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Neurobiology of vulnerability to drug dependence.

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Specificity of Genetic and Environmental Risk Factors for Use and Abuse/Dependence of Cannabis, Cocaine, Hallucinogens, Sedatives, Stimulants, and Opiates in Male Twins

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Objective: Data on use and misuse of six classes of illicit substances by male twin pairs were used to examine whether genetic and shared environmental risk factors for substance use disorders are substance-specific or -nonspecific in their effect.

Method: Lifetime history of use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates was assessed at personal interview in both members of 1,196 male-male twin pairs ascertained by the Virginia Twin Registry. Multivariate twin modeling of substance-nonspecific (common) and substance-specific genetic, shared environmental, and unique environmental risk factors was performed by using the program Mx.

Results: High levels of comorbidity involving the different substance categories were observed for both use and abuse/dependence. One common genetic factor was found to have a strong influence on risk for illicit use and abuse/dependence for all six substance classes. A modest influence of substance-specific genetic factors was seen for use but not for abuse/dependence. Shared environmental factors were more important for use than for abuse/dependence and were mediated entirely through a single common factor.

Conclusions: In an adult population-based sample of male twins, both the genetic and the shared environmental effects on risk for the use and misuse of six classes of illicit substances were largely or entirely nonspecific in their effect. Environmental experiences unique to the person largely determine whether predisposed individuals will use or misuse one class of psychoactive substances rather than another.

(Am J Psychiatry 2003; 160:687–695)

TABLE 1. Lifetime Prevalence of Use and Abuse/Dependence of Six Illicit Substance Classes by Monozygotic and Dizygotic Twins From a Population-Based Registry

	Prevalence (%)					
Behavior and Group	Cannabis	Cocaine	Hallucinogens	Sedatives	Stimulants	Opiates
Use						
Monozygotic twins (N=1,408)	51.5	16.5	13.2	10.7	18.2	6.1
Dizygotic twins (N=984)	57.5	18.7	16.7	11.9	20.4	6.0
Total (N=2,392)	54.0	17.4	14.6	11.2	19.1	6.1
Abuse/dependence						
Monozygotic twins (N=1,408)	16.9	4.9	3.4	2.4	7.0	1.5
Dizygotic twins (N=984)	20.2	6.0	3.3	4.2	8.5	2.5
Total (N=2,392)	18.3	5.3	3.3	3.1	7.6	1.9

TABLE 2. Within-Individual Tetrachoric Correlations for Lifetime Use and Abuse/Dependence Among Six Illicit Substance Classes in Monozygotic and Dizygotic Twins (N=2,392 Individuals) From a Population-Based Registry[a]

	Tetrachoric Correlation					
Substance Class	Cannabis	Cocaine	Hallucinogens	Sedatives	Stimulants	Opiates
Cannabis	—	0.85	0.85	0.69	0.76	0.60
Cocaine	0.80	—	0.82	0.79	0.78	0.72
Hallucinogens	0.83	0.83	—	0.79	0.78	0.78
Sedatives	0.78	0.77	0.81	—	0.82	0.85
Stimulants	0.73	0.74	0.74	0.85	—	0.77
Opiates	0.67	0.70	0.79	0.81	0.69	—

[a] Correlations for substance use are shown in the shaded areas above the diagonal; correlations for abuse/dependence are shown in the clear areas below the diagonal.

TABLE 4. Estimated Proportions of Variance Accounted for by Factors From the Best-Fit Models for Liability to Lifetime Use and Abuse/Dependence of Six Illicit Substance Classes by Monozygotic and Dizygotic Twins (N=2,392 Individuals) From a Population-Based Registry

	Proportion of Variance									
	Additive Genetic Factors			Shared Environmental Factors			Unique Environmental Factors			
							Common[c]			
Behavior and Substance	Common	Substance-Specific[a]	Total	Common	Substance-Specific[b]	Total	Factor 1	Factor 2[d]	Substance-Specific	Total
Use										
Cannabis	0.34	0.01	0.35	0.35		0.35	0.00	0.30	0.00	0.30
Cocaine	0.49	0.07	0.56	0.14		0.14	0.03	0.16	0.10	0.29
Hallucinogens	0.45	0.10	0.55	0.29		0.29	0.03	0.08	0.04	0.15
Sedatives	0.51	0.08	0.59	0.07		0.07	0.26	0.05	0.03	0.34
Stimulants	0.55	0.04	0.59	0.08		0.08	0.08	0.09	0.16	0.33
Opiates	0.37	0.00	0.37	0.17		0.17	0.33	0.00	0.13	0.46
Abuse/dependence										
Cannabis	0.73		0.73	0.01		0.01	0.09		0.17	0.26
Cocaine	0.63		0.63	0.00		0.00	0.15		0.22	0.37
Hallucinogens	0.63		0.63	0.05		0.05	0.24		0.09	0.33
Sedatives	0.51		0.51	0.07		0.07	0.34		0.08	0.42
Stimulants	0.57		0.57	0.06		0.06	0.16		0.21	0.37
Opiates	0.23		0.23	0.00		0.00	0.64		0.14	0.78

Behavior and Substance	Additive Genetic Factors		
	Common	Substance-Specific[a]	Total
Use			
Cannabis	0.34	0.01	0.35
Cocaine	0.49	0.07	0.56
Hallucinogens	0.45	0.10	0.55
Sedatives	0.51	0.08	0.59
Stimulants	0.55	0.04	0.59
Opiates	0.37	0.00	0.37
Abuse/dependence			
Cannabis	0.73		0.73
Cocaine	0.63		0.63
Hallucinogens	0.63		0.63
Sedatives	0.51		0.51
Stimulants	0.57		0.57
Opiates	0.23		0.23

The Structure of Genetic and Environmental Risk Factors for Common Psychiatric and Substance Use Disorders in Men and Women

Kenneth S. Kendler, MD; Carol A. Prescott, PhD; John Myers, MS; Michael C. Neale, PhD

Background: Patterns of comorbidity suggest that the common psychiatric and substance use syndromes may be divisible into 2 broad groups of internalizing and externalizing disorders. We do not know how genetic and environmental risk factors contribute to this pattern of comorbidity or whether the etiologic structure of these groups differ in men and women.

Methods: Lifetime diagnoses for 10 psychiatric syndromes were obtained at a personal interview in more than 5600 members of male-male and female-female twin pairs ascertained from a population-based registry. Multivariate twin modeling was performed using the program Mx.

Results: We first fit models to the following 7 syndromes: major depression, generalized anxiety disorder, phobia, alcohol dependence, drug abuse/dependence, adult antisocial behavior, and conduct disorder. The full model, which could be constrained to equality in male and female subjects, identified 2 genetic factors. The first had strongest loadings on alcohol dependence, drug abuse/dependence, adult antisocial behavior, and conduct disorder; the second, on major depression, generalized anxiety disorder, and phobia. Alcohol dependence and drug abuse/dependence had substantial disorder-specific genetic risk factors. Shared environmental factors were most pronounced for conduct disorder and adult antisocial behavior. No clear internalizing/externalizing structure was seen for the unique environmental common factors. We then fit models to 5 internalizing syndromes. The full model, which could also be constrained to equality in men and women, revealed one genetic factor loading most heavily on major depression and generalized anxiety disorder and another loading most strongly on animal and situational phobia.

Conclusions: The underlying structure of the genetic and environmental risk factors for the common psychiatric and drug abuse disorders in men and women is very similar. Genetic risk factors predispose to 2 broad groups of internalizing and externalizing disorders. Within the internalizing disorders, 2 genetic factors are seen that predispose to disorders dominated by anxious-misery and fear. Substance use disorders have disorder-specific genetic risks. The externalizing disorders of conduct disorder and adult antisocial behavior are significantly influenced by the shared environment. The pattern of lifetime comorbidity of common psychiatric and substance use disorders results largely from the effects of genetic risk factors.

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Table 1. Prevalence Rates and Comorbidity Between 7 Major Psychiatric and Substance Use Disorders*

	Lifetime Prevalence, %		Assessed Comorbidity, Tetrachoric Correlations (OR)						
Disorder	Men	Women	MD	GAD	Phobia	AD	DAD	AASB	CD
MD	28.5	40.4	. . .	0.50 (4.57)	0.22 (1.80)	0.35 (2.70)	0.25 (1.97)	0.26 (2.11)	0.18 (1.67)
GAD†	14.6	25.9	0.50 (4.14)	. . .	0.37 (3.12)	0.29 (2.45)	0.26 (2.22)	0.36 (3.17)	0.18 (1.72)
Phobia	21.8	30.0	0.26 (1.88)	0.29 (2.22)	. . .	0.17 (1.58)	0.17 (1.50)	0.12 (1.44)	0.19 (1.75)
AD	23.9	8.2	0.33 (2.84)	0.22 (2.01)	0.28 (2.43)	. . .	0.43 (3.29)	0.45 (3.66)	0.32 (2.43)
DAD	22.4	11.0	0.29 (2.36)	0.21 (1.91)	0.22 (1.81)	0.59 (8.17)	. . .	0.57 (5.13)	0.43 (3.01)
AASB	15.1	6.1	0.29 (2.69)	0.33 (2.99)	0.23 (2.16)	0.45 (5.55)	0.58 (8.18)	. . .	0.56 (5.78)
CD	19.1	4.4	0.33 (3.42)	0.21 (2.08)	0.21 (2.15)	0.42 (4.67)	0.50 (5.24)	0.61 (11.81)	. . .

Abbreviations: AASB, adult antisocial behavior; AD, alcohol dependence; CD, conduct disorder; DAD, drug abuse/dependence; GAD, generalized anxiety disorder; MD, major depression; OR, odds ratio.

*Results for men were above the diagonal; for women, below. All correlation and ORs are significant at $P<.05$.

†Indicates broad diagnostic criteria.

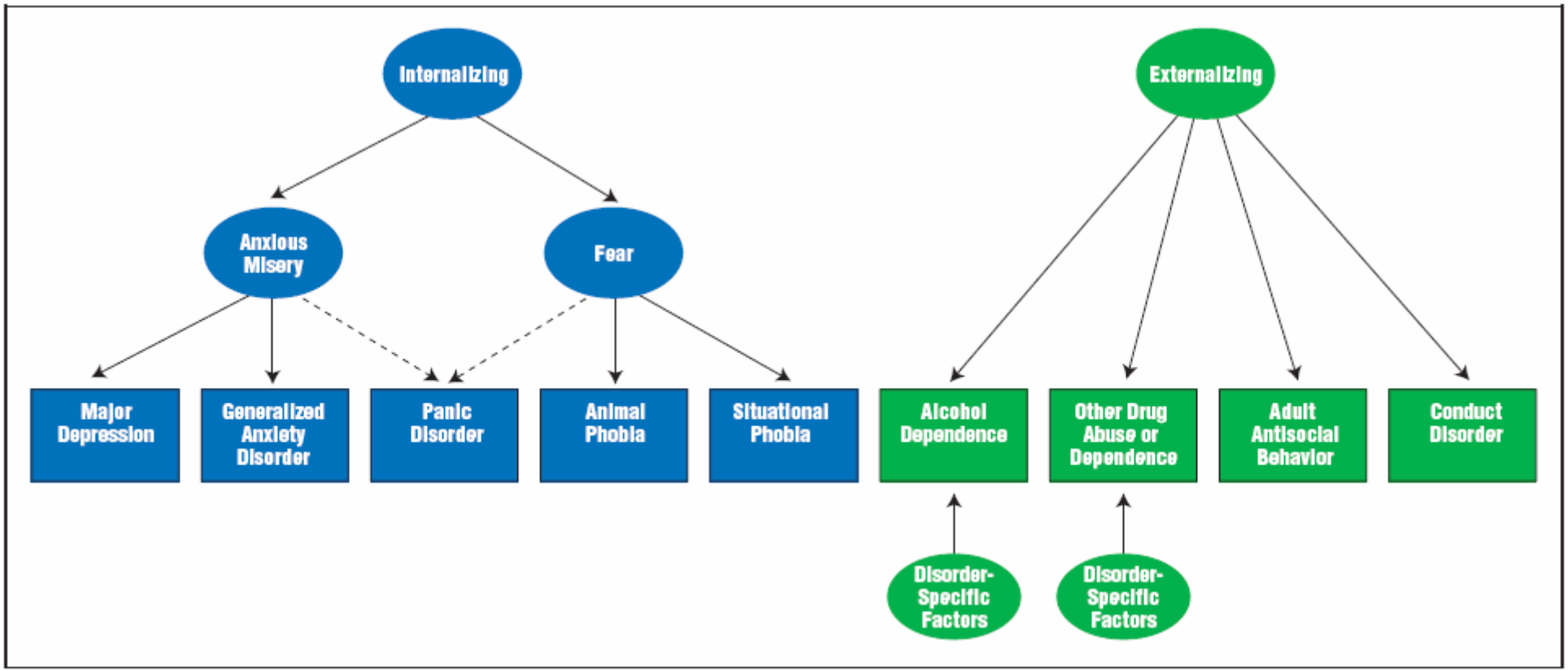

Figure 3. A proposed structure for the genetic risk factors for common psychiatric and substance use disorders in men and women. Strong relationships are depicted by solid lines and, in the case of panic disorder only, weaker relationships by dotted lines. This model exaggerates the clarity of the factor structure obtained in our analyses, as the evidence suggests that internalizing disorders load weakly on the externalizing common factor and vice versa.

Shared Genetic Risk of Major Depression, Alcohol Dependence, and Marijuana Dependence

Contribution of Antisocial Personality Disorder in Men

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Background: Little is known about genetic factors that underlie the interrelationships among antisocial personality disorder (ASPD), major depression (MD), alcohol dependence (AD), and marijuana dependence (MJD). We examined the contribution of genetic effects associated with ASPD to the comorbidity of MD and substance use disorders.

Methods: The Vietnam Era Twin Registry is a general population registry of male veteran twins constructed from computerized Department of Defense files and other sources. A telephone diagnostic interview was administered to eligible twins from the Registry in 1992. Of 5150 twin pairs who served on active military duty during the Vietnam era, 3360 pairs (1868 monozygotic and 1492 dizygotic) in which both members completed the pertinent diagnostic interview sections were included. The main outcome measures were lifetime *DSM-III-R* ASPD, MD, AD, and MJD.

Results: Structural equation modeling was performed to estimate additive genetic, shared environmental, and nonshared environmental effects common and specific to each disorder. The heritability estimates for lifetime ASPD, MD, AD, and MJD were 69%, 40%, 56%, and 50%, respectively. Genetic effects on ASPD accounted for 38%, 50%, and 58% of the total genetic variance in risk for MD, AD, and MJD, respectively. After controlling for genetic effects on ASPD, the partial genetic correlations of MD with AD and with MJD were no longer statistically significant. Genetic effects specific to MD and AD and familial effects specific to MJD remained statistically significant. Nonshared environmental contributions to the comorbidity in these disorders were small.

Conclusions: In this sample, the shared genetic risk between MD and both AD and MJD was largely explained by genetic effects on ASPD, which in turn was associated with increased risk of each of the other disorders.

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Genetic effects on ASPD accounted for 38%, 50%, and 58% of the total genetic variance in risk for MD, AD, and MJD, respectively. After controlling for genetic effects on ASPD, the partial genetic correlations of MD with AD and with MJD were no longer statistically significant. Genetic effects specific to MD and AD and familial effects specific to MJD remained statistically significant. Nonshared environmental contributions to the comorbidity in these disorders were small.

Conclusions: In this sample, the shared genetic risk between MD and both AD and MJD was largely explained by genetic effects on ASPD, which in turn was associated with increased risk of each of the other disorders.

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Decision-making and addiction (part I): impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences

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Abstract

Some substance dependent individuals (SDI) suffer from a decision-making impairment akin to that seen in neurological patients with lesions of the ventromedial (VM) prefrontal cortex. The somatic-marker hypothesis posits that decision-making is a process that depends on emotion and that deficits in emotional signaling will lead to poor decision-making. In this study, we tested the hypothesis that SDI who perform disadvantageously on a decision-making instrument, the gambling task (GT), have a deficit in the somatic signals that help guide their decision in the advantageous direction. Since deficits in decision-making/somatic markers can also result from dysfunctional amygdala, we asked indirectly (i.e. via tests sensitive to VM or amygdala dysfunction) whether such a deficit in SDI is restricted to VM dysfunction or includes the amygdala. Using the GT, and skin conductance response (SCR) as an index of somatic state activation, we studied groups of SDI ($n = 46$), normal controls ($n = 49$), and VM patients ($n = 10$). A subgroup of SDI showed defective performance on the GT coupled with impaired anticipatory SCR, but normal SCR to punishment, and normal acquisition of conditioned SCR to an aversive loud sound. This supports the hypothesis that the poor decision-making in some SDI is associated with defective somatic state activation that is linked to a dysfunctional VM cortex. Thus, the dysfunctional VM cortex underlying the "myopia" for the future in some SDI may be one of the principle mechanisms underlying the transition from casual substance taking to compulsive and uncontrollable behavior. © 2002 Elsevier Science Ltd. All rights reserved.

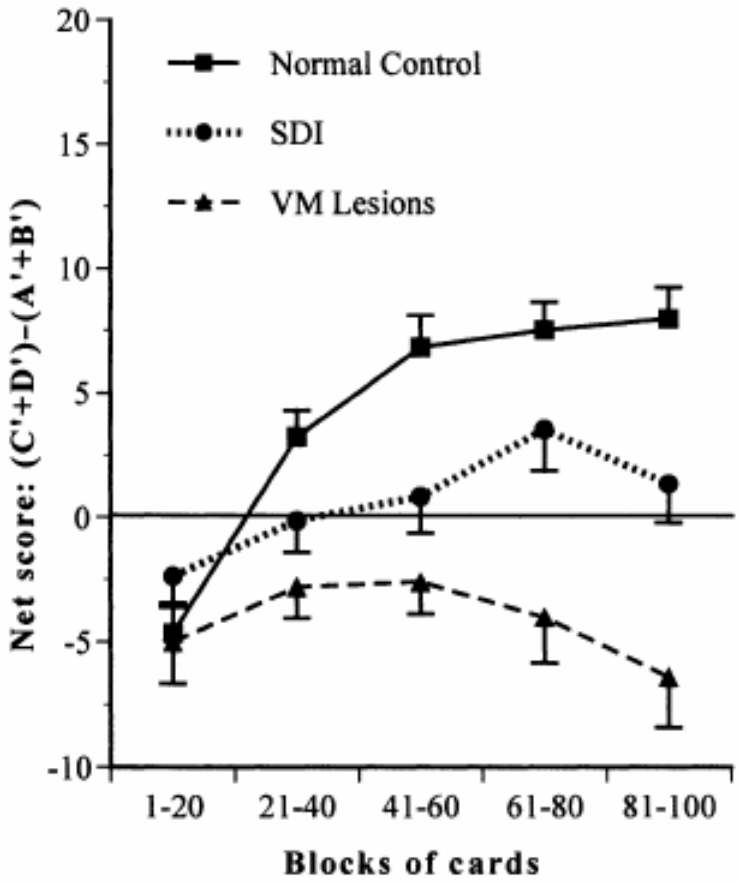

Fig. 1. Relative to normal control subjects, substance dependent individuals (SDI) were impaired in their performance on the GT, but the impairment was not as severe as that seen in VM patients. The figure shows net scores $((C' + D') - (A' + B'))$ of cards selected by each group across different blocks expressed as mean $\pm$ S.E.M. Positive net scores reflect advantageous performance while negative net scores reflect disadvantageous performance.

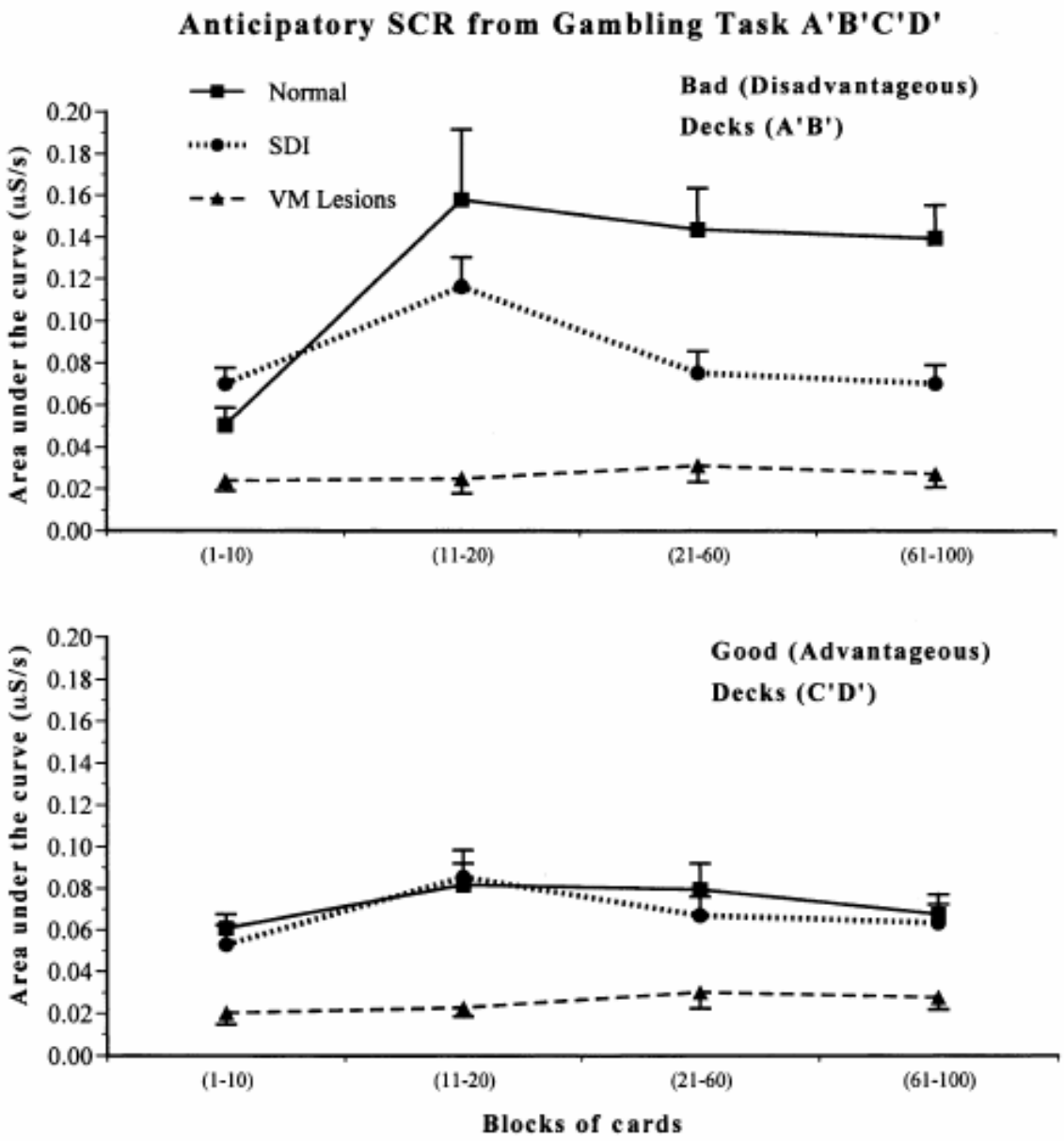

Fig. 2. Anticipatory SCRs are presented as the mean ± S.E.M. of the average area under the curve of responses generated prior to selecting cards from the disadvantageous decks (decks A′ and B′) or the advantageous decks (decks C′ and D′).

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Decision-making and addiction (part II): myopia for the future or hypersensitivity to reward?

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Received 26 March 2001; received in revised form 13 December 2001; accepted 20 December 2001

Abstract

On a decision-making instrument known as the "gambling task" (GT), a subgroup of substance dependent individuals (SDI) opted for choices that yield high immediate gains in spite of higher future losses. This resembles the behavior of patients with ventromedial (VM) prefrontal cortex lesions. In this study, we addressed the possibility that hypersensitivity to reward may account for the "myopia" for the future in this subgroup of SDI. We used a variant version of the GT, in which the good decks yielded high immediate punishment but higher delayed reward. The bad decks yielded low immediate punishment and lower delayed reward. We measured the skin conductance response (SCR) of subjects after receiving reward (reward SCR) and during their pondering from which deck to choose (anticipatory SCR). A subgroup of SDI who was not impaired on the original GT performed normally on the variant GT. The subgroup of SDI who was impaired on the original GT showed two levels of performance on the variant GT. One subgroup (36% of the sample) performed poorly on the variant GT, and showed similar behavioral and physiological impairments to VM patients. The other subgroup of SDI (64% of the sample) performed normally on the variant task, but had abnormally large physiological responses to reward, i.e. large SCR after receiving reward (reward SCR) and large SCR in anticipation of outcomes that yield large reward. Thus, the combined cognitive and physiological approach of assessing decision-making characterizes three sub-populations of SDI. One sub-population is without impairments that can be detected by any measure of the GT paradigm. Another sub-population is similar to VM patients in that they are insensitive to the future, both positive and negative. A third sub-population is hypersensitive to reward, so that the presence or the prospect of receiving, reward dominates their behavior. © 2002 Elsevier Science Ltd. All rights reserved.

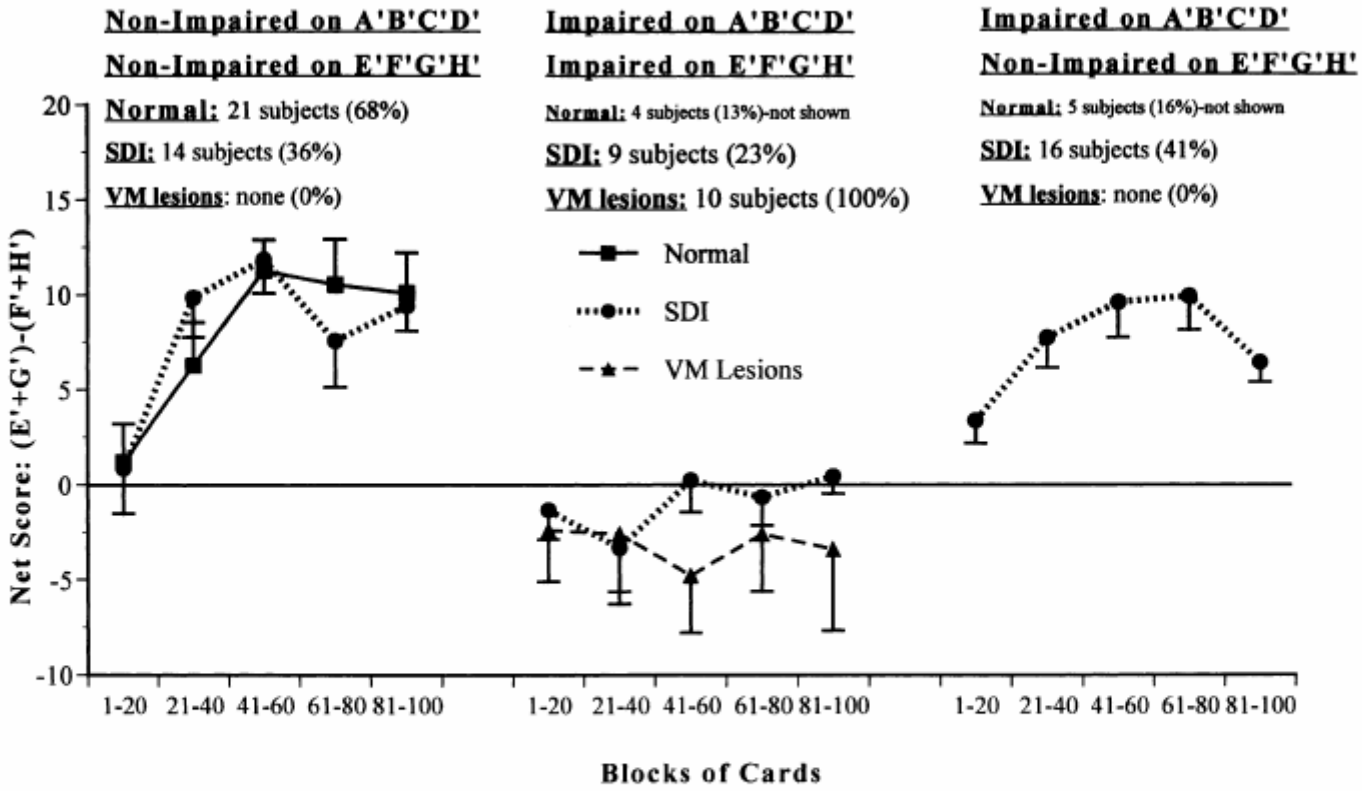

Fig. 3. Net scores of performance on the variant gambling task (E′F′G′H′). Groups are divided according to non-impaired or impaired behavioral performance on both the original (A′B′C′D′) and variant (E′F′G′H′) versions of the GT. The criteria for impaired or non-impaired performance are based on cut off scores between the performance of normal controls and patients with VM lesions. For the original task, the impaired net score is <10. For the variant task, the impaired score is <8. Data are presented as mean ± S.E.M.We note that of the 13% of normal subjects who behaved like VM patients on the GT, 50% of them (two subjects) showed abnormal behavior, but they generated anticipatory SCRs, suggesting that their deficit is not identical to that of VM patients. Only one of the subjects who was impaired on the GT and had abnormal anticipatory SCRs also showed impairment on other executive function tests, i.e. the WCST.

Activation of Orbital and Medial Prefrontal Cortex by Methylphenidate in Cocaine-Addicted Subjects But Not in Controls: Relevance to Addiction

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Drugs of abuse are rewarding to addicted and nonaddicted subjects, but they trigger craving and compulsive intake only in addicted subjects. Here, we used positron emission tomography (PET) and [^{18}F]deoxyglucose to compare the brain metabolic responses (marker of brain function) of cocaine-addicted subjects ($n = 21$) and controls ($n = 15$) to identify brain regions that are uniquely activated in addicted subjects by intravenous methylphenidate (a drug that cocaine-addicted subjects report to be similar to cocaine). In parallel, we also measured the changes in dopamine (DA) induced by intravenous methylphenidate (using PET and [^{11}C]raclopride) in the striatum and in the thalamus. Metabolic responses between groups differed significantly only in the right medial orbital prefrontal cortex [Brodmann's area (BA) 25 and medial BA 11], where methylphenidate increased metabolism in addicted subjects but decreased metabolism in controls. These changes were associated in all subjects with increased "desire for methylphenidate" and in the addicted subjects with "cocaine craving." In addicted subjects, increases in BA 25 were also associated with mood elevation. Methylphenidate-induced increases in metabolism in the medial orbital prefrontal cortex were associated with its increase of DA in the thalamus but not in the striatum. These findings provide evidence that enhanced sensitivity of BA 25 (region involved with emotional reactivity) and BA 11 (region involved with salience attribution and motivation) in cocaine-addicted subjects may underlie the strong emotional response to the drug and the intense desire to procure it that results in craving and compulsive drug intake. It also suggests that the mesothalamic DA pathway may contribute to these processes.

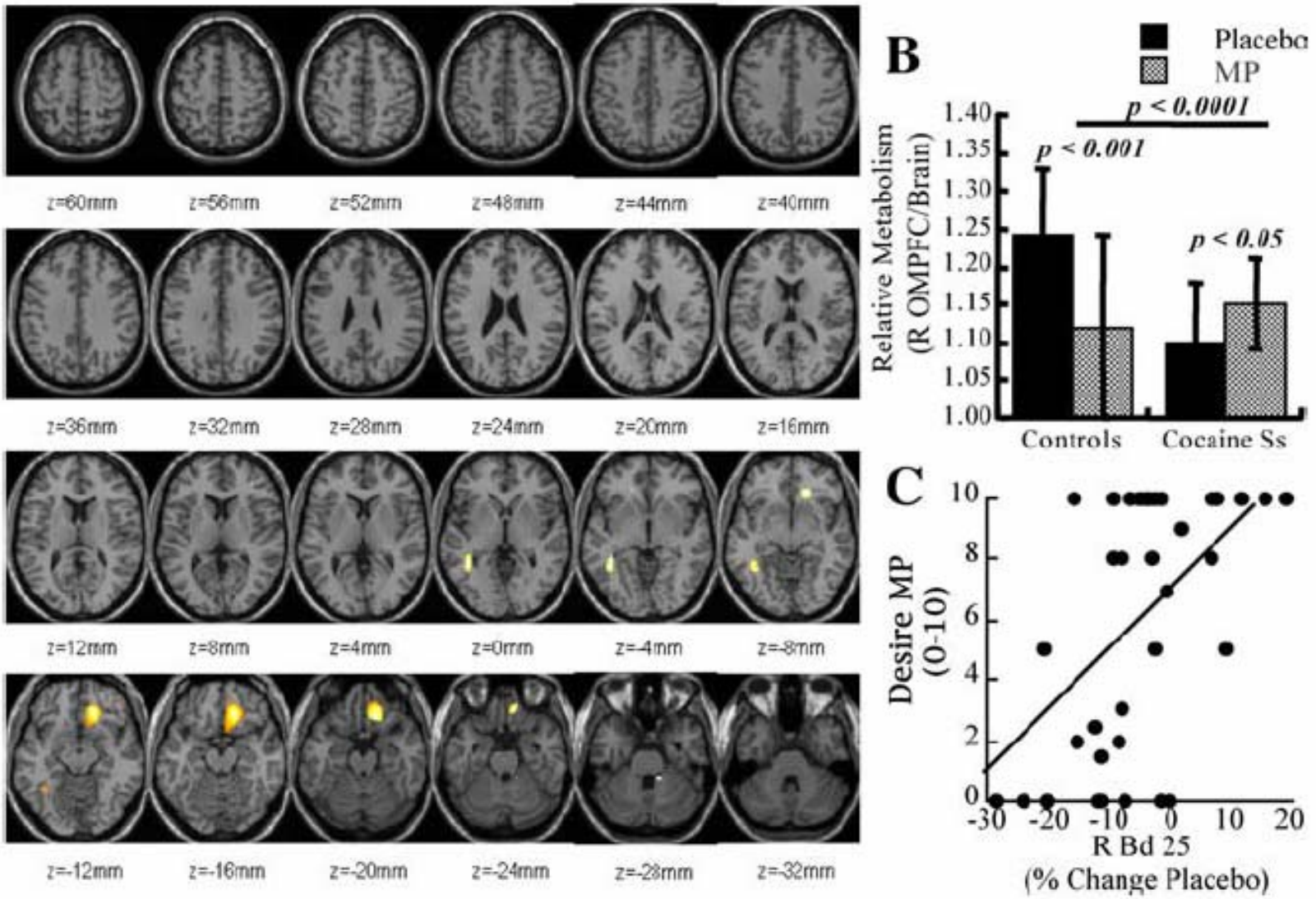
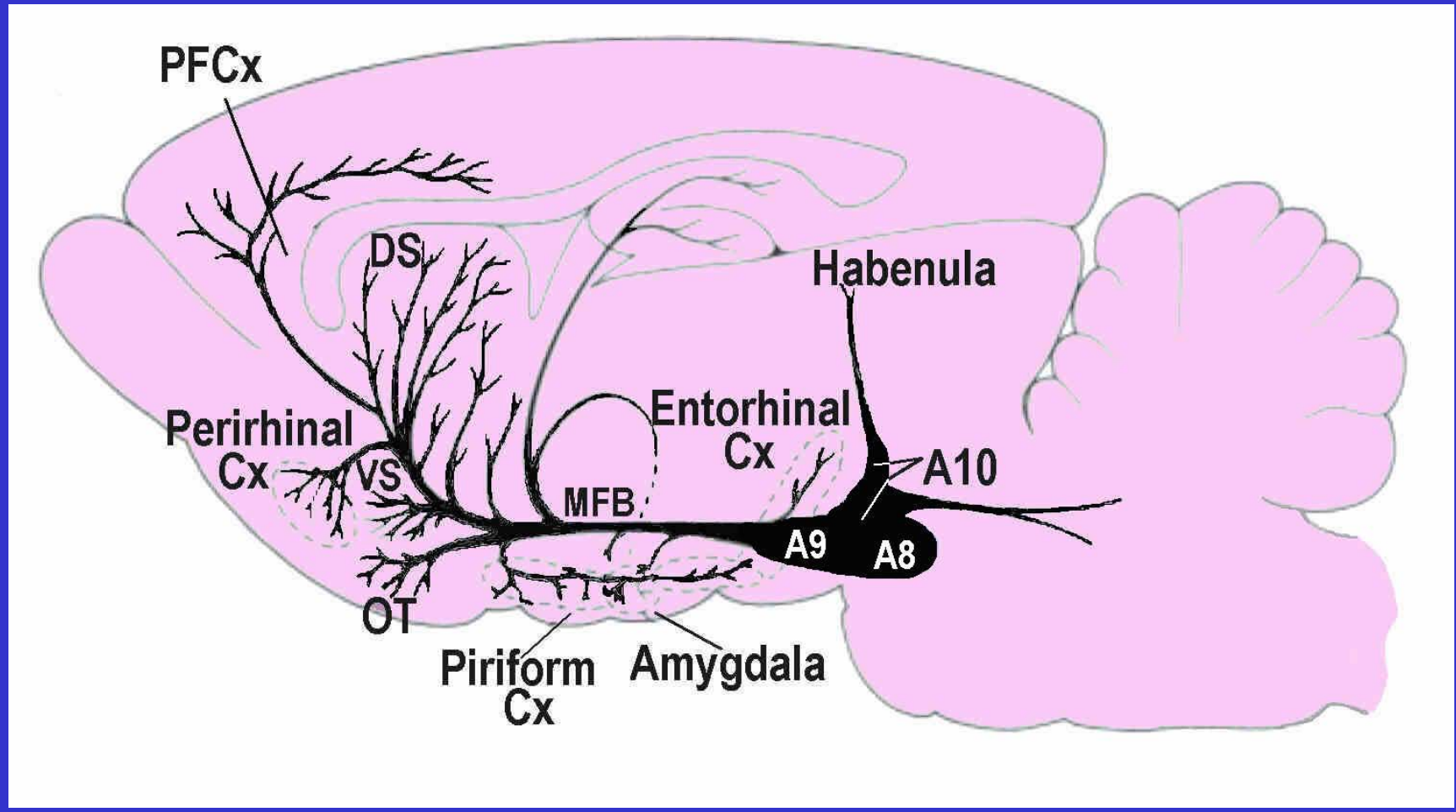


Figure 3. ***A***, Brain regions where the response to MP differed between controls and cocaine-addicted subjects. The results are presented with respect to the controls. ***B***, Relative metabolic measures in the right OMPFC in controls and in cocaine-addicted subjects for the placebo and for MP conditions. Metabolism was significantly lower in addicted subjects than in controls for the placebo condition. MP decreased metabolism in controls but increased metabolism in addicted subjects (values correspond to means and SDs). R OMPFC, Right OMPFC. ***C***, Relationship between the changes in metabolism induced by MP and the self-reports for desire for MP ($r = 0.55$; $p < 0.0005$). R Bd 25, Right Brodmann area 25.


PFCx
DS
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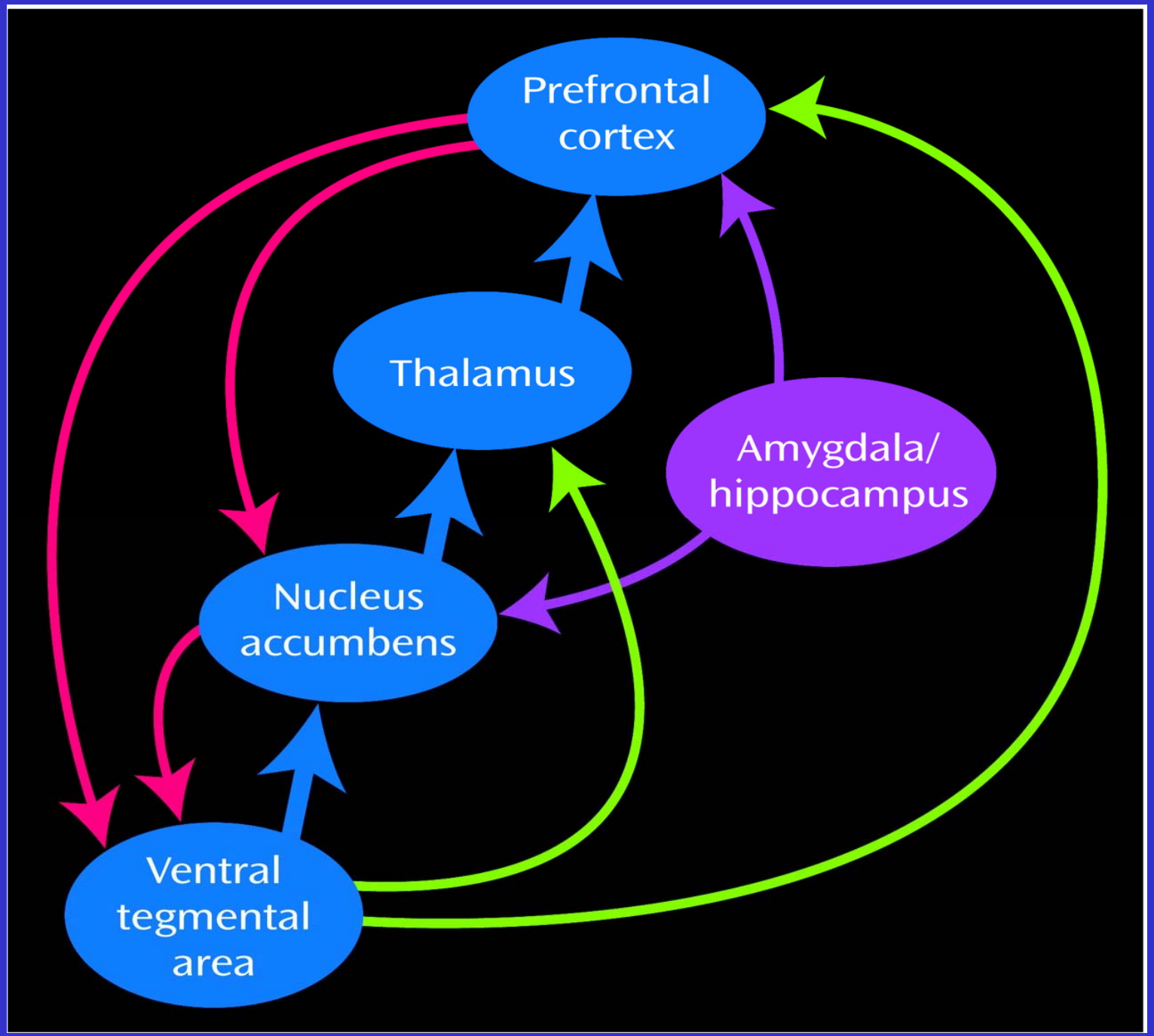
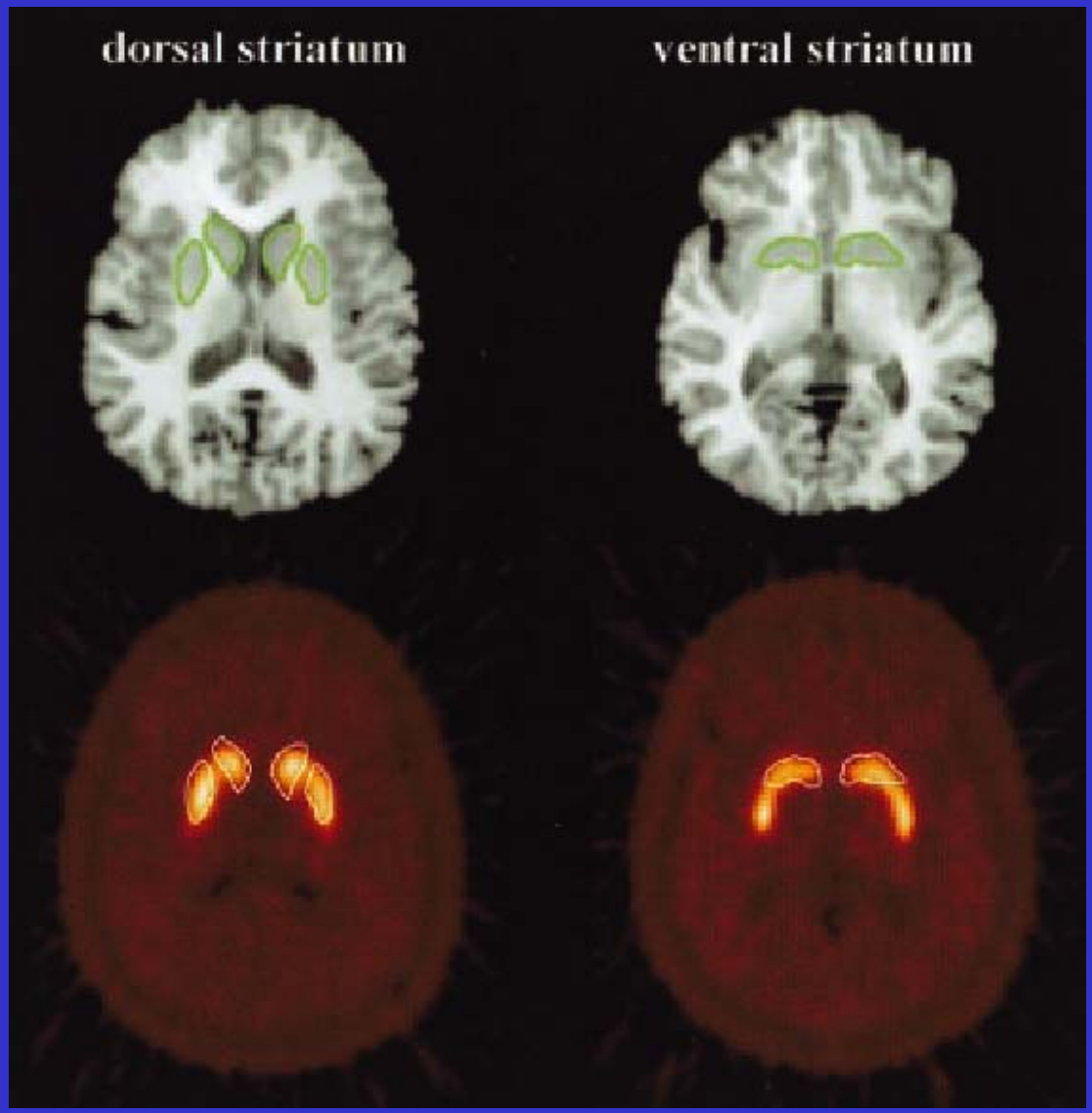

Prefrontal cortex
Thalamus
Amygdala/ hippocampus
Nucleus accumbens
Ventral tegmental area

W.C. Drevets, C. Gautier, J.C. Price, D.J. Kupfer, P.E. Kinahan, A.A. Grace, J.L. Price, and C.A. Mathis

Amphetamine-Induced Dopamine Release in Human Ventral Striatum Correlates with Euphoria

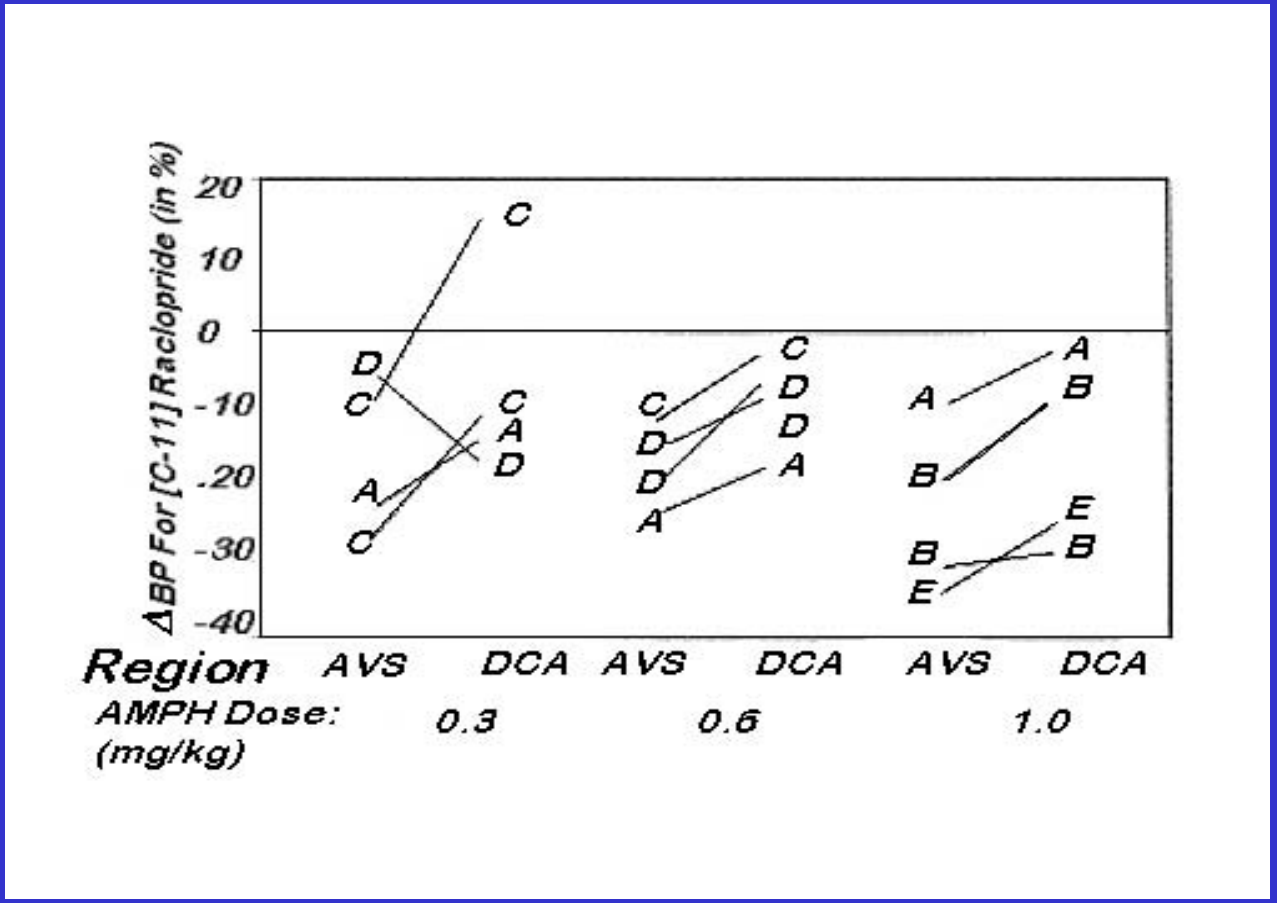
Biol. Psychiatry **2001;49:81–96**



Wayne C. Drevets, M.D., Julie C. Price, Ph.D., David J. Kupfer, M.D., Paul E. Kinahan, P
Brian Lopresti, B.S., Daniel Holt, B.S., and Chester Mathis, Ph.D

PET Measures of Amphetamine-Induced Dopamine Release in Ventral versus Dorsal Striatum

NEUROPSYCHOPHARMACOLOGY 1999–VOL. 21, NO. 6



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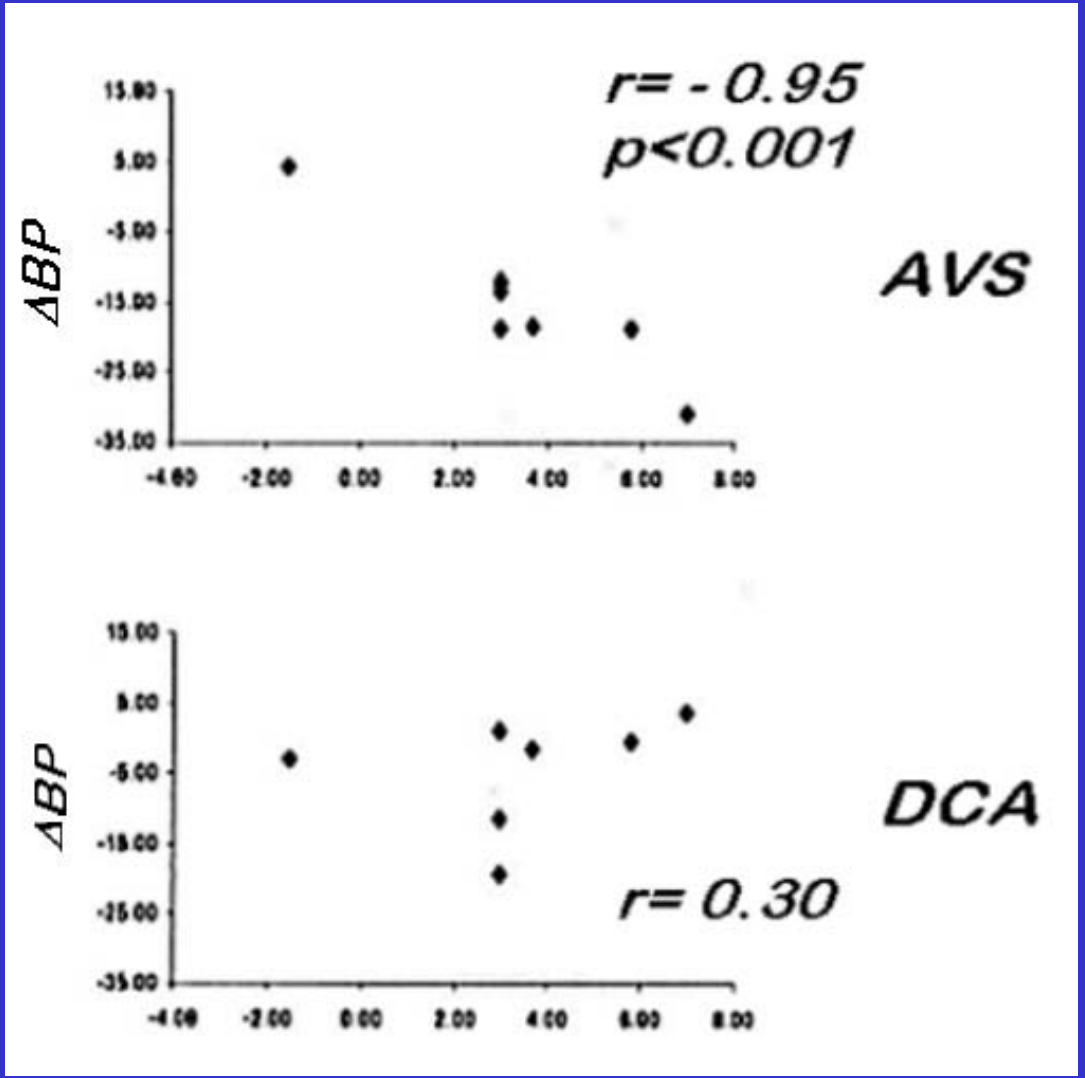

Amphetamine-Induced Increases in Extracellular Dopamine, Drug Wanting, and Novelty Seeking: A PET/[^{11}C]Raclopride Study in Healthy Men

Marco Leyton, Isabelle Boileau, Chawki Benkelfat, Mirko Diksic, Glen Baker, and Alain Dagher

Eight healthy men underwent two positron emission tomography (PET) [^{11}C]raclopride scans, one following placebo, the second following d-amphetamine (0.30 mg/kg, p.o.). PET data were analyzed using: (1) brain parametric maps to statistically generate regions of significant change; and (2) a priori identified regions of interest (ROI) manually drawn on each individual's co-registered magnetic resonance (MR) images. Compared with placebo, d-amphetamine decreased [^{11}C]raclopride binding potential (BP) with significant effects in ventral but not dorsal striatum. Change in BP in the statistically generated cluster correlated with self-reported drug-induced 'drug wanting' ($r = 0.83$, $p = .01$) and the personality trait of Novelty Seeking-Exploratory Excitability ($r = 0.79$, $p = .02$). The same associations were seen in the manually drawn ROI in ventral striatum but not in dorsal putamen or caudate. Changes in extracellular dopamine (DA) did not correlate with mood. Mesolimbic DA might mediate interest in obtaining reward rather than reward, per se. Individual differences in amphetamine-induced DA release might be related to predispositions to drug and novelty seeking.

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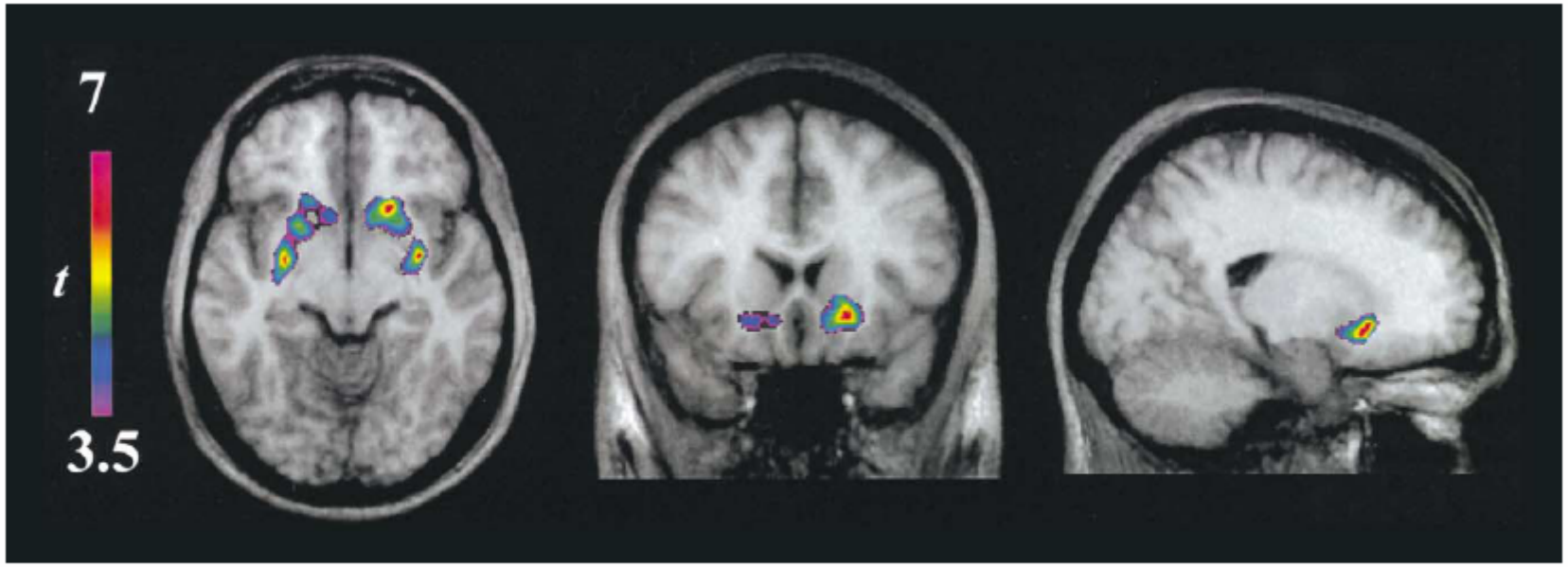


Figure 2. Statistically generated t-map of d-amphetamine–induced changes in [^{11}C]raclopride binding potential superimposed on average MRI. Right side on right.

Table 3. [^{11}C]Raclopride binding potential values on test days with placebo or d-amphetamine (0.3 mg/kg, p.o.). Newman-Keuls *post hoc* tests.

Test Day	Ventral Striatum	Caudate	Putamen
Placebo	1.44 ± 0.5†	1.97 ± 0.2*	2.45 ± 0.3*†
d-Amphetamine	1.26 ± 0.4$^{\#\dagger}$	1.94 ± 0.2*	2.45 ± 0.3*†

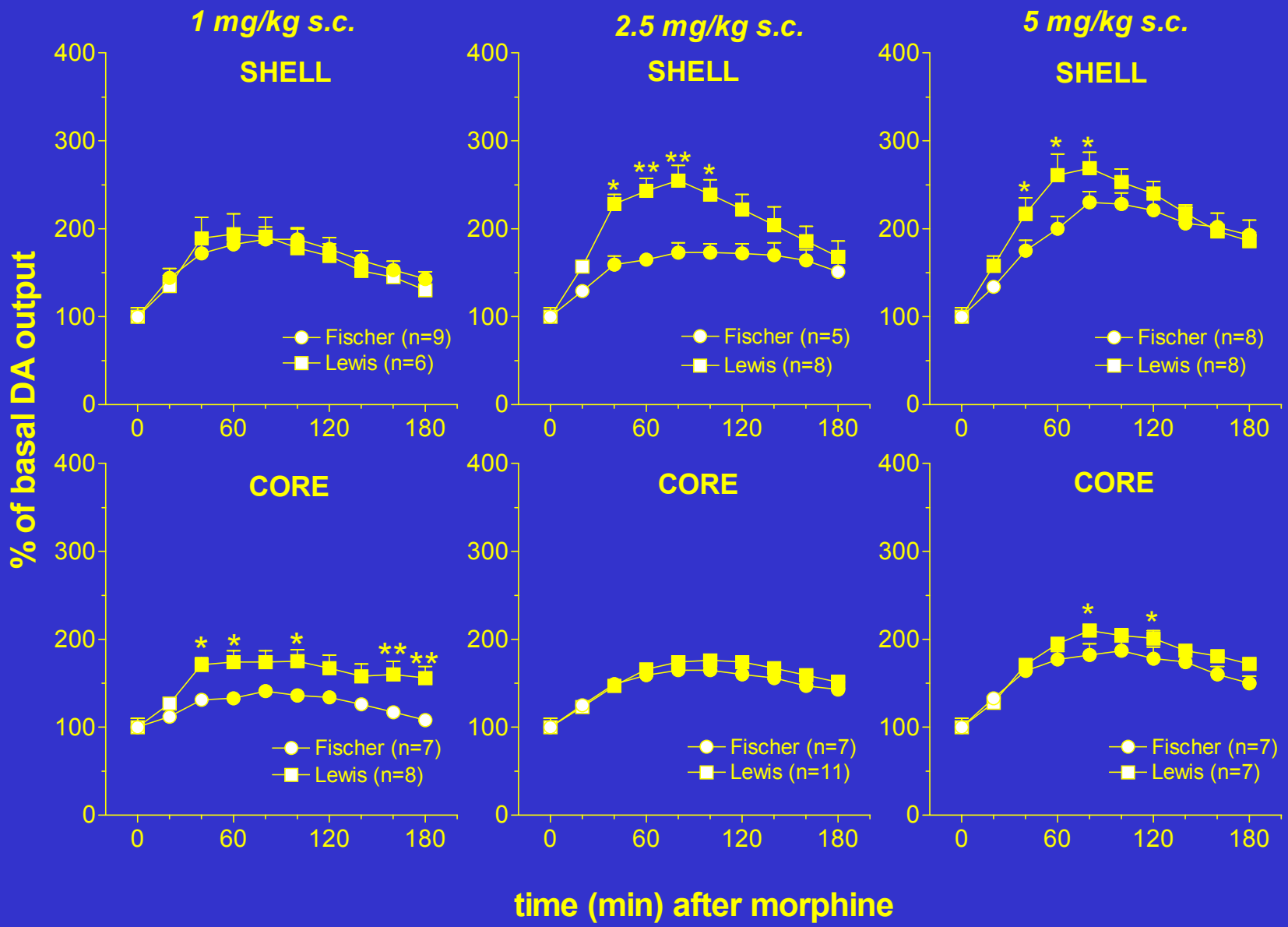
$^{\#}$Different from placebo, p = .05.
* Different from ventral striatum, $p < .001$.
† Different from caudate, $p < .001$.

Table 4. Pearson correlations with change in [^{11}C]raclopride binding potential.

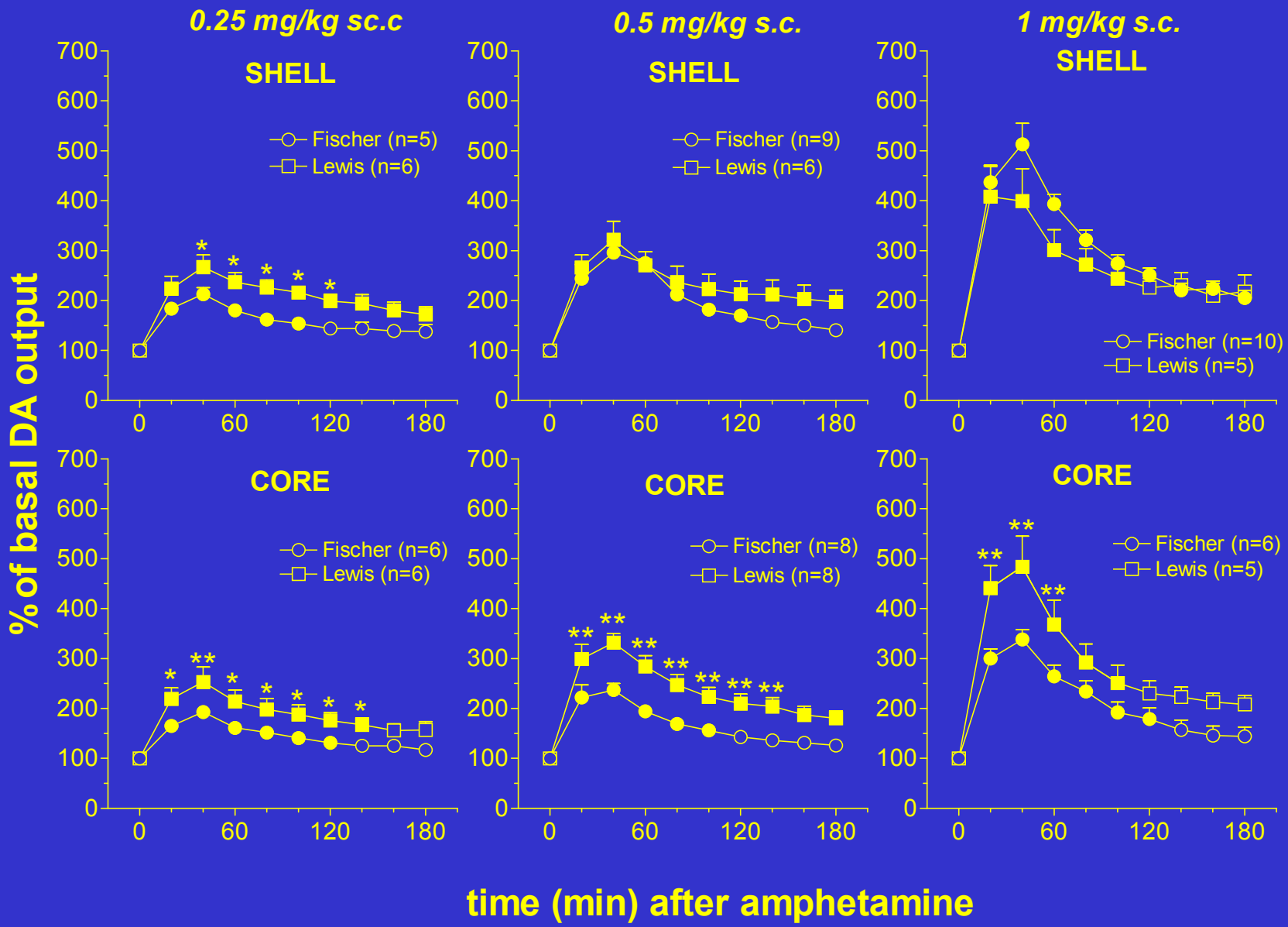
ROI	Want Drug	NS	NS-1	HA	RD	RD-2
T-Map	0.83**	0.43	0.79*	0.06	0.06	−0.01
Ventral Striatum	0.62†	0.75*	0.74*	0.16	−0.03	−0.28
Caudate	−0.14	−0.13	0.08	−0.25	−0.13	−0.24
Putamen	−0.19	−0.09	0.09	−0.34	−0.07	−0.14

† $p \leqslant .10$, * $p \leqslant .05$, ** $p \leqslant .01$. 'Want Drug': Self-reported drug wanting on the amphetamine administration test day. T-Map: statistically generated cluster of change; NS: Novelty Seeking; NS-1: Exploratory Excitability; HA: Harm Avoidance; RD: Reward Dependence; RD-2: Persistence

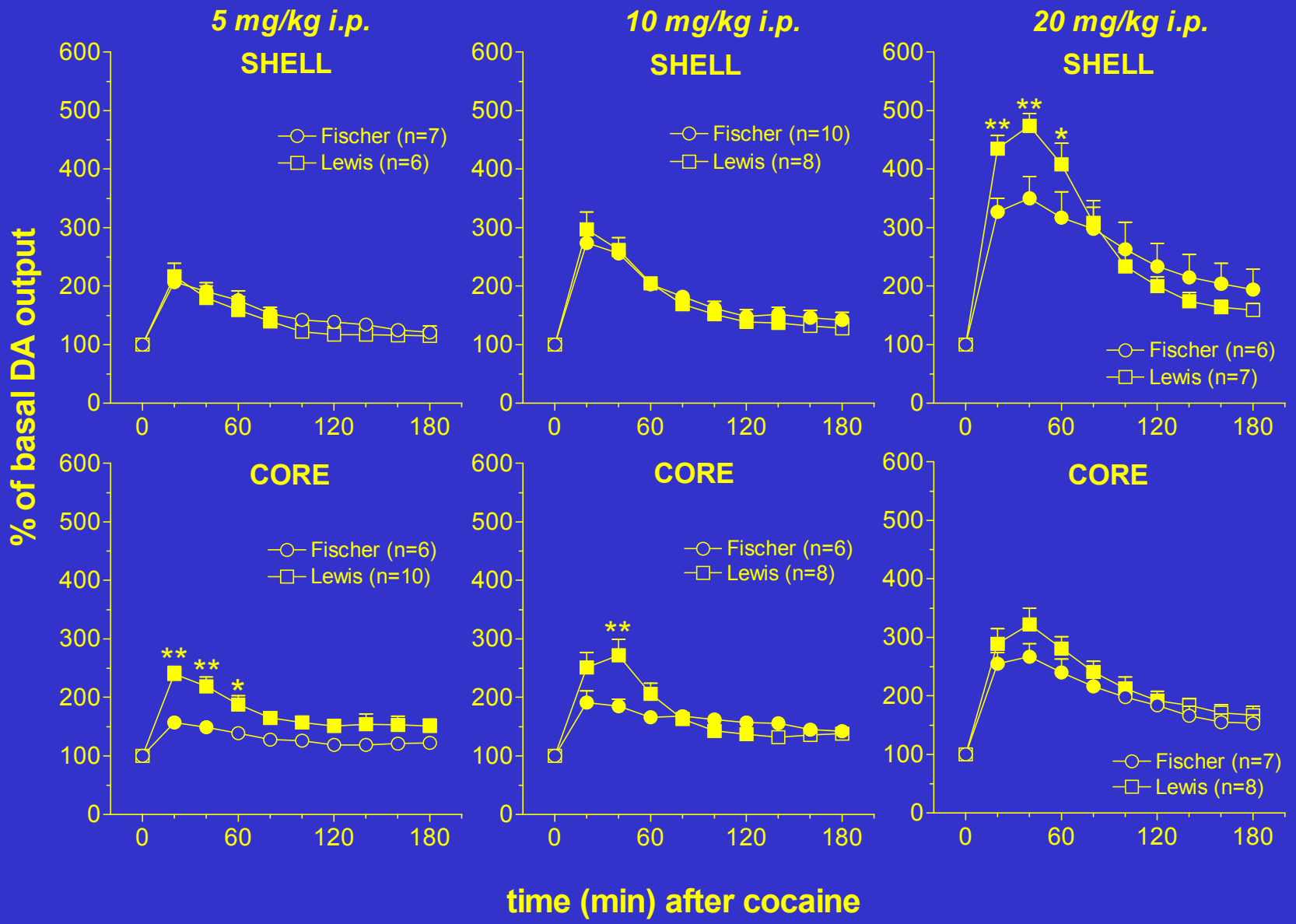
Morphine on dialysate dopamine in n.accumbens shell and core



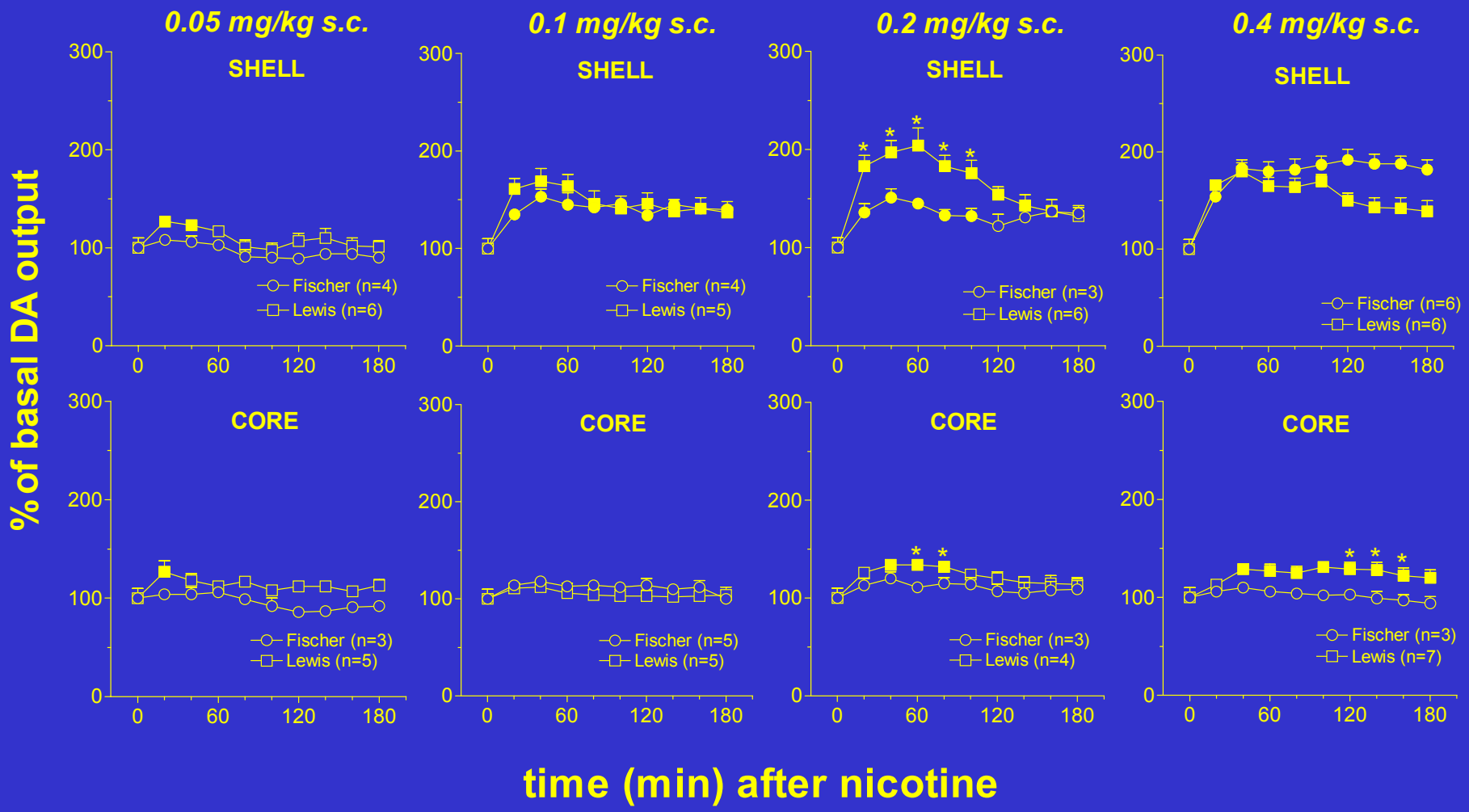
Amphetamine on dialysate dopamine in n.accumbens shell and core

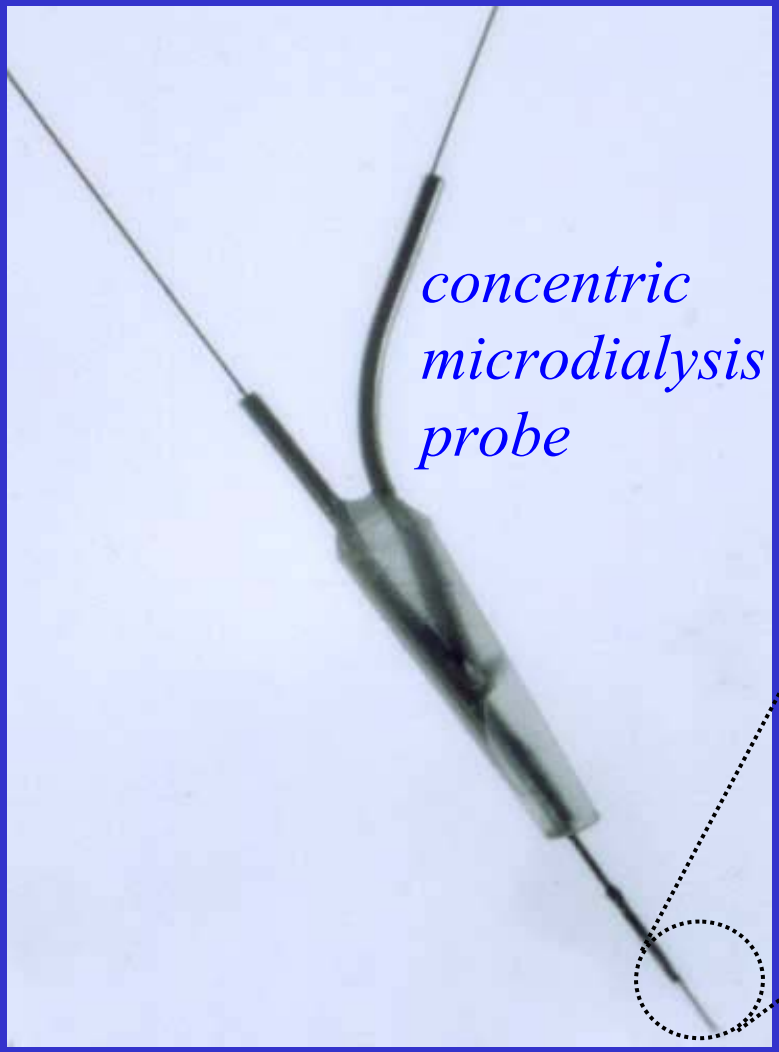


Cocaine on dialysate dopamine in n.accumbens shell and core

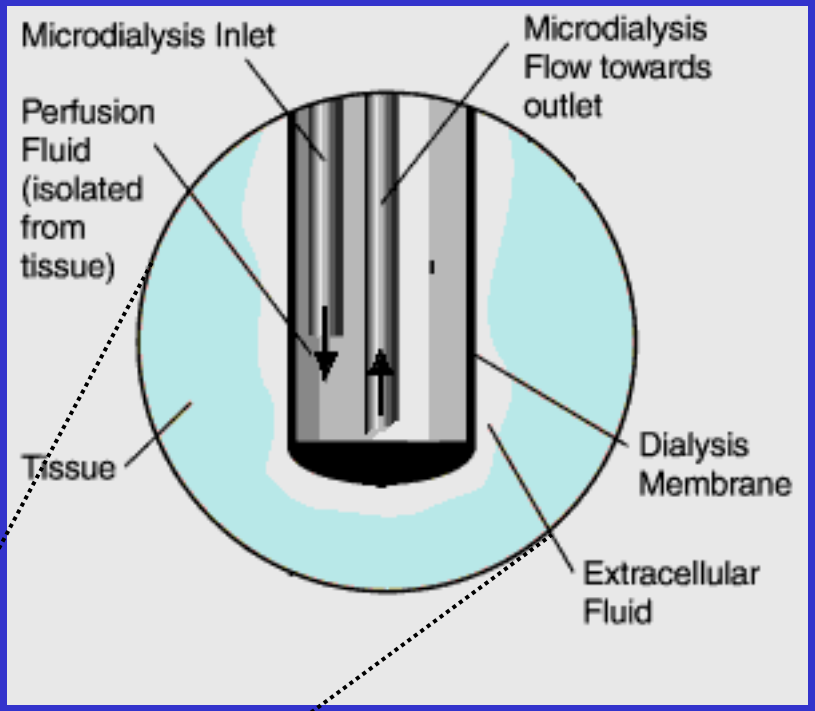


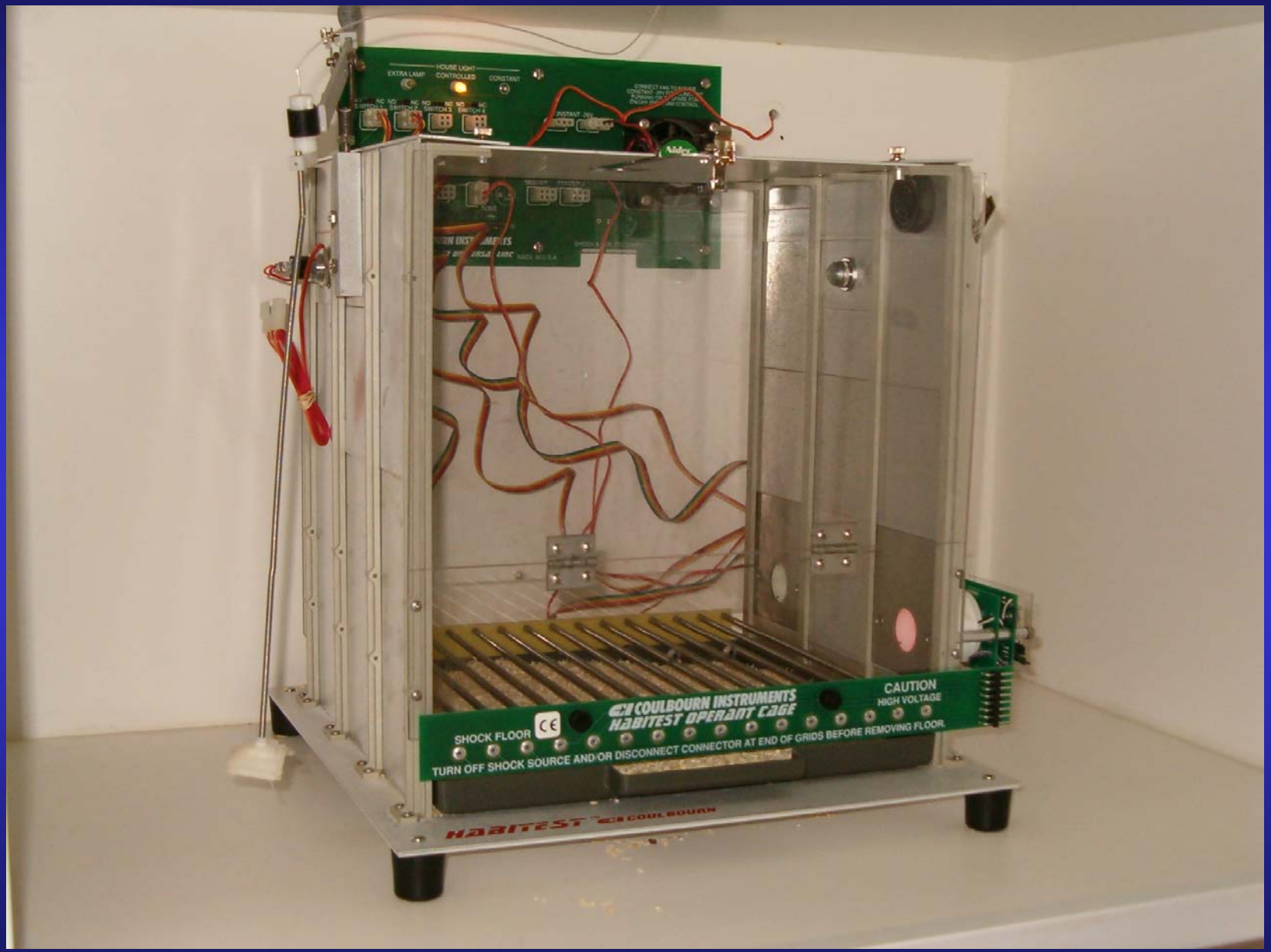
Nicotine on dialysate dopamine in n.accumbens shell and core

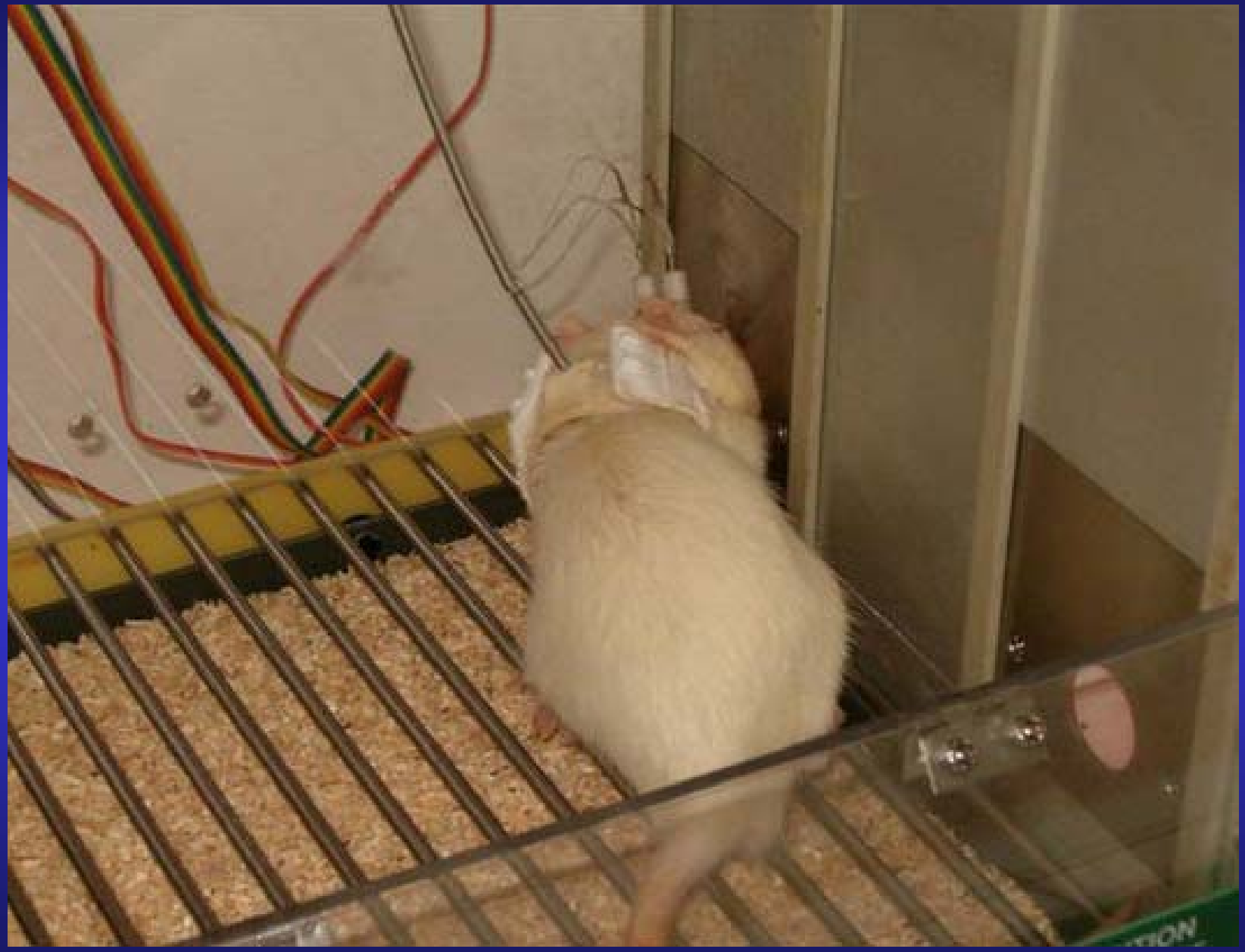


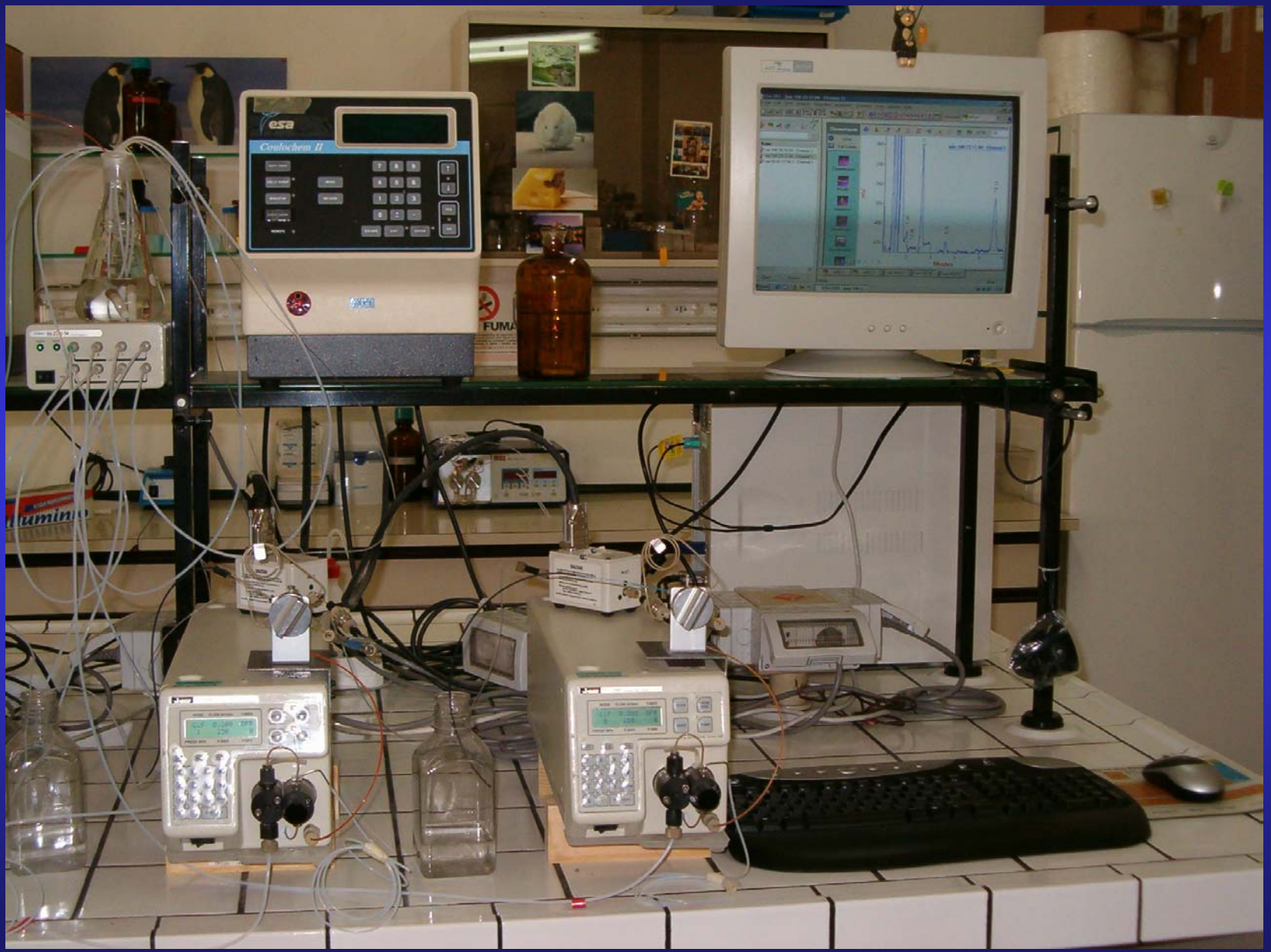


concentric microdialysis probe

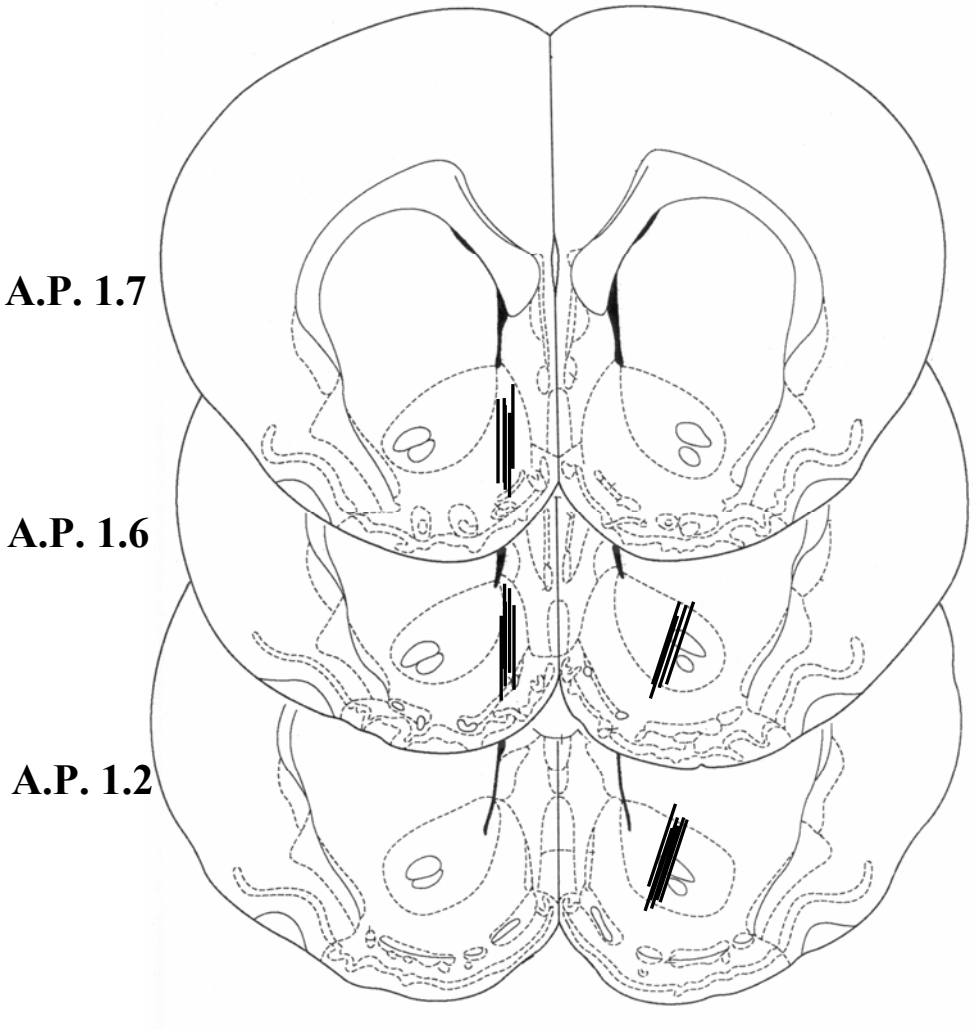


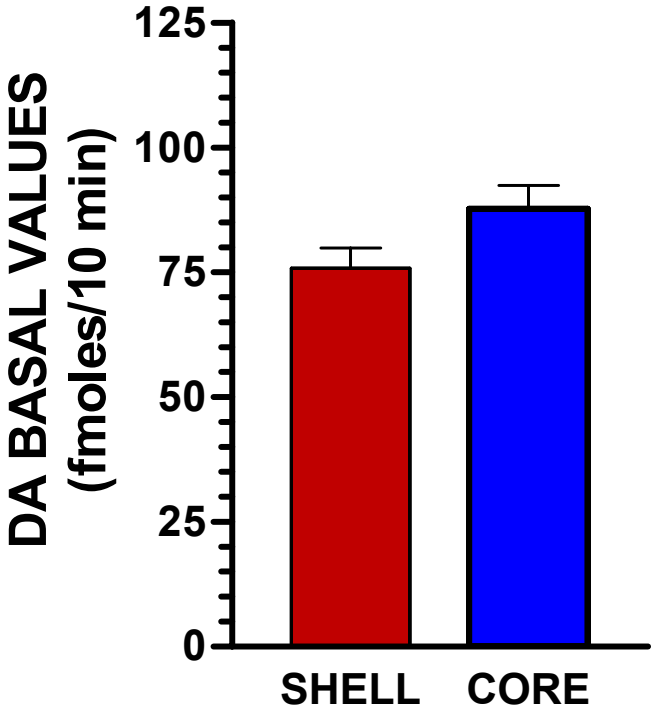

HOUSE LIGHT
EXTRA LAMP
CONTROLLED
CONSTANT
COULBOURN INSTRUMENTS
HABITEST OPERANT CAGE
SHOCK FLOOR
CAUTION
HIGH VOLTAGE
TURN OFF SHOCK SOURCE AND/OR DISCONNECT CONNECTOR AT END OF GRIDS BEFORE REMOVING FLOOR.
HABITEST
COULBOURN



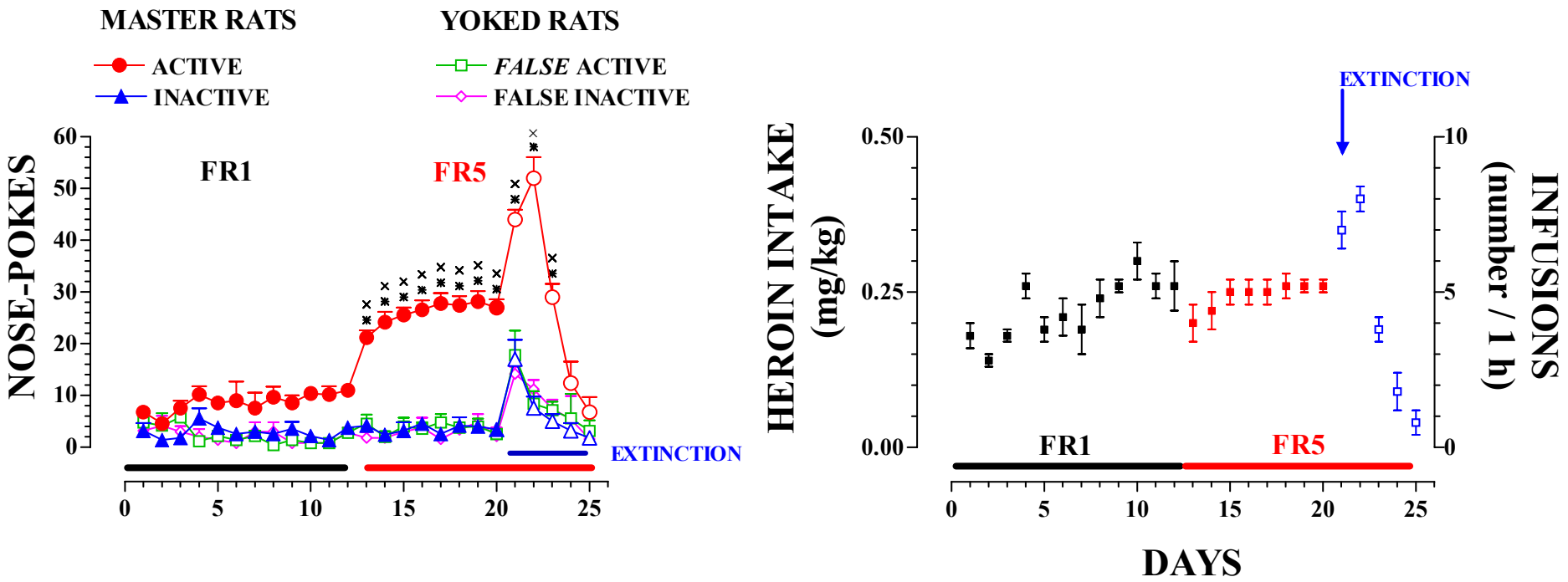

esa
Coulochem II

Location of microdialysis probes in rats responding for i.v. cocaine

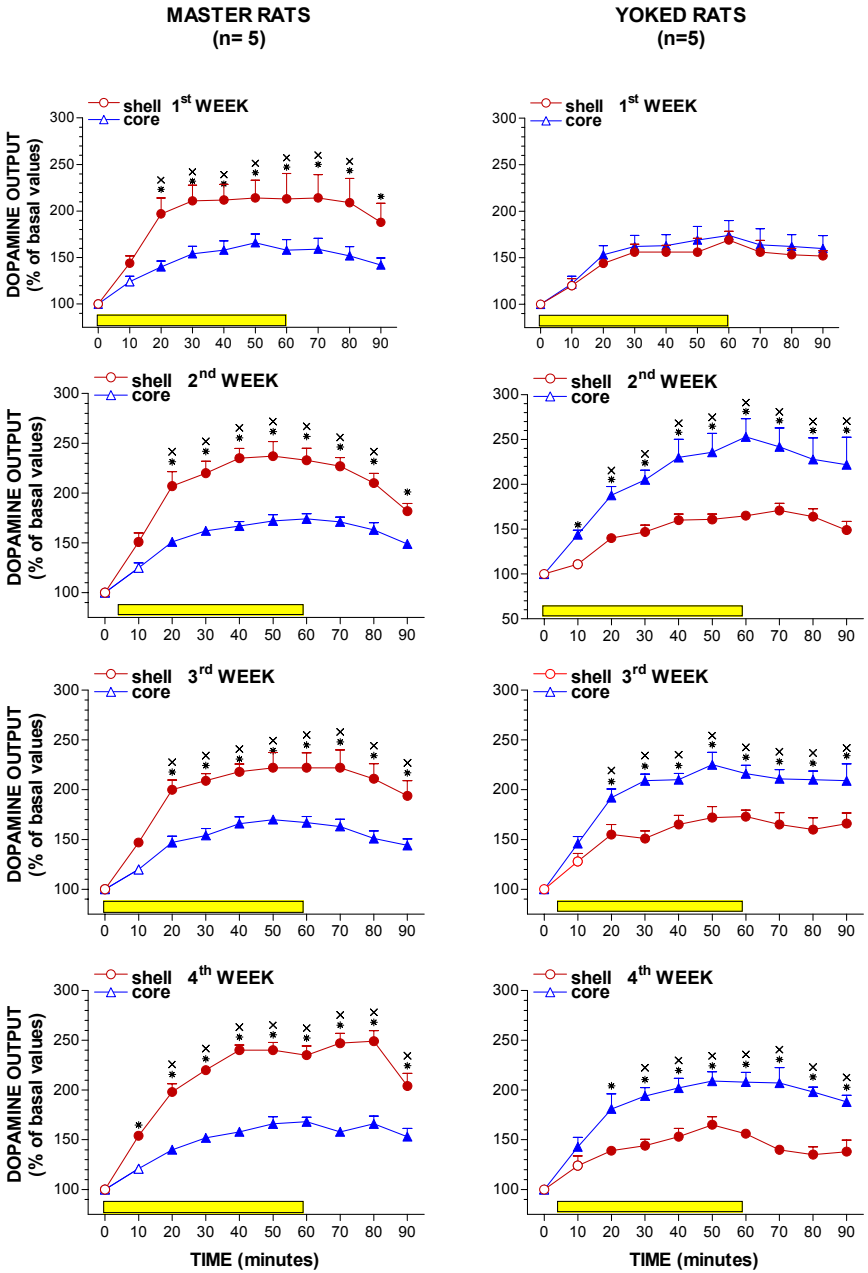




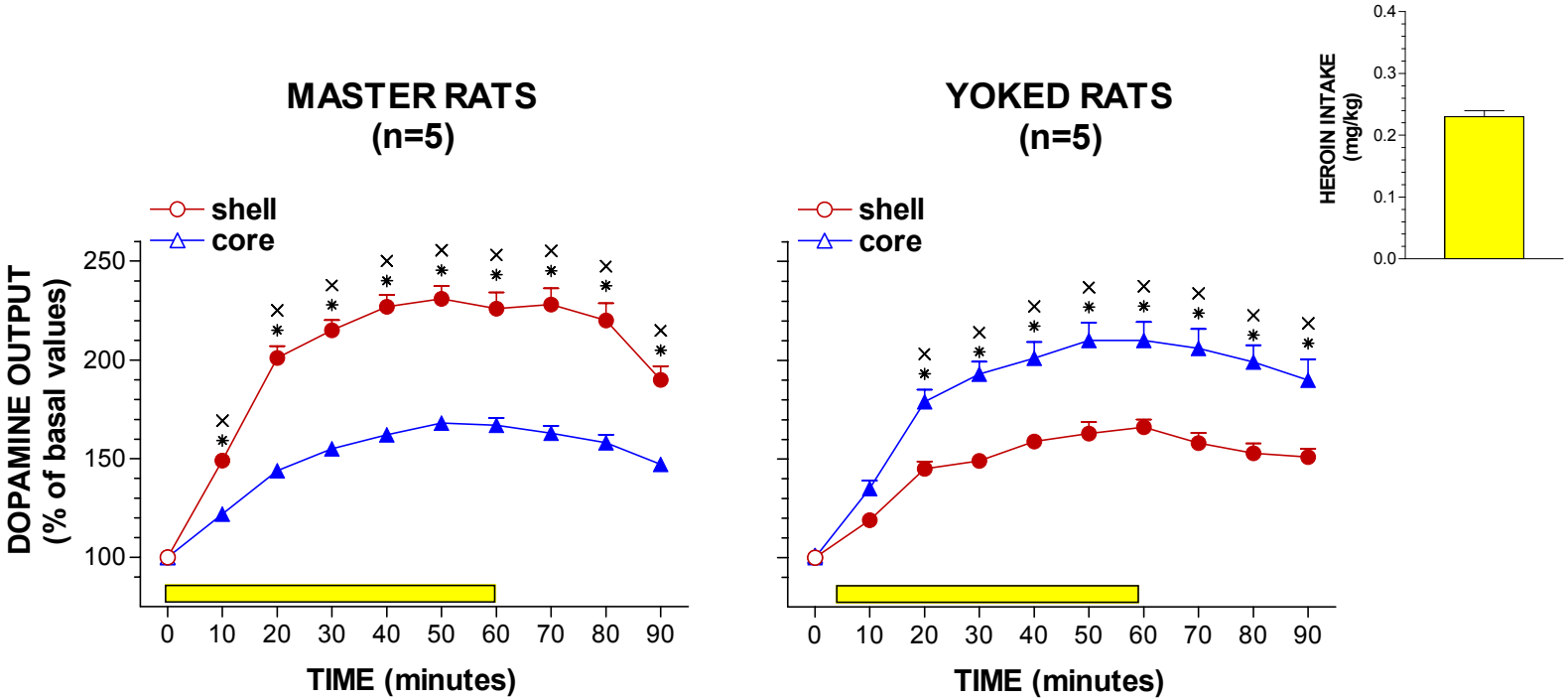
Lecca et al



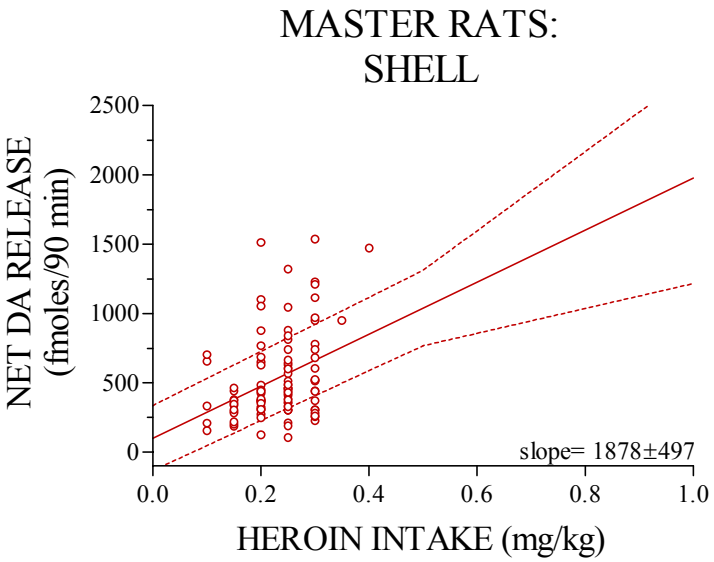
*: p<0.05 vs. respective inactive
x: p<0.05 vs. yoked *false active* nose-poke

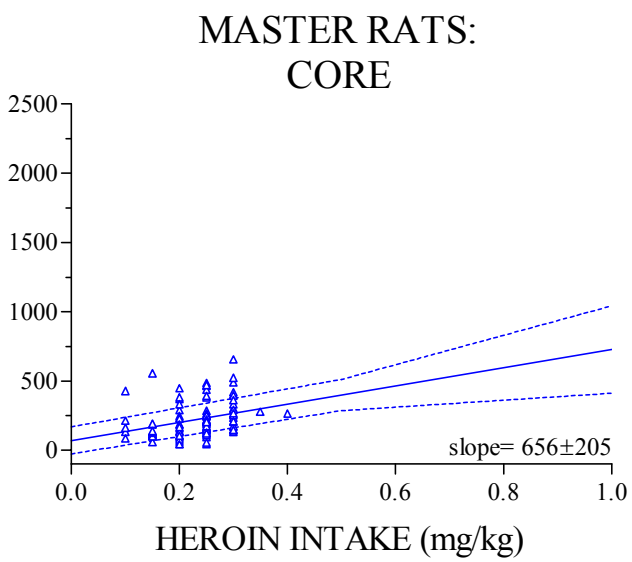


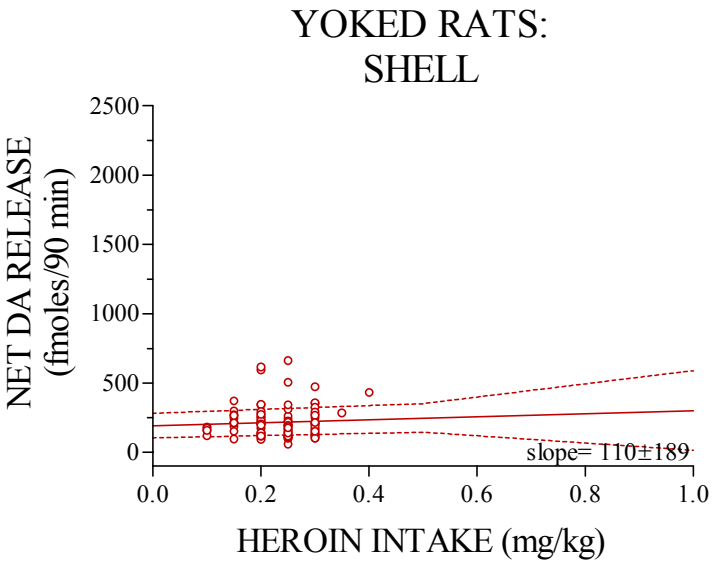
Filled symbols: p<0.05 vs basal values;
*: p<0.05 vs core [master rats] or vs shell [yoked rats]
x: p<0.05 vs yoked shell or vs master core

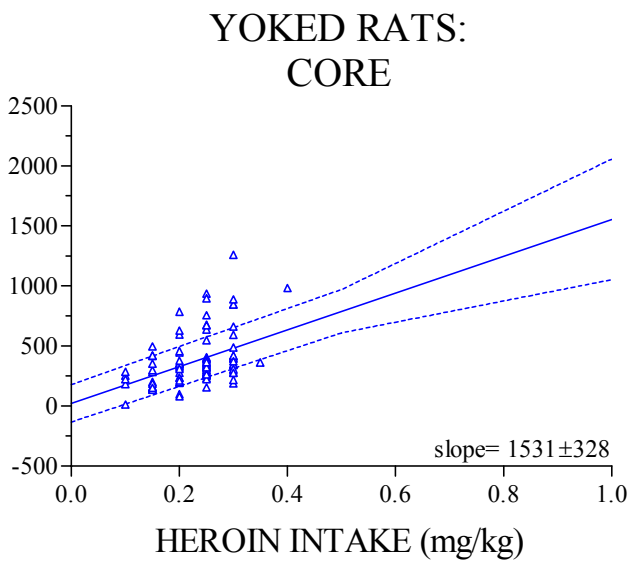


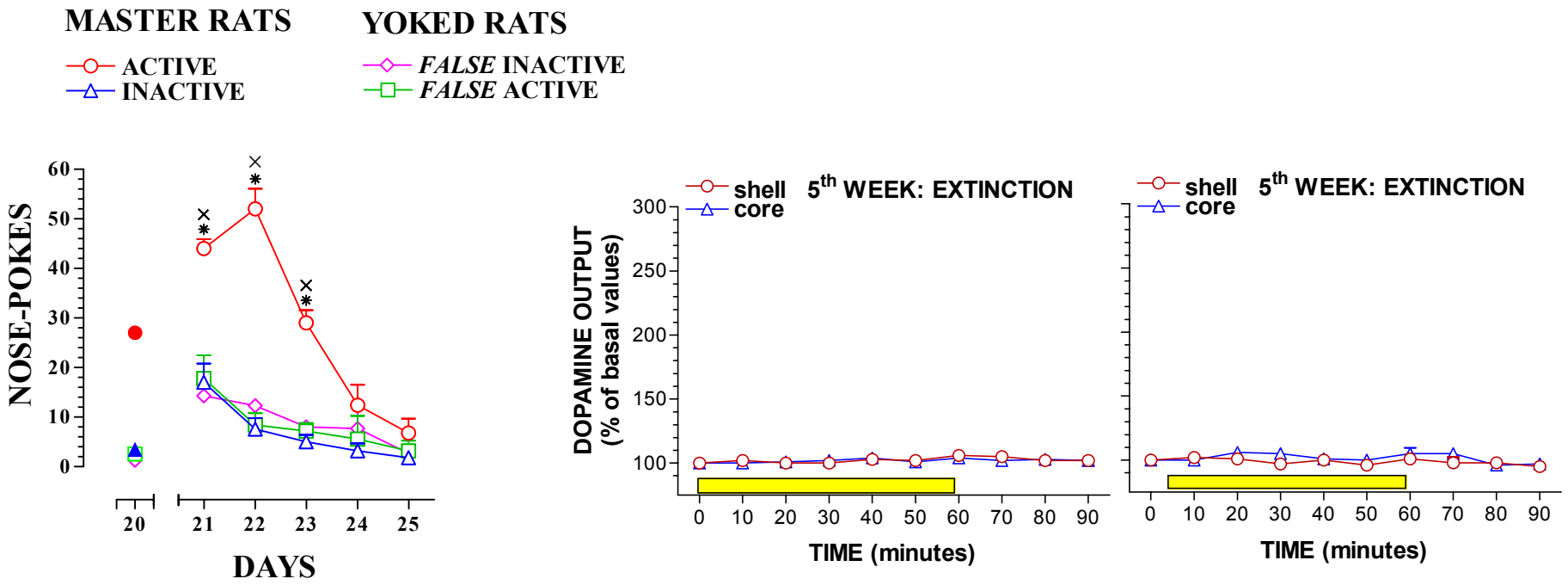
Filled symbols: p<0.05 vs basal values;
*: p<0.05 vs core [master rats] or vs shell [yoked rats]
x: p<0.05 vs yoked shell or vs master core


MASTER RATS:
SHELL
NET DA RELEASE
(fmoles/90 min)
2500
2000
1500
1000
500
0
slope= 1878±497
0.0
0.2
0.4
0.6
0.8
1.0
HEROIN INTAKE (mg/kg)


MASTER RATS:
CORE
2500
2000
1500
1000
500
0
slope= 656±205
0.0
0.2
0.4
0.6
0.8
1.0
HEROIN INTAKE (mg/kg)


YOKED RATS:
SHELL
NET DA RELEASE
(fmoles/90 min)
2500
2000
1500
1000
500
0
slope= 110±189
0.0
0.2
0.4
0.6
0.8
1.0
HEROIN INTAKE (mg/kg)


YOKED RATS:
CORE
2500
2000
1500
1000
500
0
-500
slope= 1531±328
0.0
0.2
0.4
0.6
0.8
1.0
HEROIN INTAKE (mg/kg)



*: p<0.05 vs. respective inactive

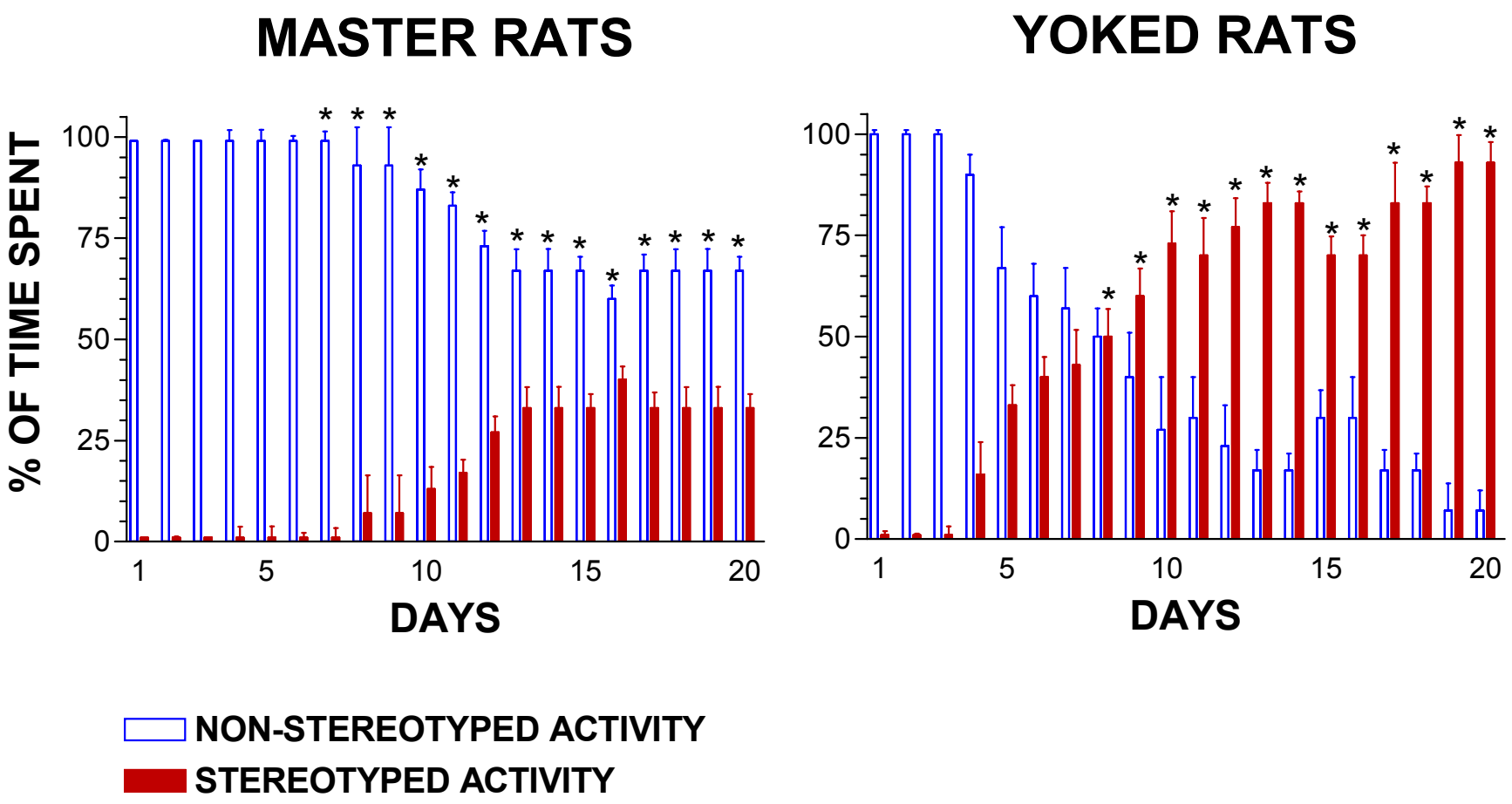
x: p<0.05 vs. yoked *false active* nose-poke

Non-stereotyped activity

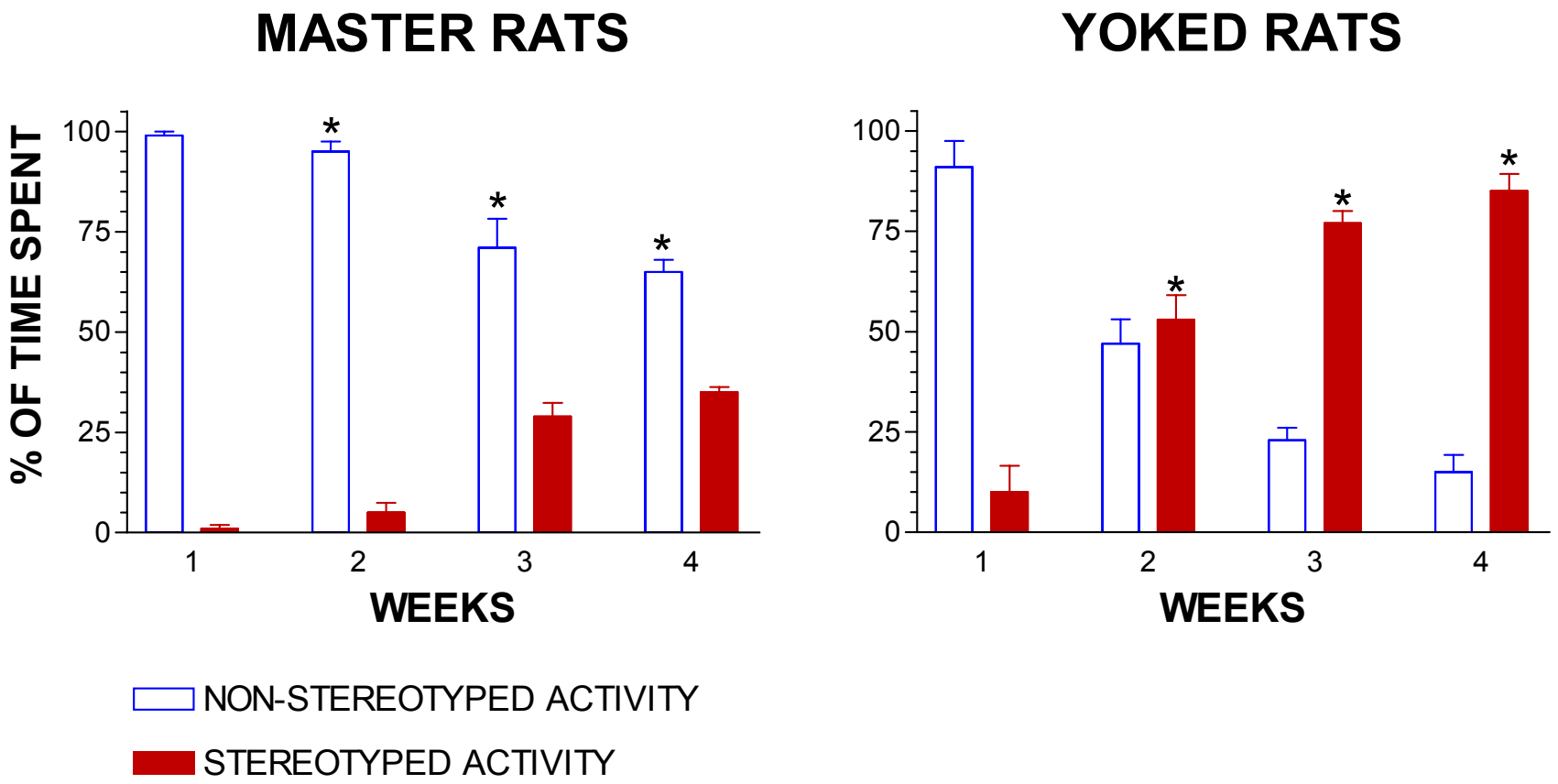
- Still
- Locomotion
- Sniffing upward
- Grooming
- Rearing

Stereotyped activity

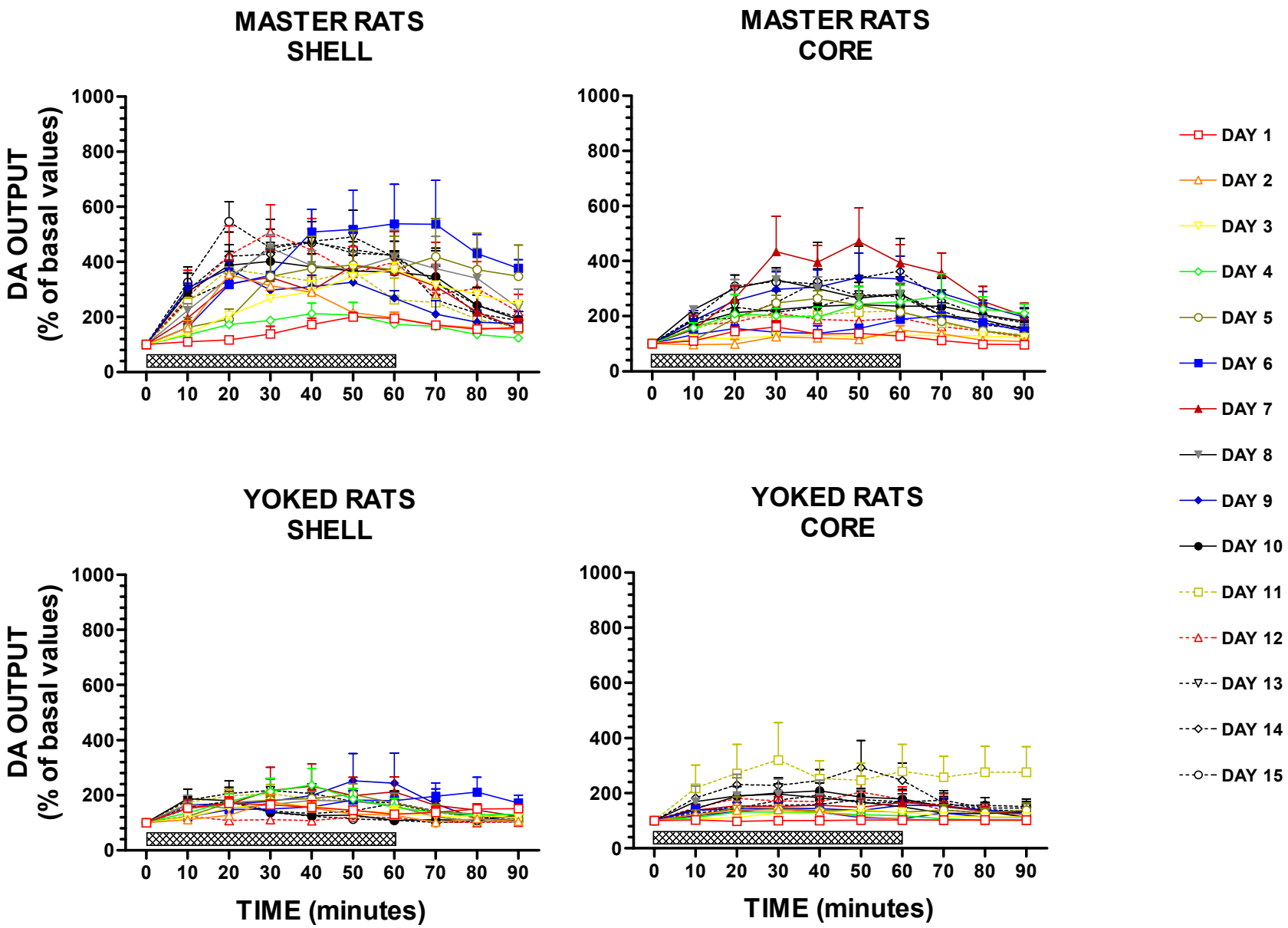
- Gnawing (self-mutilation)
- Gnawing confined
- Sniffing down confined
- Licking

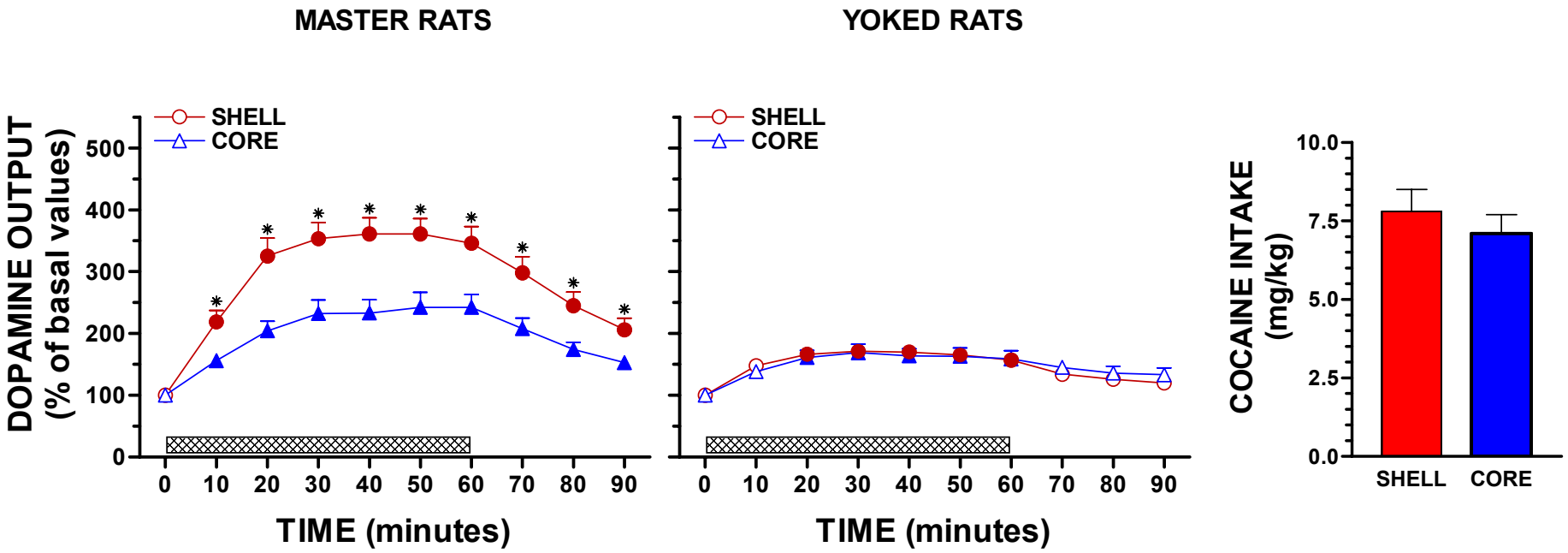


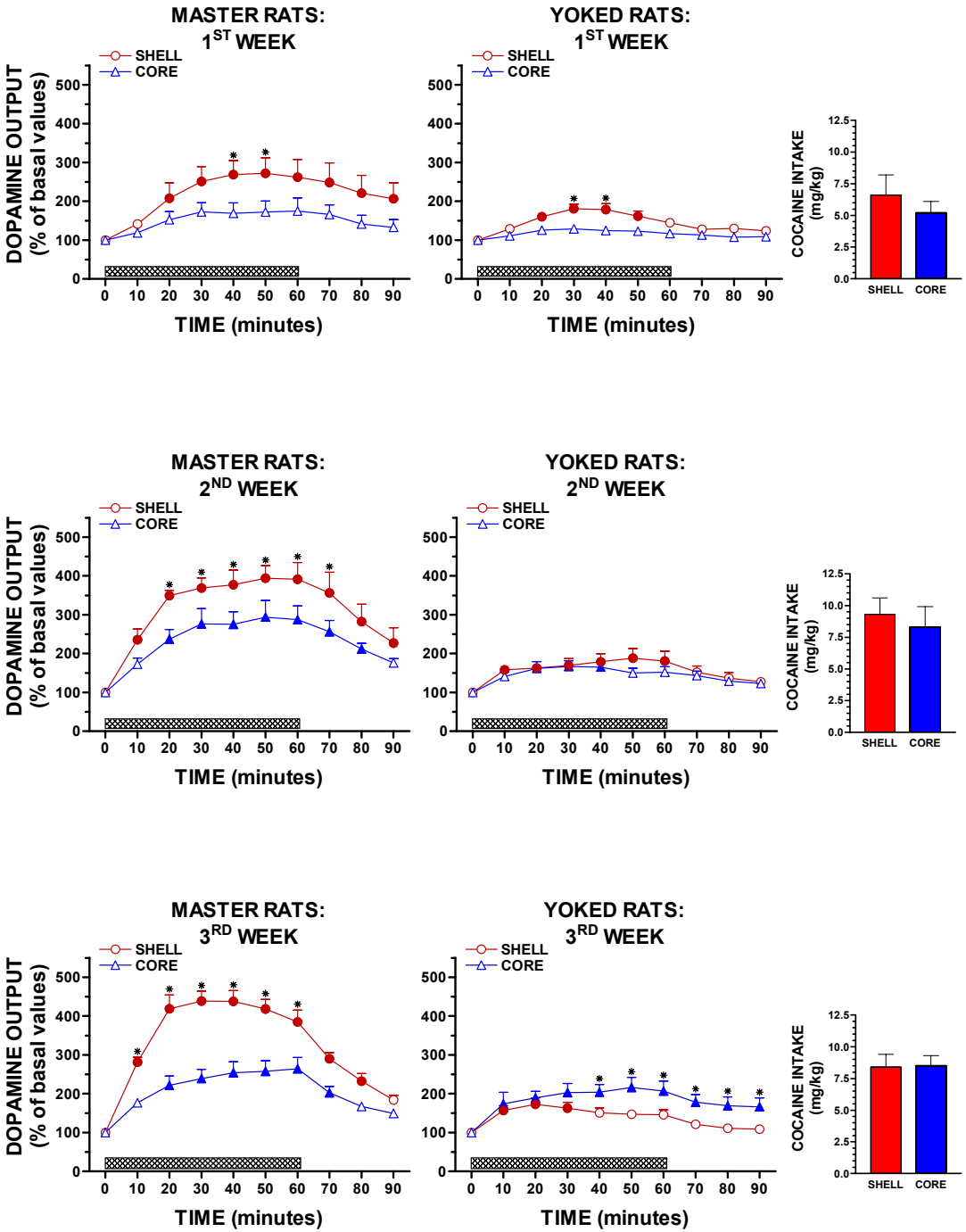
* P < 0.05 VS. CORRESPONDING DAY-MATCHED COUNTERPART RATS ACTIVITY



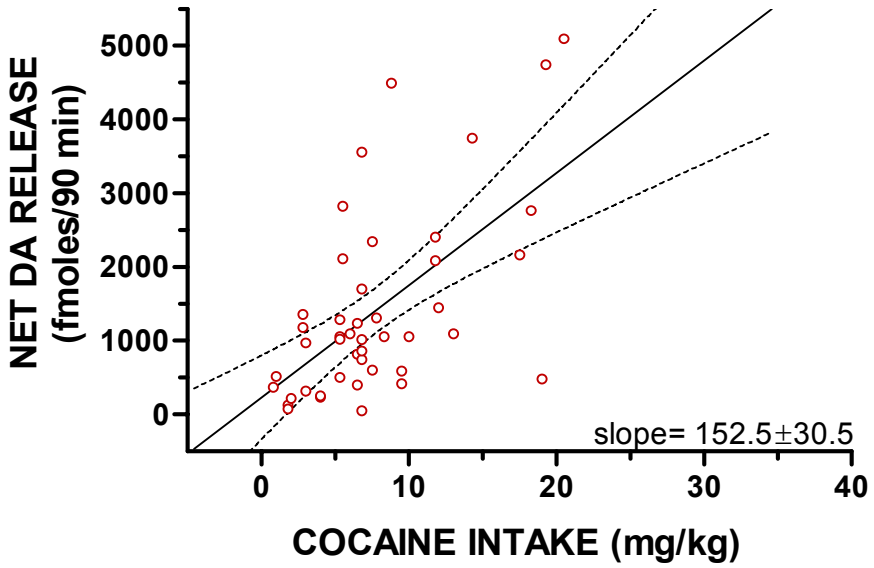
* P < 0.05 VS. CORRESPONDING WEEK-MATCHED COUNTERPART RATS ACTIVITY


MASTER RATS
SHELL
MASTER RATS
CORE
YOKED RATS
SHELL
YOKED RATS
CORE
DA OUTPUT
(% of basal values)
TIME (minutes)
0
200
400
600
800
1000
0
10
20
30
40
50
60
70
80
90
DAY 1
DAY 2
DAY 3
DAY 4
DAY 5
DAY 6
DAY 7
DAY 8
DAY 9
DAY 10
DAY 11
DAY 12
DAY 13
DAY 14
DAY 15

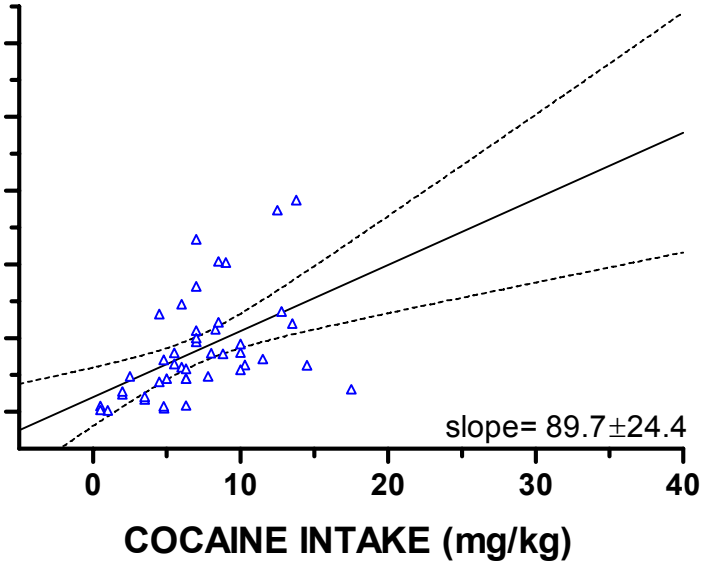

MASTER RATS
YOKED RATS
SHELL
CORE
DOPAMINE OUTPUT
(% of basal values)
500
400
300
200
100
0
0 10 20 30 40 50 60 70 80 90
TIME (minutes)
SHELL
CORE
0 10 20 30 40 50 60 70 80 90
TIME (minutes)
COCAINE INTAKE
(mg/kg)
10.0
7.5
5.0
2.5
0.0
SHELL
CORE


MASTER RATS:
1ST WEEK
YOKED RATS:
1ST WEEK
SHELL
CORE
DOPAMINE OUTPUT
(% of basal values)
TIME (minutes)
COCAINE INTAKE
(mg/kg)
MASTER RATS:
2ND WEEK
YOKED RATS:
2ND WEEK
MASTER RATS:
3RD WEEK
YOKED RATS:
3RD WEEK

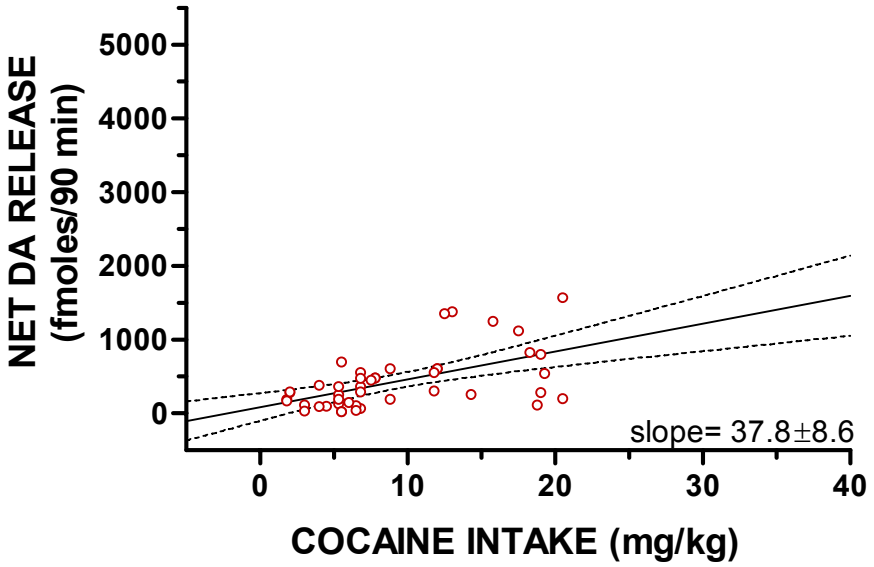
MASTER RATS: SHELL



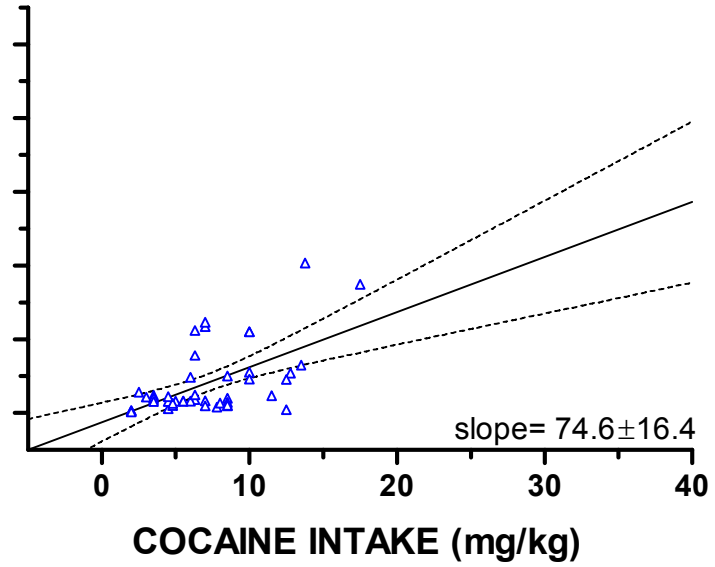
MASTER RATS: CORE



YOKED RATS: SHELL



YOKED RATS: CORE

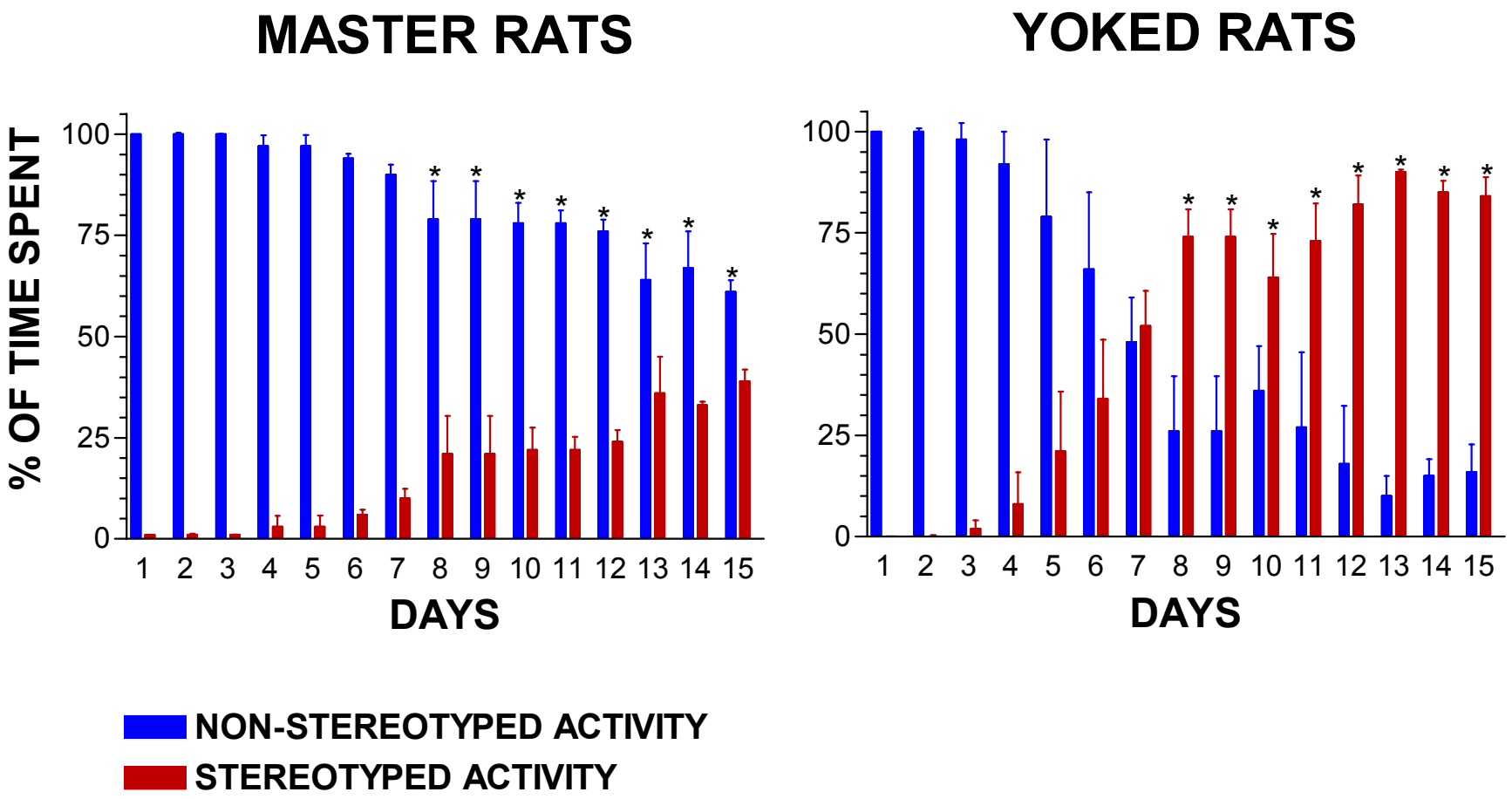


Non-stereotyped activity

- Still
- Locomotion
- Sniffing upward
- Grooming
- Rearing

Stereotyped activity

- Sniffing down
- Gnawing
- Head bobbing
- Licking



* P < 0.05 VS. THE CORRESPONDING DAY-MATCHED COUNTERPART RATS ACTIVITY

Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects

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* *Medical and ‡ Chemistry Departments, Brookhaven National Laboratory, Upton, New York 11973, USA*

† *Department of Psychiatry, State University of New York at Stony Brook, Stony Brook, New York, 11794, USA*

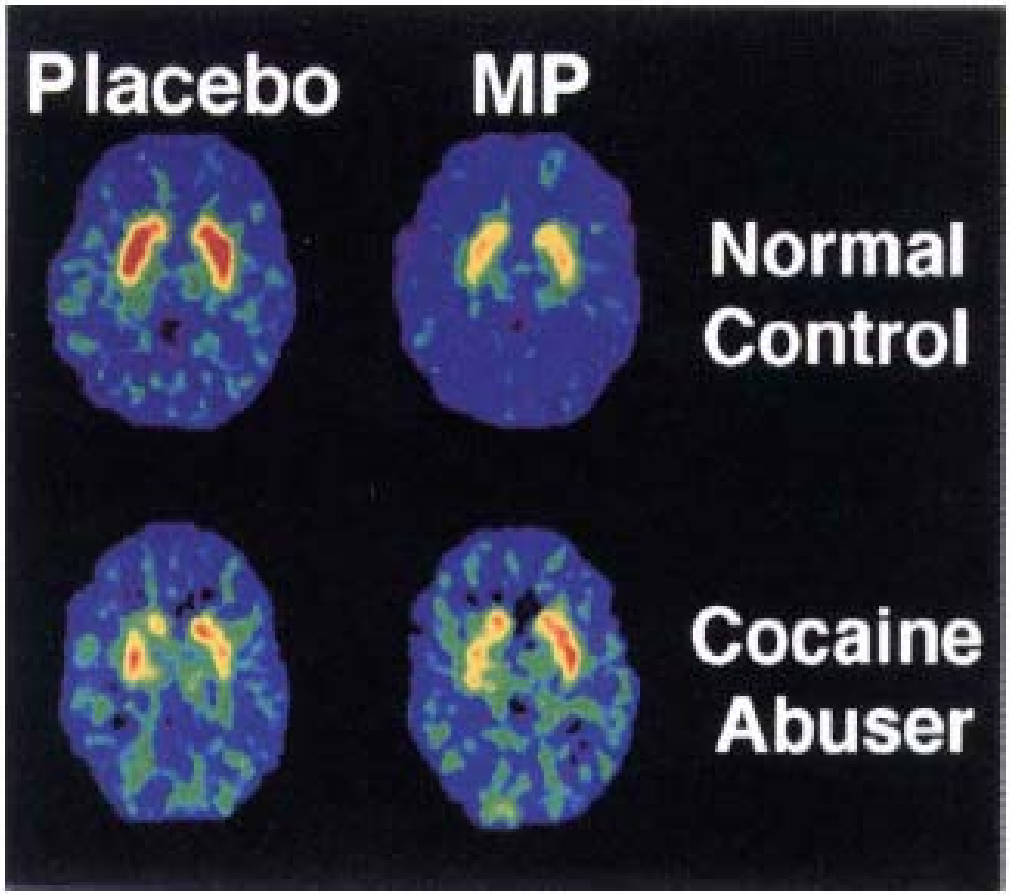

Figure 1 Distribution volume images of [^{11}C]raclopride at the level of the striatum in a normal control and in a cocaine-dependent subject tested after placebo (baseline) and after methylphenidate (MP) administration. Baseline binding for [^{11}C]raclopride in striatum and the reductions in striatal binding with MP were lower in the cocaine-dependent subject than in the control.

Table 1 Mean and standard deviations (±) for self reports of drug-induced (placebo or methylphenidate) behavioural effects in controls and in cocaine-dependent subjects

	Normal controls		Cocaine dependent		MP effect
	Placebo	MP	Placebo	MP	*P*
Alert	7 ± 1	9 ± 1	8 ± 1	9 ± 2	NS
Anxiety	2 ± 2	4 ± 3	4 ± 3	6 ± 4	NS
Distrustful	0	1 ± 2	1 ± 1	2 ± 3	NS
High*	1 ± 1	6 ± 3	0	4 ± 3	$P < 0.005$
Restlessness**	2 ± 2	7 ± 2	2 ± 2	5 ± 4	$P < 0.0001$
Craving***	0	1 ± 2	3 ± 3	8 ± 3	$P < 0.001$

Self reports were recorded 27 min after administration of placebo or of methylphenidate (MP). MP significantly increased self reports for high, restlessness and cocaine craving. Behavioural responses to MP were significantly larger in controls for restlessness and high whereas for cocaine craving responses were larger in the cocaine-dependent subjects. ANOVA interaction effect (diagnosis × drug): *$P < 0.05$, **$P < 0.005$, ***$P < 0.001$. NS, not significant.