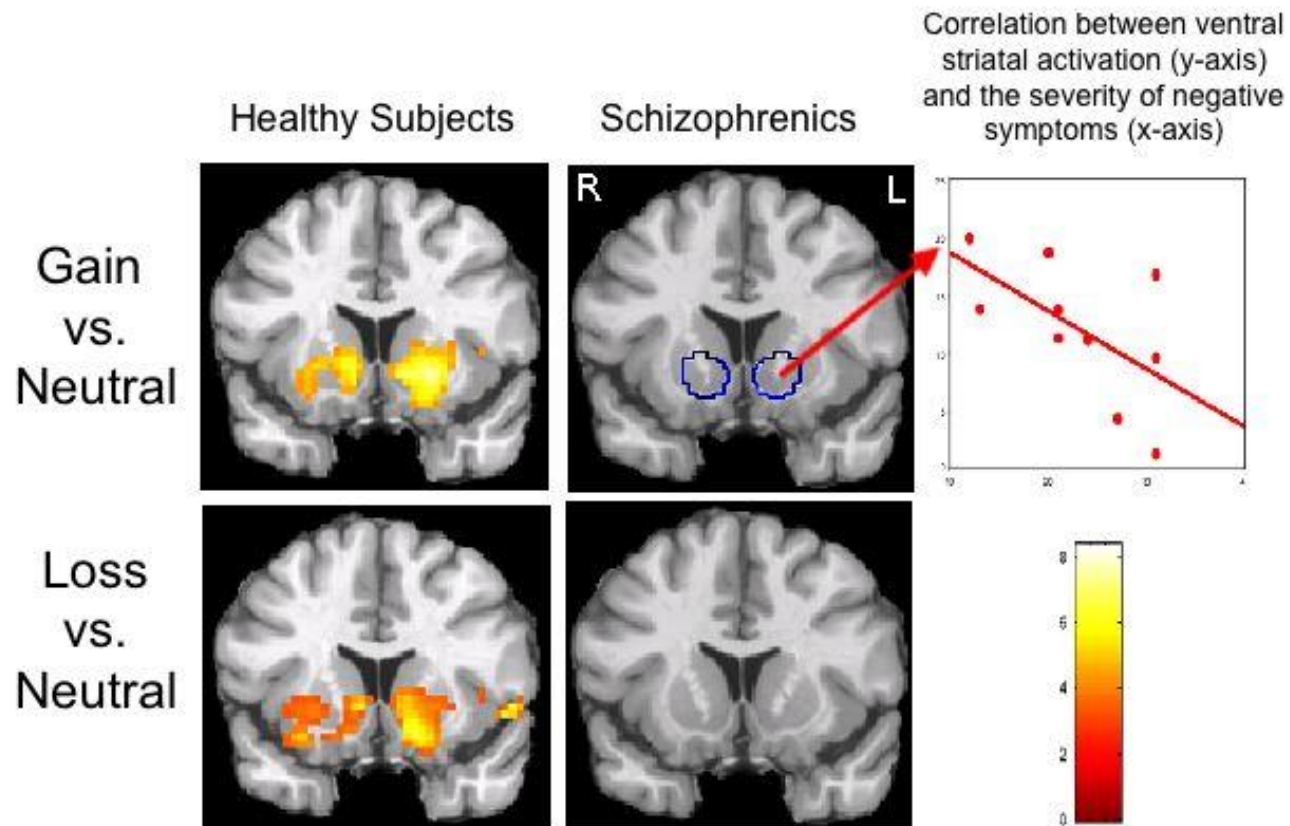
More Immediate Reward
But Disadvantageous
“High Risk”



SZ: Prefer Smoking to Natural Rewards (Spring et al. *AJP* 2003)



Ventral Striatal Activation Deficit During Anticipation of Reward/Punishment in Schizophrenia: Correlation with Negative Symptoms... Substance Abuse?

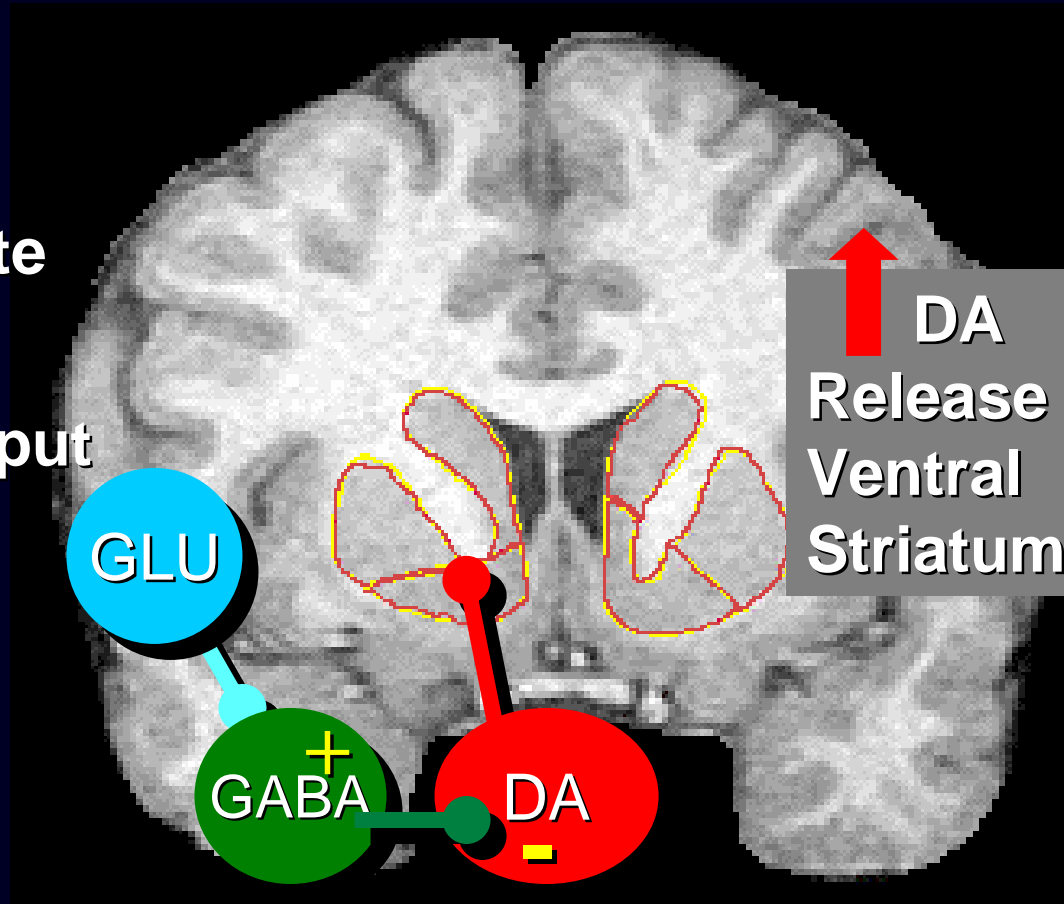


Juckel et al. NeuroImage 2005

A Simplified Circuitry for Reward-Related Striatal Dysfunction in Schizophrenia: Would reduced NMDA receptor function enhance DA function?

↓ NMDA -
Glutamate
Cortico-
limbic Input

↓ GABA
Tone in
VTA



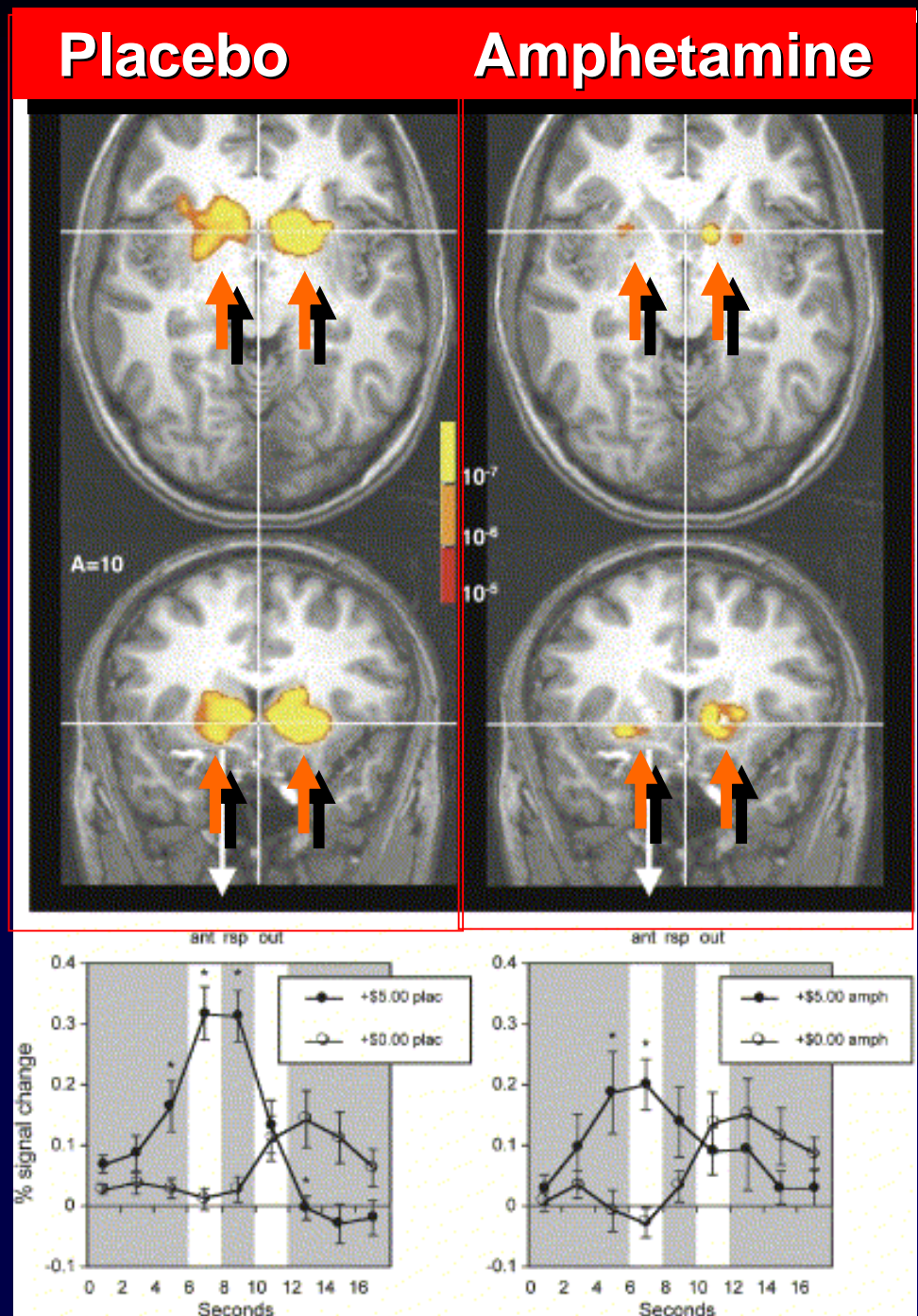
Modified from D. Martinez

A link between reductions in NMDA-R, increased striatal dopamine activation and negative symptoms?

- Ketamine increases amphetamine-stimulated dopamine release in humans (Kegeles et al. Biol Psychiatry 2000)
- Ketamine occupancy of NMDA-R in many brain regions is correlated with production of negative symptoms (J. Stone et al. Psychopharm 2008)

Amphetamine *Reduces* Ventral Striatal Activation During Anticipation of Reward in Healthy Subjects

Knutson et al.
Neuron 2004



Do Negative Symptoms Promote *AND* Protect Against Substance Abuse? (reviewed in Krystal et al. Neurotoxicol Res 2006)

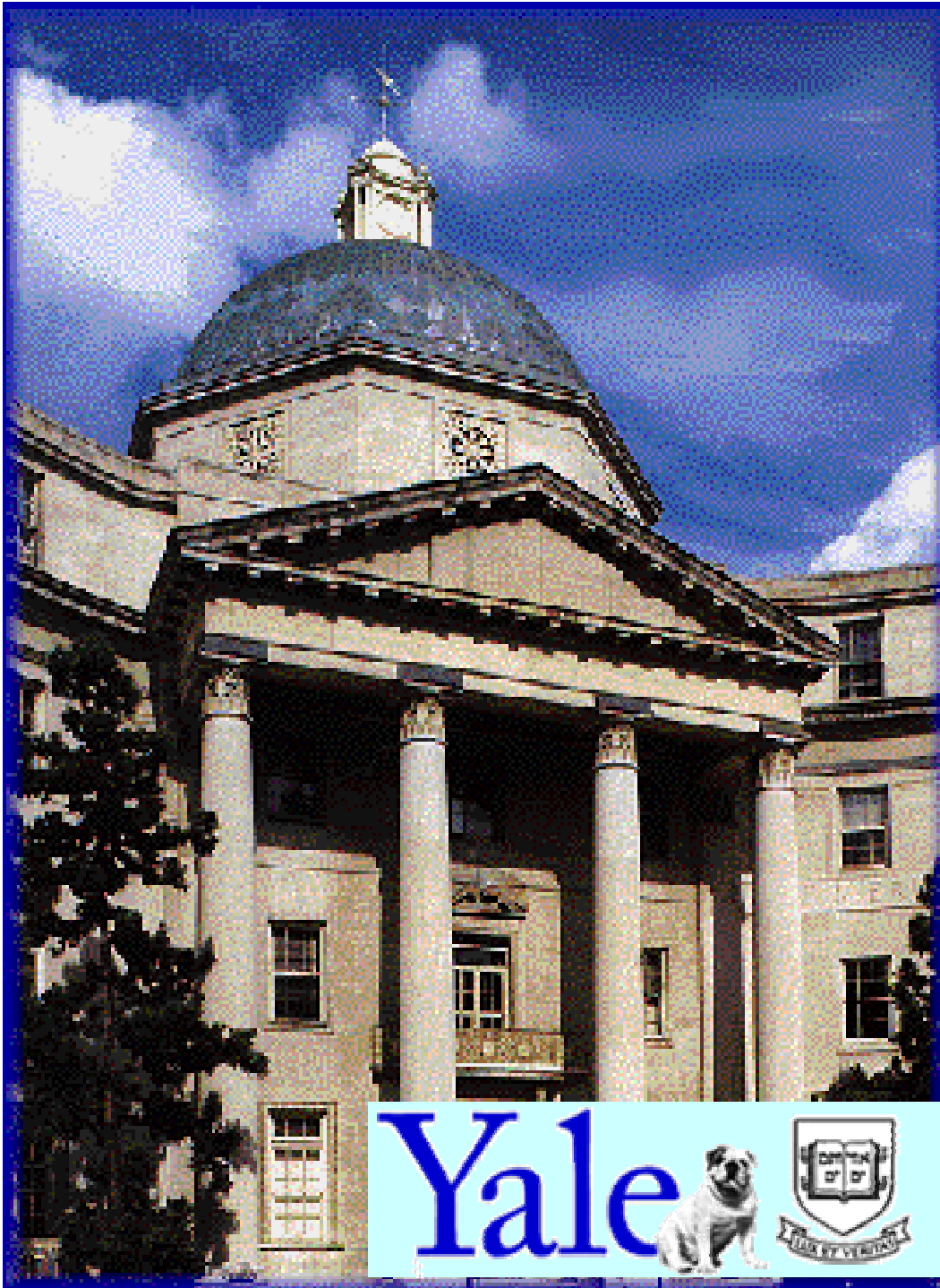
- Negative symptoms correlated with ventral striatal dysfunction
- However: Negative symptoms are not a prominent target for self-medication and high levels are protective against substance abuse in schizophrenia
- Are the component negative symptoms (motivation deficit vs. anhedonia) differentially associated with substance abuse?

Opposing changes in NMDA/DA similar dysfunction in circuitry related to reward/motivation

- Alcoholism: increased NMDA-R function, reduced dopamine release:
 - Treat with NMDA antagonist? D1 agonist?
- Schizophrenia: reduced NMDA-R function, increased dopamine release:
 - Treat with strategies that enhance NMDA receptor function? Clozapine?

Treatment:

- Normalize DA systems (clozapine; A. Green et al.)
- Block opiate (naltrexone; I. Petrakis et al.)
- Block AChR? (mecamylamine; T. George et al.)



Collaborators

Yale

D. Cyril D'Souza
Ismene Petrakis
Godfrey Pearlson
Mark Potenza
Stephanie O'Malley

Columbia

Anissa Abi-Dargham
Diana Martinez
Marc Laruelle

IOP - UK

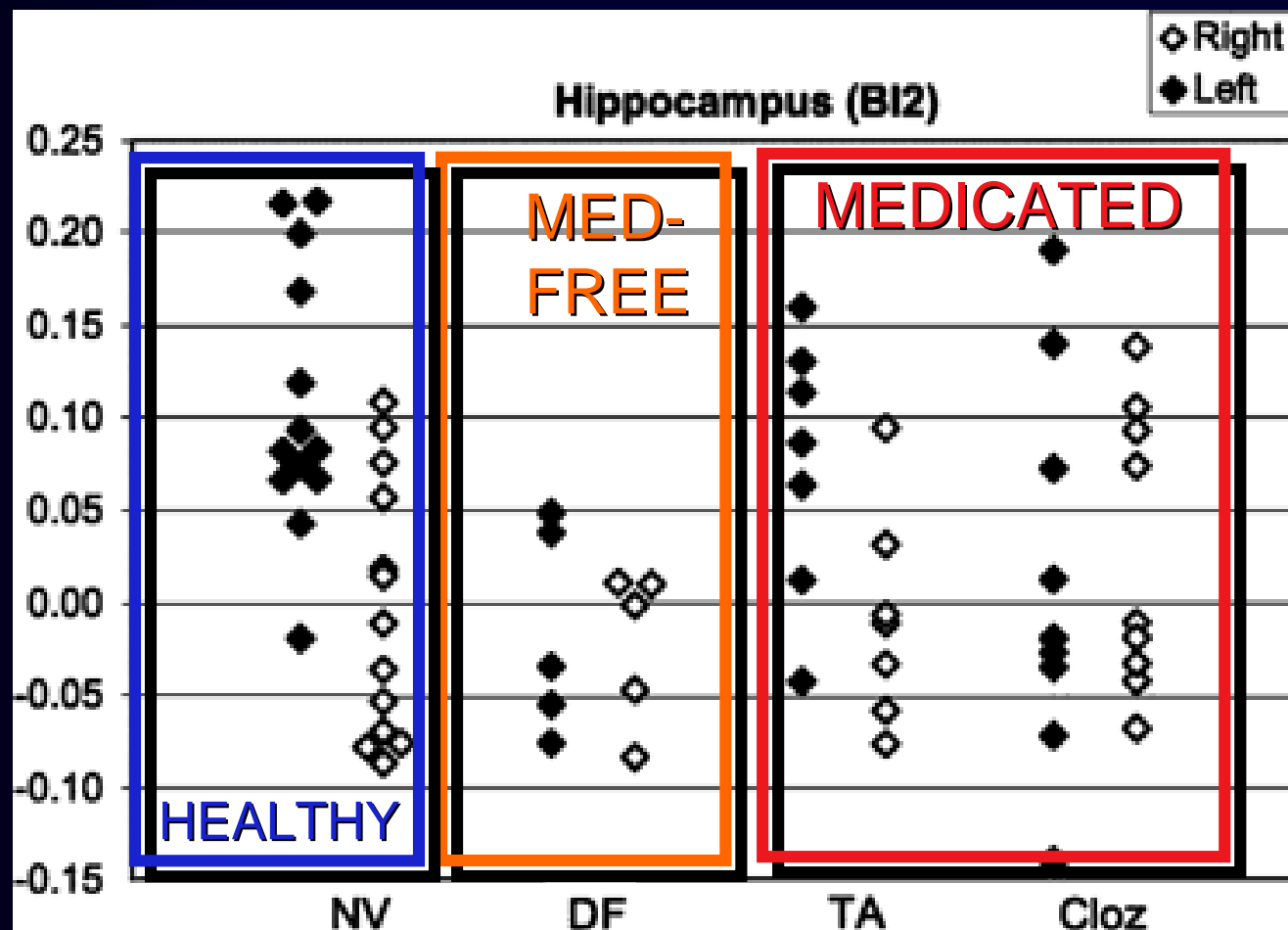
Lyn Pilowsky
James Stone

Supported by:

NIAAA, NIMH
Dept. Veterans Affairs
NARSAD



**Treatment implications: Are reductions in NMDA receptor density somewhat normalized by clozapine?
123I-CNS1261 in schizophrenia
(Pilowsky et al. *Mol Psychiatry* 2005)**



Link between reduced NMDA-R function and negative symptoms: Occupancy of NMDA receptors by ketamine (displacement of 123I-CNS1261) correlates with **NEGATIVE Sx** in Healthy Subjects (n=10)

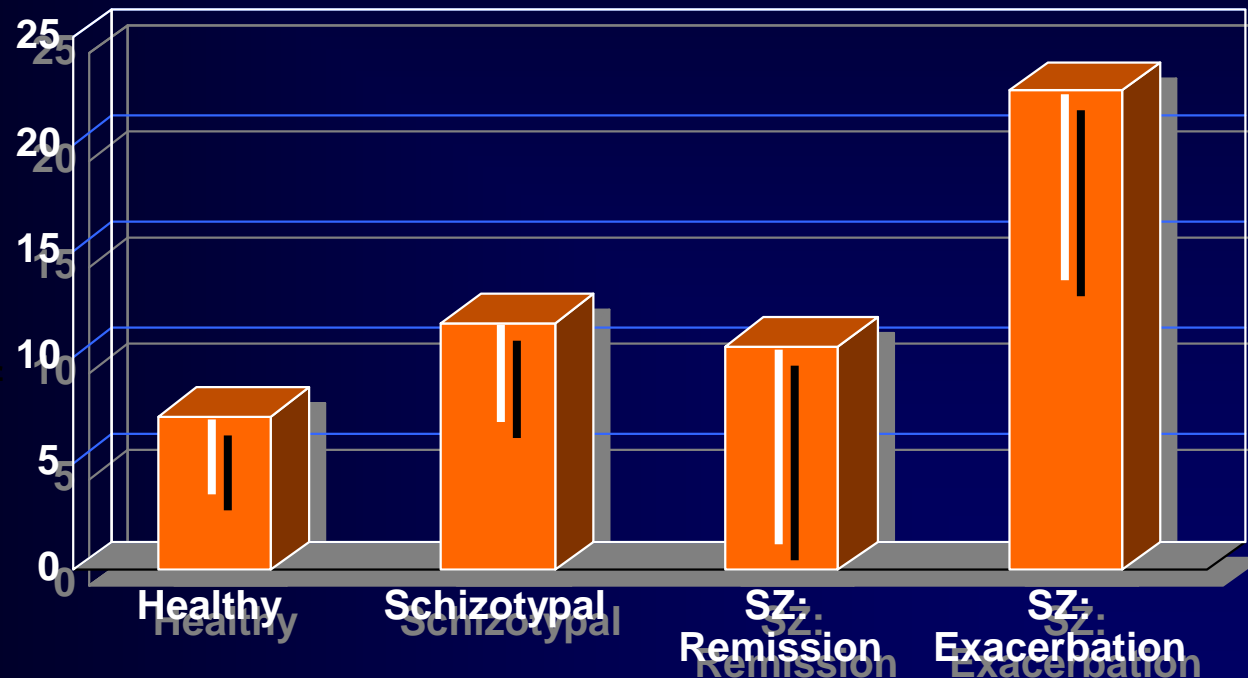
(J Stone et al. Psychopharm 2008)

	Total BPRS	Positive	Negative	Manic	Anxiety
Thalamus	-.4	-.4	-.8	-.2	-.03
Caudate	-.2	-.1	-.7	.3	-0.03
Putamen	-.2	-.1	-.9	0.4	-.4
Lenticular N	-.2	-.1	-.8	.3	-.1
Angular Gyr	-.2	-.1	-.8	.4	-.4
Sup PFC	-.3	-.2	-.7	.2	-.3

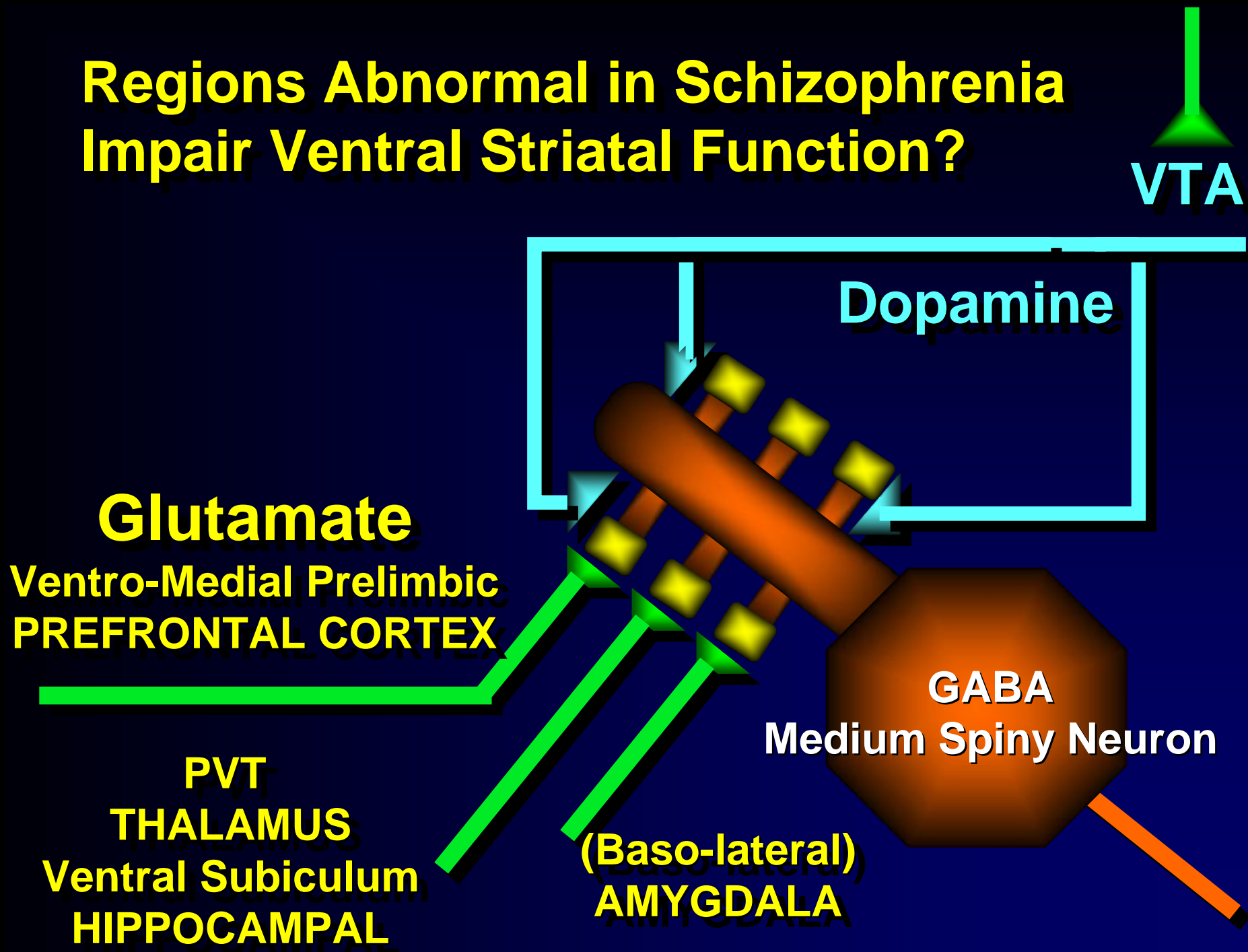
All correlations significant ($p < .05$)

Striatal DA Release is Not Always Increased in Schizophrenia: Which Phases or Patient Subtypes Are Associated with Increased Substance Abuse Risk?

Amount of
Dopamine
Released by
Amphetamine:
Displacement of
[¹¹C]raclopride -
 ΔV_3

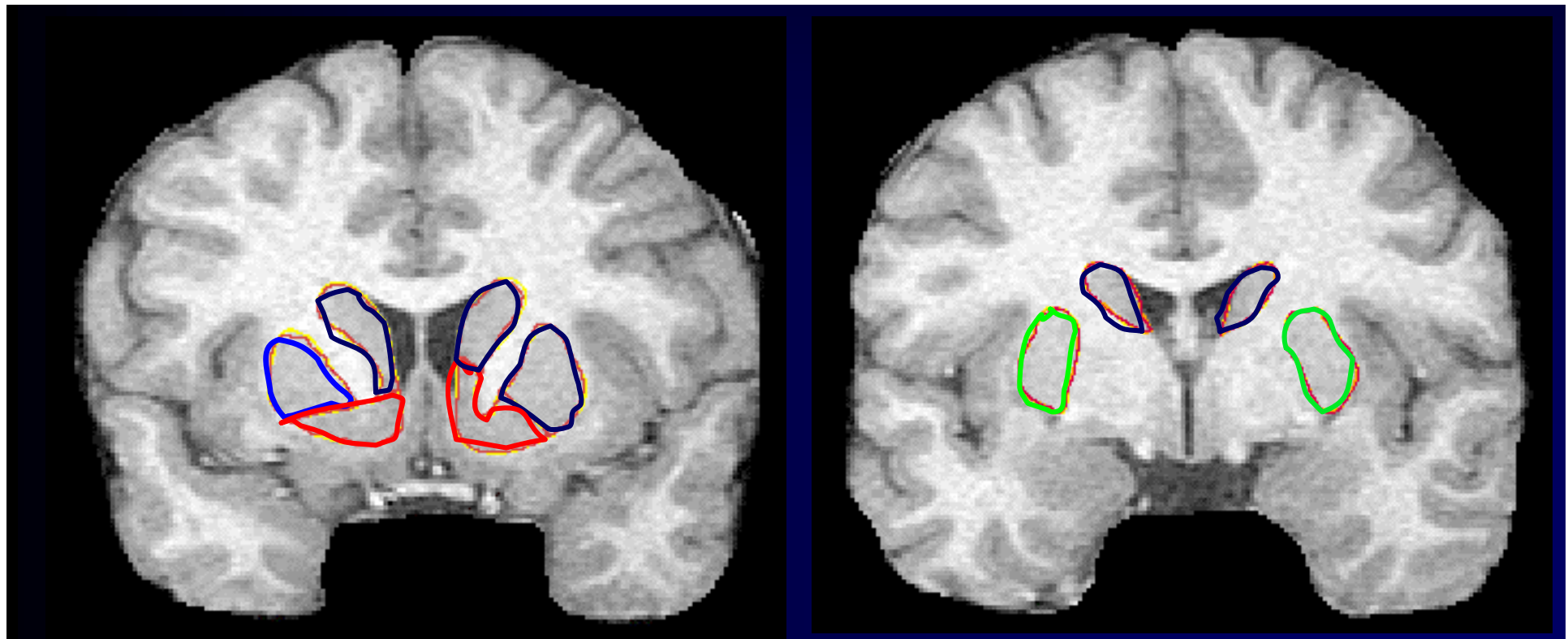


Regions Abnormal in Schizophrenia Impair Ventral Striatal Function?



Divisions of the Human Striatum

■ Limbic (NAc) ■ Cognitive (Caud/Put) ■ Motor (Putamen)



From: Martinez, Abi-Dargham, Laruelle after S. Haber

Ventral Striatal Deficits with Healthy Individuals with Family History of Alcohol Dependence (FHP): Contribute to Motivation Deficits with *Delayed* Punishment and Reward (P4: Pearlson; n=6 pairs)

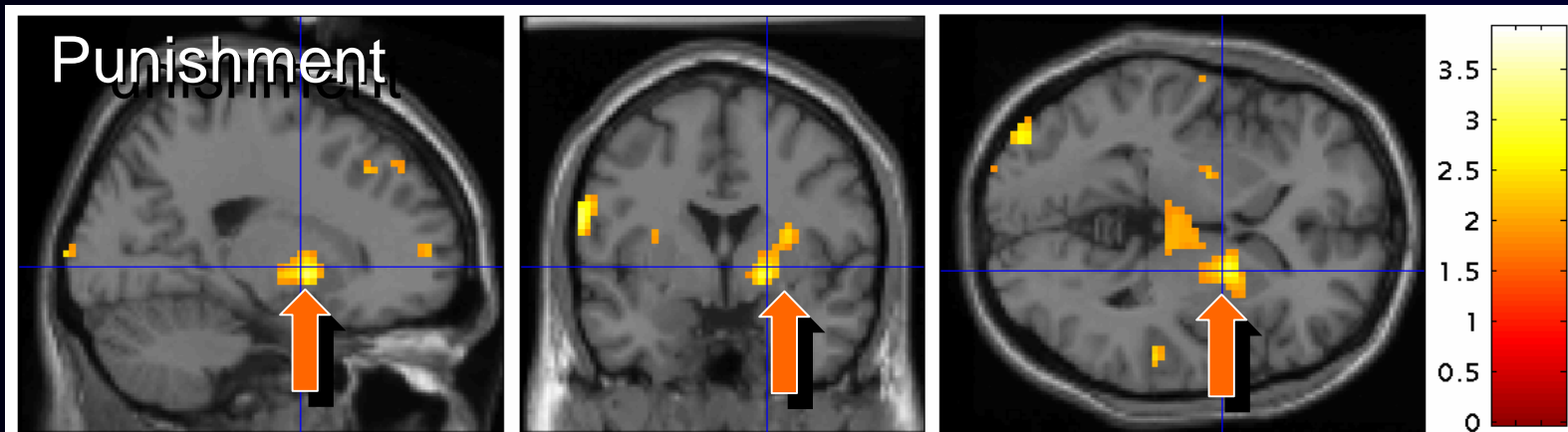


Fig. 6: FHN > FHP for anticipation of punishment. $p < 0.05$ uncorrected.

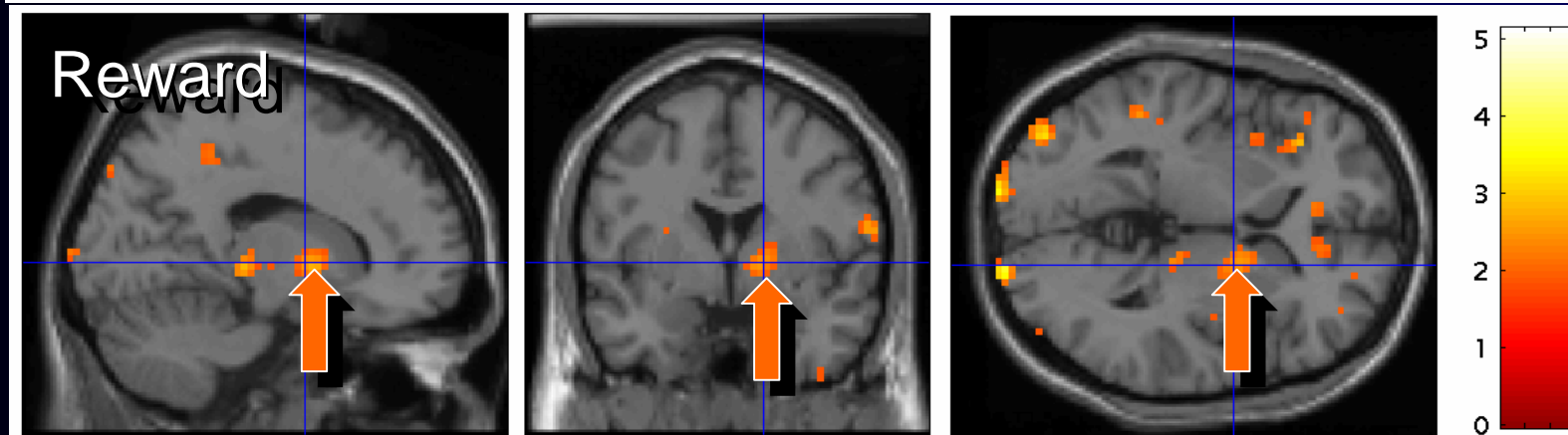
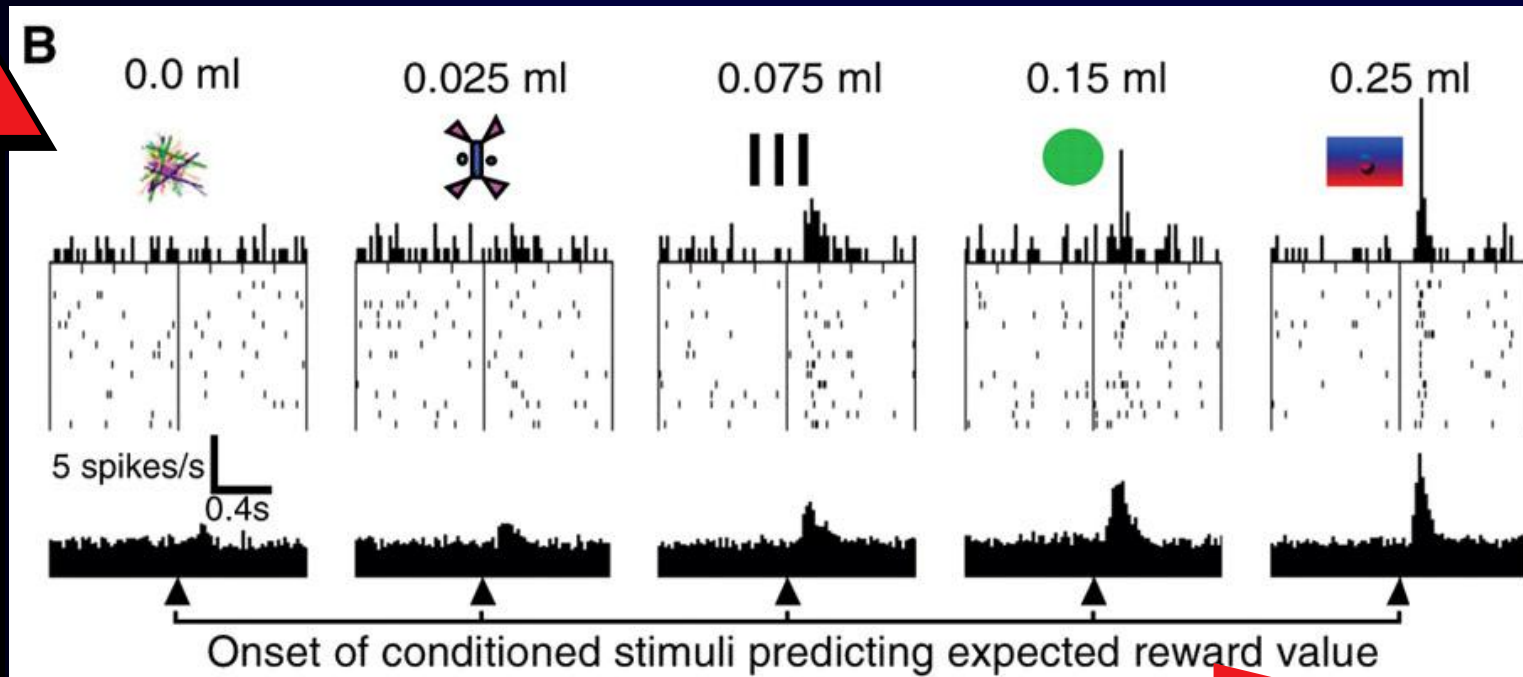


Fig. 7: FHN > FHP for anticipation of reward. $p < 0.05$ uncorrected.

Link Between Ventral Striatal Dysfunction and Dopamine Release?

Larger Anticipated Delayed Rewards Produce Greater Activation of DA Input to Ventral Striatum
(Tobler Science 2005)

Increasing DA Activation

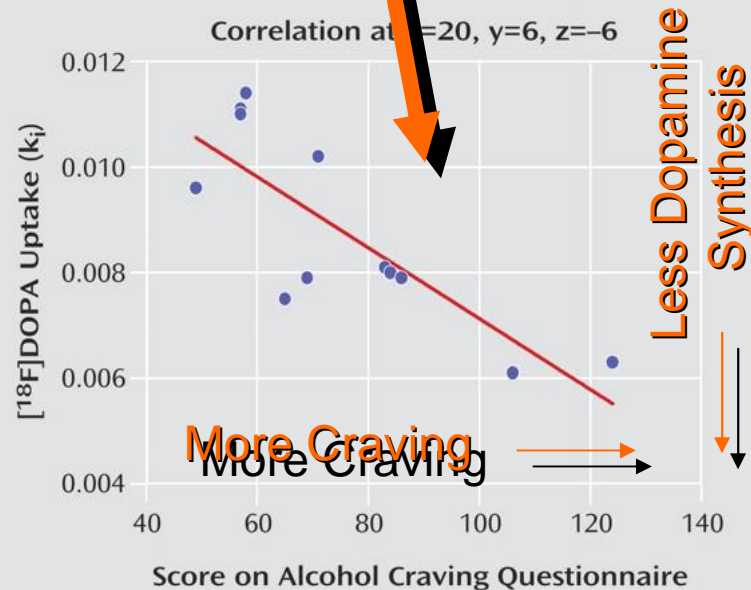
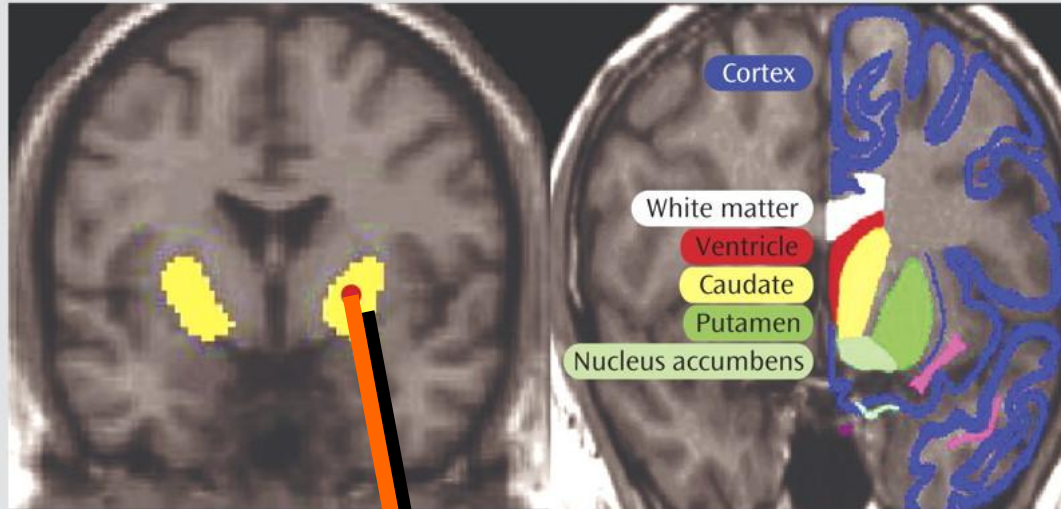


Increasing Anticipated Reward Magnitude

Reduced Basal Caudate Dopamine Synthesis: Association with Greater Alcohol Craving

Statistical Parametric Mapping Overlay

Talairach Atlas



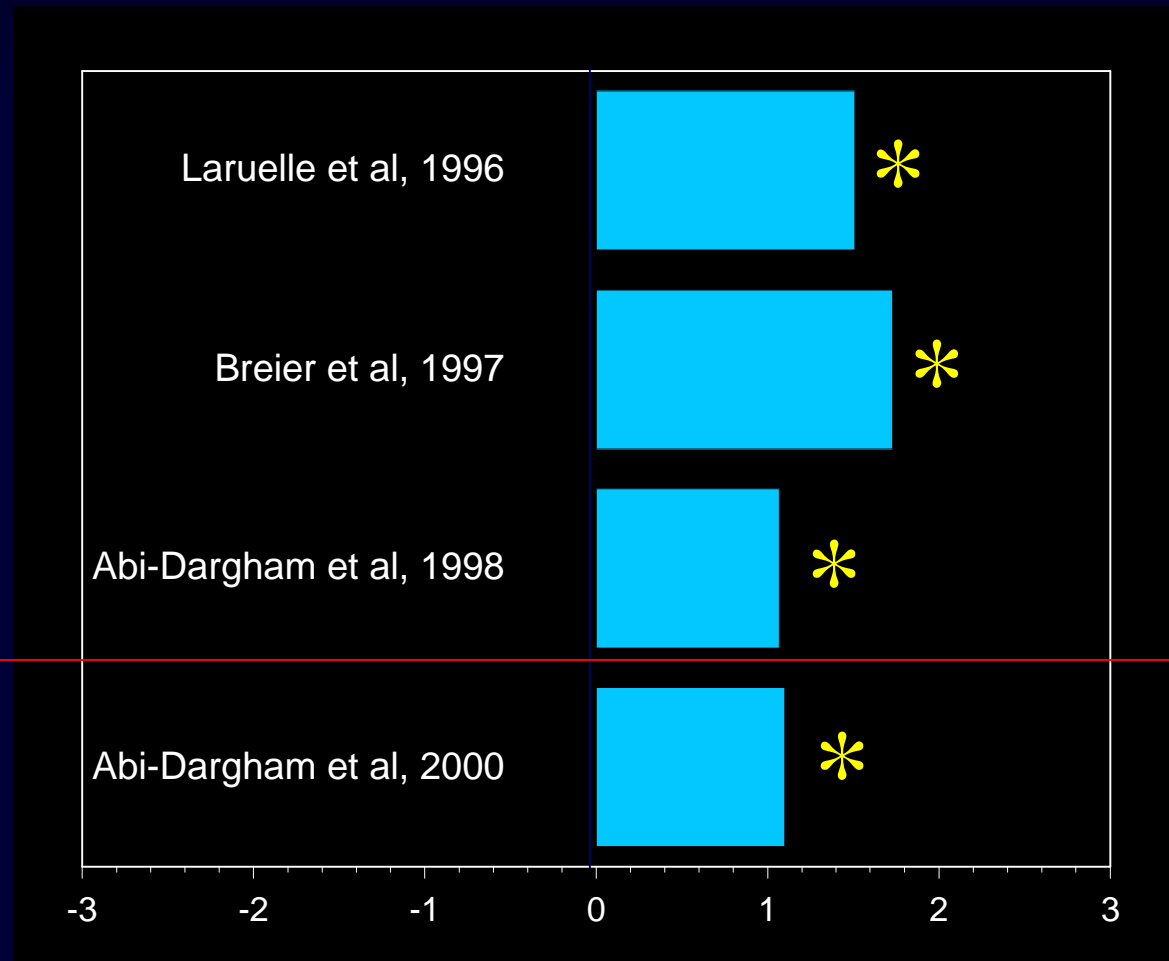
Heinz et al. AJP 2005

But, increased dopamine release in schizophrenia (from M. Laruelle)

Effect Size

*Increased dopamine release capacity:
Increased D2 receptor tracer displacement by amphetamine*

*Increase basal dopamine release:
Greater increase D2 receptor tracer binding by dopamine depletion*



Dopamine: Therapeutic Implications?

- If similar ventral striatal dopamine deficits in addiction and schizophrenia, is there value of limbic-selective pro-dopaminergic therapies?
- If hyperdopaminergic, what antidopaminergic treatment is necessary? (D1? D3? D4?)

Schizophrenic Patients Show Less Light Smoking (Blue) and More Heavy Smoking (Orange) Compared to Others (McRreadie et al. 2002)

	Schizophrenic	Non-Schizophrenic
Number of cigarettes	Subjects (n=125)	Subjects (n=82)
	N (%)	N (%)
<10	9 (7%)	19 (24%)
10-29	66 (53%)	55 (66%)
≥30	50 (40%)	8 (10%)

Association of schizophrenia and heavy smoking: $\chi^2=27.23$, $p<.0001$

When Smoking Similar Numbers of Cigarettes, Schizophrenic Patients Extract More Nicotine Than Other Smokers (N=13/grp)

Healthy Schizophrenic

Cigarettes/day	28±11	26±10
Pack-years	35±26	27±15
Pl. Nicotine (ng/ml)	10±10	28±18 ^{***}
Pl. Cotinine (ng/ml)	245±156	453±245 ^{***}

Jacobsen et al. *Biol Psychiatry* 2004

Smoking By Schizophrenic Patients

- Smoke more cigarettes
- Extract more nicotine from each cigarette

Dalack and Meador-Woodruff Am J Psychiatry 1996

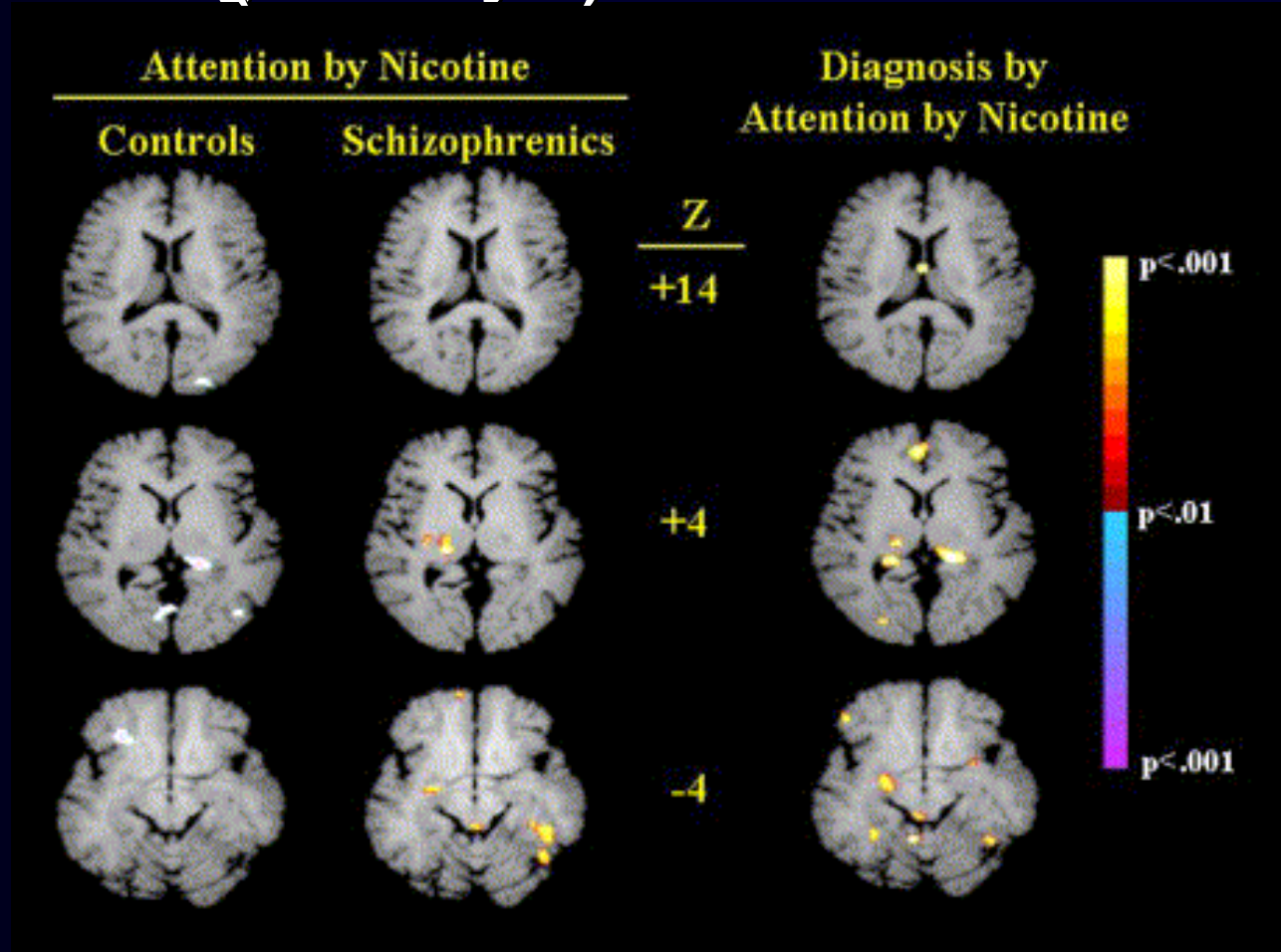
Altered Nicotine Response

- Failure to upregulate high-affinity nAChR's ($\alpha_4\beta_2$) with smoking
- Genetic and physiological evidence implicating alpha-7 subunit
- Cognitive effects, but unclear differential euphoria or dysphoria

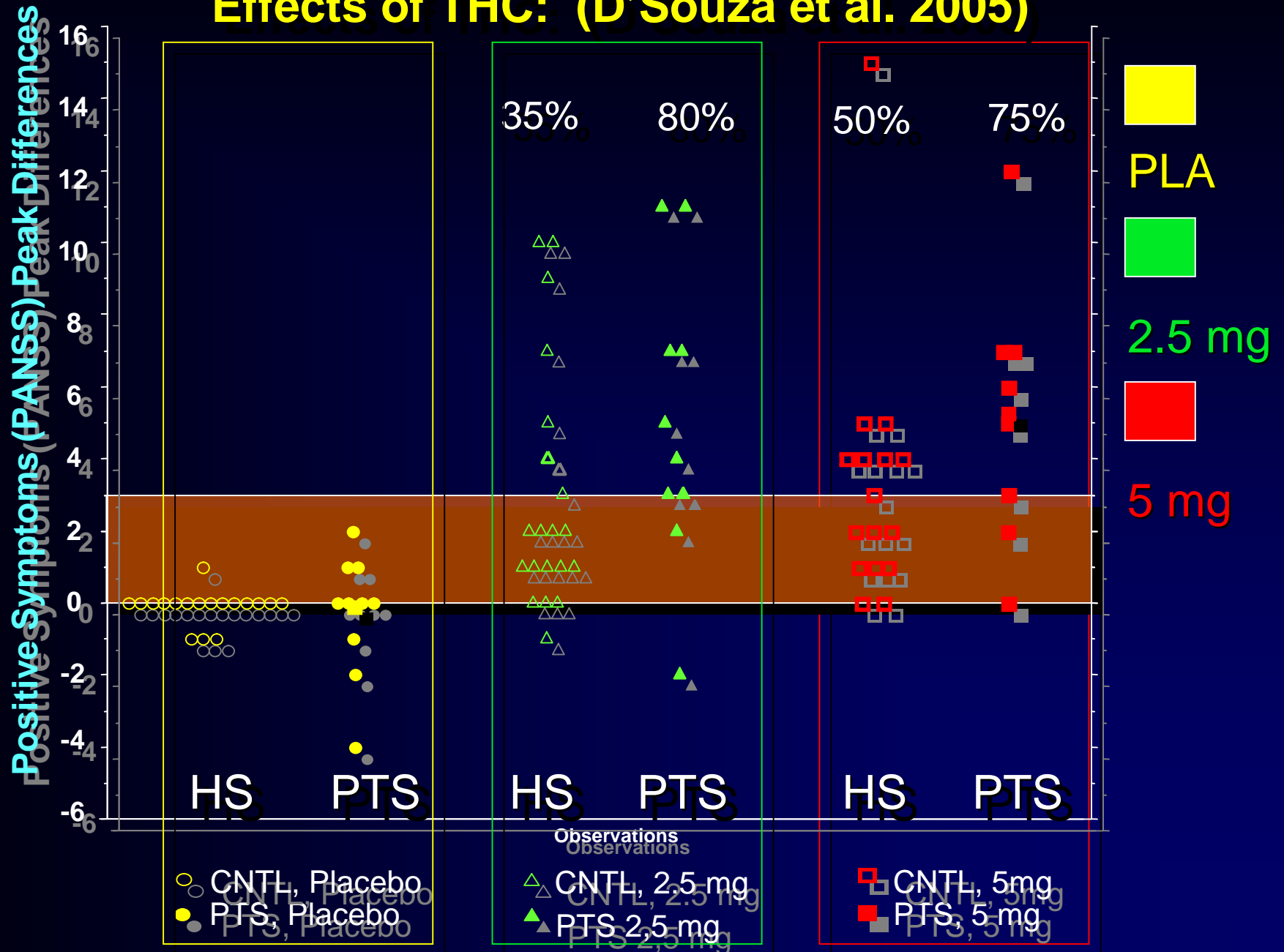
RC Smith et al. 2002, 2005, K Sacco et al 2005, Tregallas et al. 2005, De Luca et al. 2004, Patkar et al. 2002, George et al. 2002, Dalack et al. 1998

Nicotine Patch (Jacobsen et al. *Biol Psychiatry* 2004)

Attention (Distraction) Related Effects of Nicotine



Schizophrenic Patients More Sensitive to Psychotic Effects of THC: (D'Souza et al. 2005)



Ventral Striatal Deficits with Healthy Individuals with Family History of Alcohol Dependence (FHP): Contribute to Motivation Deficits with *Delayed* Punishment and Reward (MIDT) (P4: Pearlson; n=6 pairs)

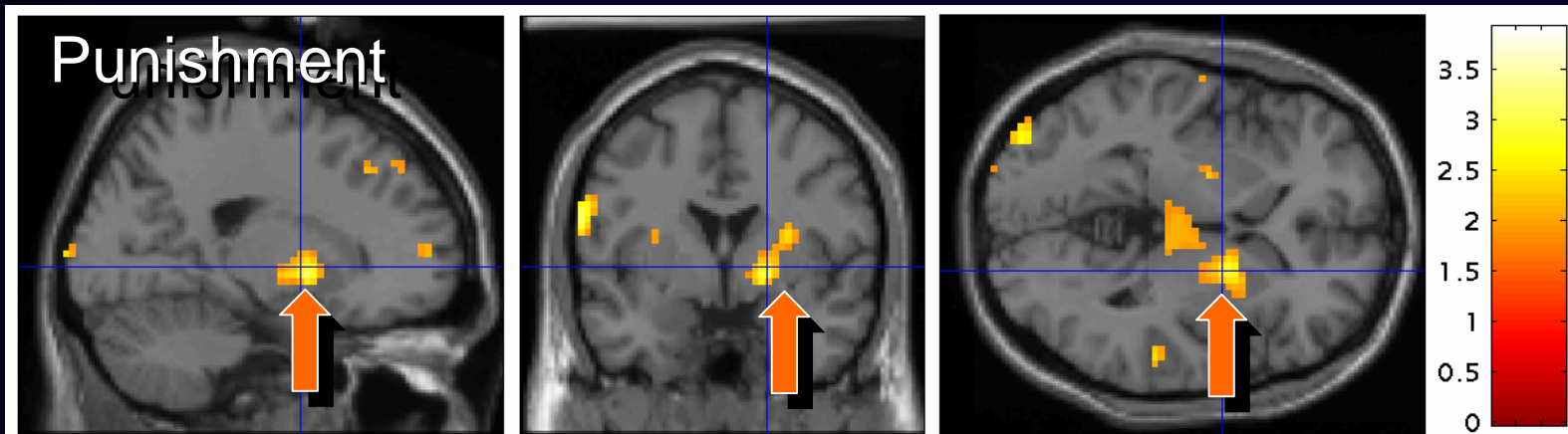


Fig. 6: FHN > FHP for anticipation of punishment. $p < 0.05$ uncorrected.

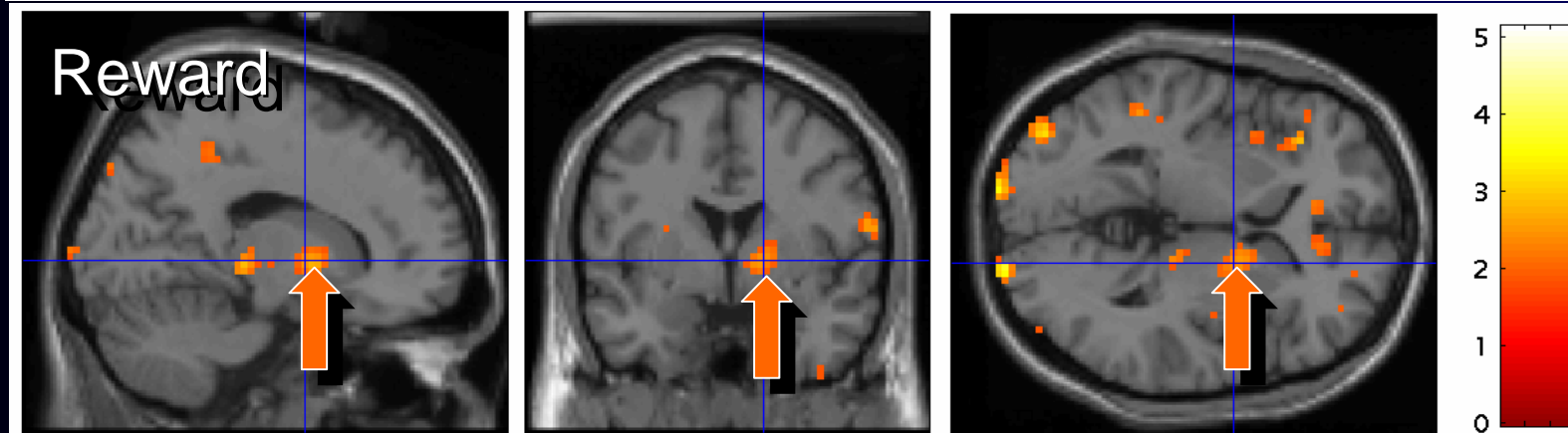


Fig. 7: FHN > FHP for anticipation of reward. $p < 0.05$ uncorrected.

Differential Effects of Treatment?

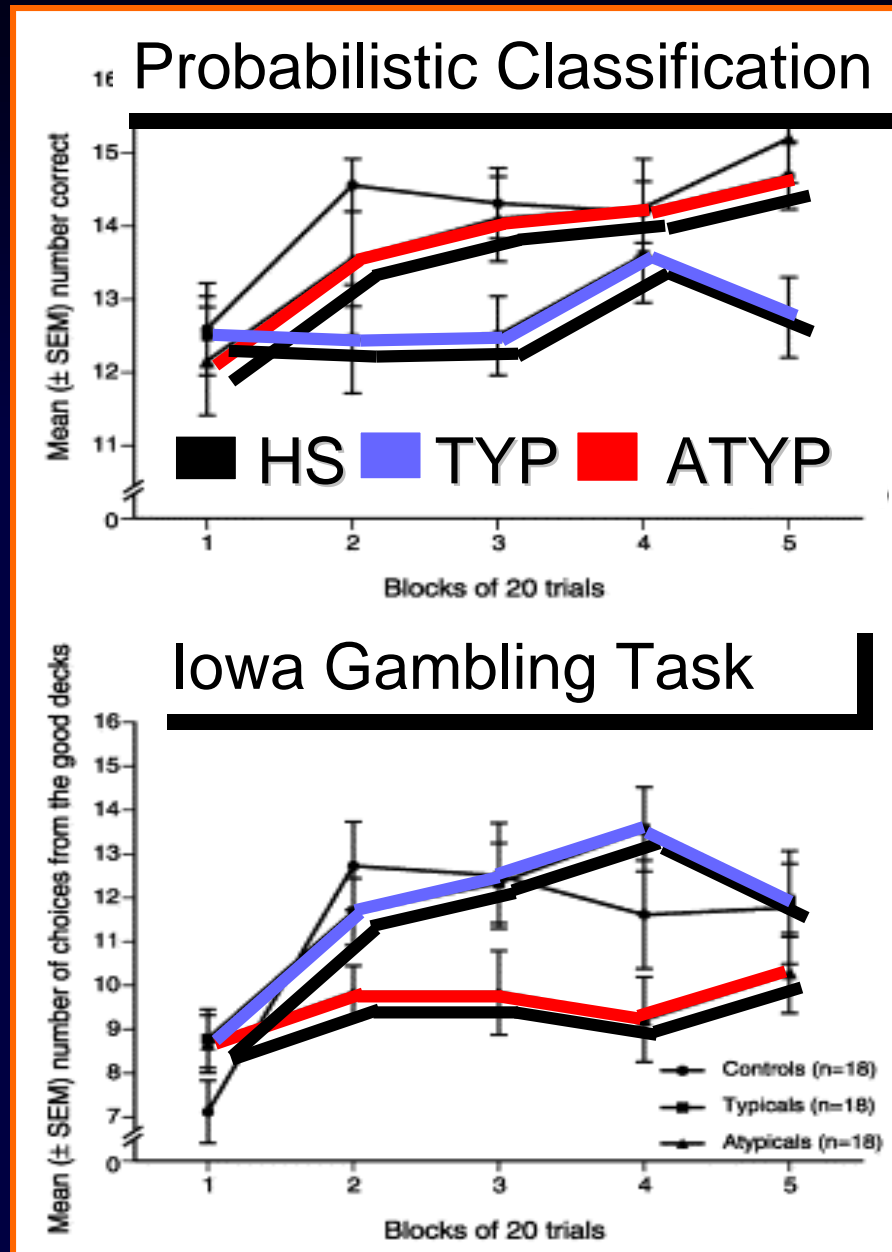
“Striatal” Task

Atypicals antipsychotics better than typicals

“Cortical” Task:

Typicals better than Atypicals

R. Beninger et al.
Schiz Res 2003



Correct

Better Choices

Sources of *Excess* Substance Abuse Risk in Schizophrenia

- Contribution of self-medication
- Contributions of the pathophysiology or treatment of schizophrenia
- Secondary reinforcement (withdrawal suppression)

Top 5 Reasons Given For Substance Abuse by Schizophrenic Patients

	Opiate (n=11)	ETOH (n=9)	Cannabis (n=5)
Get High	100%	56%	80%
Reduce Depression	36%	78%	40%
Relax	64%	56%	80%
Increase Pleasure	64%	44%	100%
Increase Energy	64%	22%	40%

S. Goswami et al. *Am J Addictions* 2004