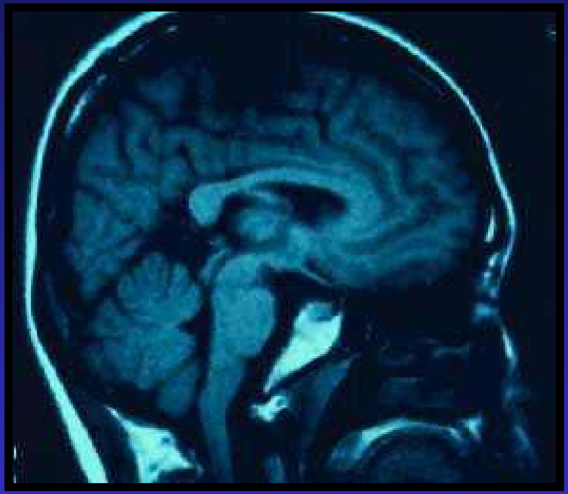
LE NEUROSCIENZE COGNITIVE NELLA TOSSICODIPENDENZA E NELL'ALCOLISMO

LA PRESA IN CARICO MULTIPLA:
Gli Aspetti Psicocomportamentali e i Correlati di Neuroimaging nell'uso di Sostanze
Frescada di Preganziol - Treviso - 28 Ottobre 2005



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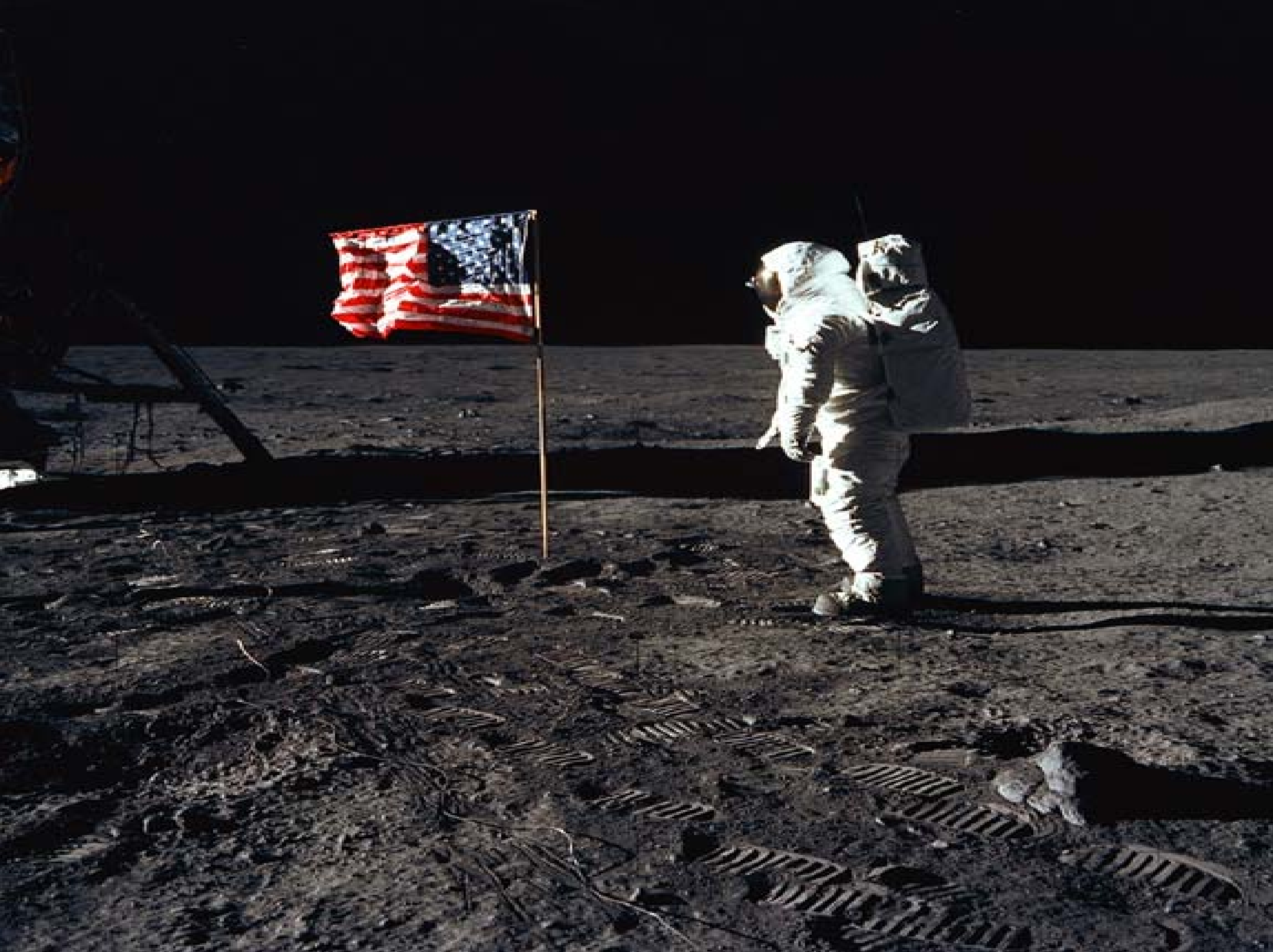

La tossicodipendenza e l'alcolismo sono dei comportamenti appresi alla cui base vi è una alterazione dei sistemi della gratificazione e della motivazione

Illustration by J.R. Sanchez-Ramos, M.D.

from: *The Psychiatric Times*, February (1990) 20-22.

Studi di neuroimaging: contributi

- ✓ Il ruolo della dopamina negli effetti gratificanti indotti dagli stimoli primari e delle sostanze d'abuso
- ✓ La distinzione neurobiologica fra desiderio e effetti gratificanti
- ✓ L'implicazione di diverse aree cerebrali nei fenomeni di intossicazione, dipendenza ed astinenza
- ✓ La dipendenza come apprendimento appreso
- ✓ Il *craving* come memoria del piacere
- ✓ Il legame fra *craving* e disforia

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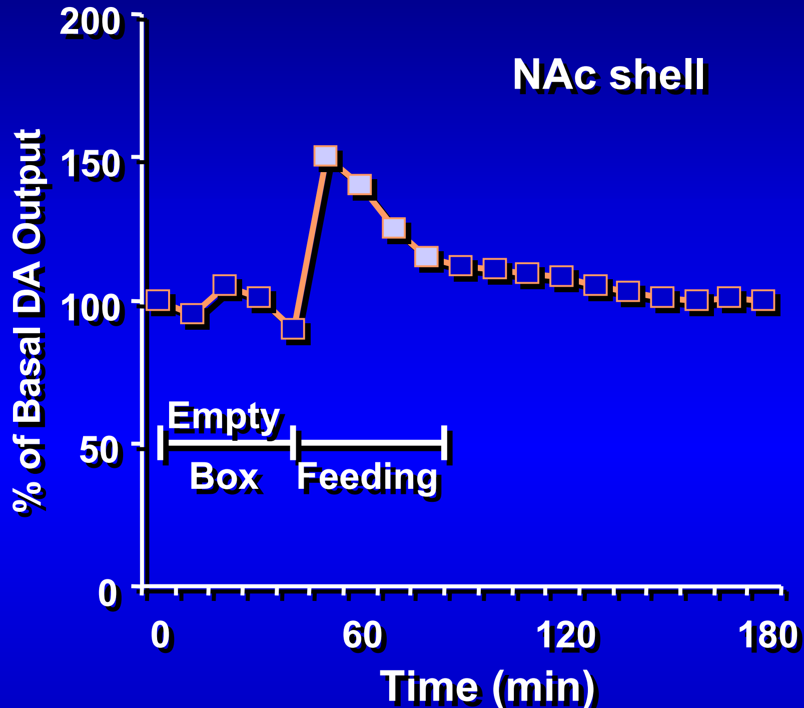
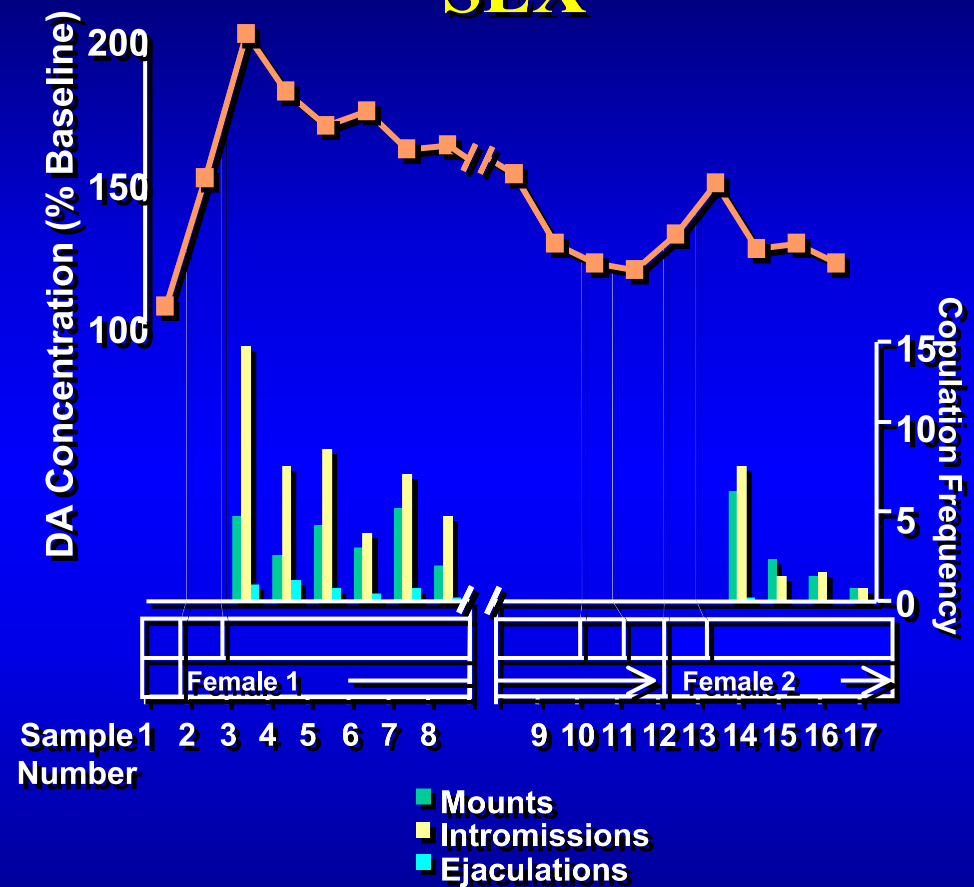
Natural Rewards Elevate Dopamine Levels

FOOD

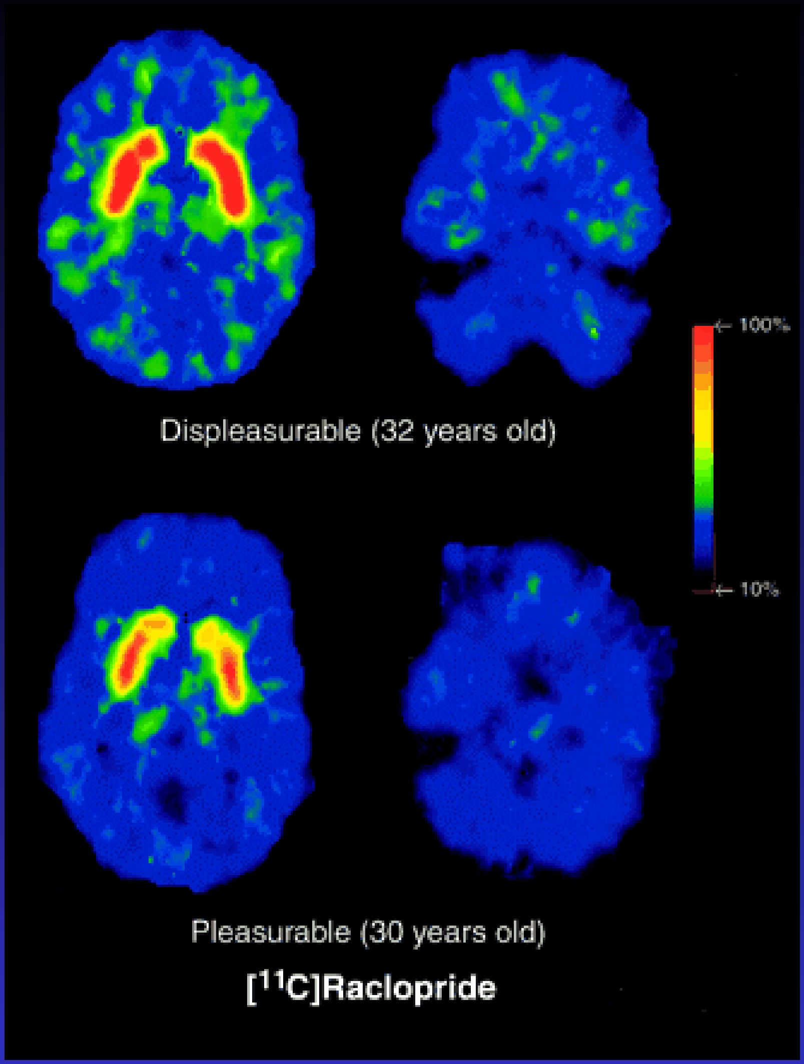


Source: Di Chiara et al.

SEX



Source: Fiorino and Phillips



Distribution Volume Images of [^{11}C]Raclopride at the Levels of the Striatum (left) and Cerebellum (right) in a Healthy Male Subject Who Reported the Effects of Methylphenidate as Pleasant and in a Healthy Male Subject Who Reported Them as Unpleasant[a]

From: Volkow et al., 1999

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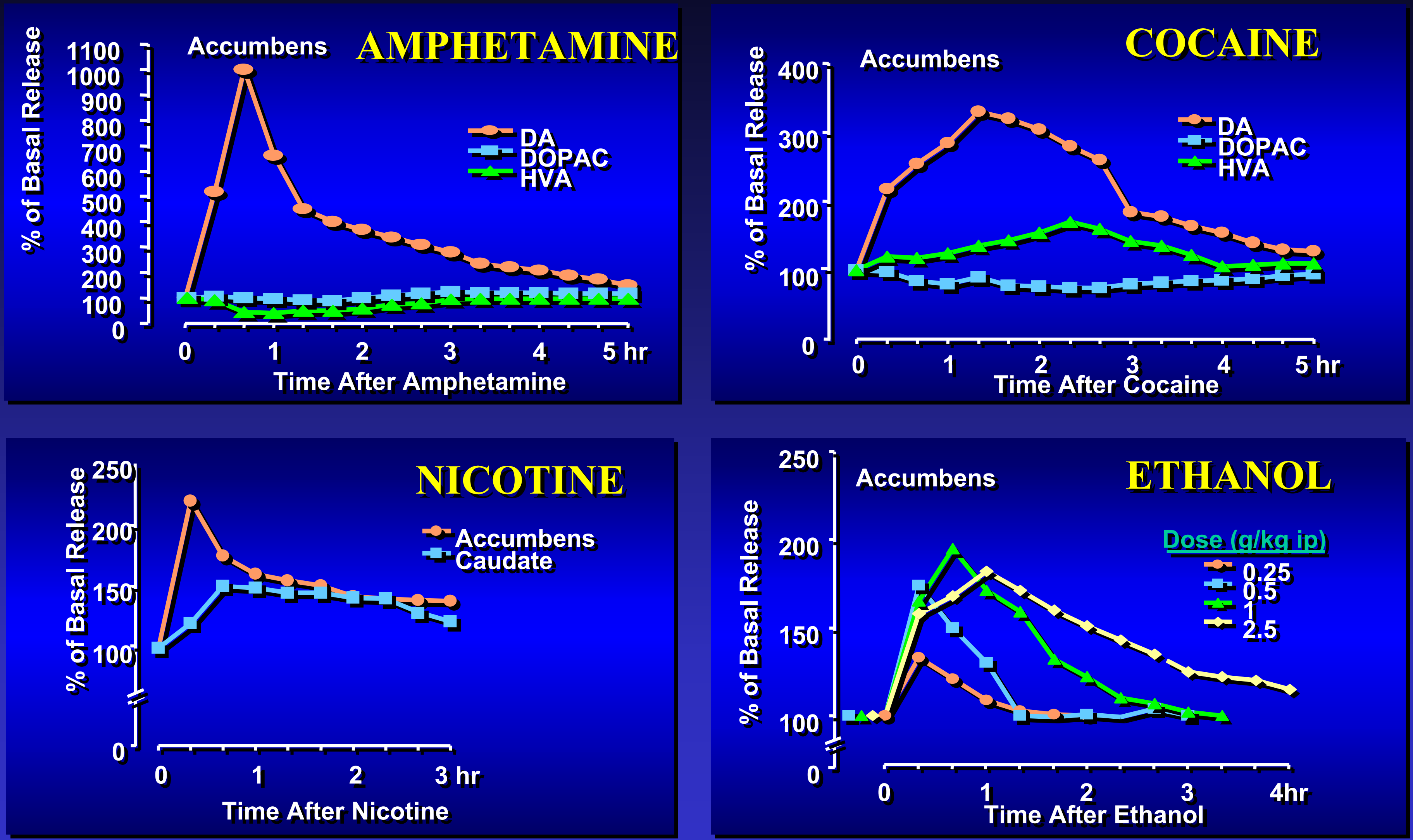
Effects of Drugs on Dopamine Levels



Source: Di Chiara and Imperato

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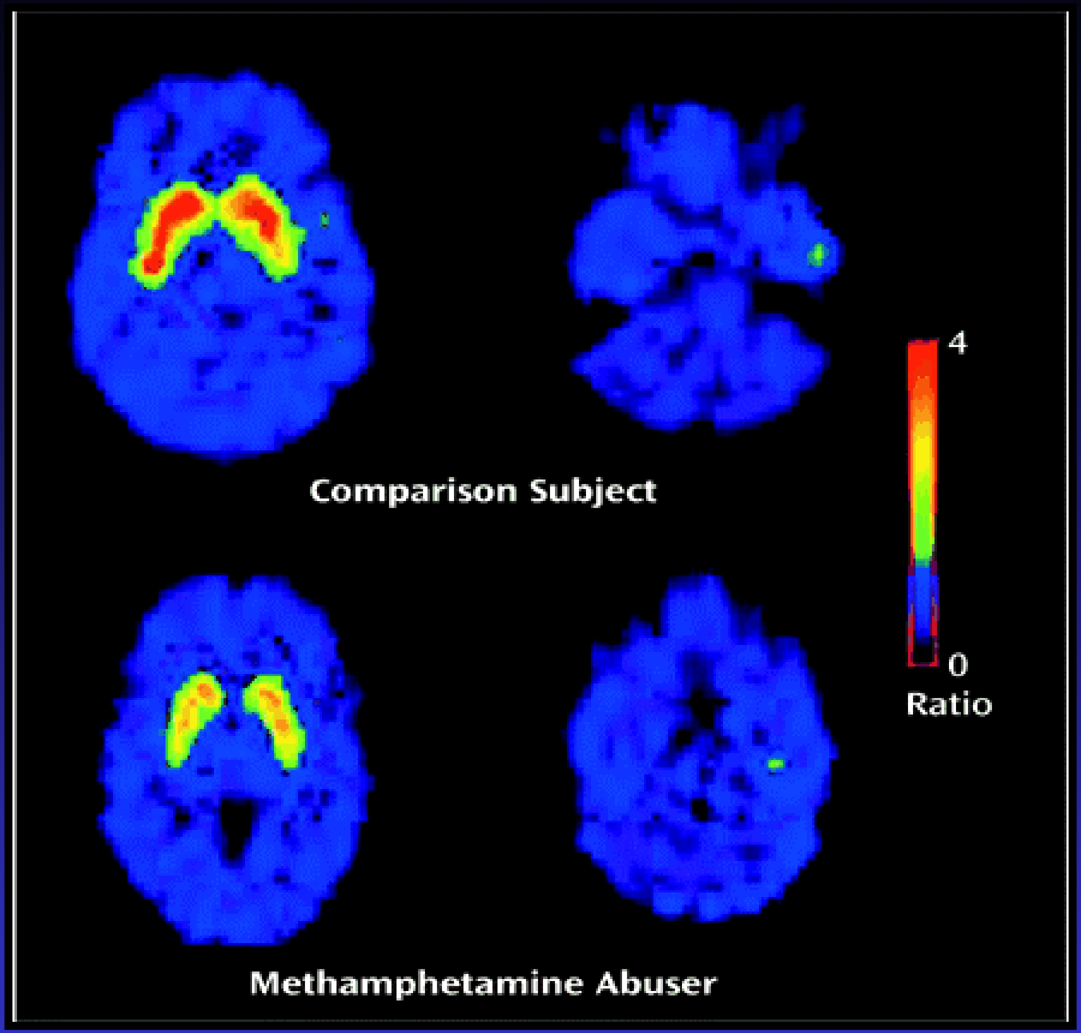
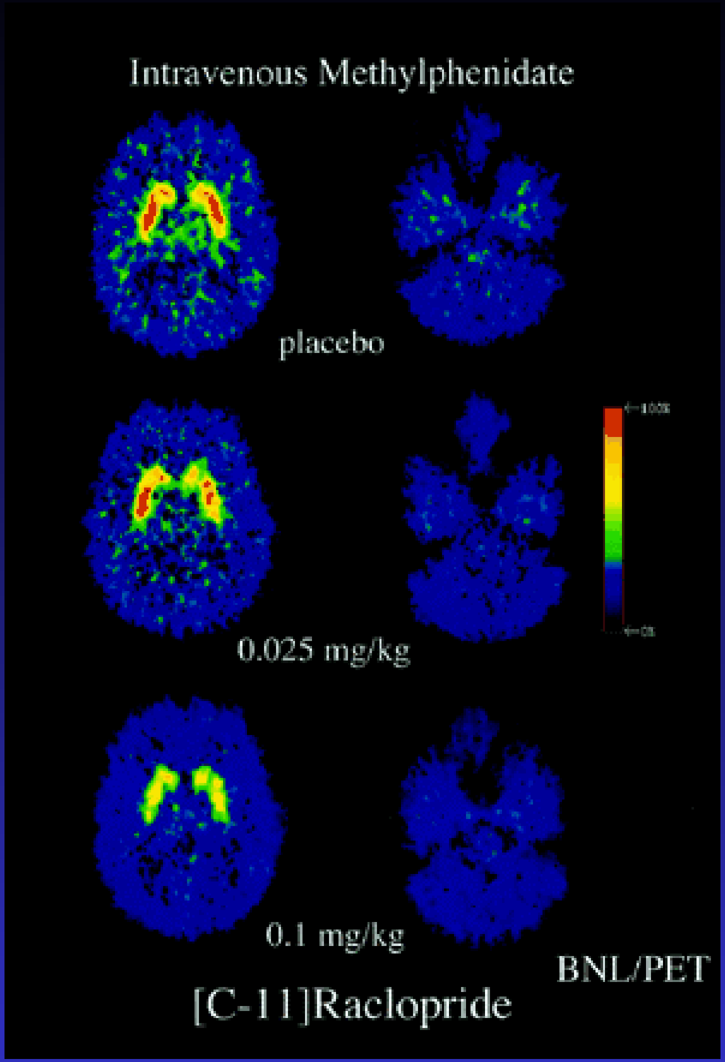


Ratio of the Distribution Volume of [^{11}C]Raclopride in the Striatum Normalized to the Distribution Volume in the Cerebellum in a Non-Drug-Abusing Comparison Subject and a Methamphetamine Abuser

From: Volkow wt al., 2001



DV images of [^{11}C]raclopride at the level of the ST and at the level of the CB for one of the subjects at baseline and after administration of 0.1 and 0.025 mg/kg i.v. of MP. MP reduced binding of [^{11}C]raclopride in the ST where it competes with DA for binding to DA D_2 receptors, but not in CB, where binding is predominantly nonspecific

From: Volkow et al., 1999

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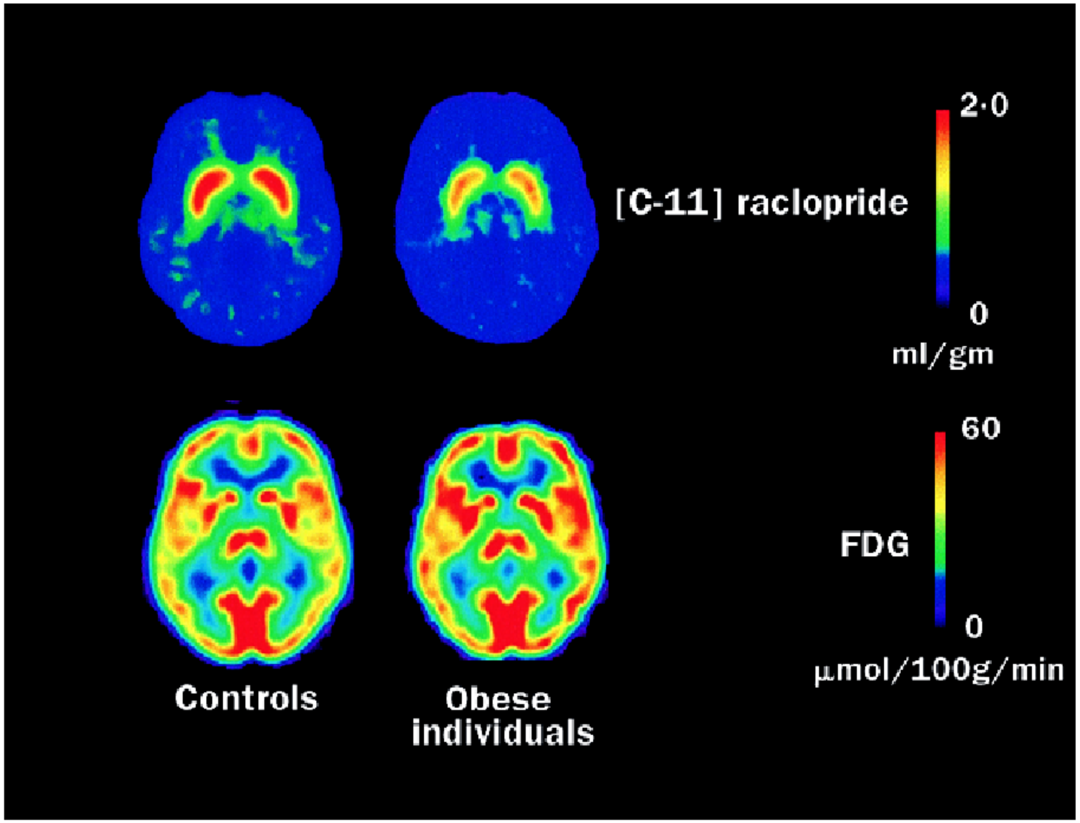

Figure 1: **Group average images of [C-11]raclopride (distribution volume image) and FDG (metabolic image) PET for obese individuals and controls at the level of the basal ganglia**

The images are scaled with respect to the maximum value obtained from the controls and presented by means of the rainbow scale. For [C-11]raclopride, red represents the highest value (2·0) and dark violet represents the lowest value (0 ml/Gm). For FDG, highest value is 60 μmol and lowest value is 0 μmol/100 g/min.

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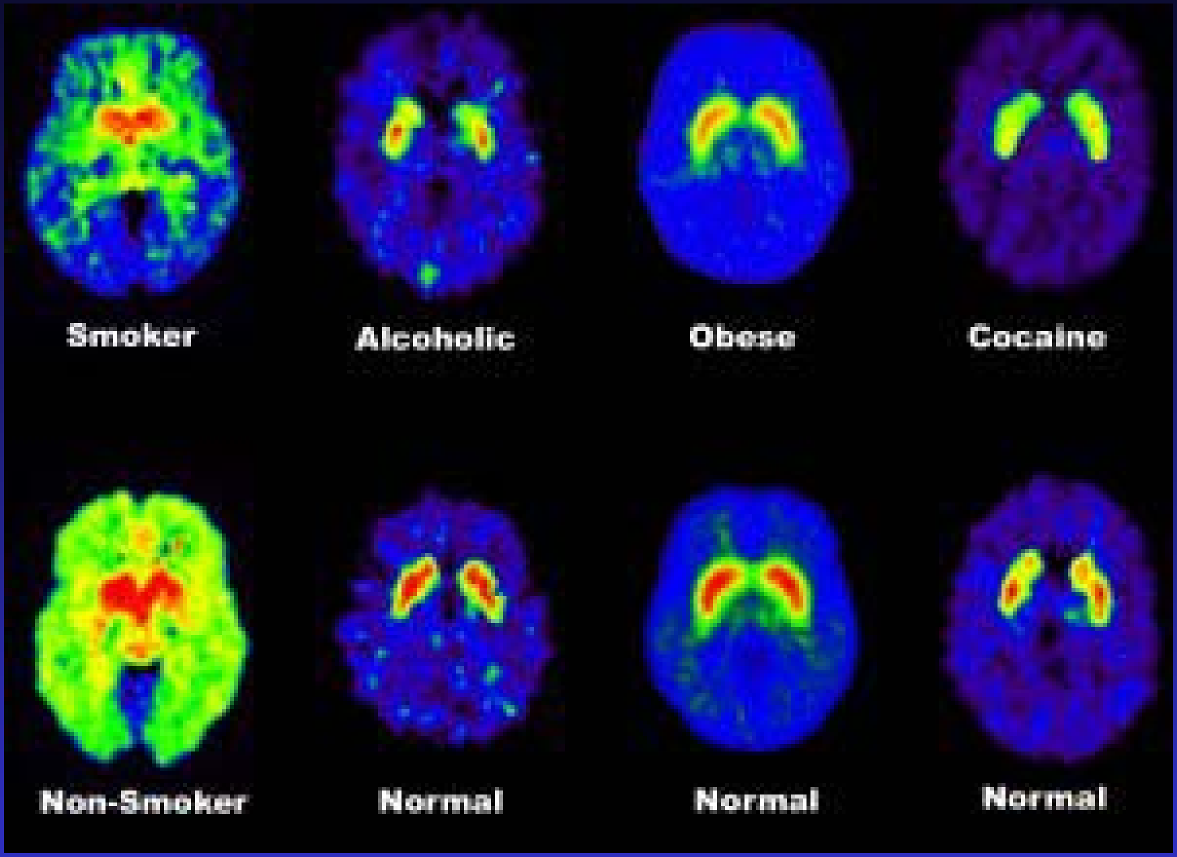
Wang et al., 2001


Smoker
Alcoholic
Obese
Cocaine
Non-Smoker
Normal
Normal
Normal

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Le sostanze d'abuso condividono con gli stimoli primari le proprietà gratificanti attraverso l'iperattività dopaminergica del sistema limbico

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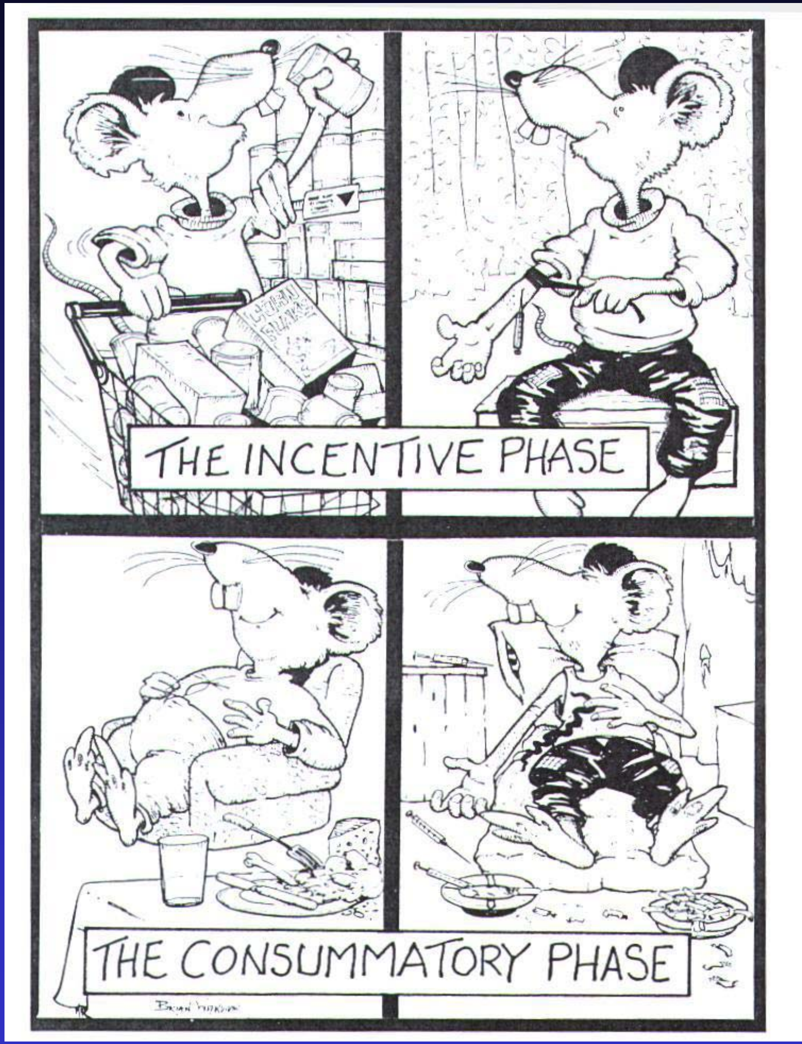

“Wanting” = Dopamine

“Liking” = Opioid System

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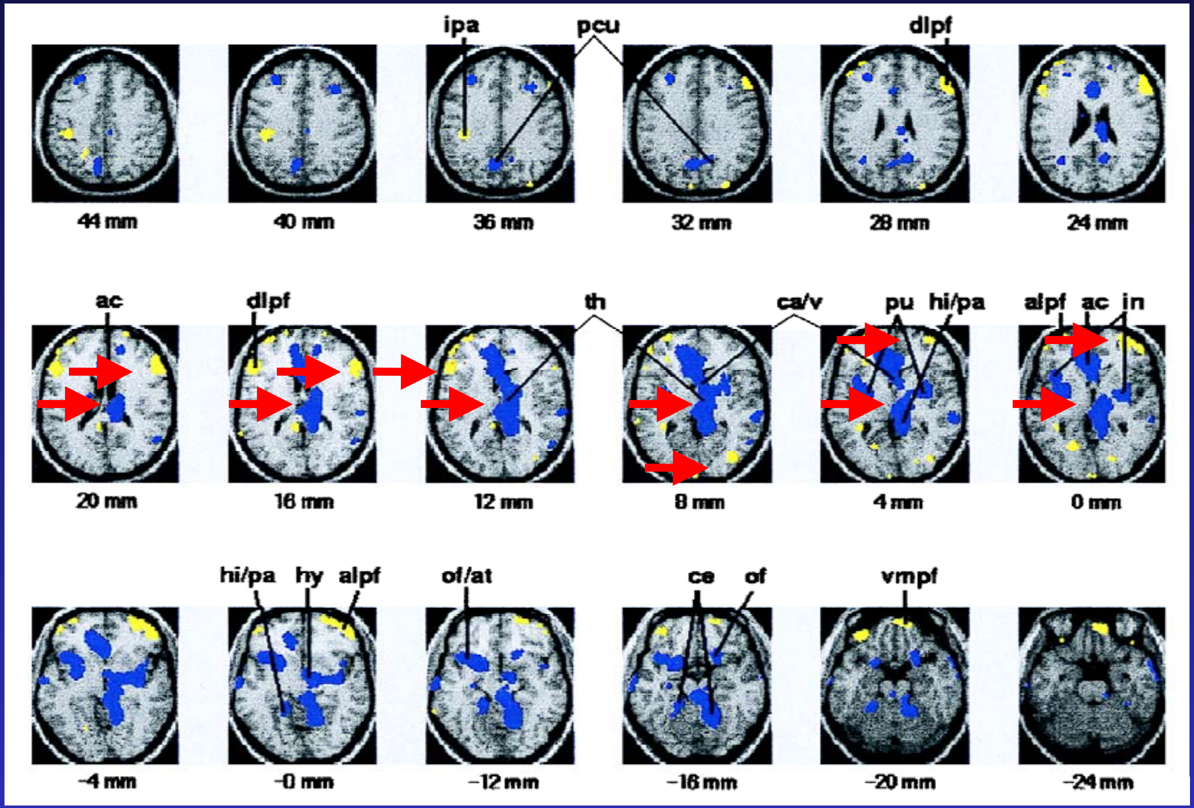
Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography

Satiation
Hunger



Images of brain activation in response to hunger and satiation. Brain regions with significant decrease in Cerebral Blood Flow (rCBF) in response to hunger are shown in blue; brain regions with significant increase in rCBF in response to satiation are shown in yellow.

In comparison with satiation, hunger was associated with increased rCBF in the vicinity of the hypothalamus and insular cortex and in additional paralimbic and limbic areas (anterior cingulate cortex, parahippocampal and hippocampal formation, and a region that includes the anterior temporal and posterior orbitofrontal cortex), thalamus, caudate, precuneus, putamen, and cerebellum. In comparison with hunger, satiation was associated with increased rCBF bilaterally in the vicinity of the ventromedial prefrontal cortex, dorsolateral prefrontal cortex, and the inferior parietal lobule

From: Tataranni et al., 1999

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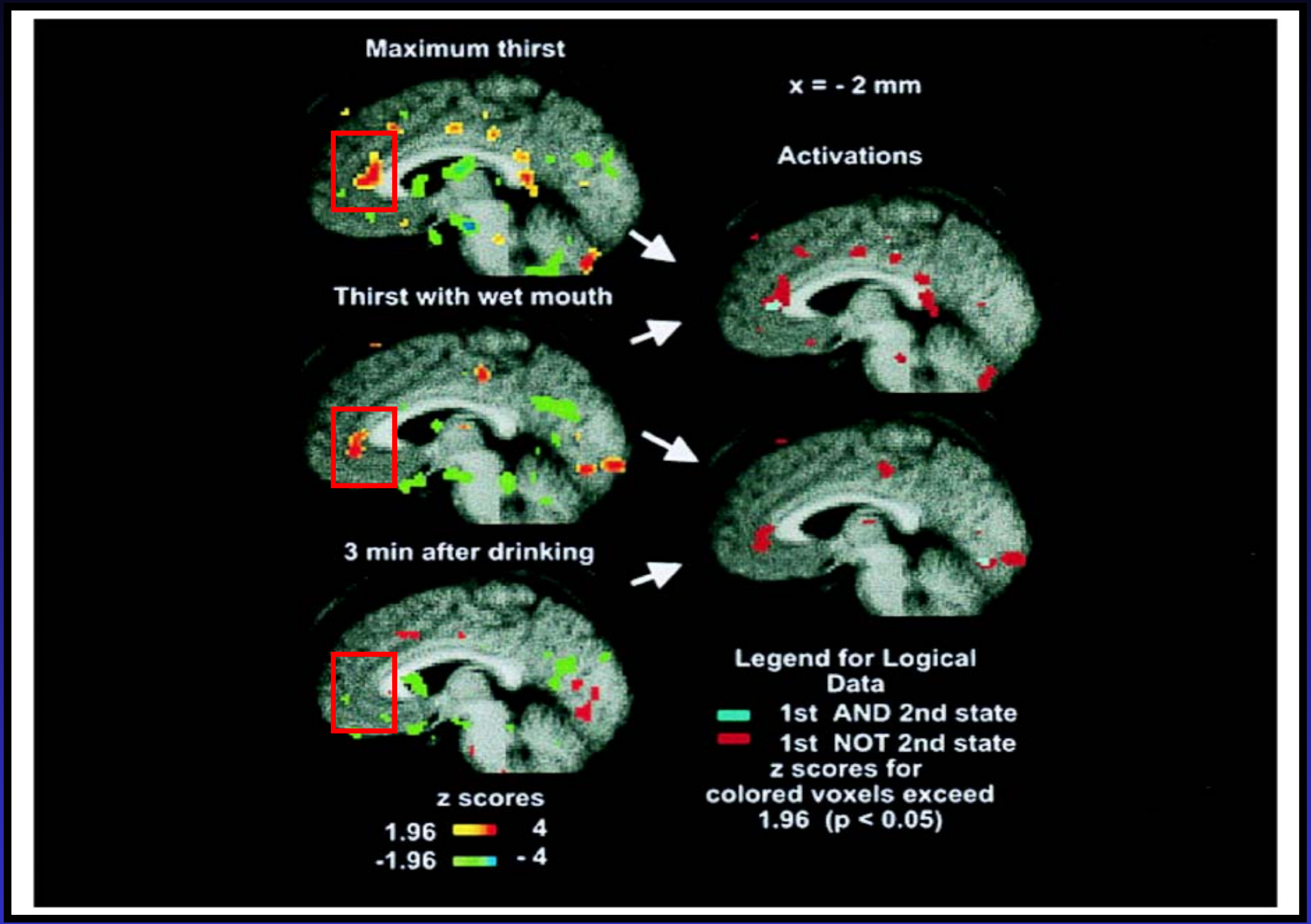
Consciousness of thirst, a primal vegetative emotion, and satiation of thirst appear to be subserved by phylogenetically ancient brain regions



The salient change in the brain associated with the development of moderate-to-severe thirst (maximum thirst minus baseline) occurred predominantly in the cingulate gyrus. Maximum thirst was associated with parietal activation. Irrigating the mouth with water caused reduction of cingulate activation. Wetting the mouth caused a number of strong frontal activations. By 3 min after drinking water to satiation, the major activations in the cingulate had disappeared

From: Denton et al., 1999

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Desiderio = Aree Corticali
Soddisfacimento = Aree Diencefaliche (+ ancestrali)

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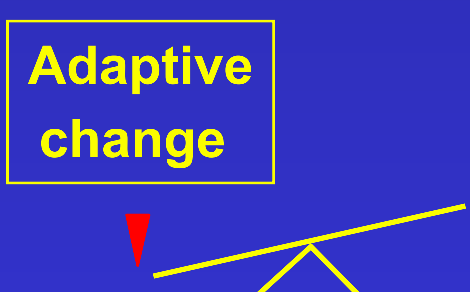
Effetti Clinici delle Sostanze d'Abuso

Effetti +

Effetti + +

Tolleranza



Effetti -

Effetti acuti

- Attivazione delle aree corticali orbito-frontali
- Attivazione dell'amigdala
- Attivazione delle aree striatali

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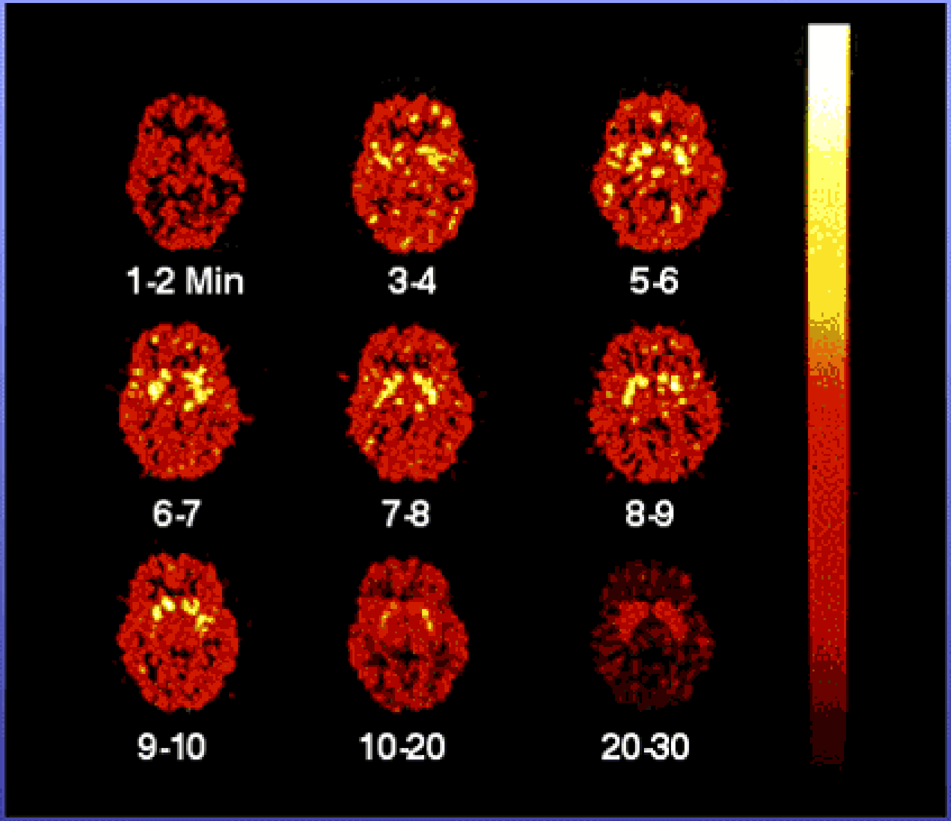
Your Brain on Drugs



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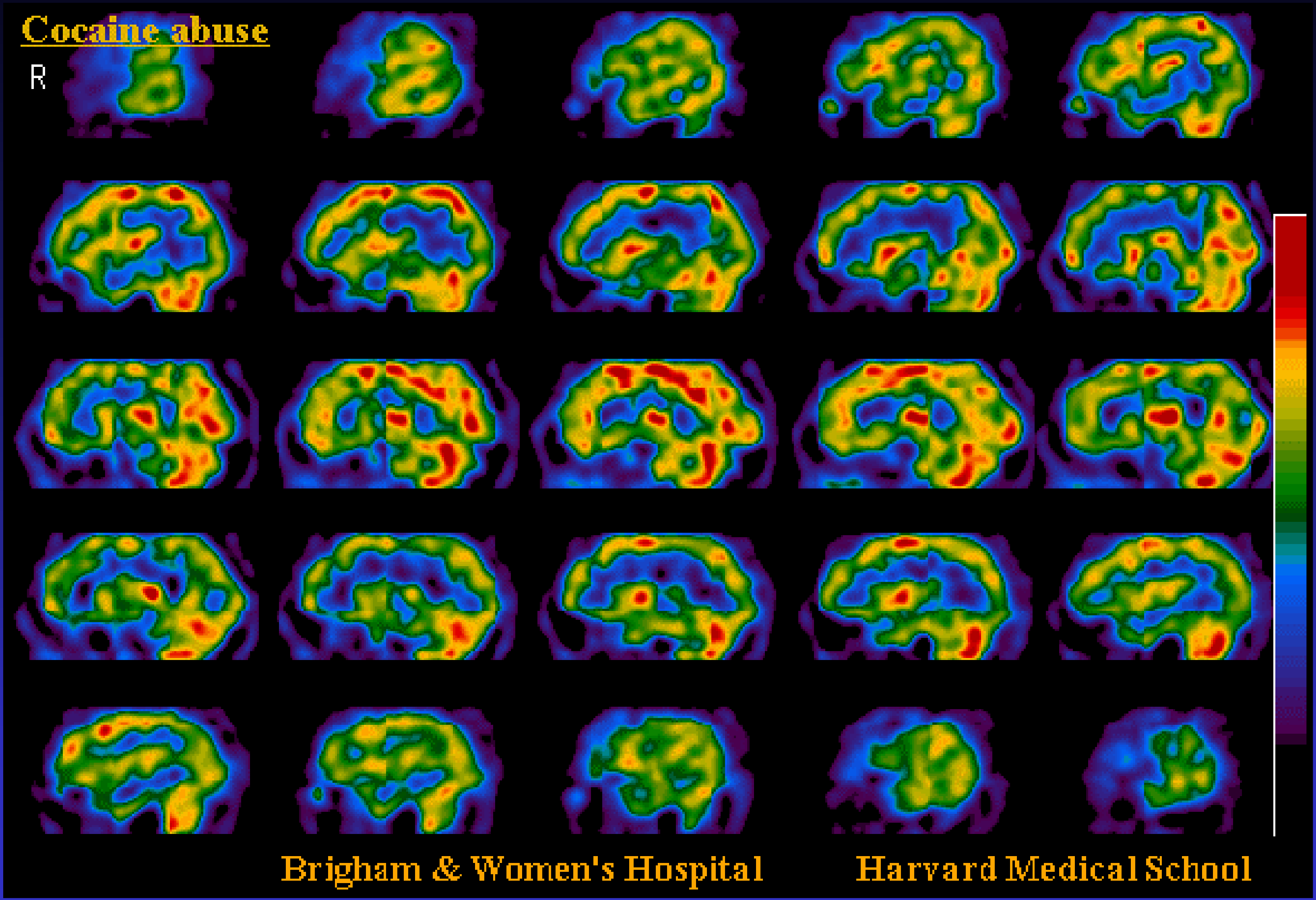
Cocaine abuse
R
Brigham & Women's Hospital
Harvard Medical School

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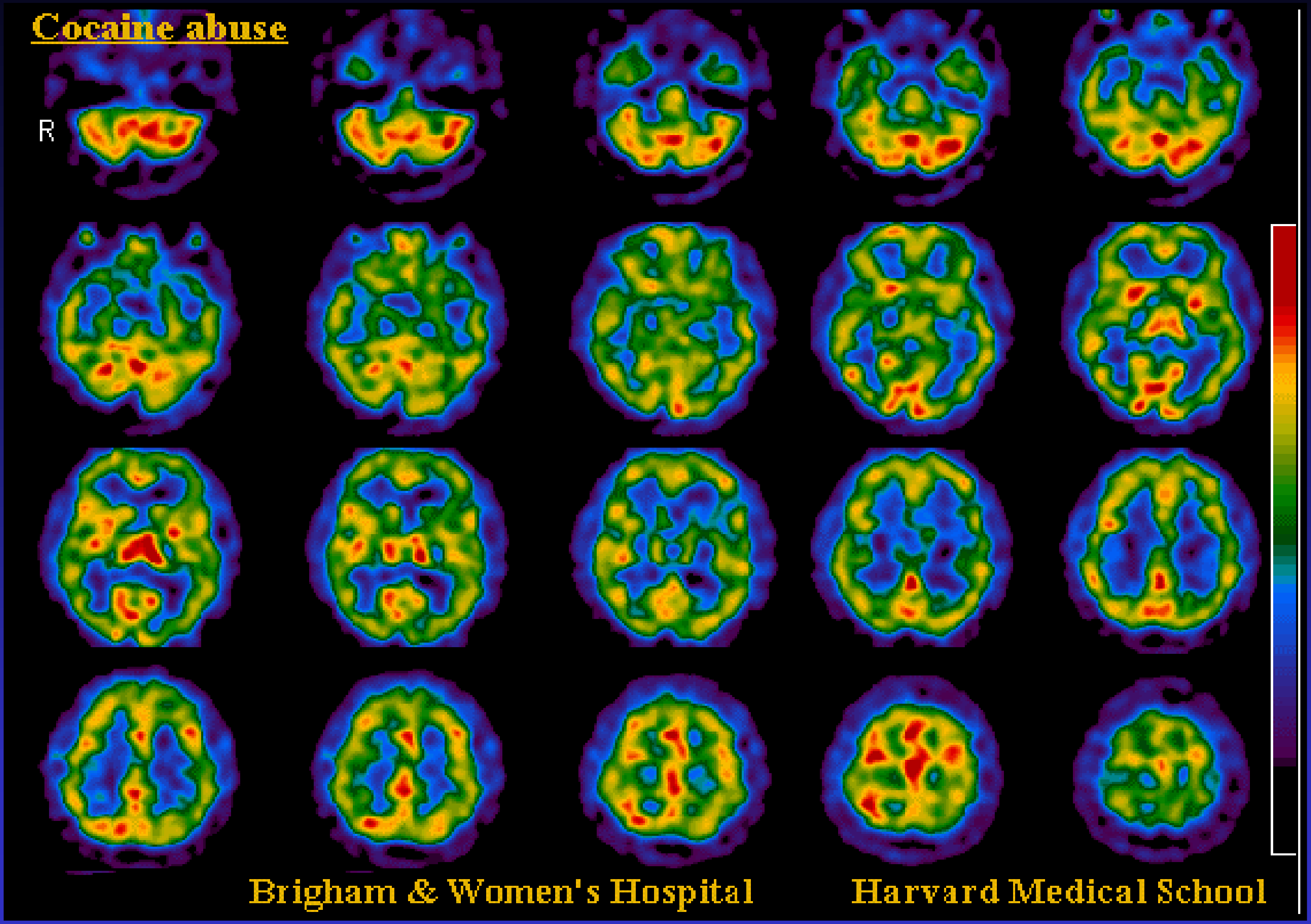
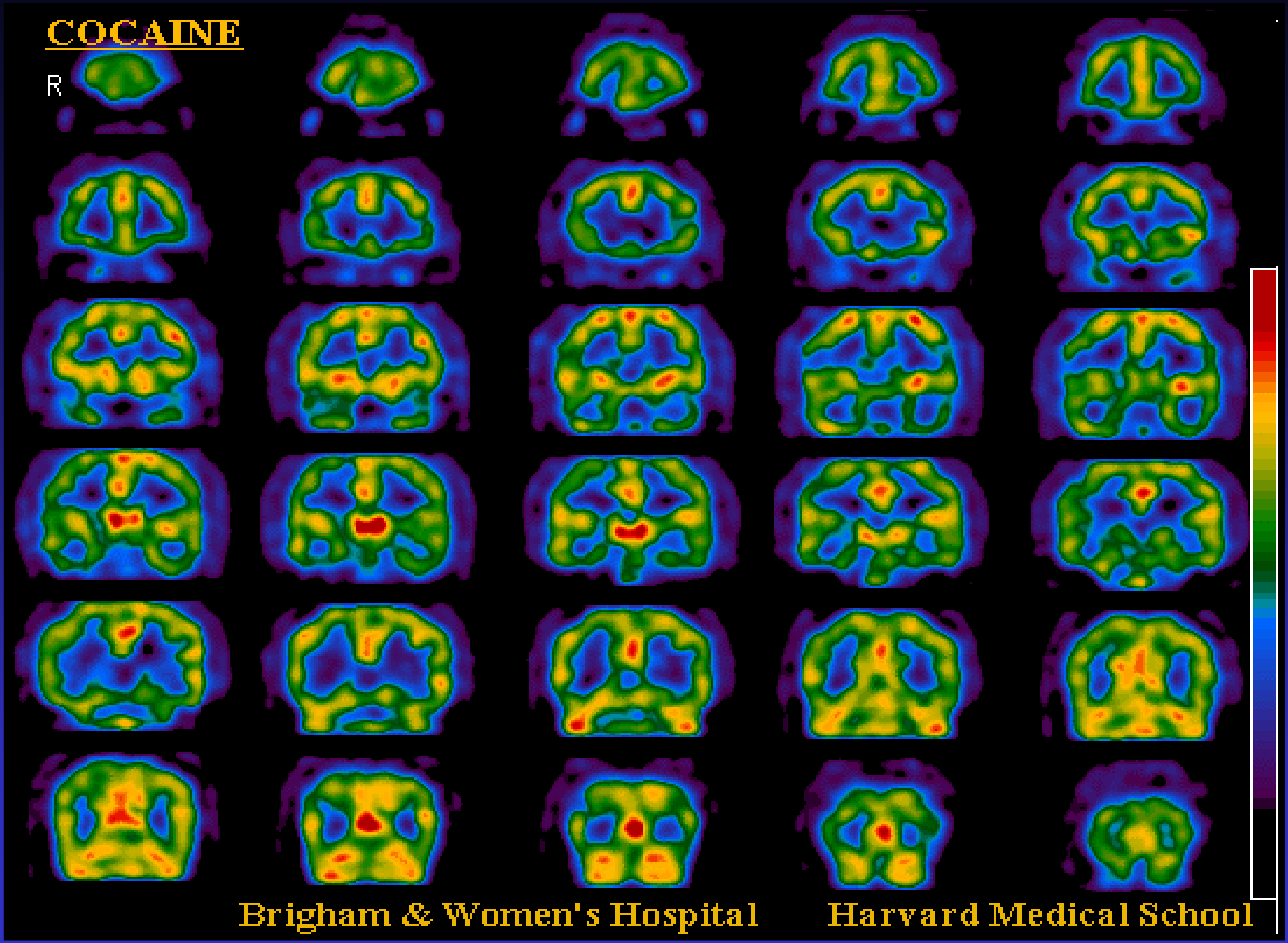
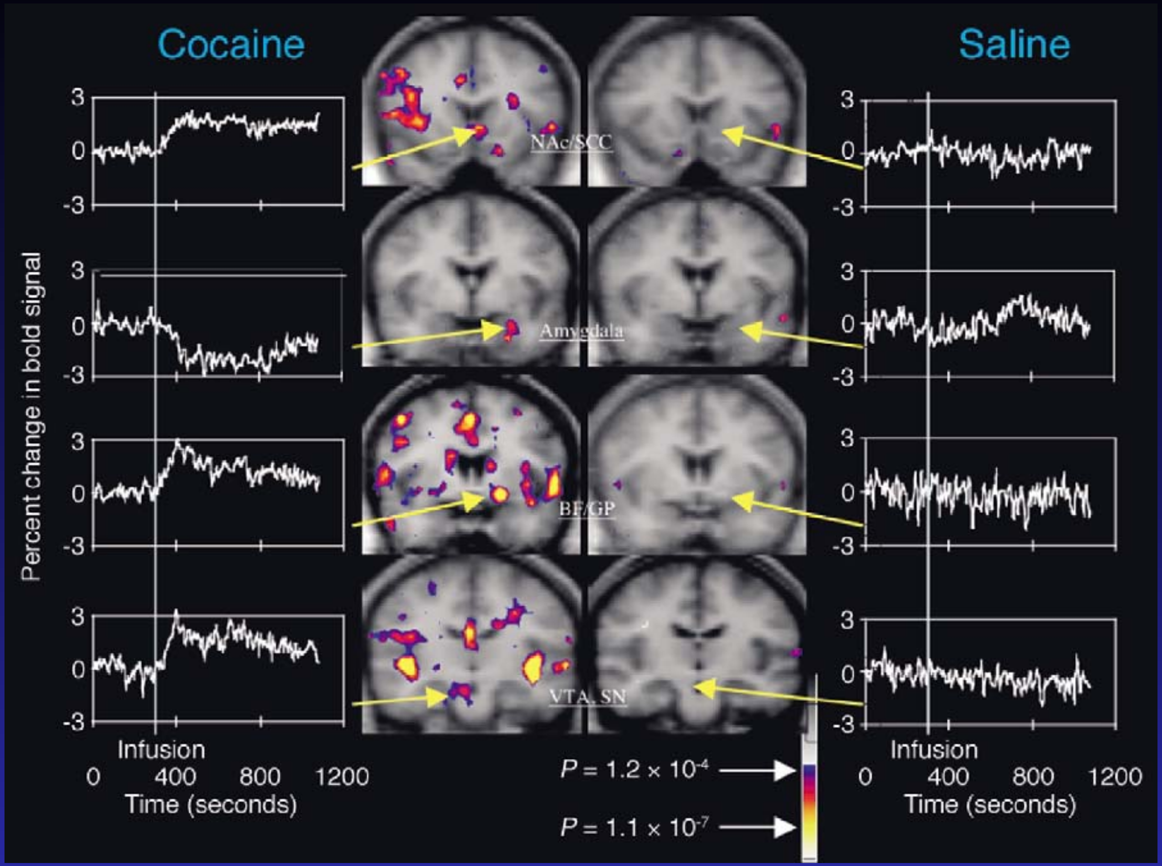

Cocaine abuse
R
Brigham & Women's Hospital
Harvard Medical School

F. Nava, 2005



F. Nava, 2005



Images of coronal sections obtained with fMRI, showing areas of brain activation and deactivation during cocaine intoxication compared with those after saline administration. During intoxication there is a complex pattern of activation and/or deactivation that includes the ventral tegmental area (VTA) and the substantia nigra (SN), where DA cells are located, as well as regions involved with reward (nucleus accumbens, NAc; basal forebrain, BF; globus pallidus, GP), with memory (amygdala), and with motivation (subcallosal cortex, SCC). The color scale indicates the level of significance (*P* value) of the change in activation of the bold signal.

From: Volkow et al., 2001

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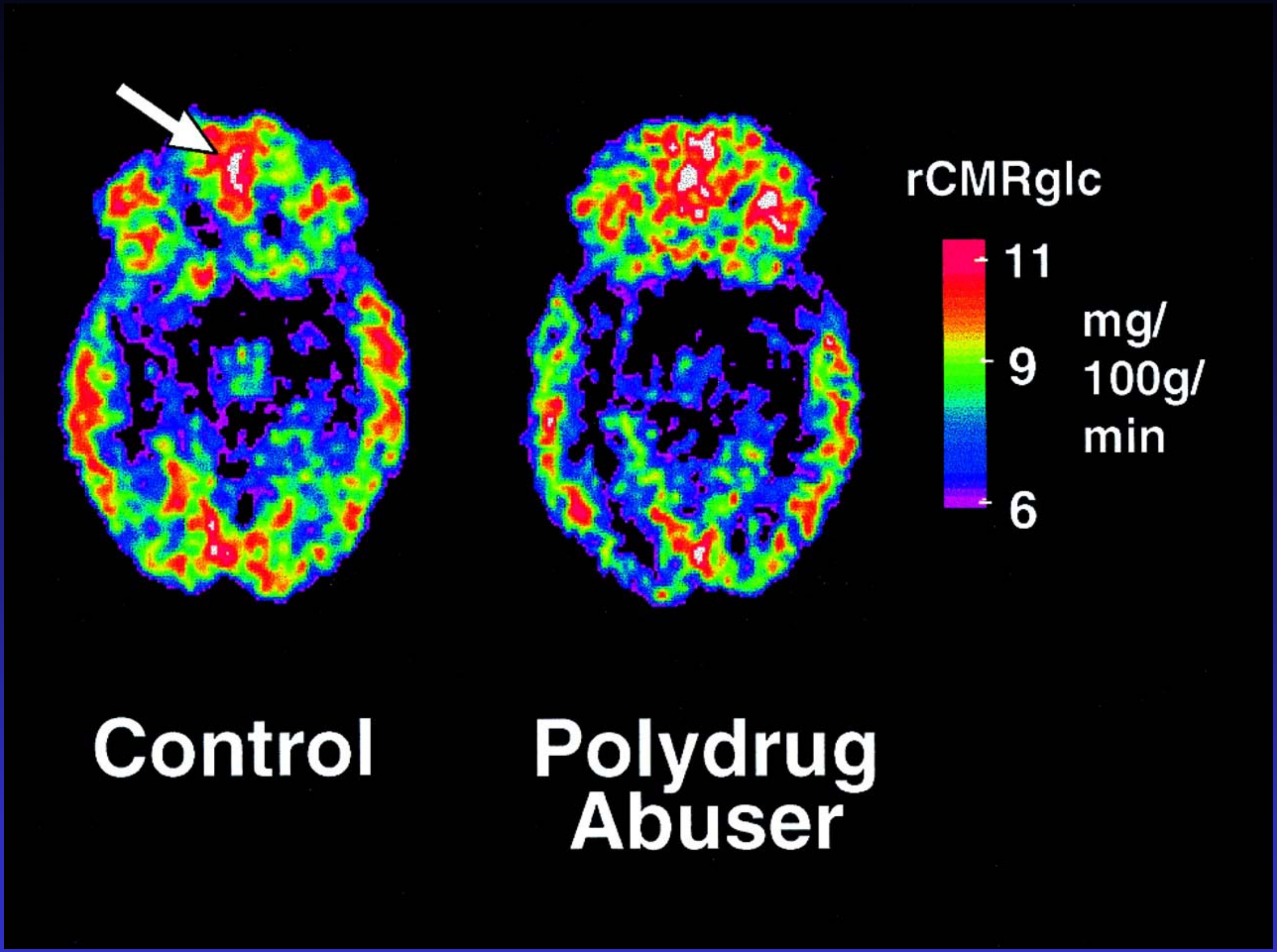

From: London et al., 2001

Effetti in *ex abusers*

- Attivazione delle aree corticali parietali
- Attivazione del talamo
- Attivazione delle aree striatali

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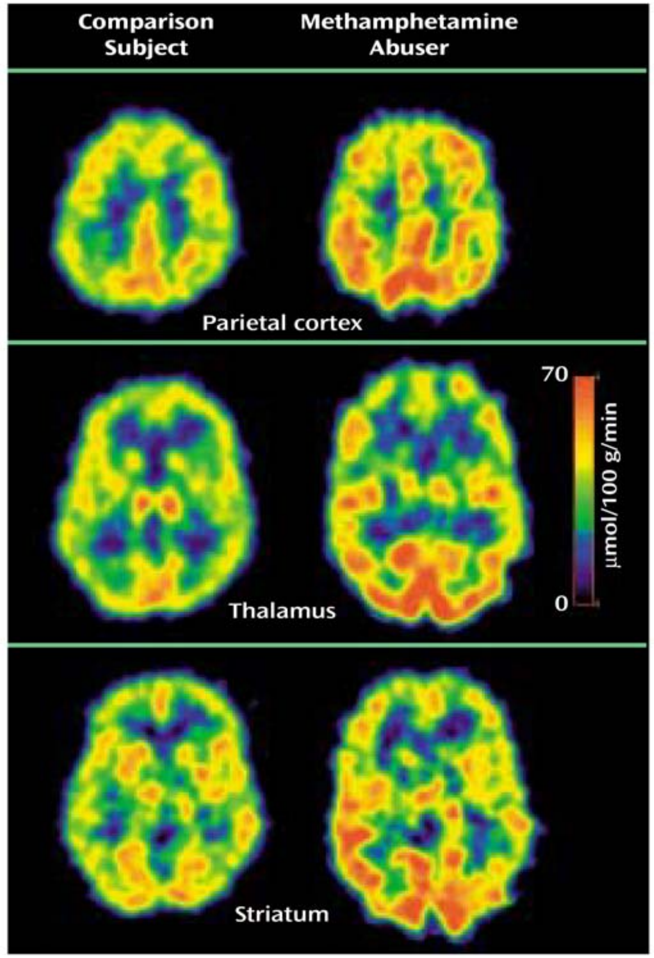
FIGURE 1. Parietal Cortex, Thalamic, and Striatal Metabolism in a Detoxified Methamphetamine Abuser and in an Age-Matched Comparison Subject With No History of Drug Abuse[a]



[a] The upper images were taken at the level of the centrum semiovale, where the parietal cortex can be visualized. Note the higher metabolism in the cortex and the lower metabolism in the thalamus and the caudate in the methamphetamine abuser.

From: Volkow et al., 2001

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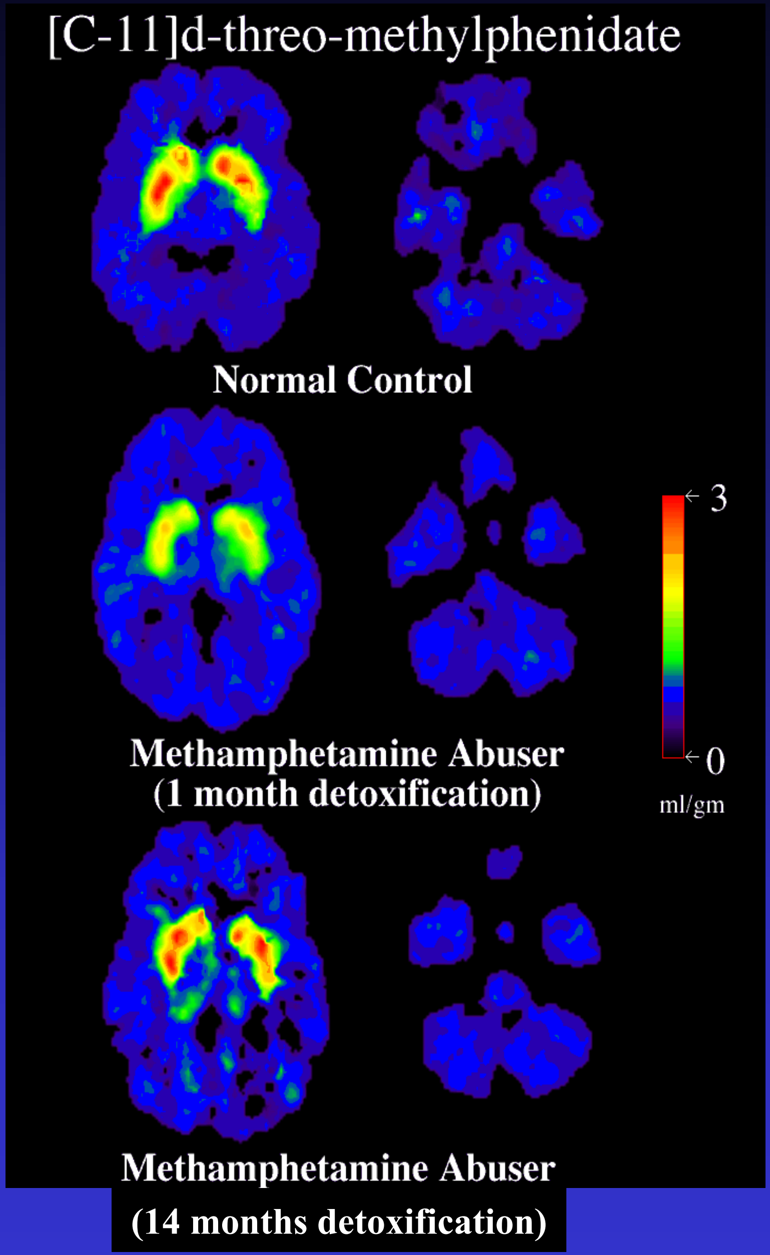
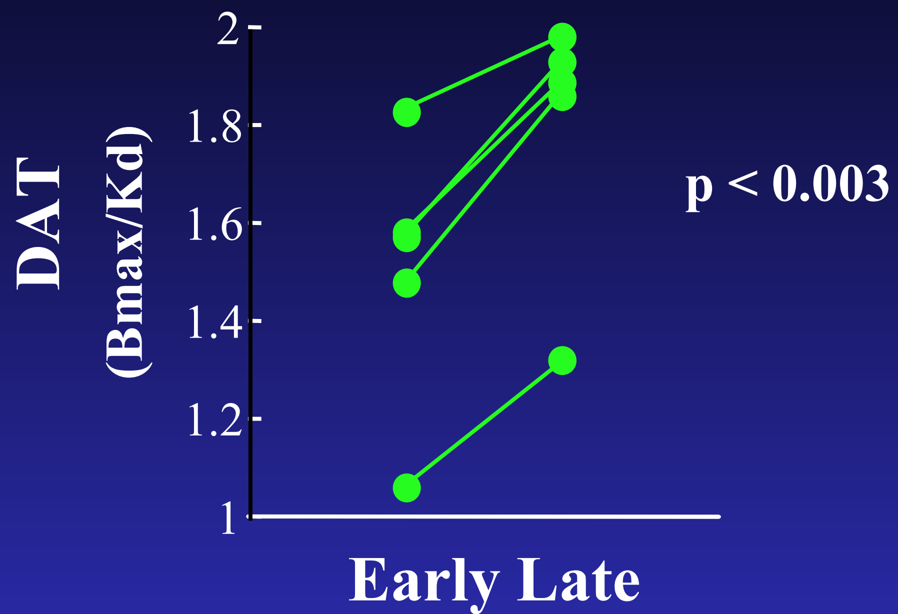
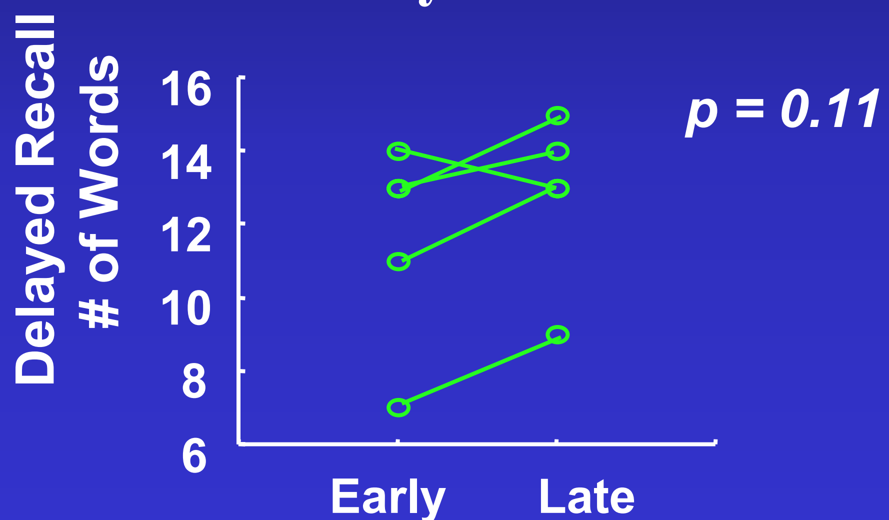
Detoxification Leads to Partial Recovery of Neurobiology and Function







Effetti cronici

- Ipoattività delle aree corticali orbito-frontali

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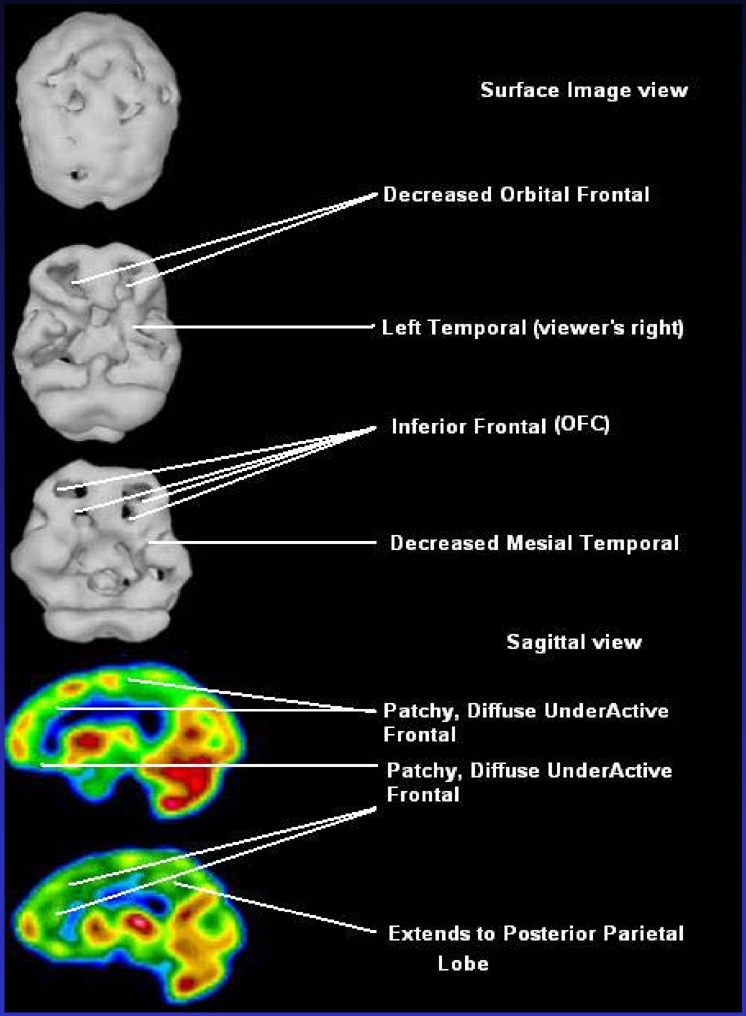
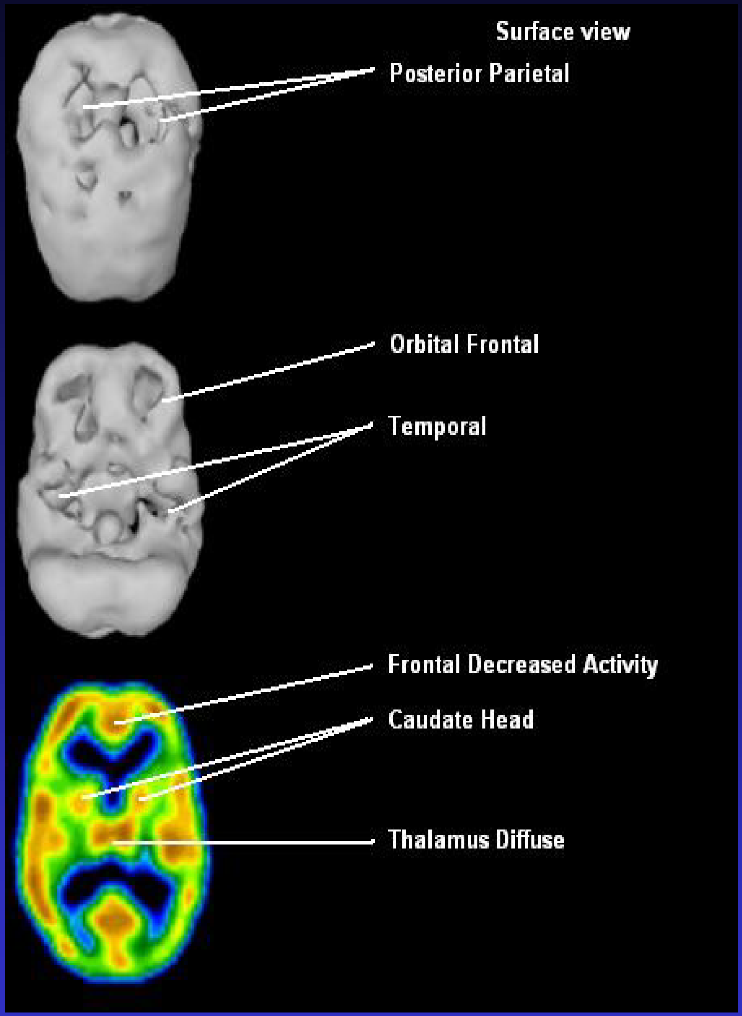
SPECT



Alcohol chronic abuse



Ecstasy chronic abuse

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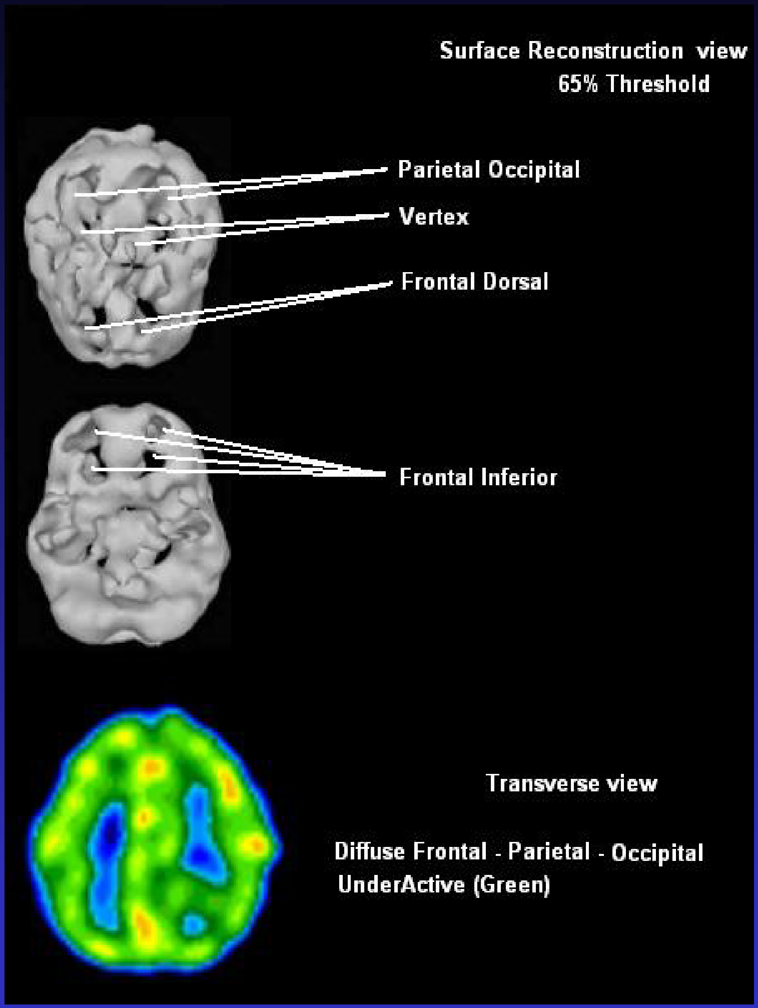
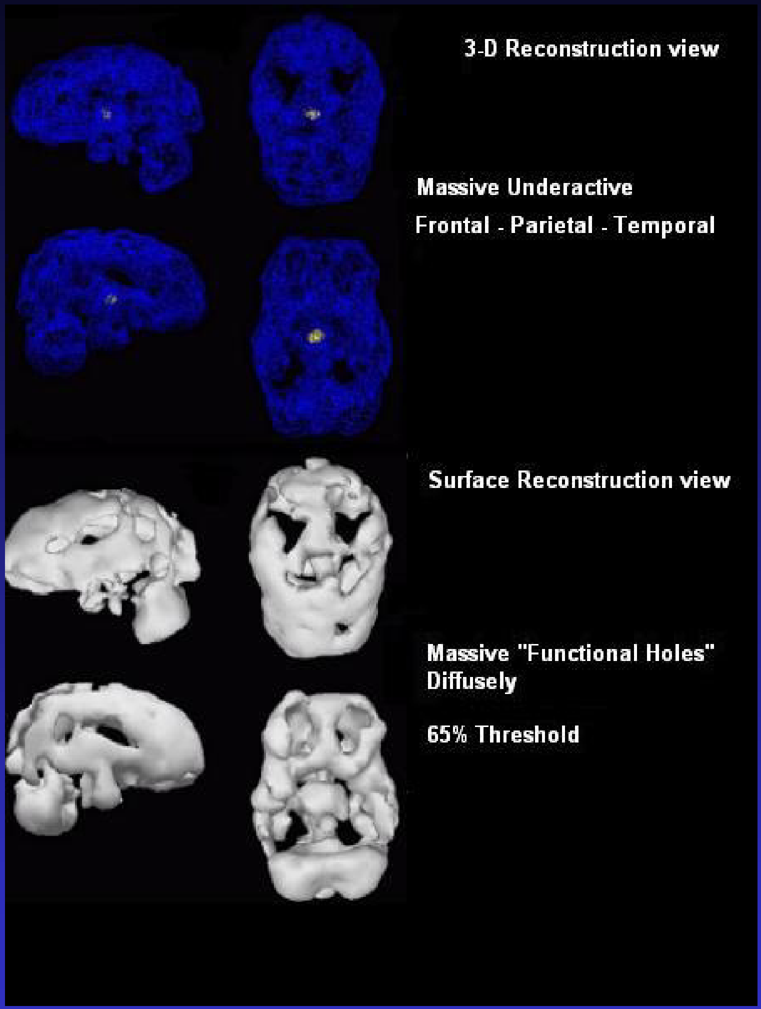
From: www.brain-spect.com

SPECT





Marijuana chronic abuse

Heroin + Hallucinogen chronic abuse

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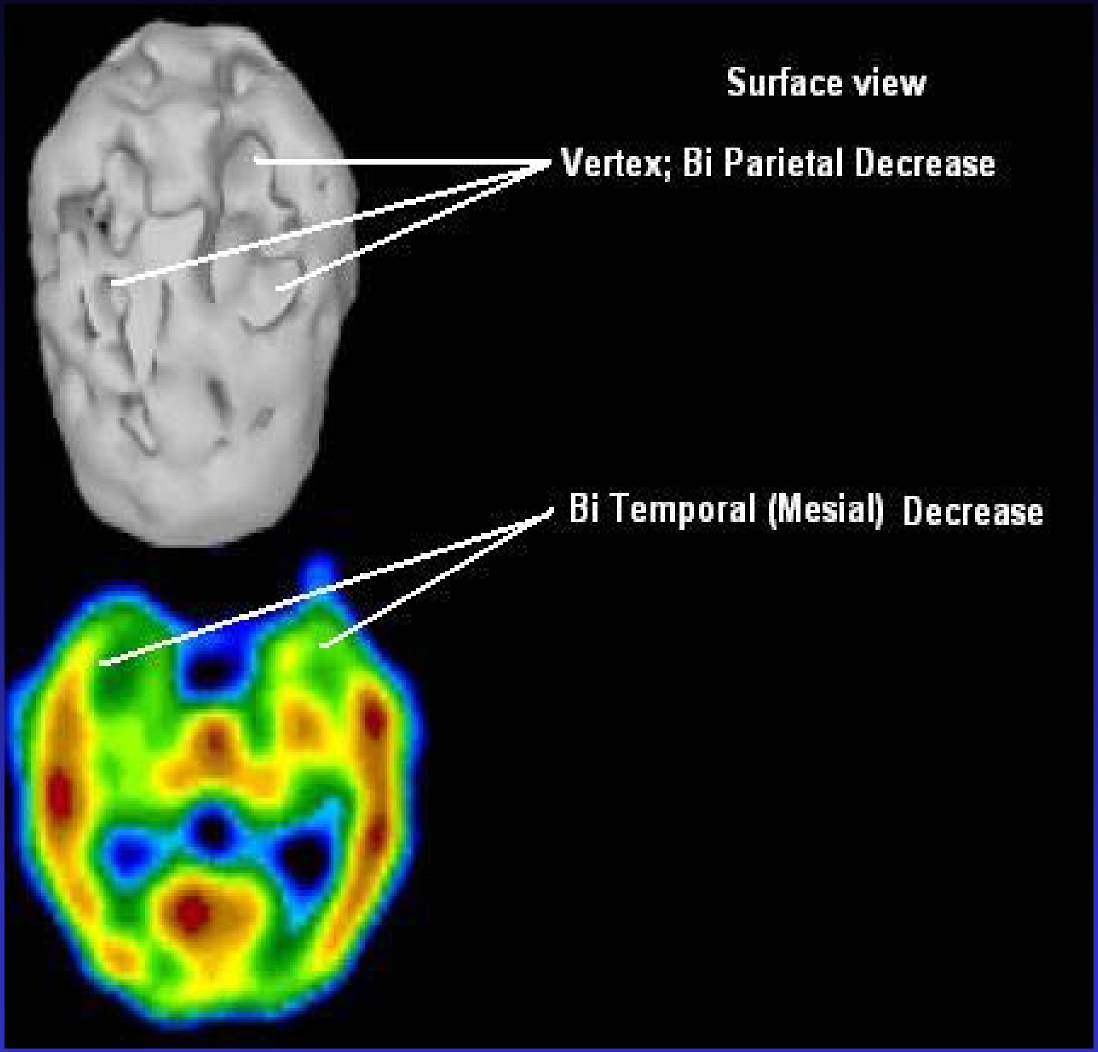
From: www.brain-spect.com

SPECT



Methamphetamine + Alcohol chronic abuse

From: www.brain-spect.com

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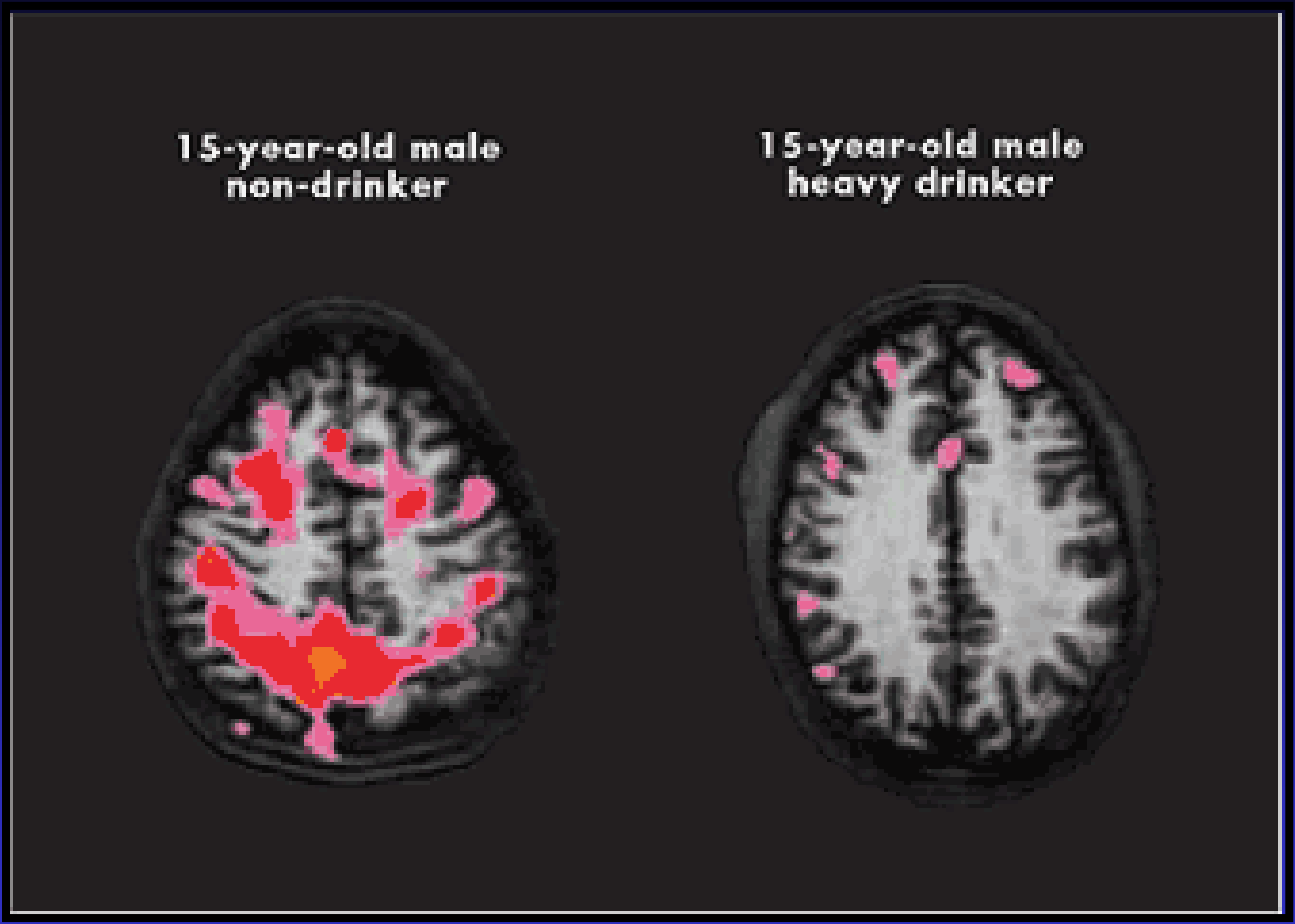

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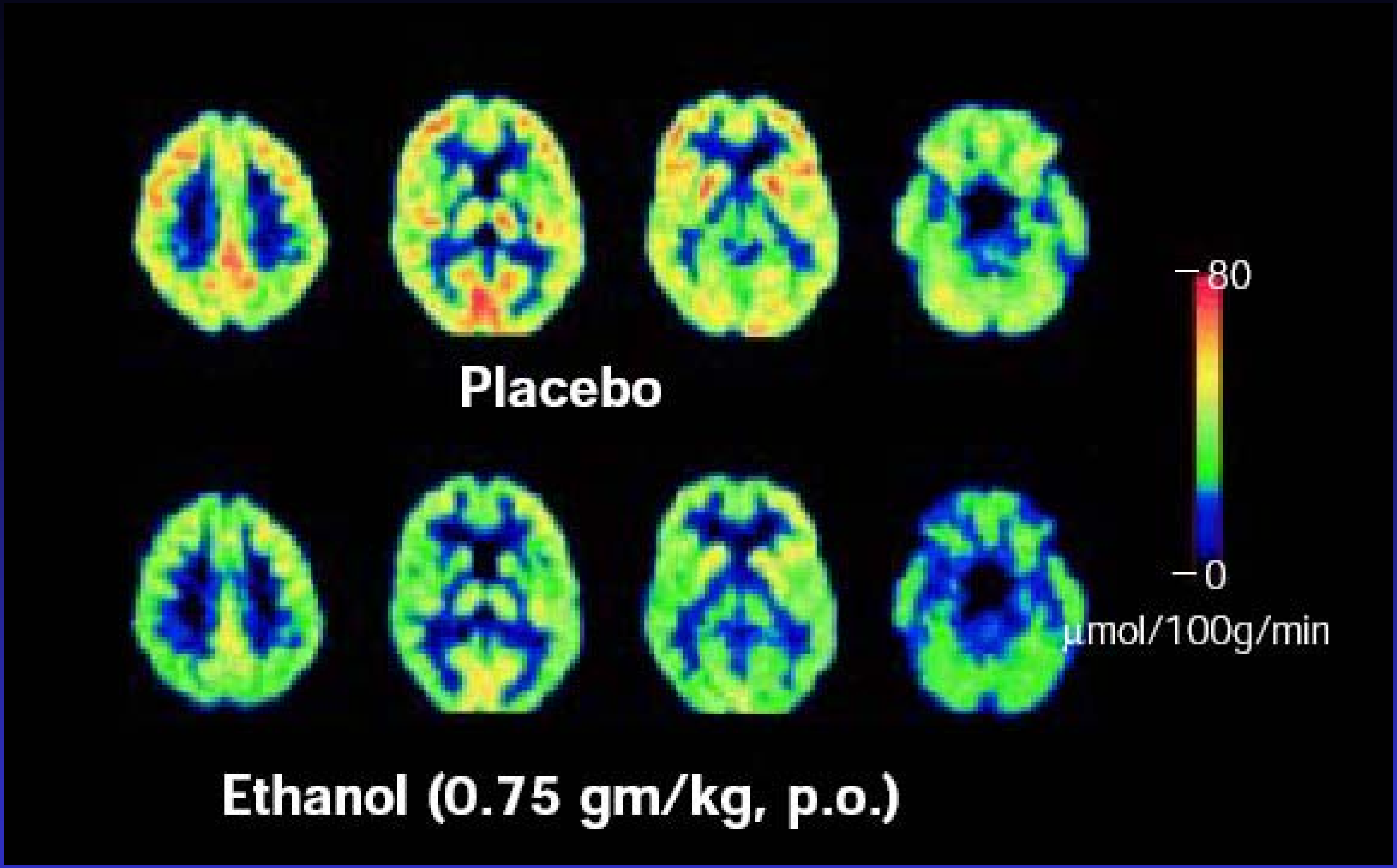
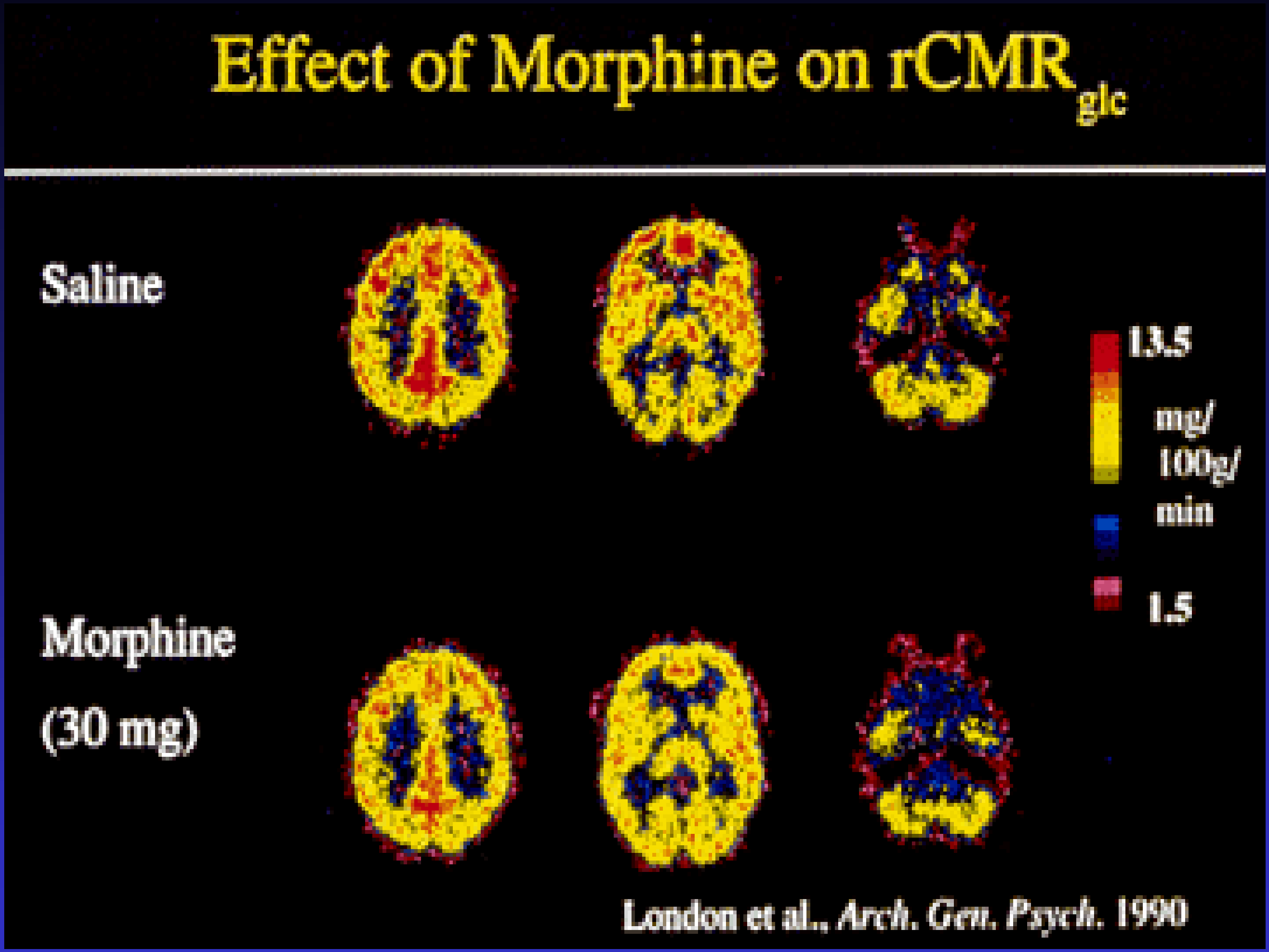
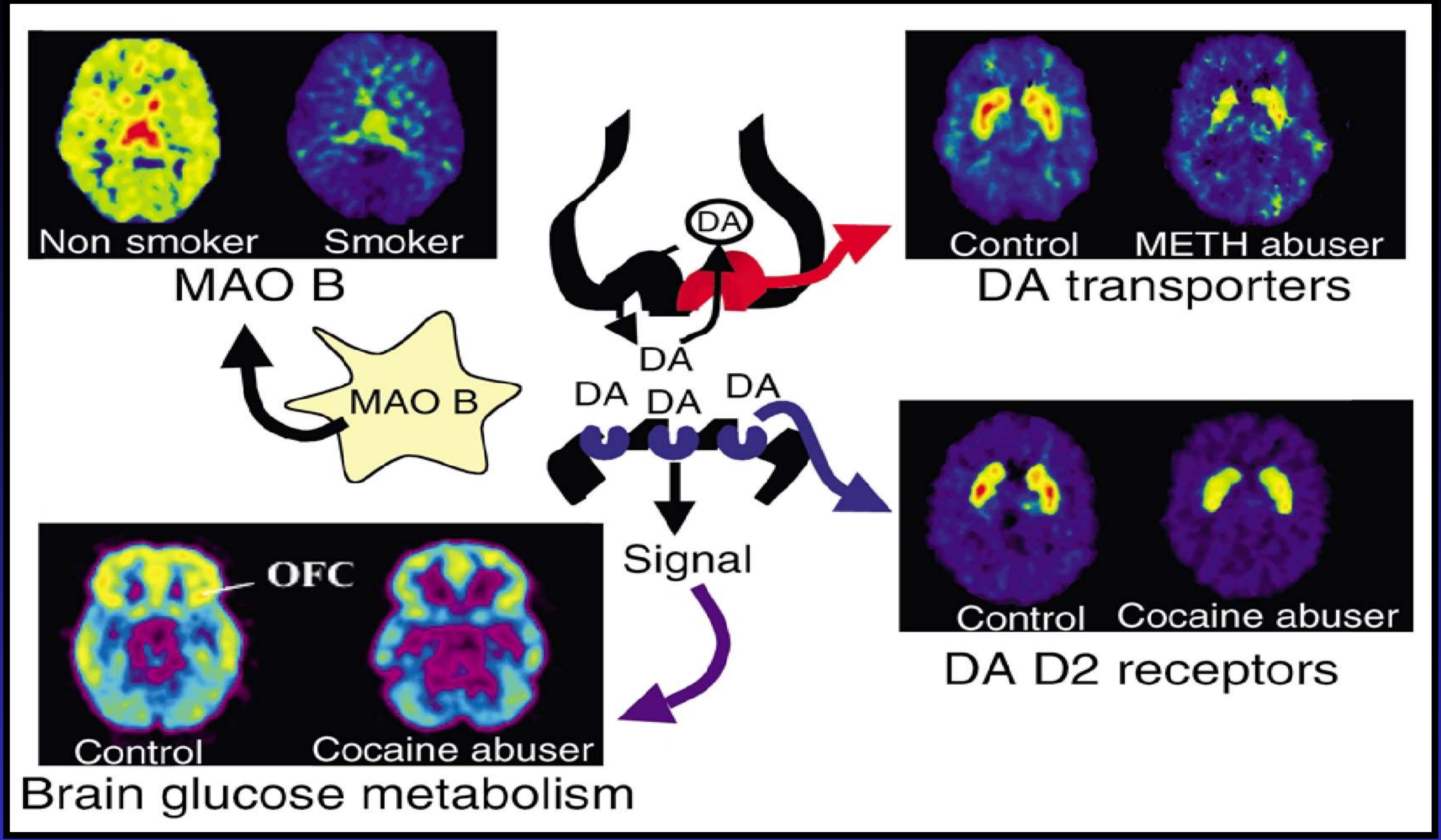


From: Wang et al., 2002

F. Nava, 2005


Effect of Morphine on $rCMR_{glc}$
Saline
Morphine
(30 mg)
13.5
mg/
100g/
min
1.5
London et al., *Arch. Gen. Psych.* 1990

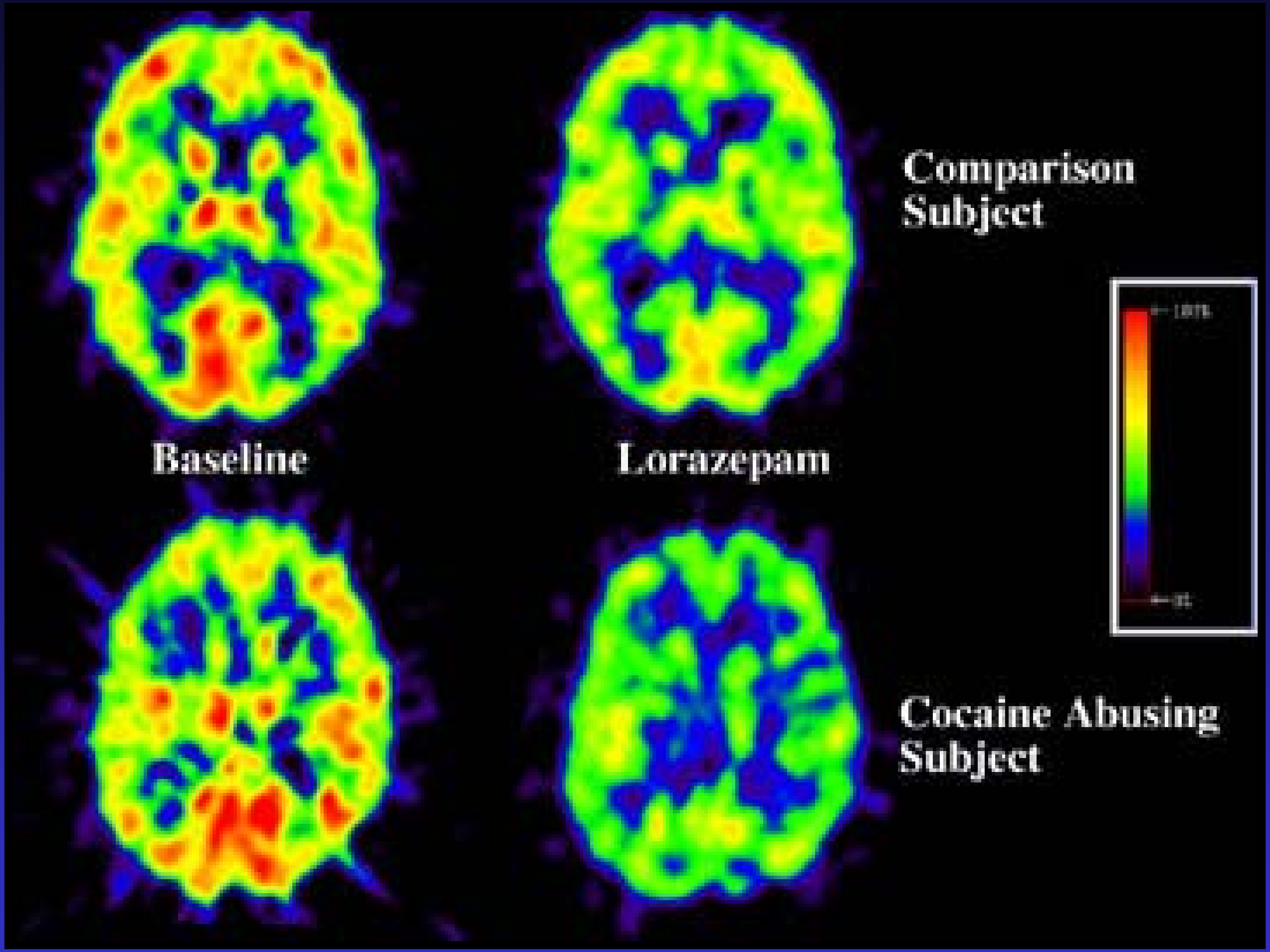
F. Nava, 2005



Images obtained with PET (axial sections) that show the effects of chronic drug exposure on various proteins involved in dopamine (DA) neurotransmission and on brain function (as assessed by brain glucose metabolism). <u>While some effects are common to many drugs of abuse, such as decreases in DA D2 receptors in striatal neurons and decreased metabolic activity in the orbitofrontal cortex (OFC), others are more specific</u>. These include the decrease in DA transporters in striatum in methamphetamine (METH) abusers (possibly the result of neurotoxicity to DA terminals) and the decrease in brain monoamine oxidase B (MAO B; the enzyme involved in DA metabolism) in cigarette smokers. The rainbow scale was used to code the PET images; radiotracer concentration is displayed from higher to lower as red > yellow > green > blue.

From: Volkow et al., 2002

F. Nava, 2005


Comparison
Subject
Baseline
Lorazepam
Cocaine Abusing
Subject

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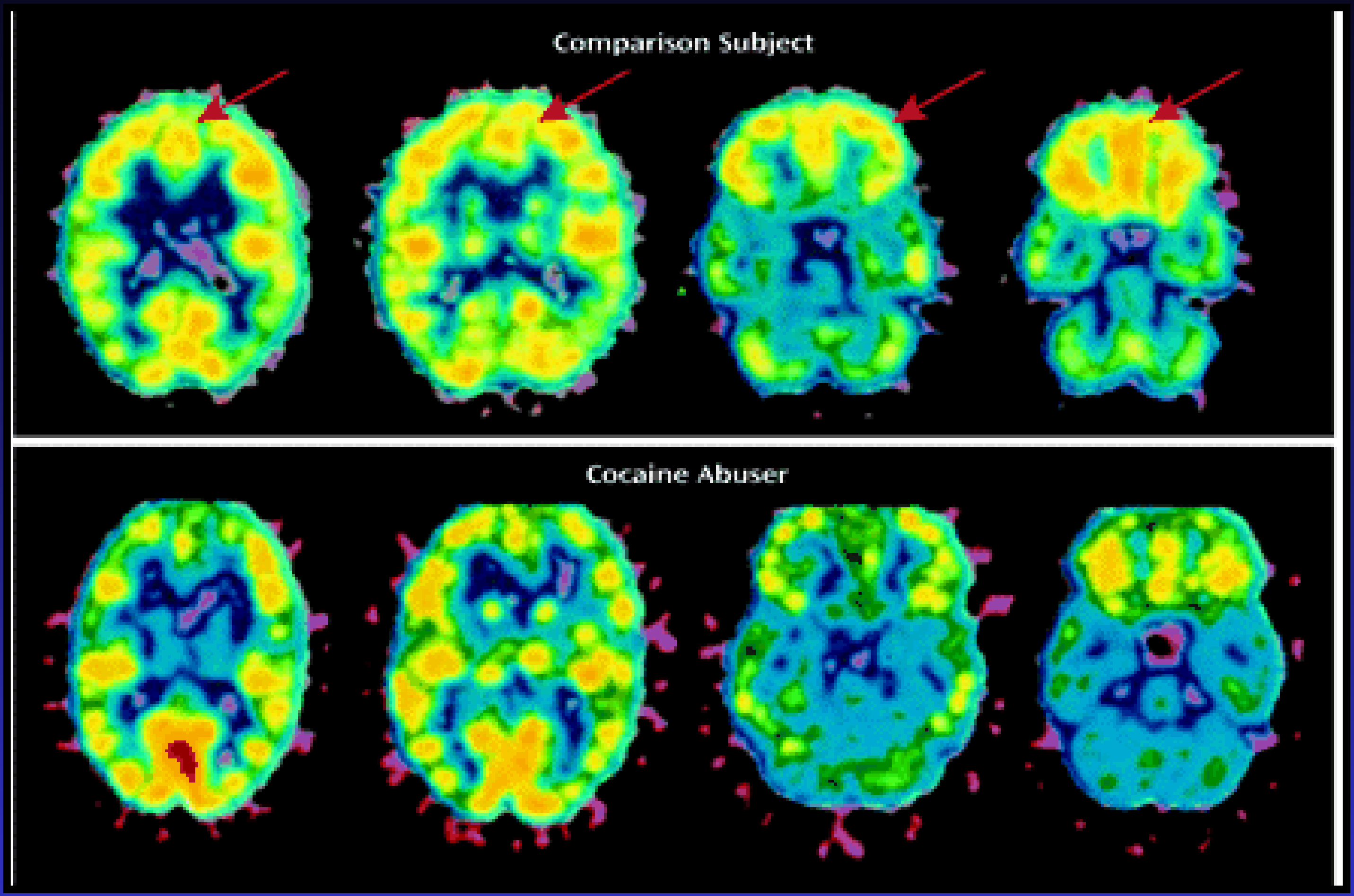
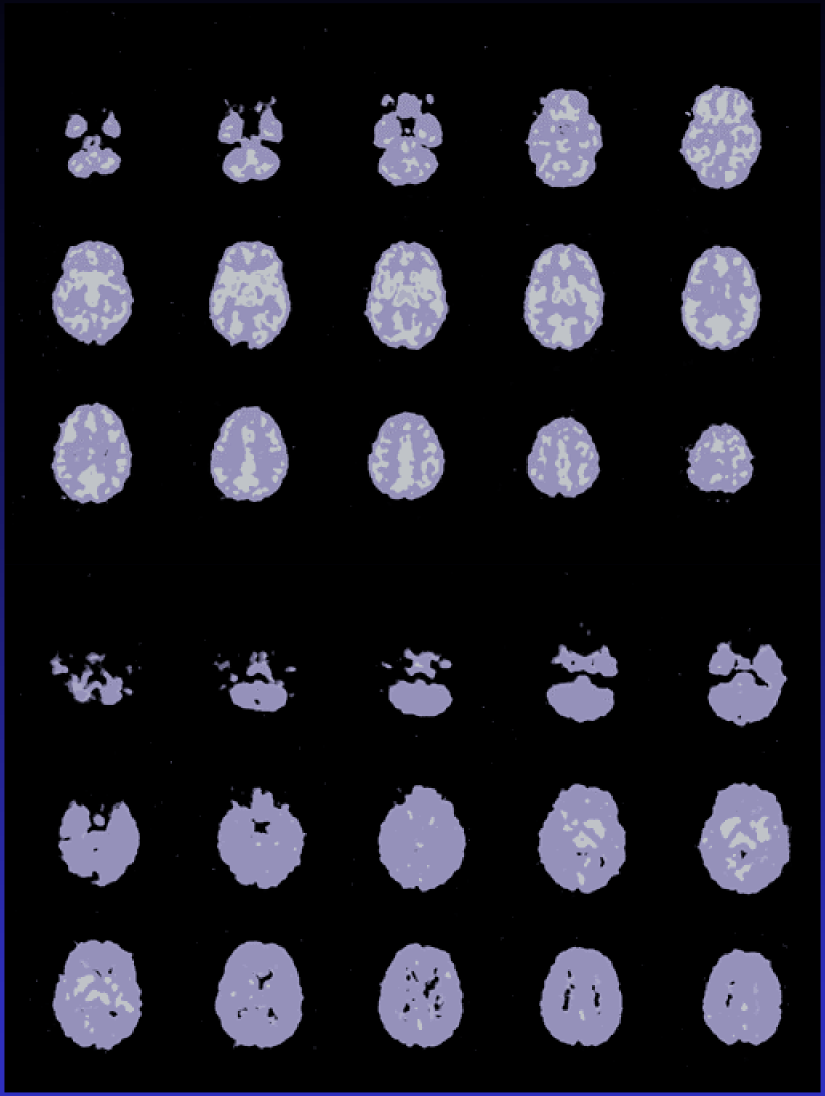


Lower Relative Glucose Metabolism in the Prefrontal Cortex and Anterior Cingulate Gyrus of a Cocaine Abuser Than in a Normal Comparison Subject.

From: Goldstein and Volkow, 2002



These brain scans show the amount of serotonin activity over a 40-minute period in a non-MDMA user (top) and an MDMA user (bottom). Dark areas in the MDMA user's brain show damage due to chronic MDMA use

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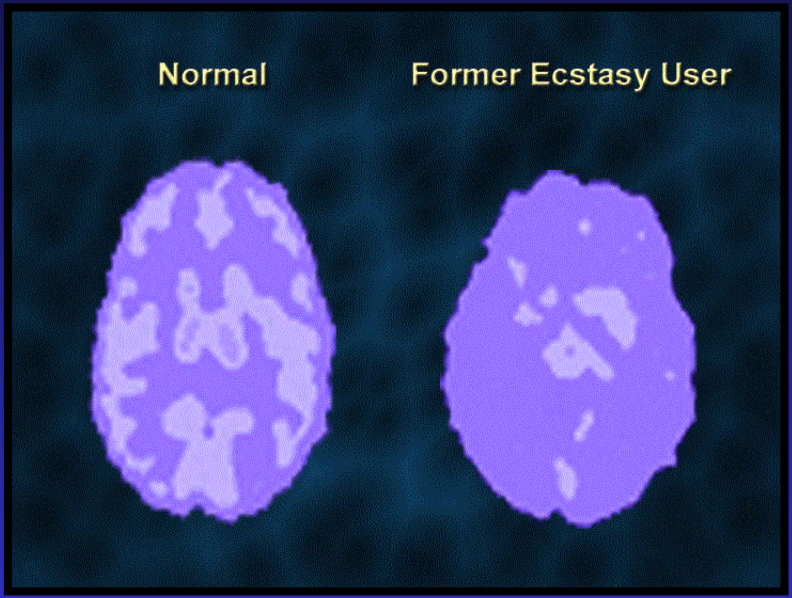
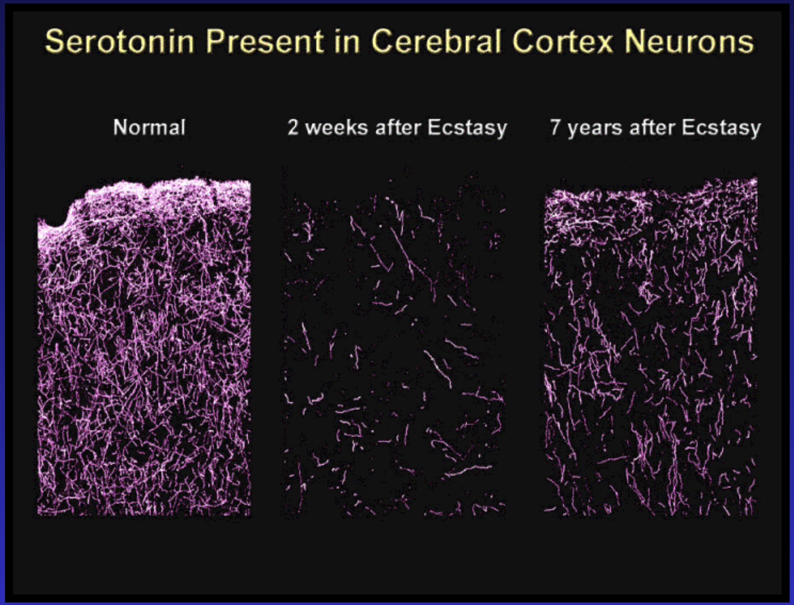

Normal
Former Ecstasy User


Serotonin Present in Cerebral Cortex Neurons
Normal
2 weeks after Ecstasy
7 years after Ecstasy

Effetti acuti e cronici determinano attivazione di diverse aree cerebrali

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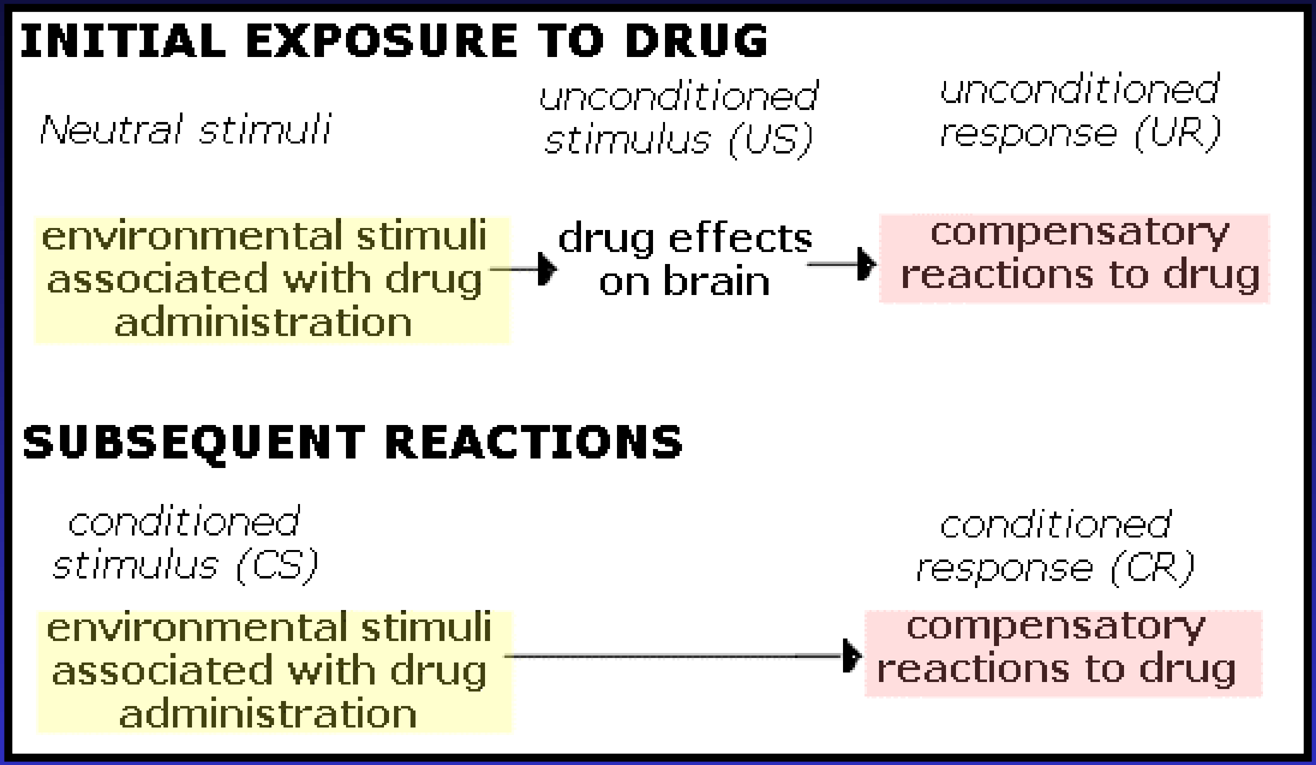
INITIAL EXPOSURE TO DRUG
Neutral stimuli
unconditioned stimulus (US)
unconditioned response (UR)
environmental stimuli associated with drug administration
drug effects on brain
compensatory reactions to drug
SUBSEQUENT REACTIONS
conditioned stimulus (CS)
conditioned response (CR)
environmental stimuli associated with drug administration
compensatory reactions to drug

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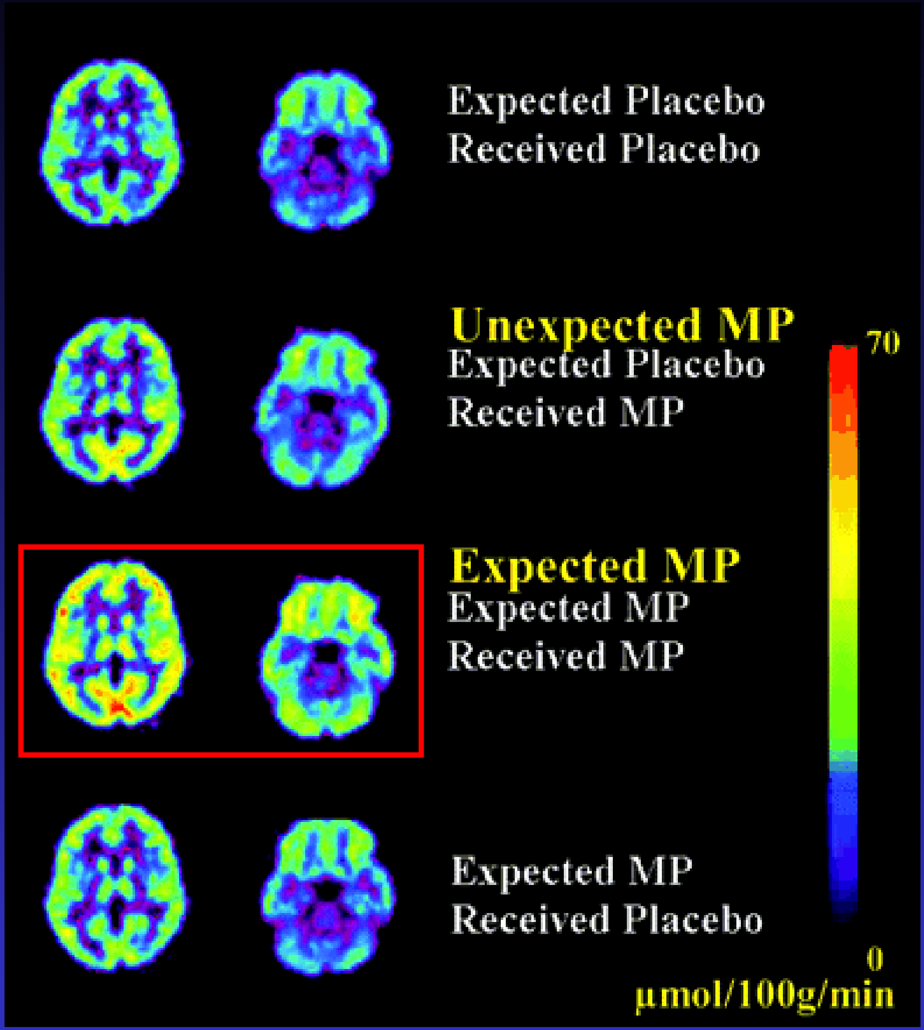
Expectation enhances brain response to drugs of abuse



Brain metabolic images at the thalamic and cerebellar levels for the four conditions: (1) expected placebo received placebo, (2) expected placebo received MP, (3) expected MP received MP, and (4) expected MP received placebo. Scale is to the right and reflects micromoles/100 gm per minute. Note the larger increases in metabolism when MP was expected than when it was not expected

From: Volkow et al., 2003

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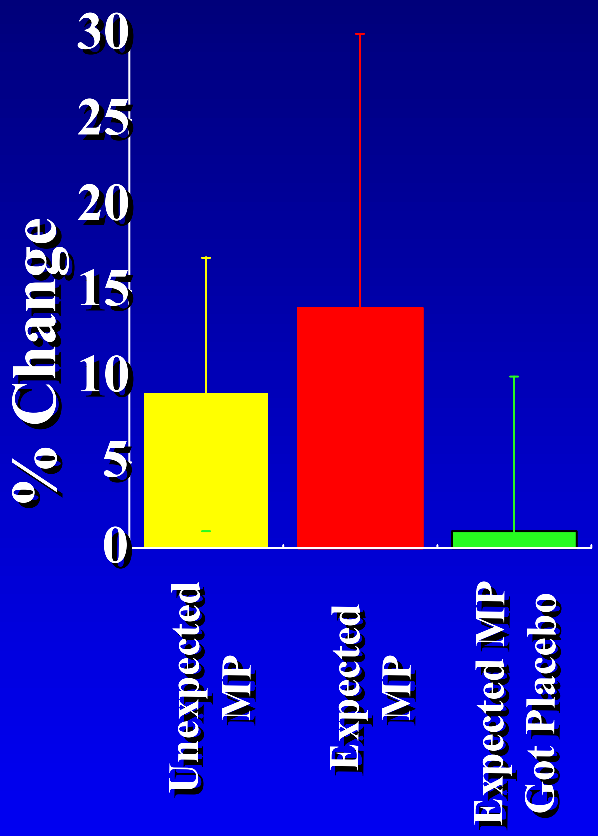
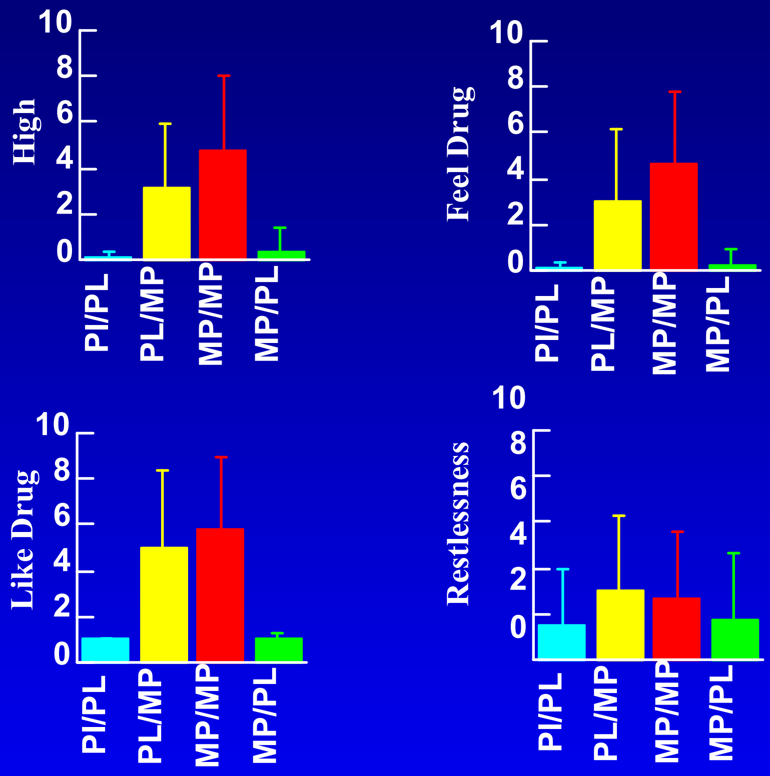
Effects of Expectation on the Response to MP on Brain Glucose Metabolism and Behavior

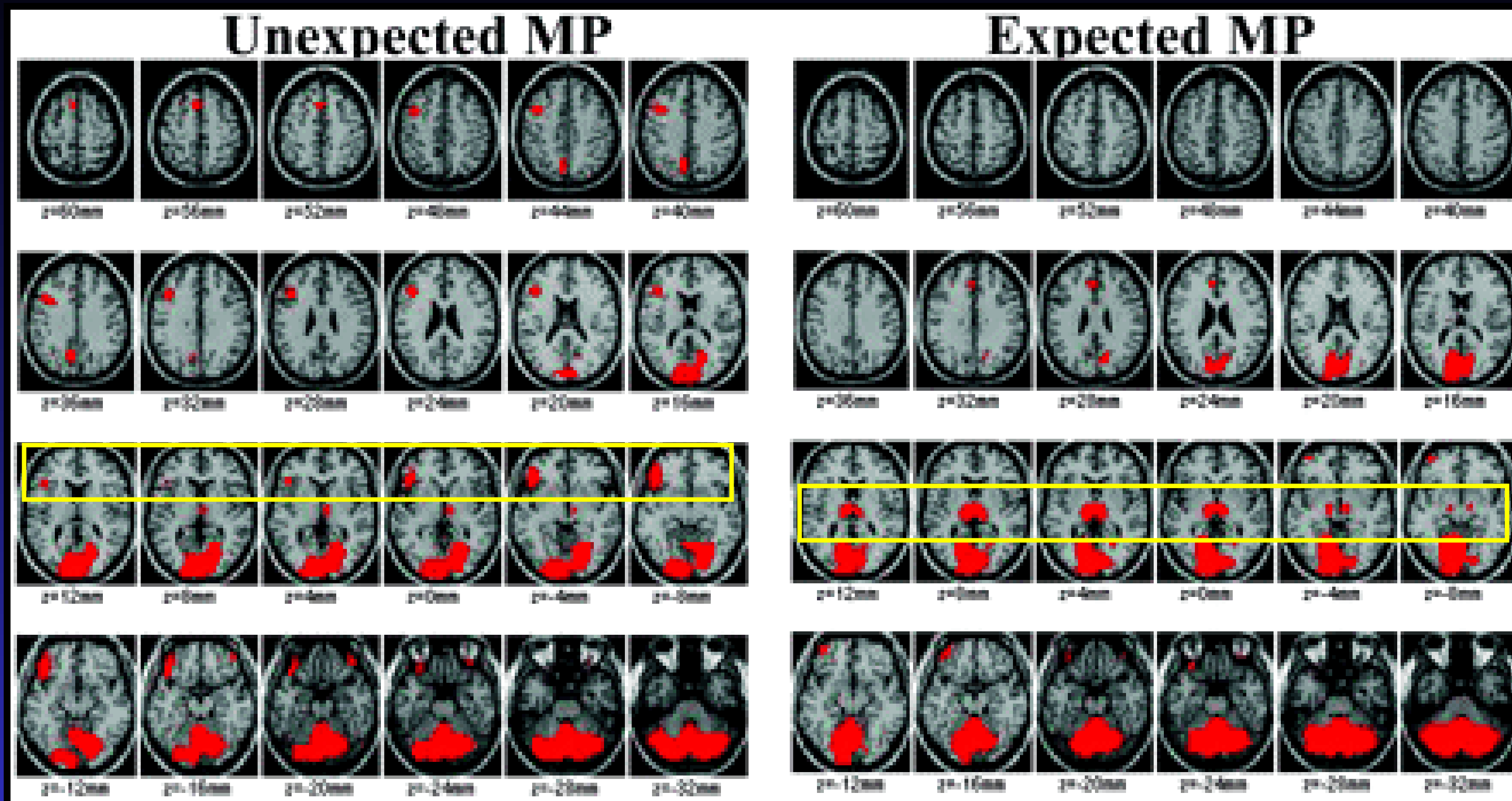




Increases in Metabolism Were About 50% Larger When MP Was Expected Than Unexpected

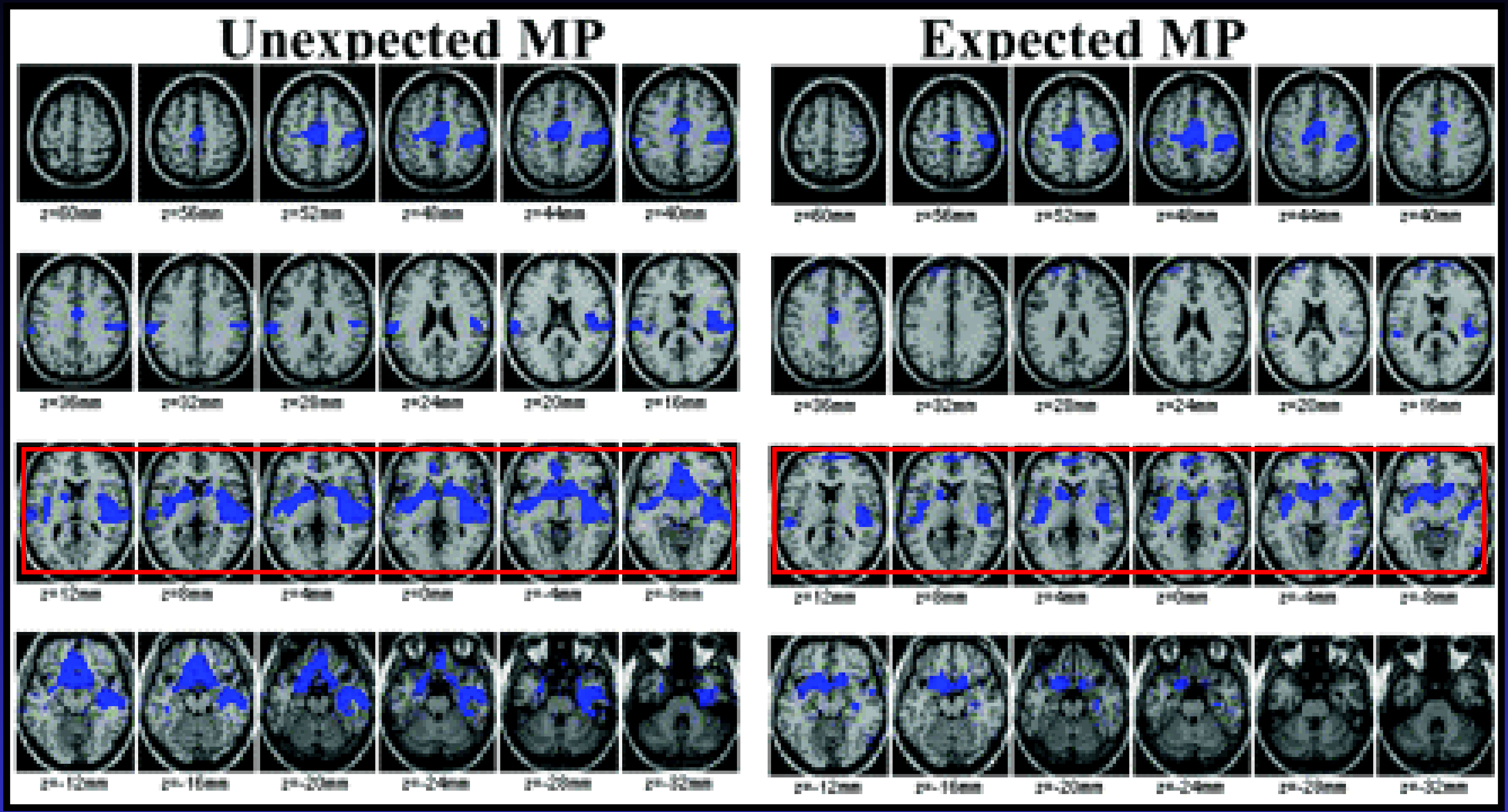
"High" Was About 50% Greater When MP Was Expected Than Unexpected

Source: Volkow, ND et al., Journal of Neuroscience, 23, pp. 11461-11468, December 2003.



Brain maps obtained with SPM after normalization for the global metabolic increases to reveal the areas where MP induced the largest increases in metabolism both for unexpected and expected MP (areas in red). Comparisons are with the "expected placebo received placebo" condition, and significance was set at $p < 0.005$. <u>Note that the largest increases with MP occurred in cerebellum, occipital cortex, and thalamus. Note also the much larger areas of activation in thalamus for expected MP and in lateral orbitofrontal cortex for unexpected MP</u>

From: Volkow et al., 2003



Brain maps obtained with SPM after normalization for the global metabolic increases to reveal the areas where MP induced relative decreases in metabolism for both unexpected and expected MP (areas in blue). Comparisons are with the expected placebo received placebo condition, and significance was set at *p* < 0.005. <u>Note the relative decreases for both conditions in limbic regions (NAc, Brodmann area 25, insula, amygdala) and in motor cortices</u>

From: Volkow et al., 2003

F. Nava, 2005

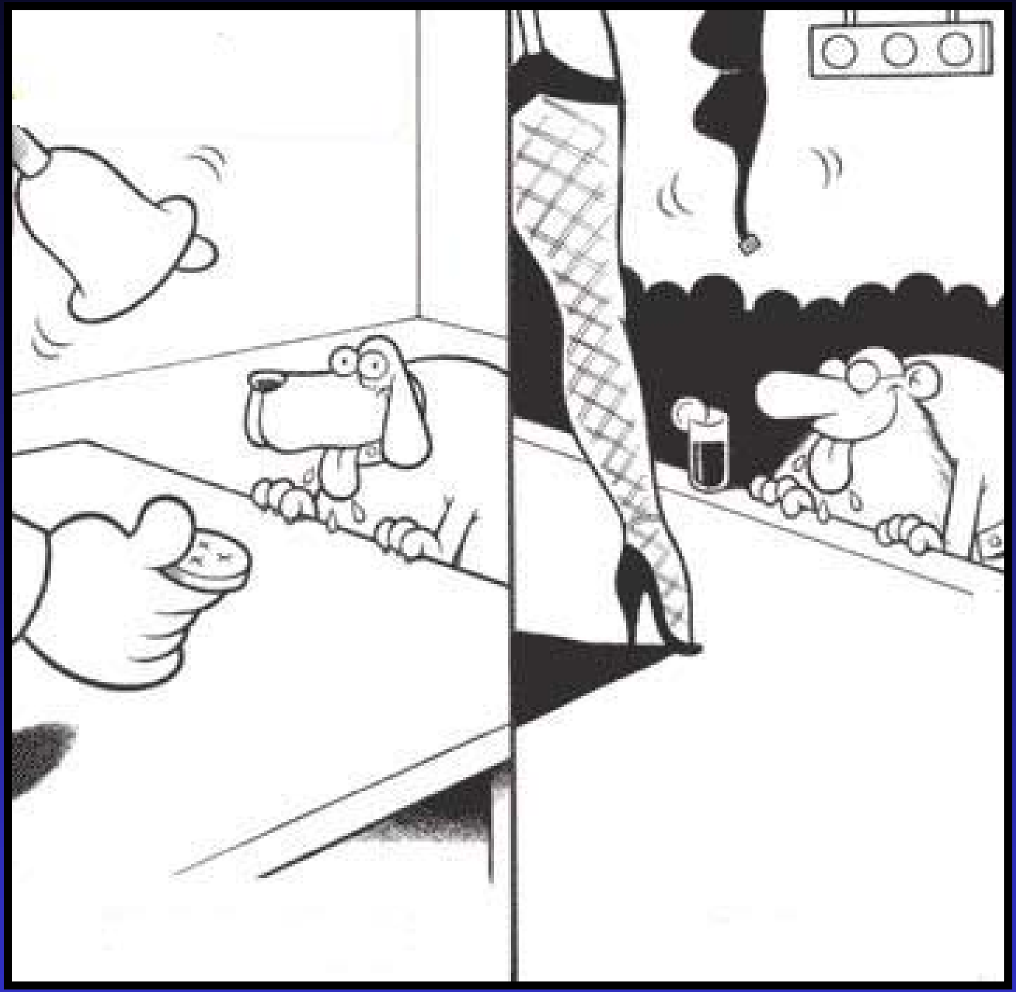
Sostanza attesa = Attività Talamo =
Risposta Condizionata in Risposta allo Stimolo Gratificante

Sostanza non attesa = Attività Corteccia Orbitofrontale =
Riconoscimento “Cognitivo Incentivo” della Sostanza

F. Nava, 2005

Studi di neuroimaging: contributi

- ✓ Il ruolo della dopamina negli effetti gratificanti indotti dagli stimoli primari e delle sostanze d'abuso
- ✓ La distinzione neurobiologica fra desiderio e effetti gratificanti
- ✓ L'implicazione di diverse aree cerebrali nei fenomeni di intossicazione, dipendenza ed astinenza
- ✓ La dipendenza come apprendimento appreso
- ✓ Il *craving* come memoria del piacere
- ✓ Il legame fra *craving* e disforia



F. Nava, 2005

Neuroimaging in Humans

- Three types of craving
  - Drug-induced
  - Cue-induced
  - Withdrawal

Drug-induced Craving

Structure	Possible function
Mesocorticolimbic pathway (NAcc, SCC, medial OFC)	Reward / Motivation
+/- Amygdala	Memory / Learning

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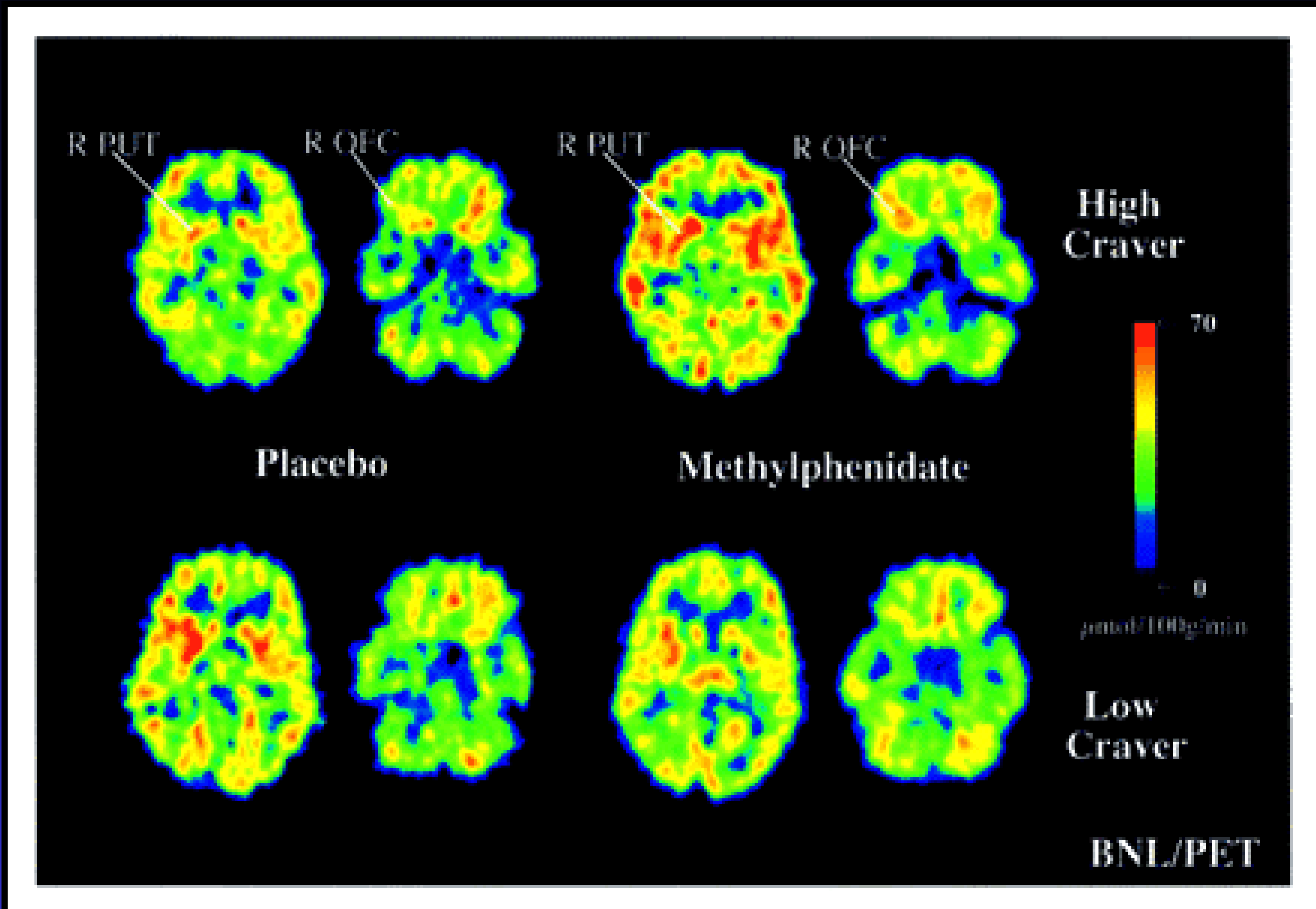


Volkow and Fowler et al., 2000

F. Nava, 2005

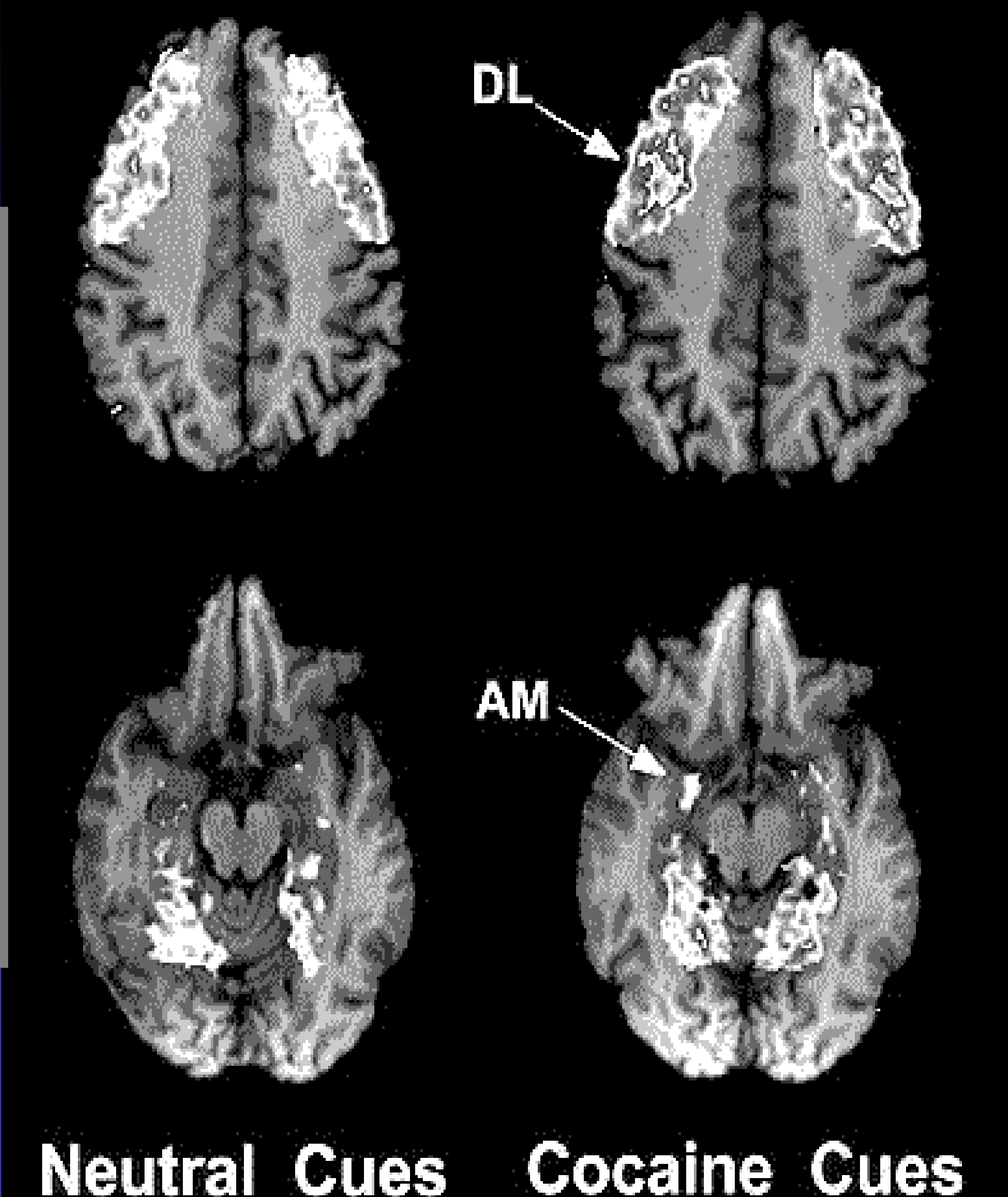
Cue-induced Craving

Structure	Possible function
Prefrontal cortex	Executive function
Lateral OFC	Inhibition / planning
Amygdala	Associative learning
Mesocorticolimbic pathway	Reward / motivation

F. Nava, 2005

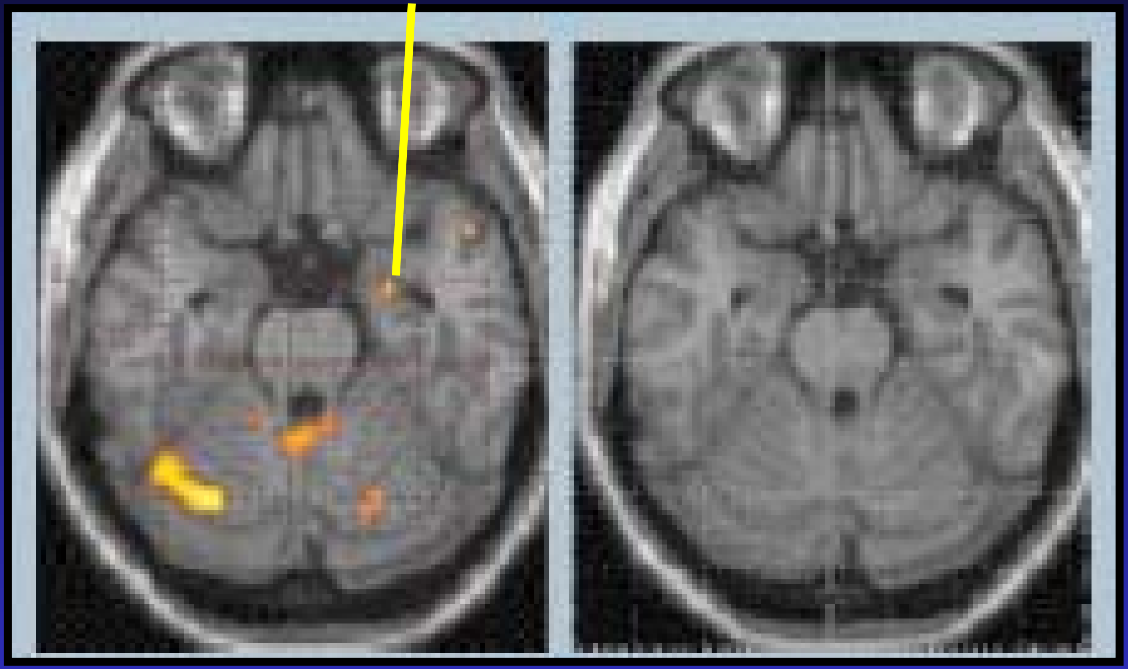
Regional increases in cerebral glucose metabolism associated with cocaine craving

Grant et al (1996) *Proc. Natl. Acad. Sci. USA*, **93**:12040-12045



F. Nava, 2005

Amygdala Activation to Ethanol Cues Before and After Treatment



Before treatment After treatment

Schneider et al, 2001

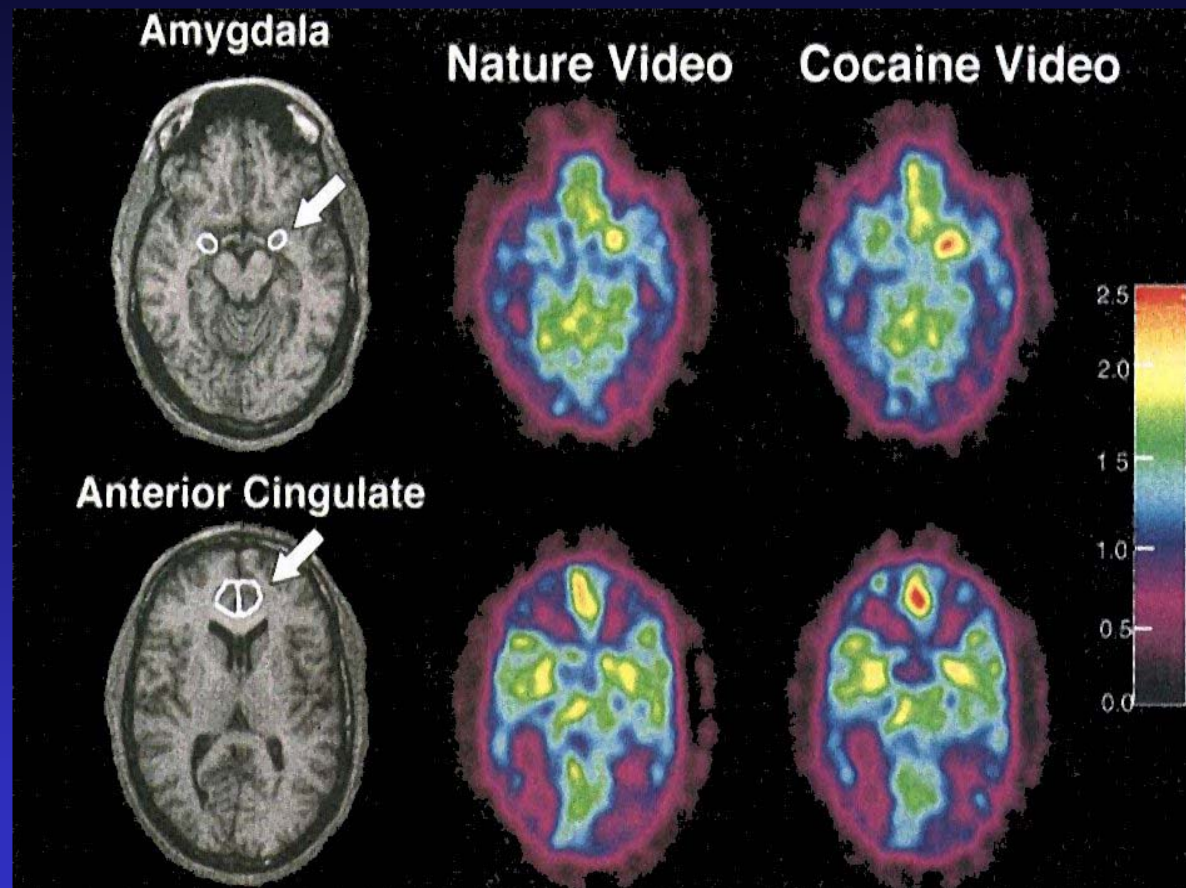
F. Nava, 2005

Changes in rCBF in response to cocaine related stimulus in detoxified users

Increase in rCBF in anterior cingulate gyrus and amygdala

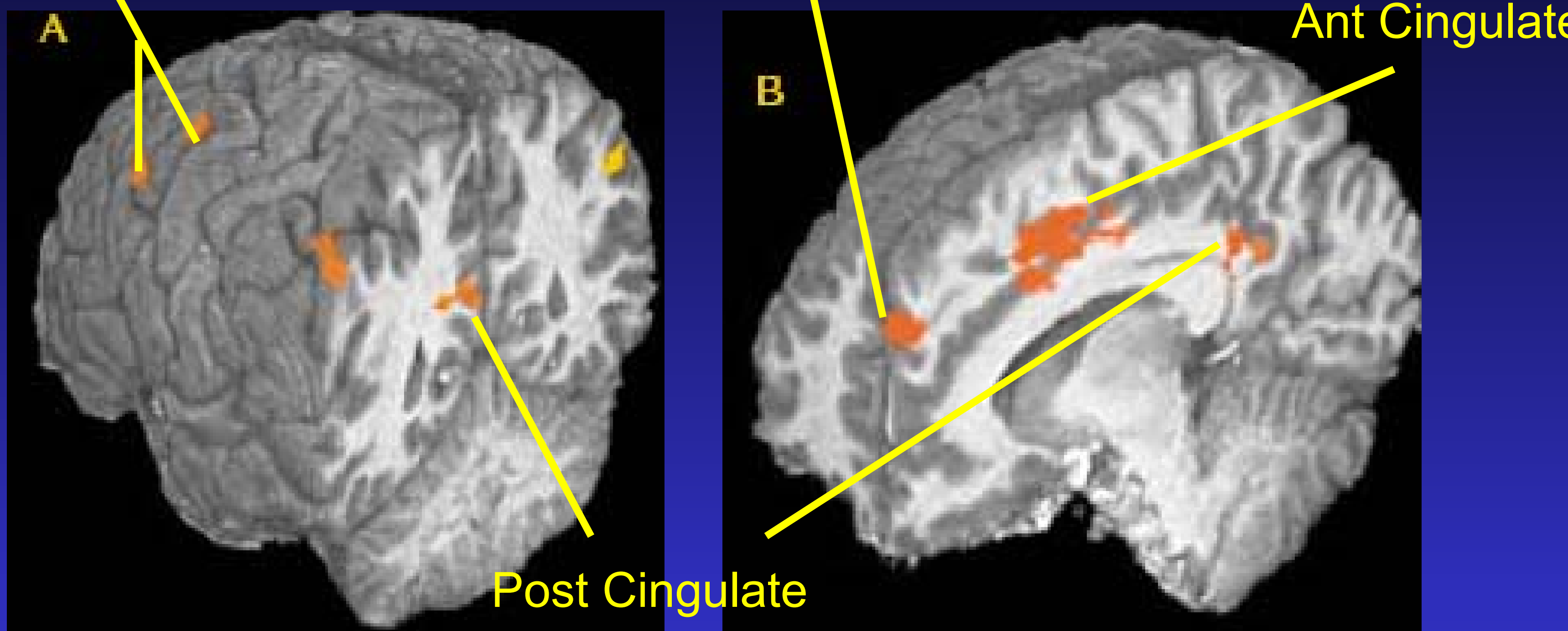
Video stimuli of cocaine related images or nature video

Changes also found in temporal pole and orbito-frontal cortex



Childress et al. 1999

Cue-induced Craving Associated ↑ in BOLD fMRI



Garavan et al, 2000

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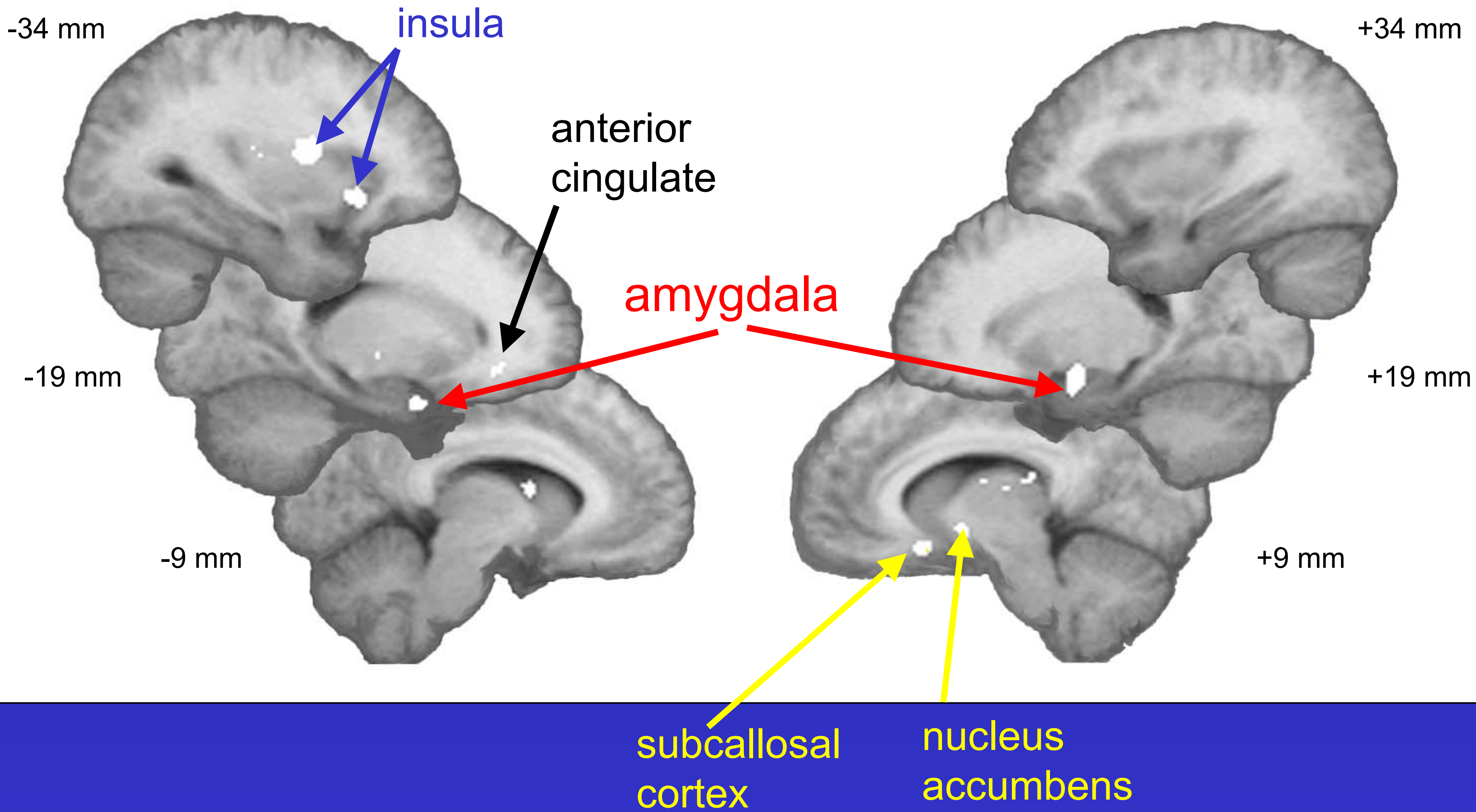
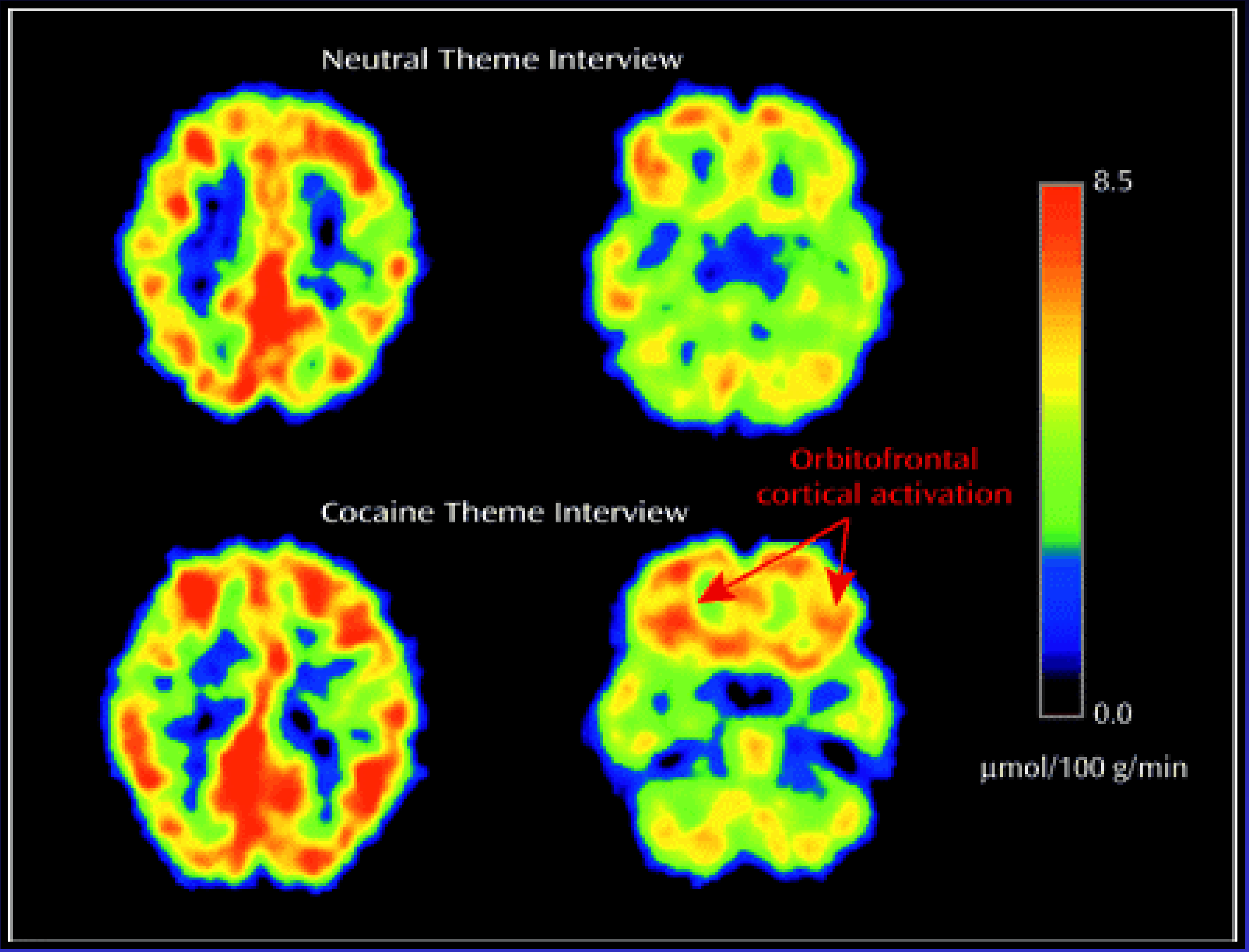
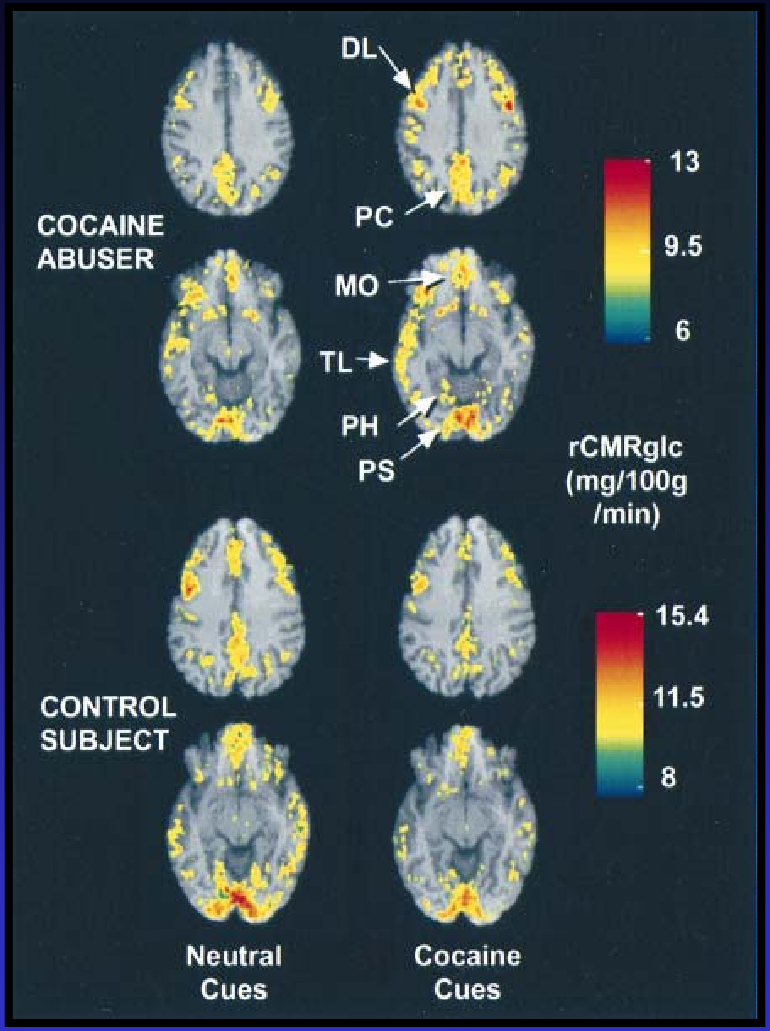
Neural Correlates of Cocaine Cue-induced Craving

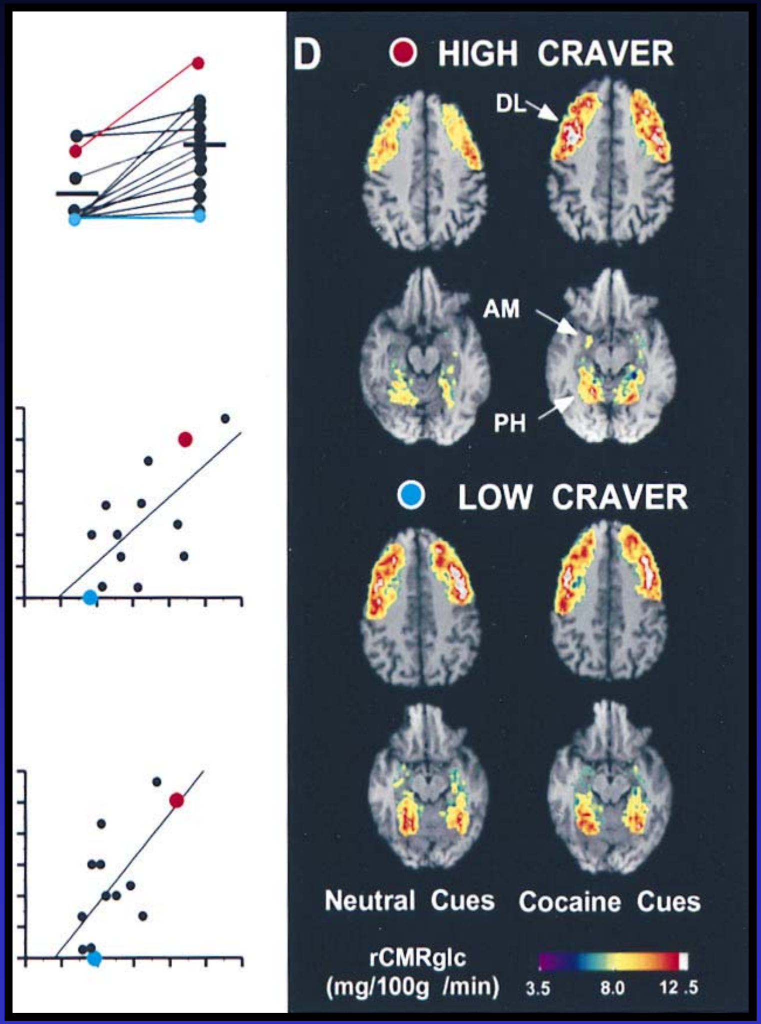


F. Nava, 2005



Goldstein and Volkow, 2002





Grant et al., 1996

F. Nava, 2005

Withdrawal-induced Craving

Structure	Possible function
Anterior Cingulate	Stimuli Perception
+/- Amygdala	Memory / Learning

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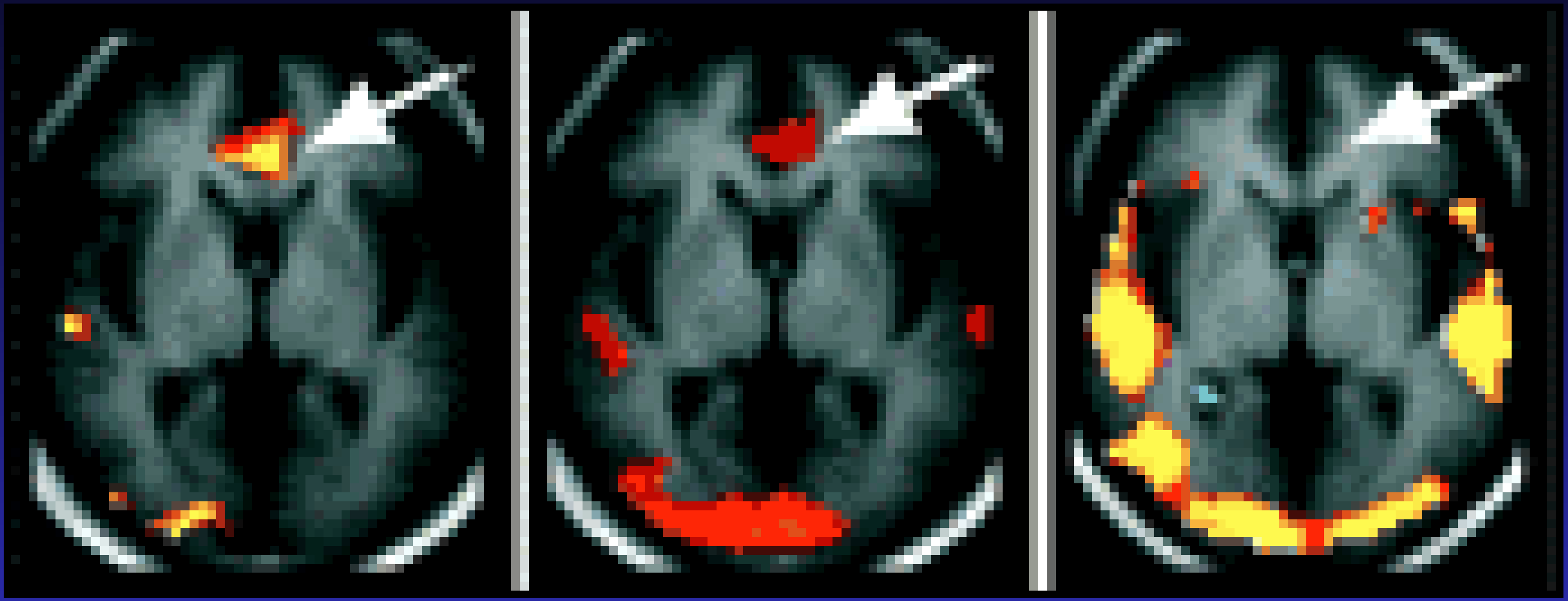
Anterior cingulate activation : fMRI of cocaine cue exposure & craving

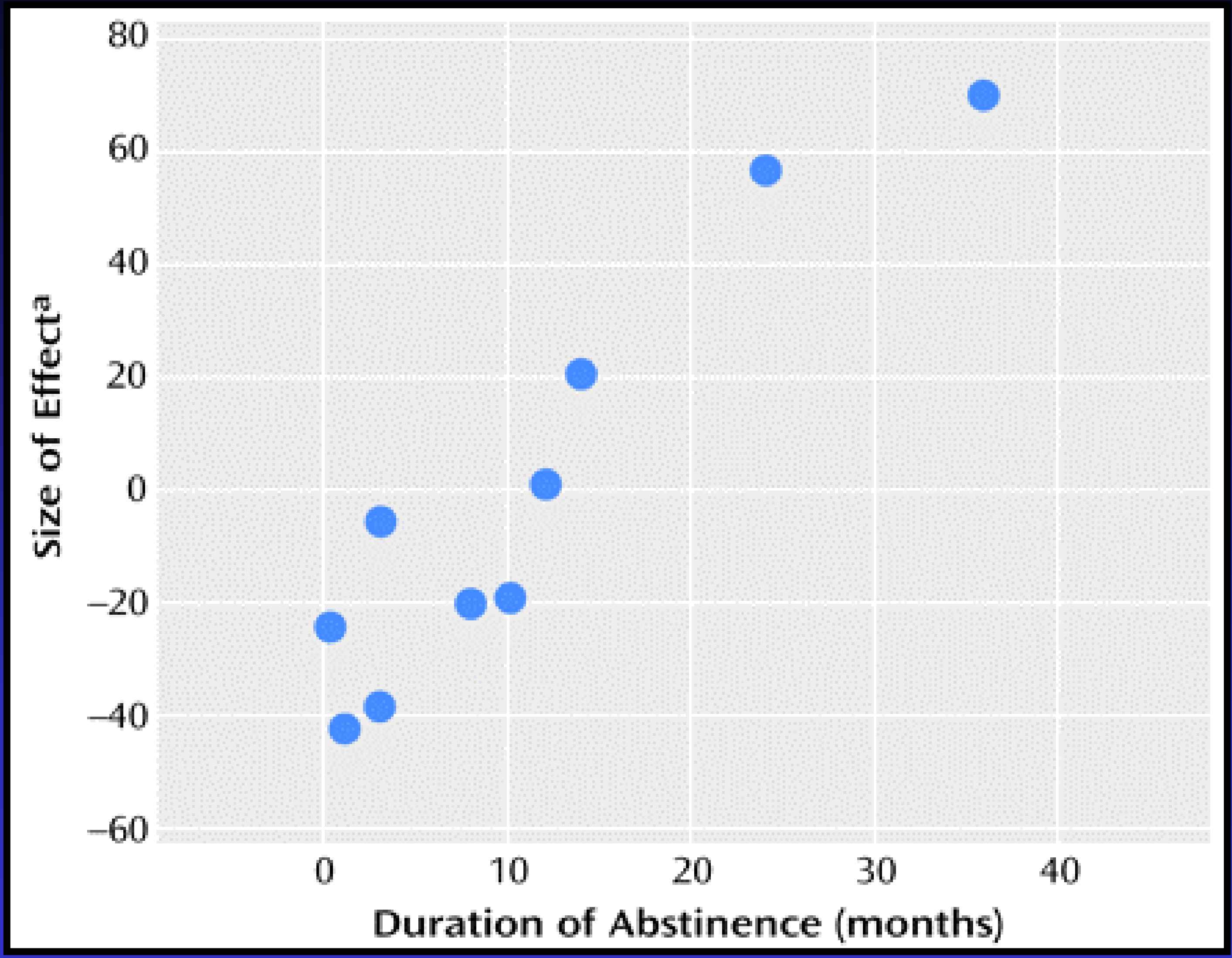


Pts : + craving | Pts : no craving | Controls

Activation of anterior cingulate cortex is seen in abstinent cocaine addicts at the start of watching a ‘cocaine video’ *before* and whether or not they experienced craving

Wexler et al. 2001

Activation in the anterior cingulate cortex is related to duration of abstinence



F. Nava, 2005

Daglish et al 2001

Drug-induced vs Cue-induced Craving vs Withdrawal-Induced Craving

Drug-induced	Cue-induced	Withdrawal-induced
Mesocorticolimbic pathway	**Mesocorticolimbic pathway**	**Anterior Cingulate**
(+/-) Amygdala	Amygdala	(+/-) Amygdala
	Prefrontal cortex	

F. Nava, 2005

Studi di neuroimaging: contributi

- ✓ **Il ruolo della dopamina negli effetti gratificanti indotti dagli stimoli primari e delle sostanze d’abuso**
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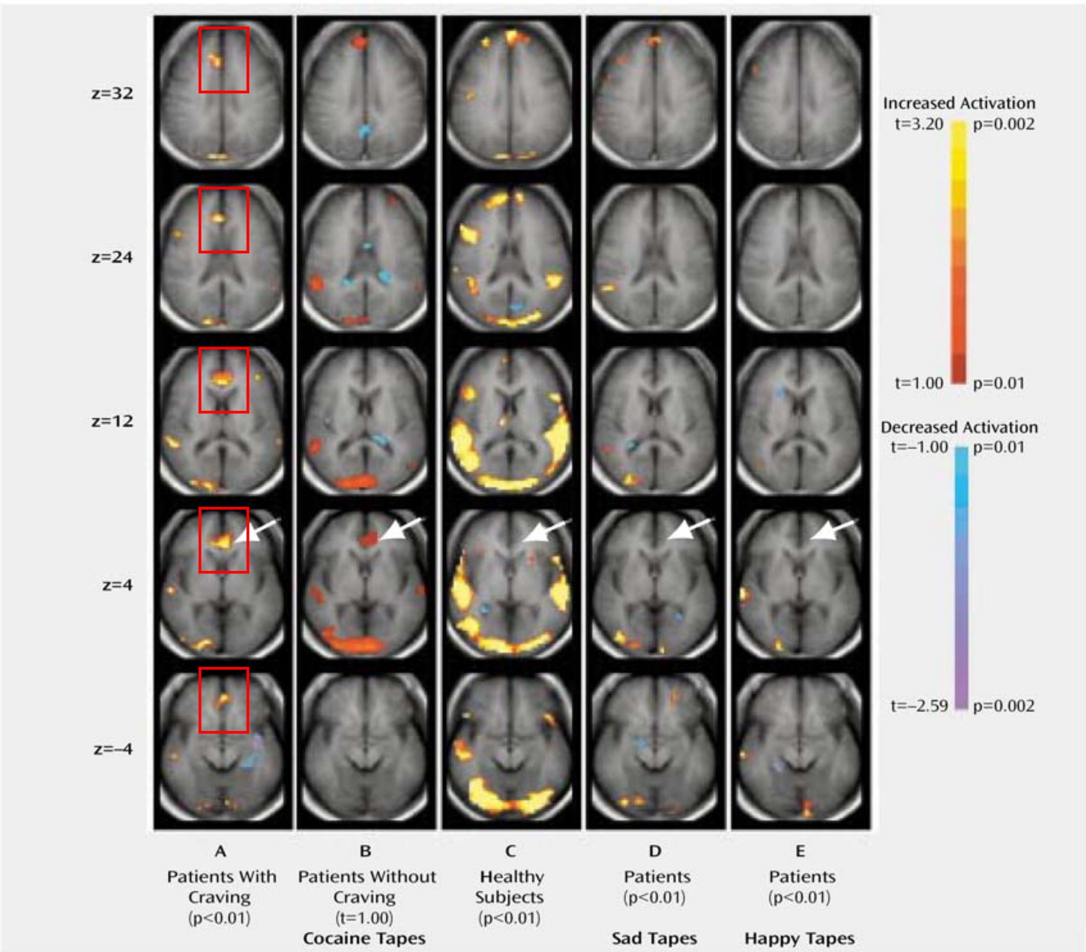
- ✓ **L’implicazione di diverse aree cerebrali nei fenomeni di intossicazione, dipendenza ed astinenza**
- ✓ **La dipendenza come apprendimento appreso**
- ✓ **Il *craving* come memoria del piacere**
- ✓ **Il legame fra *craving* e disforia**

Initial videotape viewing

FIGURE 2. fMRI Images Comparing Regional Brain Activations During Initial Videotape Viewing and at Baseline in 11 Cocaine-Dependent Patients and 20 Healthy Comparison Subjects Who Watched Videotapes Designed to Evoke Cocaine Craving, Happiness, and Sadness[a]



[a] The epochs involved are defined in Figure 1; the images represent emotion 0 minus baseline 1. The numbers of patients and healthy subjects varied among tapes. The z values indicate the distance in millimeters below or above the plane of the anterior and posterior commissures. The arrows point to anterior cingulate activity in cocaine addicts watching cocaine-cue tapes and the absence of such activity in all other conditions. The left hemisphere is on the right side of each image. The p values on the color bars refer to columns A, C, D, and E; t values refer to column B. See text for details of the data analysis.

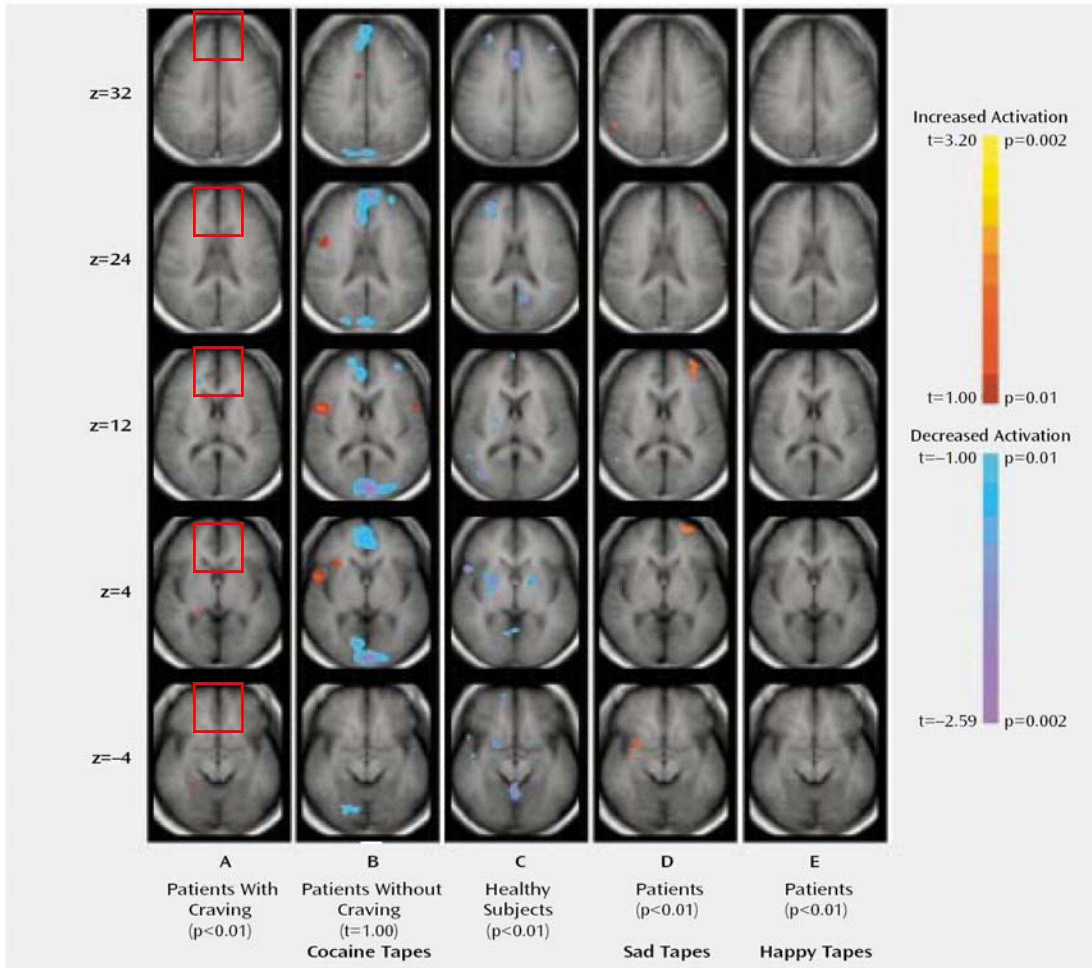
Robust activation of the anterior cingulate was evident in patients watching cocaine tapes but not in patients whacting happy or sad tapes or in healthy subjects under any condition. Anterior cingulate activation preceded the reported onset of craving and was evident in patients who did not report craving

Wexler et al., 2001

F. Nava, 2005

Videotape viewing

FIGURE 3. fMRI Images Comparing Regional Brain Activations During Initial Self-Reported Craving or Emotional Response and in Immediately Preceding Period in 11 Cocaine-Dependent Patients and 20 Healthy Comparison Subjects Who Watched Videotapes Designed to Evoke Cocaine Craving, Happiness, and Sadness[a]



[a] The epochs involved are defined in Figure 1; the images represent emotion 1 minus emotion 0. The numbers of patients and healthy subjects varied among tapes. The z values indicate the distance in millimeters below or above the plane of the anterior and posterior commissures. The left hemisphere is on the right side of each image. The p values on the color bars refer to columns A, C, D, and E; t values refer to column B. See text for details of the data analysis.

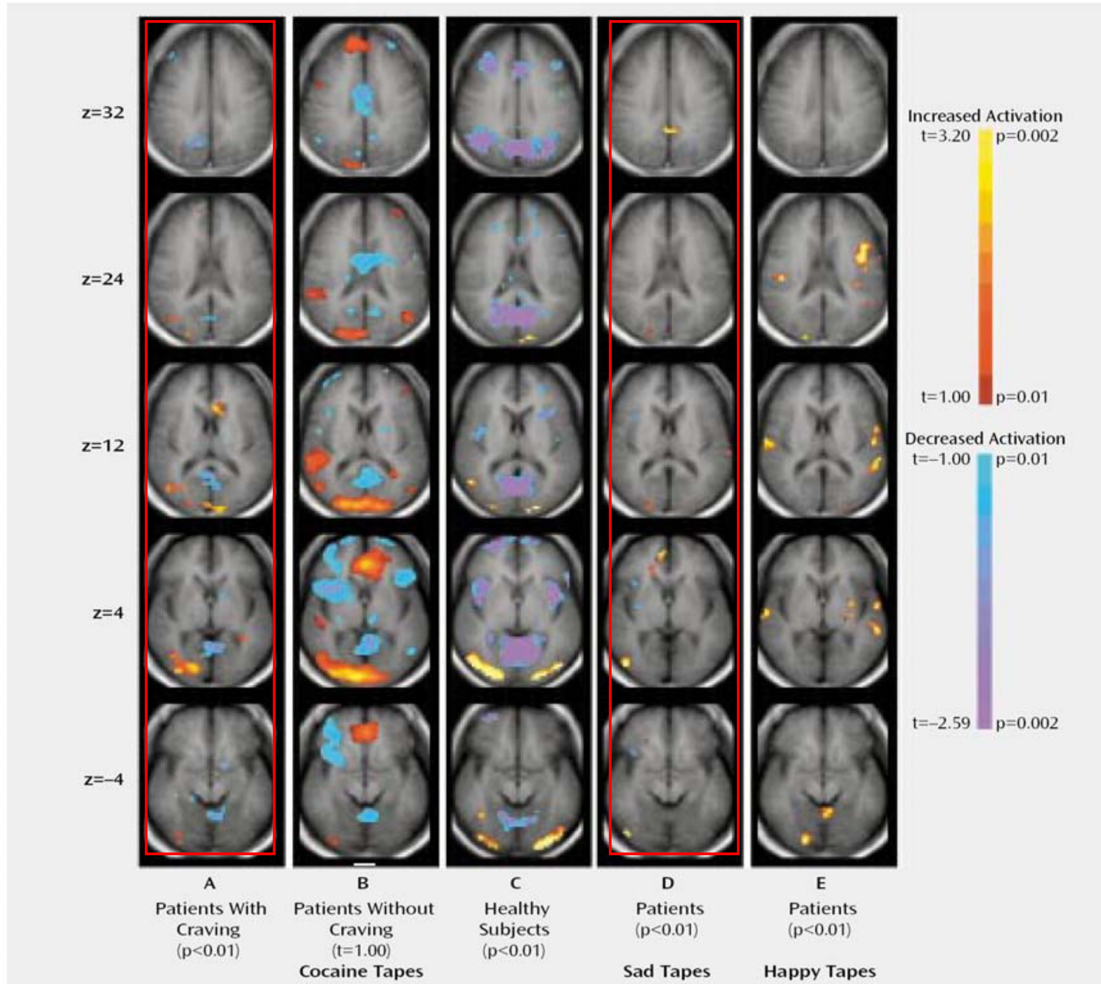
Patients with craving showed less activation than healthy subjects during cocaine-cue tapes in areas of the frontal lobes

F. Nava, 2005

Wexler et al., 2001

End of videotape viewing

FIGURE 4. fMRI Images Comparing Regional Brain Activations at the End of Videotape Viewing and at the Posttape Baseline in 11 Cocaine-Dependent Patients and 20 Healthy Comparison Subjects Who Watched Videotapes Designed to Evoke Cocaine Craving, Happiness, and Sadness[a]



[a] The epochs involved are defined in Figure 1; the images represent emotion 2 minus baseline 2. The numbers of patients and healthy subjects varied among tapes. The z values indicate the distance in millimeters below or above the plane of the anterior and posterior commissures. The left hemisphere is on the right side of each image. The p values on the color bars refer to columns A, C, D, and E; t values refer to column B. See text for details of the data analysis.

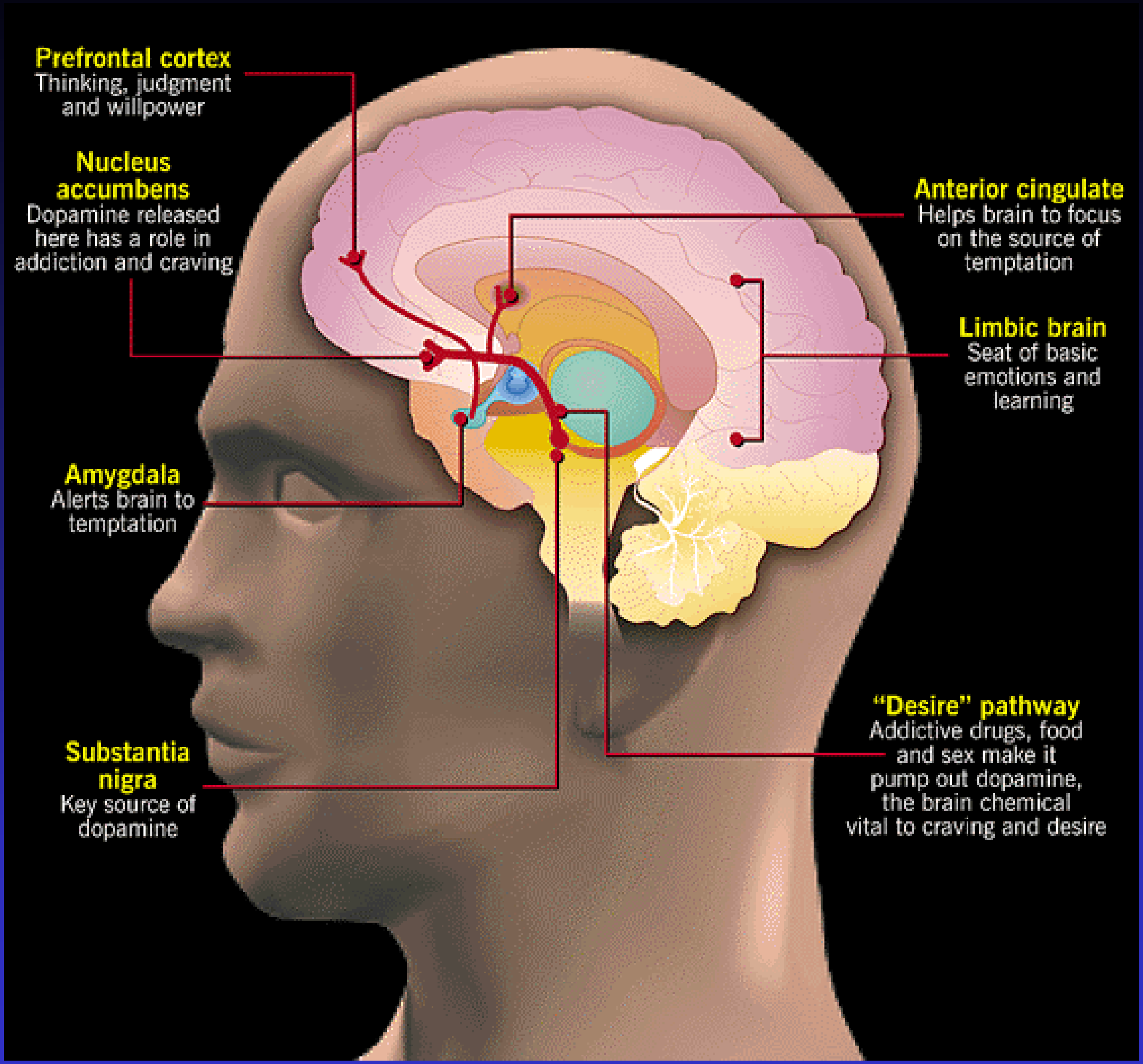
After the reported onset of craving, cocaine-dependent subjects showed greater activity than healthy subjects In regions that are more activein healthy subjects when they wacht sad tapes, suggesting a physiologic link between cocaine-cue and normal dysphoric state

Wexler et al., 2001

F. Nava, 2005

Craving is associated
with normal dysphoric state in addicts

F. Nava, 2005



Prefrontal cortex
Thinking, judgment and willpower
Nucleus accumbens
Dopamine released here has a role in addiction and craving
Anterior cingulate
Helps brain to focus on the source of temptation
Limbic brain
Seat of basic emotions and learning
Amygdala
Alerts brain to temptation
"Desire" pathway
Addictive drugs, food and sex make it pump out dopamine, the brain chemical vital to craving and desire
Substantia nigra
Key source of dopamine

F. Nava, 2005