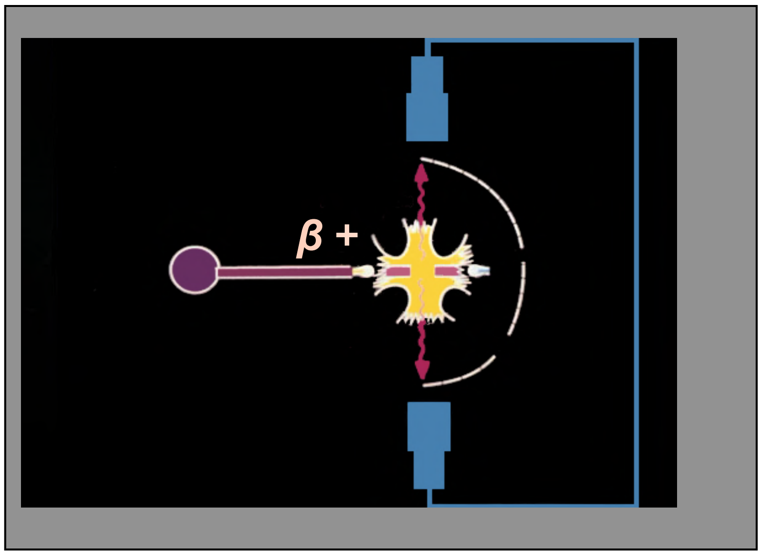
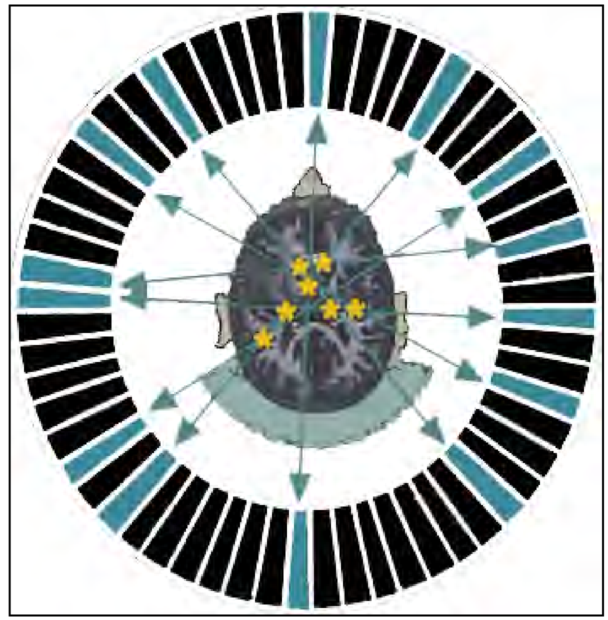
Principles of Neuroimaging

Positron Emission Tomography (PET) Applications

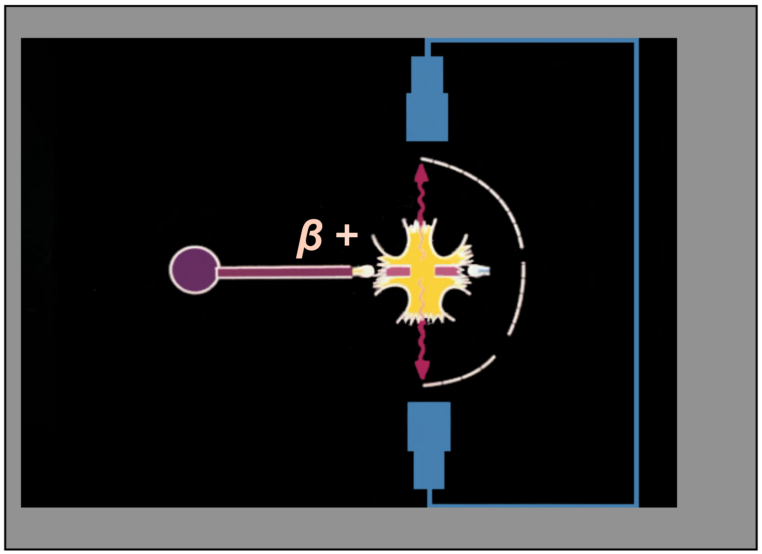




Edythe D. London, Ph.D.
elondon@mednet.ucla.edu
310-825-0606
Semel Institute C8-831

What is Positron Emission Tomography (PET)?

Tomograph is a picture of a slice

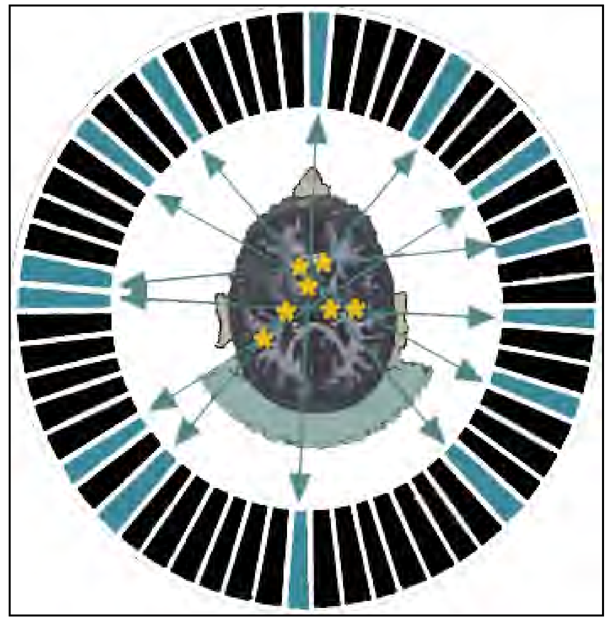


Positron emission:

• Positron leaves atomic nucleus.

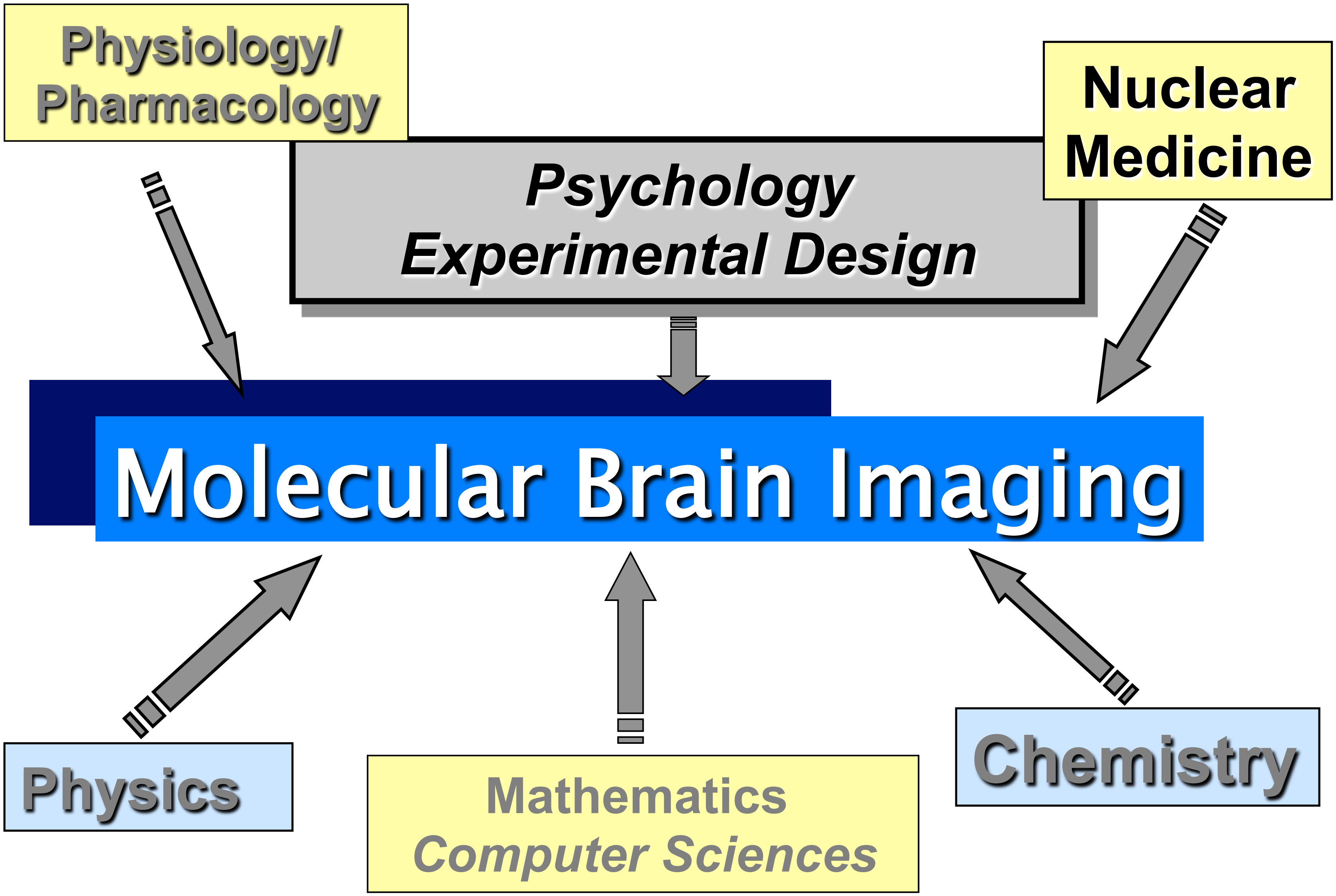
• Annihilation of positron and electron.

•Coincidence events detected



Computer system reconstructs image of annihilations.

This shows where radioactive tracer accumulated.


Physiology/
Pharmacology
Psychology
Experimental Design
Nuclear
Medicine
Molecular Brain Imaging
Physics
Mathematics
Computer Sciences
Chemistry

Goals of Molecular Imaging

Research:

Figure out how the brain works.

What circuits are activated or de-activated?

Characterize illness.

What circuits? What transmitter systems?

Advance treatment.

Rational basis to design therapies.

Evaluate treatments.

Clinical:

Diagnosis & evaluation of disease progression/recovery

What Can You Measure?

What Can You Measure?

- Indices of regional brain function:

  blood flow, glucose metabolism, O_2 *metabolism*

What Can You Measure?

- Indices of regional brain function:

  blood flow, glucose metabolism, O_2 *metabolism*
- Proteins of interest:

  neurotransmitter receptors, transporters

What Can You Measure?

- Indices of regional brain function:

  blood flow, glucose metabolism, O_2 *metabolism*
- Proteins of interest:

  neurotransmitter receptors, transporters, enzymes, inflammation
- Pharmacokinetics:

  occupancy or relevant receptors by medications

What Can You Measure?

- Indices of regional brain function:

  blood flow, glucose metabolism, O_2 metabolism
- Proteins of interest:

  neurotransmitter receptors, transporters, enzymes, inflammation
- Pharmacokinetics:

  occupancy or relevant receptors by medications
- Neurotransmitter release

What Can You Measure?

- Indices of regional brain function:

  blood flow, glucose metabolism, O_2 metabolism
- Proteins of interest:

  neurotransmitter receptors, transporters, enzymes, inflammation
- Pharmacokinetics:

  occupancy or relevant receptors by medications
- Neurotransmitter release
- Neurotransmitter turnover

What Can You Measure?

- Indices of regional brain function:
  blood flow, glucose metabolism, O_2 metabolism
- Proteins of interest:
  neurotransmitter receptors, transporters, enzymes, inflammation
- Pharmacokinetics:
  occupancy or relevant receptors by medications
- Neurotransmitter release
- Neurotransmitter turnover
- Dynamic changes in neurotransmitter function with cognition?

What Can You Measure?

- Indices of regional brain function:
  blood flow, glucose metabolism, O_2 metabolism
- Proteins of interest:
  neurotransmitter receptors, transporters
- Pharmacokinetics:
  occupancy or relevant receptors by medications
- Neurotransmitter release
- Neurotransmitter turnover
- Dynamic changes in neurotransmitter function with cognition *– to some extent*

PET vs. SPECT

PET – decay by emission of positrons

(photons released as byproducts)

short-lived isotopes – cannot be shipped

O-15 (2 min) C-11 (20 min)

F-18 (110 min)

Br-76 (16.2 h), N-13 (9.97 min)

advantage of C-11-- many compounds possible

SPECT – decay by single photons

long-lived isotopes – can be shipped

I-123 (13.3 h), TC-99m (6.01 h), In-111(67 h)

more commonly used clinically

SPECT Tracers

Cerebral Blood flow:

[Tc-99m]HMPAO, [I-123]Iodoamphetamine

D2-like Dopamine Receptor:

[I-123]Iodobenzamide, [I-123]epidipride

Dopamine transporter:

*[I-123]*β-CIT, *[Tc-99m]TRODAT*

Serotonin transporter:

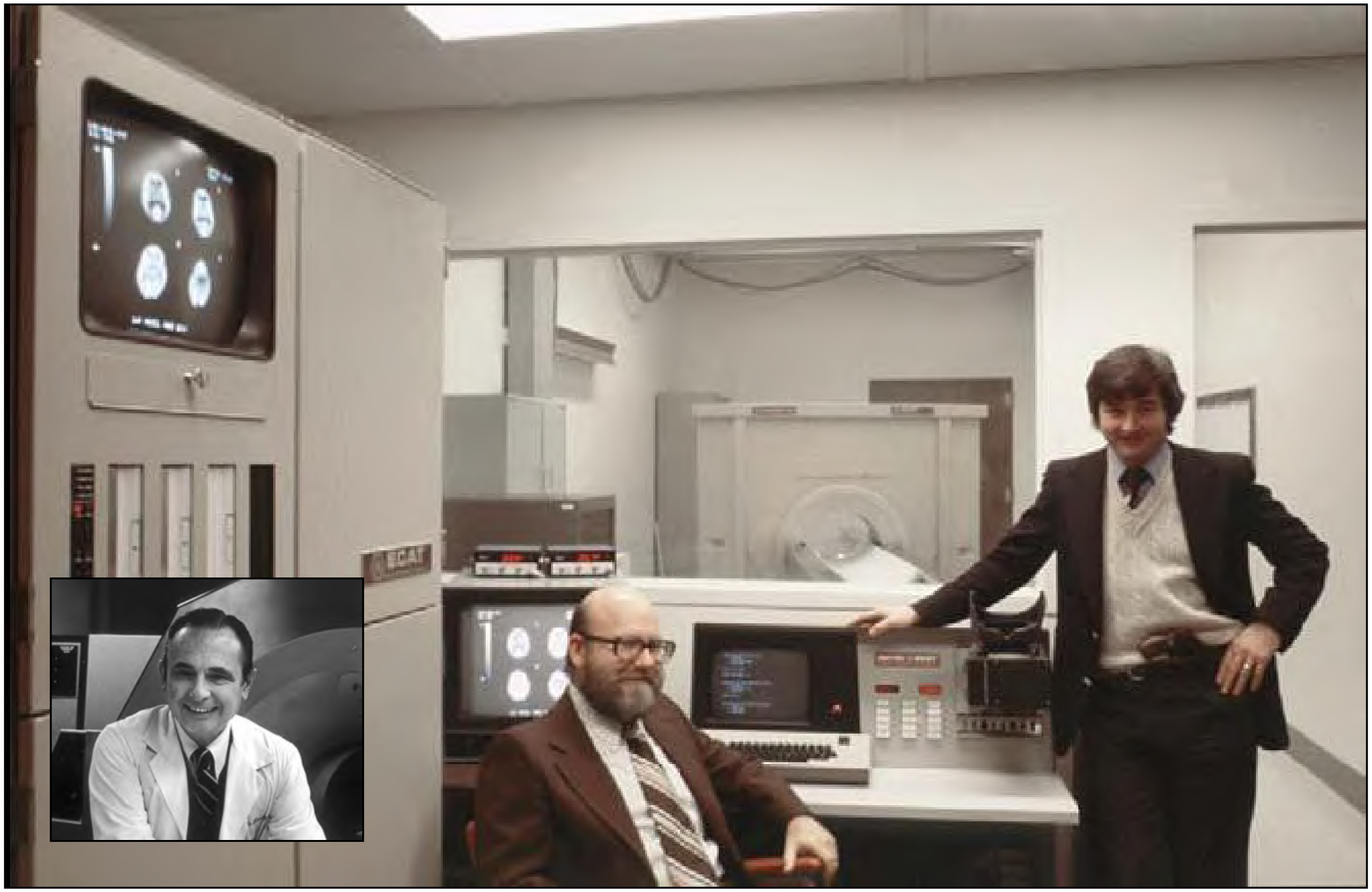
*[I-123]ADAM, [I-123]*β-CIT

Nicotinic Acetylcholine Receptor

[I-123]5-Iodo-A-85380

Development of PET

PET III built in 1974 - Washington University

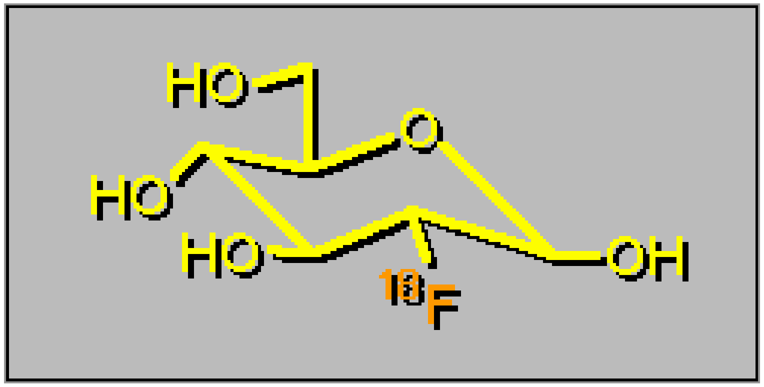


M. Ter-Pogossian　　　　**E.** Hoffman　　　　M. Phelps

Functional Imaging with PET

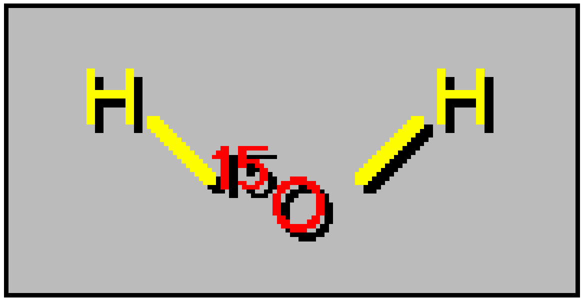
The brain uses glucose and O2 for energy.

Cerebral Glucose Metabolism



[F-18]fluorodeoxyglucose

Cerebral Blood Flow



[O-15]Water

Used less often:

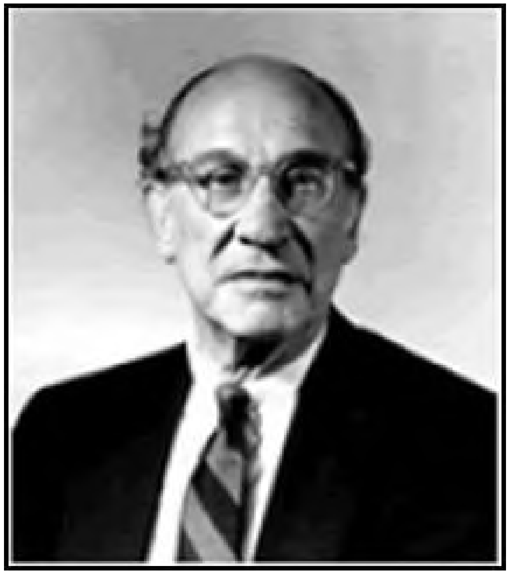
O-15 --*oxygen metabolism*

[C-11]O -- c*erebral blood volume*

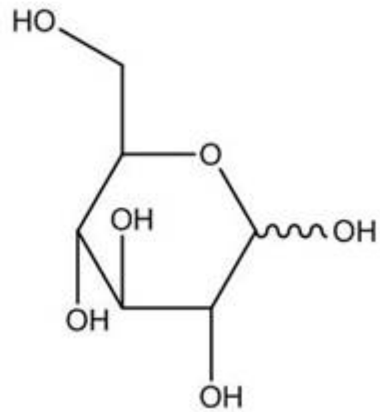
[C-11]acetate – *brain tumors*

Beginning of Functional Brain Imaging

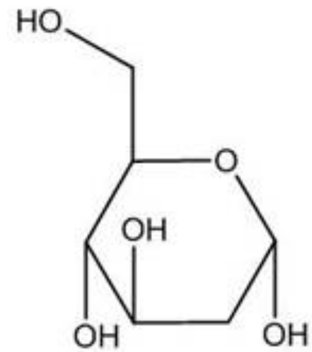
The Deoxyglucose Method 1977



L. Sokoloff



D-glucose

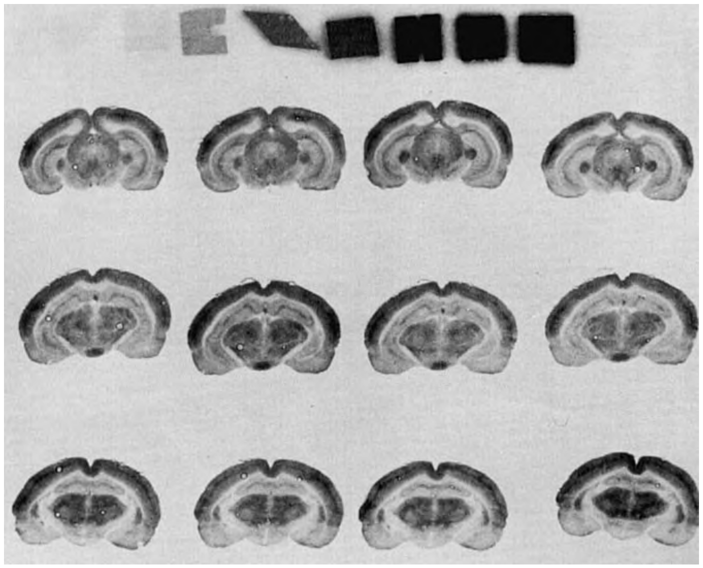


2-deoxy-D-glucose

THE [^{14}C]DEOXYGLUCOSE METHOD FOR THE MEASUREMENT OF LOCAL CEREBRAL GLUCOSE UTILIZATION: THEORY, PROCEDURE, AND NORMAL VALUES IN THE CONSCIOUS AND ANESTHETIZED ALBINO RAT

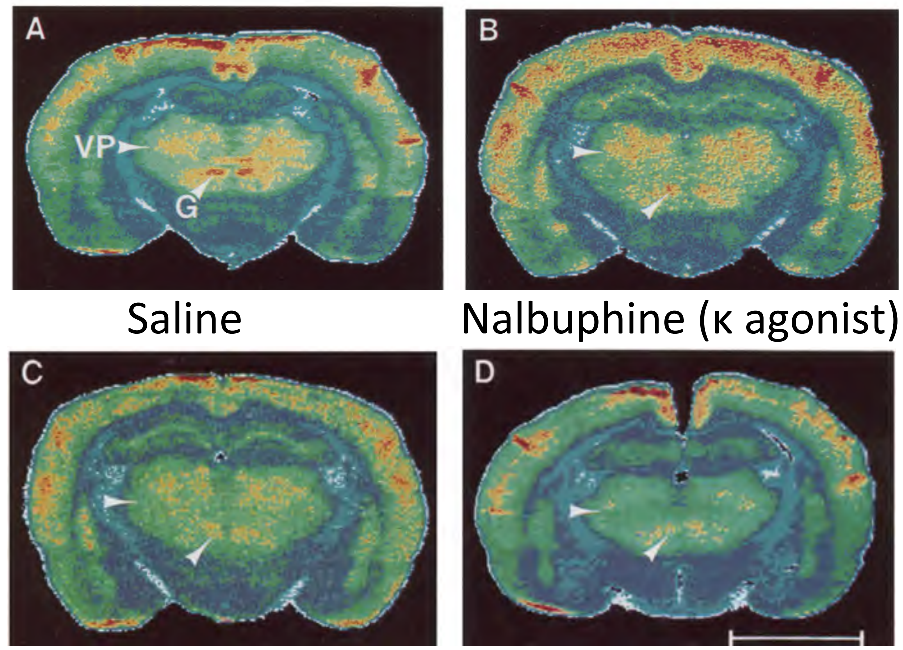
L. Sokoloff, M. Reivich, C. Kennedy, M.H. Des Rosiers, C.S. Patlak, K Pettigrew, O. Sakurada and M. Shinohara.
J. Neurochemistry, 1977

Quantitative Autoradiography Preceded PET



L. Sokoloff et al., 1977

Opioid Agonist Effects in Thalamus



Saline | Nalbuphine (κ agonist)

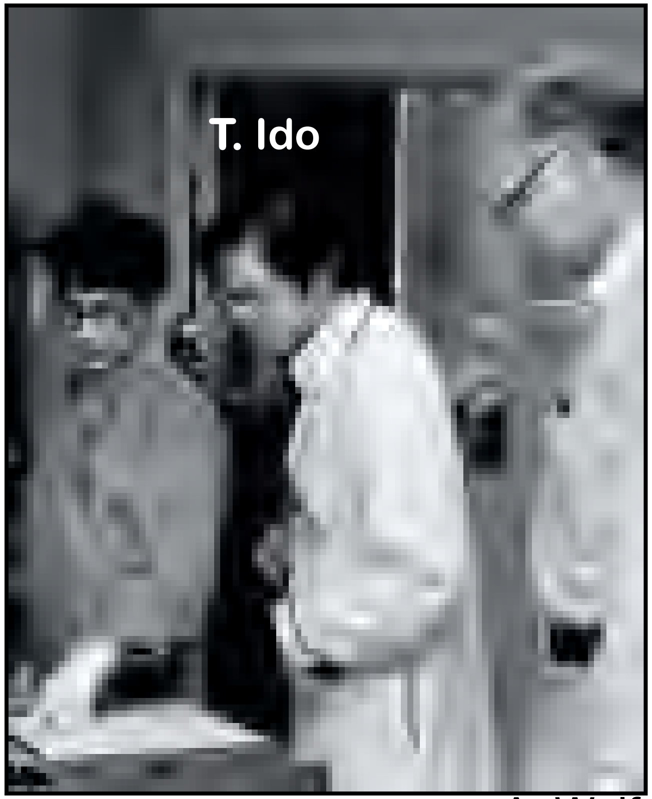
Morphine (μ agonist) | Oxymorphone (μ agonist)

V= ventral posterior n.
G = gelatinosus n.

RF Fanelli et al., 1987

Adapting the Deoxyglucose Method for PET

[^{18}F]Fluorodeoxyglucose Synthesis 1976

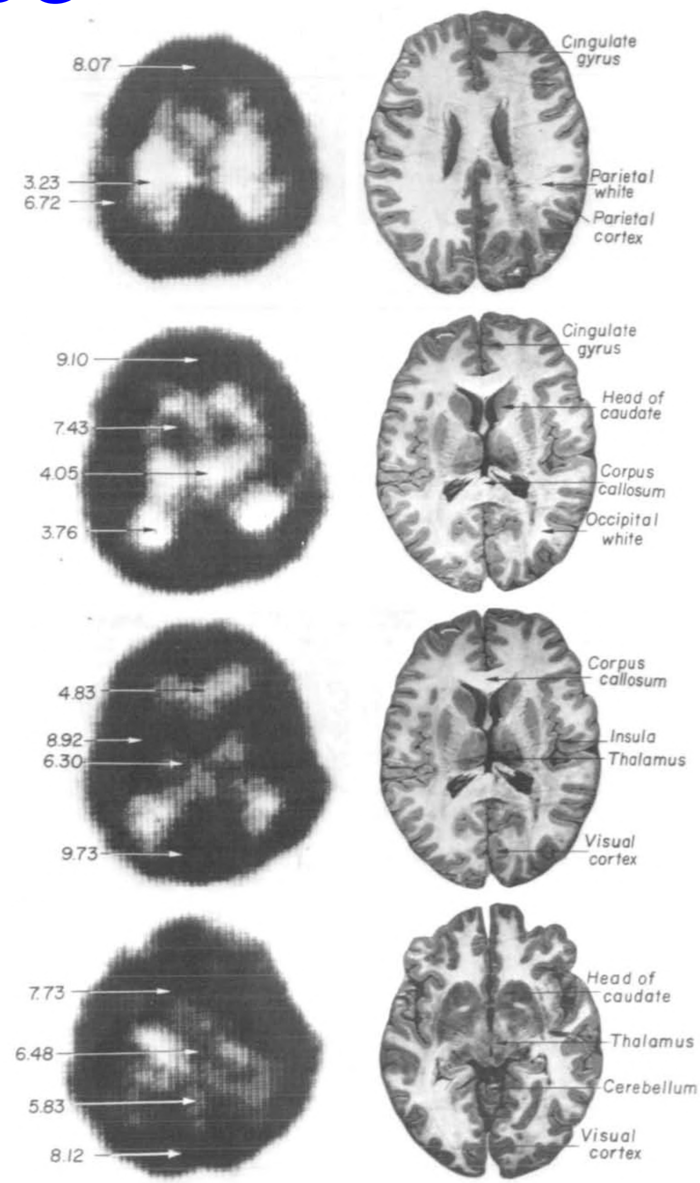


A. Wolf

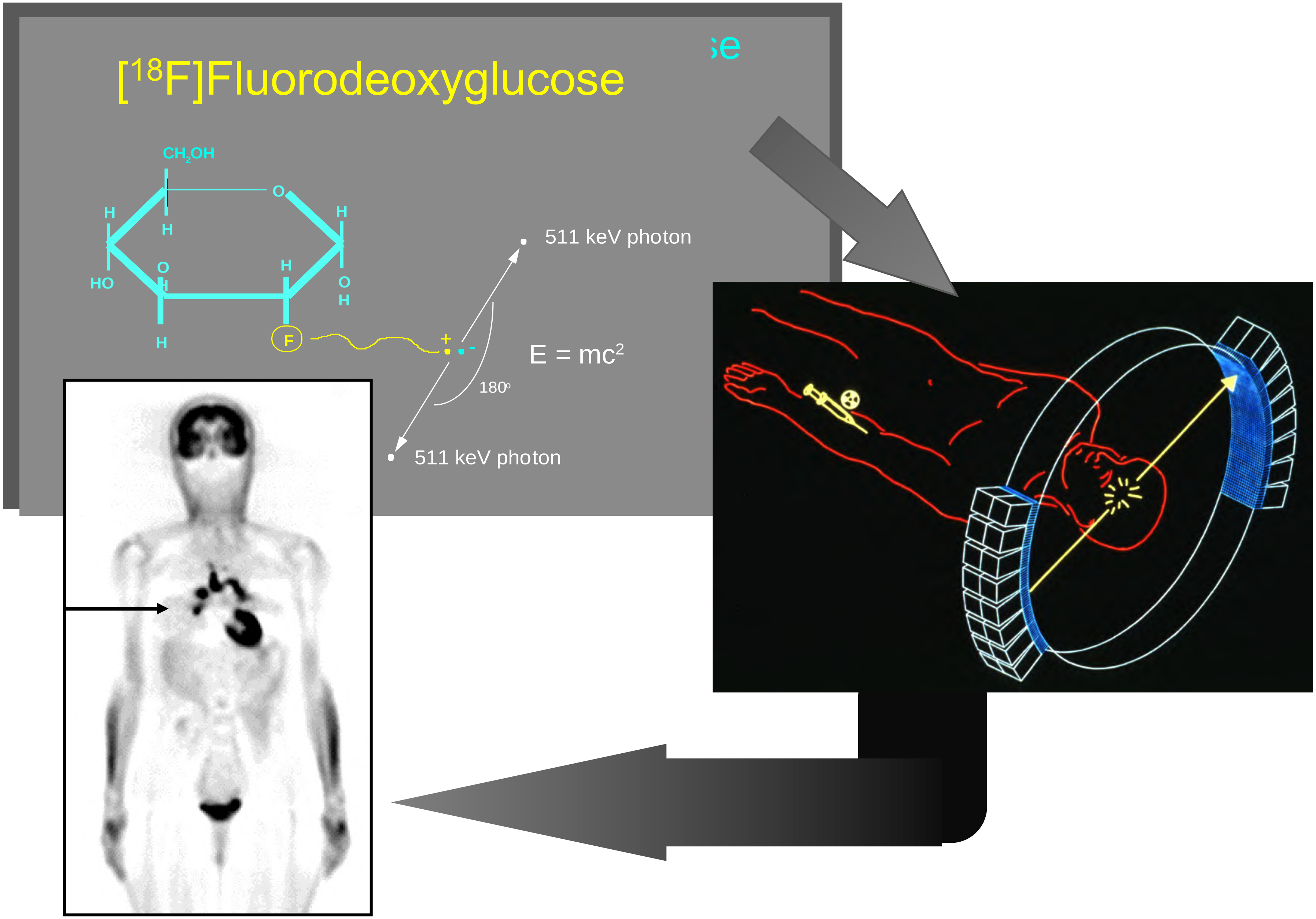
J. Fowler

T. Ido, C.-N. Wan, V. Casella, J.S. Fowler, A.P. Wolf, M. Reivich, D. Kuhl.
J. Labeled Compounds and Radiopharm., 1978

First Human Study with FDG



M. Reivich, D. Kuhl, A. Wolf, J. Greenberg, M. Phelps, T. Ido, V. Cascella, J. Fowler, E. Hoffman, A. Alavi, P. Som, L. Sokoloff.
Circ. Res, 1979


[18F]Fluorodeoxyglucose
CH2OH
O
H
HO
OH
F
+
-
511 keV photon
E = mc2
180o
511 keV photon

Tracer Kinetic Models

a mathematical framework for calculating rates of biological processes with PET

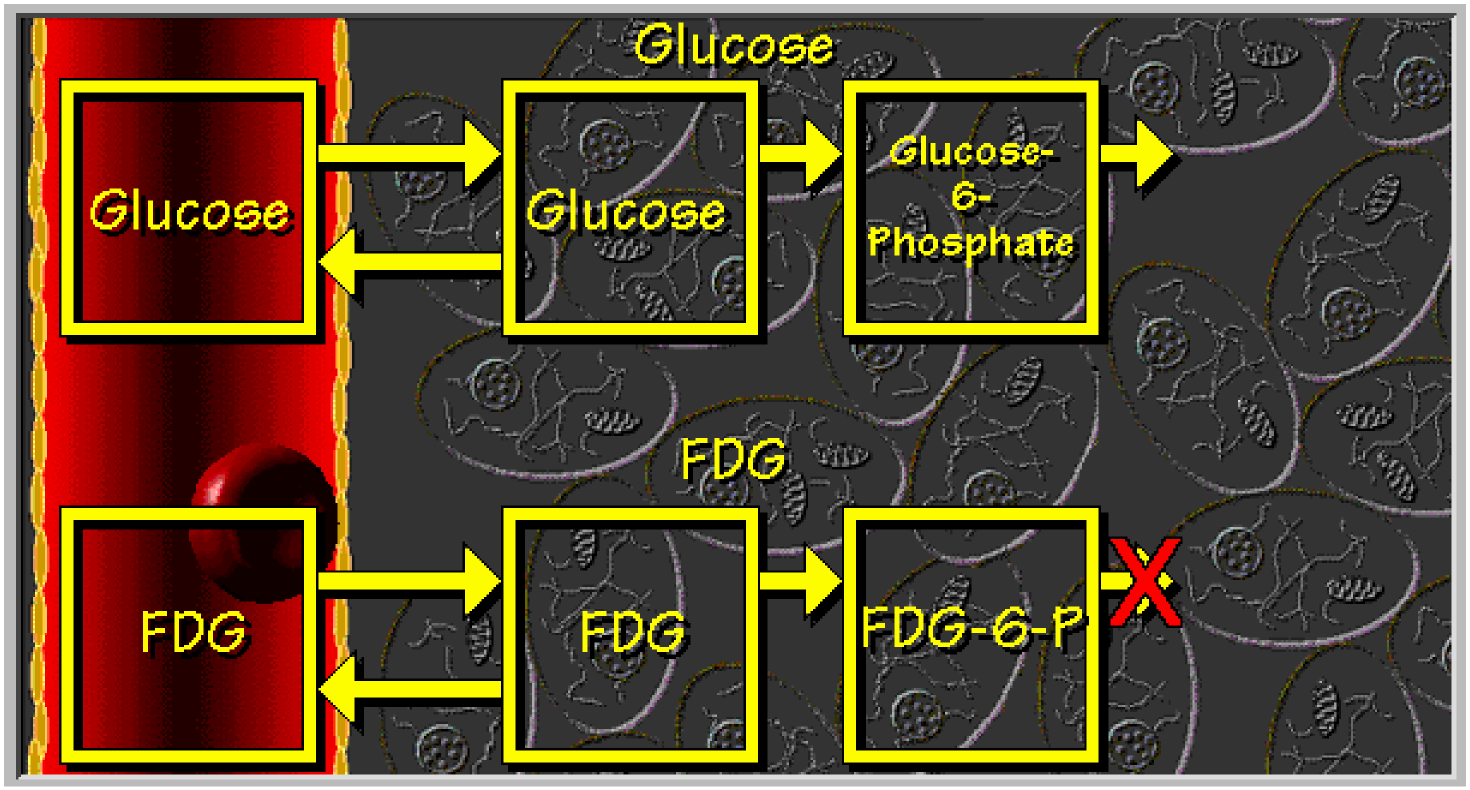
- Compartmental models - most common.
- Simplifications of biological systems.
- Formulated by differential equations describing exchange between compartments.
- Describe biochemical systems
- Require:

  - extensive biochemical studies to define them

  - simplifying approximations in their practical formulations.

FDG Model for Assay of Cerebral Glucose Metabolism

Diffusible, β^+-emitting Substrate is Converted to a Sequestered Product



The enzyme product is retained in cells.
It accumulates in proportion to glycolytic rate.

Operational Equation for Calculating Cerebral Glucose Metabolism, FDG Method

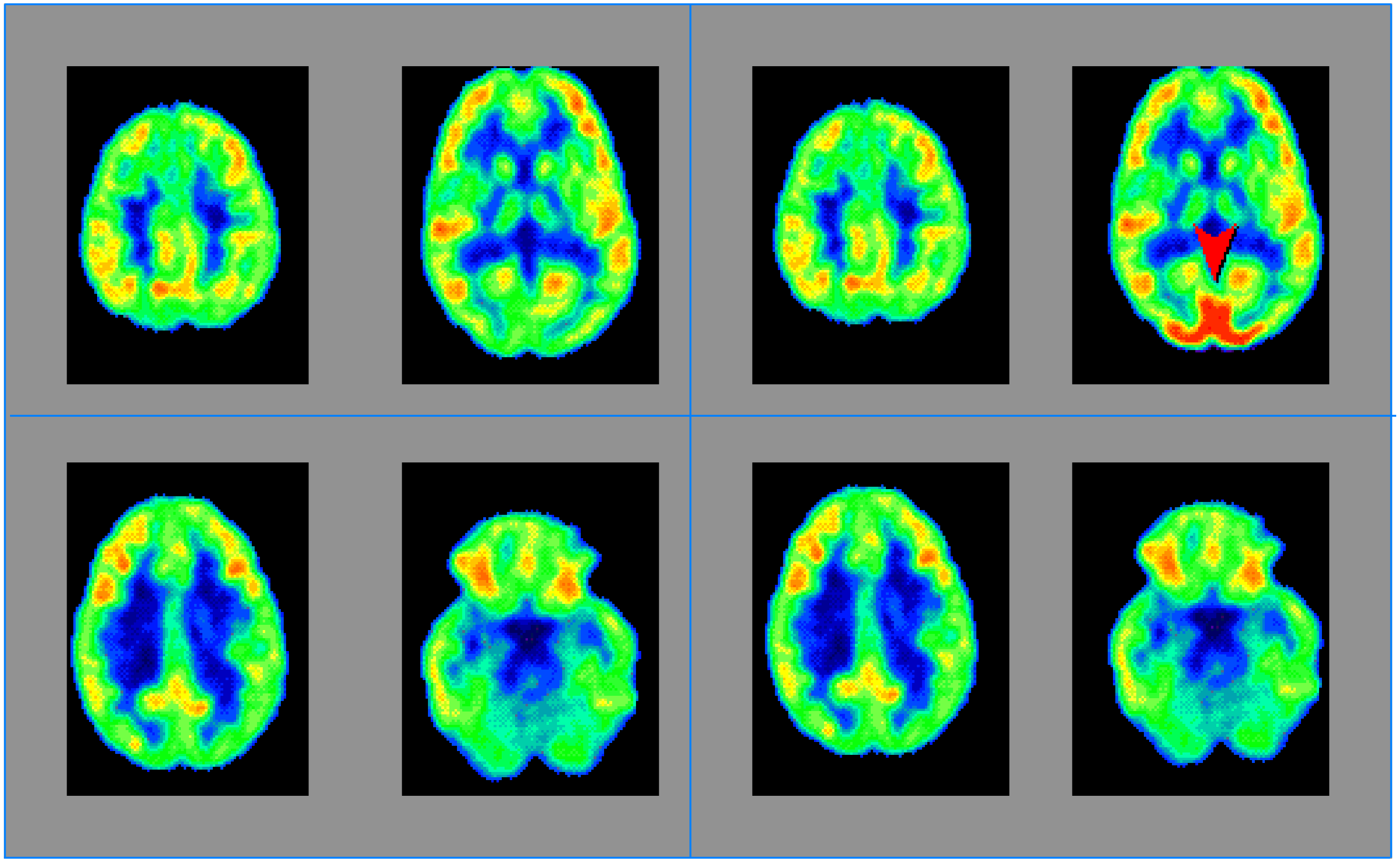
(R_i , rate of tracer incorporation)

$$R_i = \frac{C_p\left(C_i^*(T) - \frac{k_1^*}{\alpha_2 - \alpha_1}\left[(k_4^* - \alpha_1)e^{-\alpha_1 t} + (\alpha_2 - k_4^*)e^{-\alpha_2 t}\right] \otimes C_p^*(t)\right)}{LC\left(\frac{k_2^* + k_3^*}{\alpha_2 - \alpha_1}\right)\left(e^{-\alpha_1 t} - e^{-\alpha_2 t}\right) \otimes C_p^*(t)}$$

(replacing arterial with venous sampling as in original Sokoloff 1977 method)

See ME Phelps et al., Ann Neurol., 1979 for derivation and definition of terms.

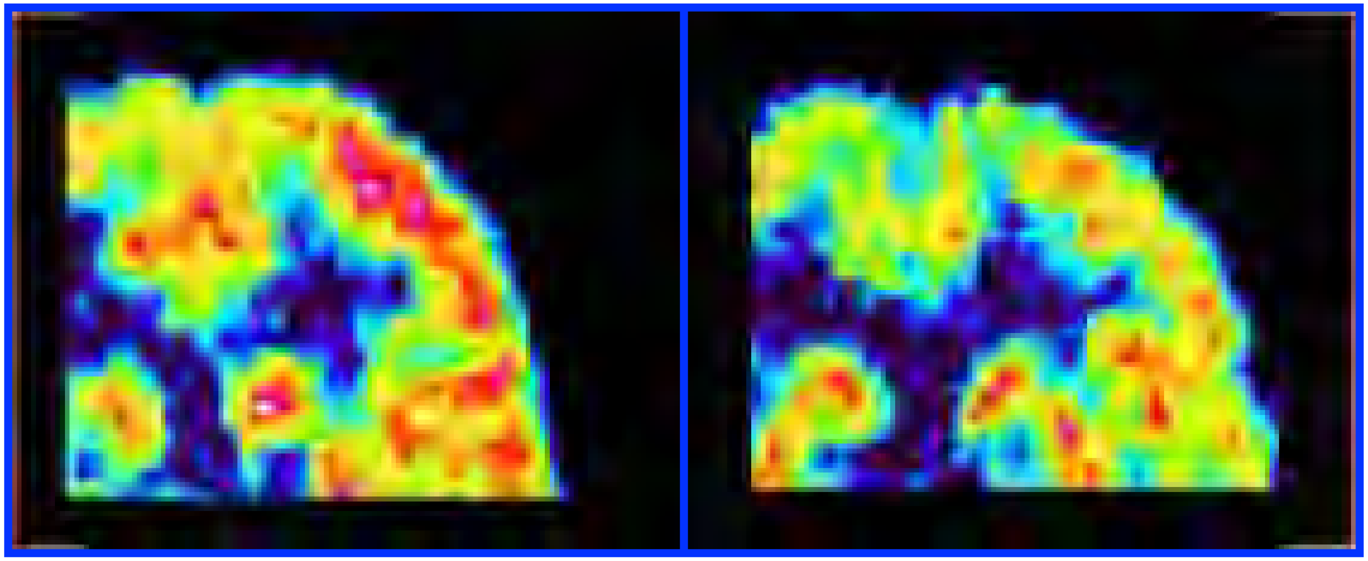
Visual Activation (FDG)



Resting Brain   Viewing a Complex Scene

FDG PET Shows Disease-Related Dysfunction

Cortical Hypometabolism in Schizophrenia



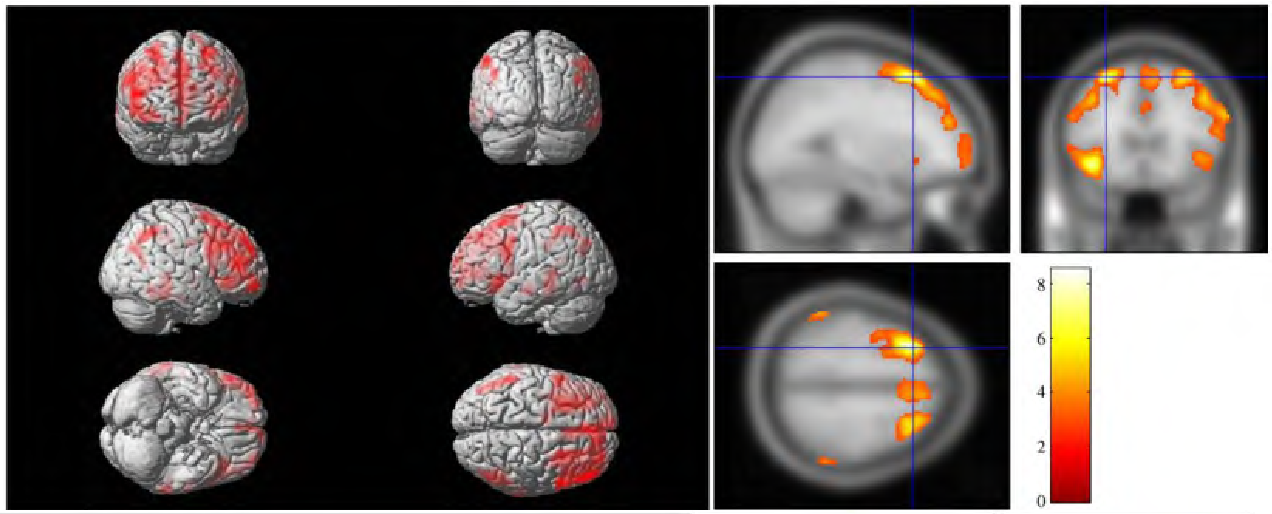
Healthy control | Schizophrenic

altered metabolic relationship between
frontal cortex, striatum & thalamus

$[^{18}F]$FDG Reveals Cortical Deficit in Glucose Metabolism Bipolar and Unipolar Depression

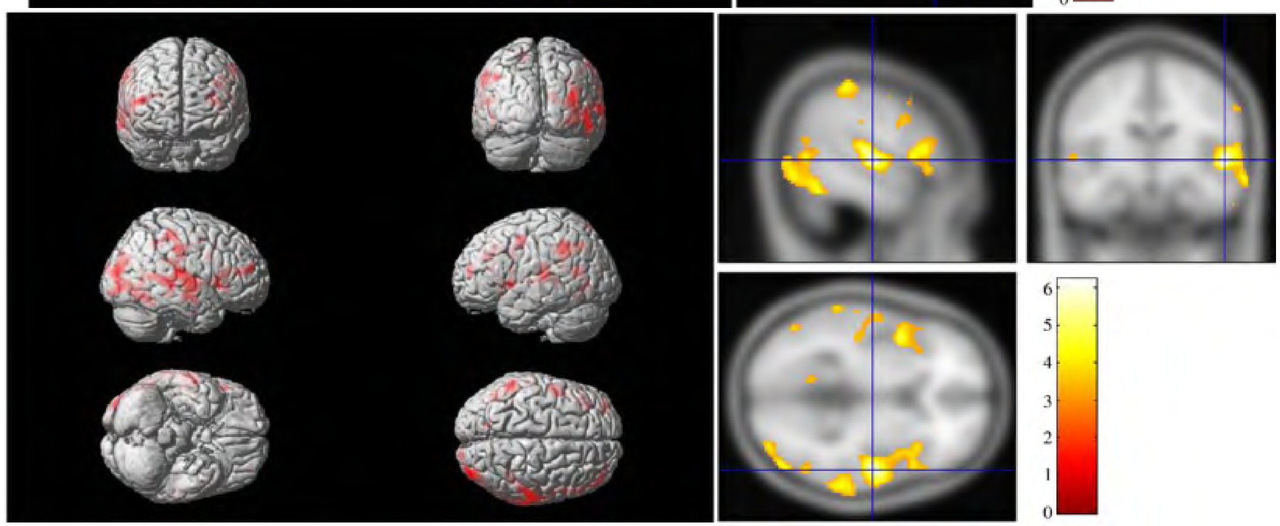
Bipolar Depression

colors indicate areas of lower glucose metabolism vs. control



Unipolar Depression

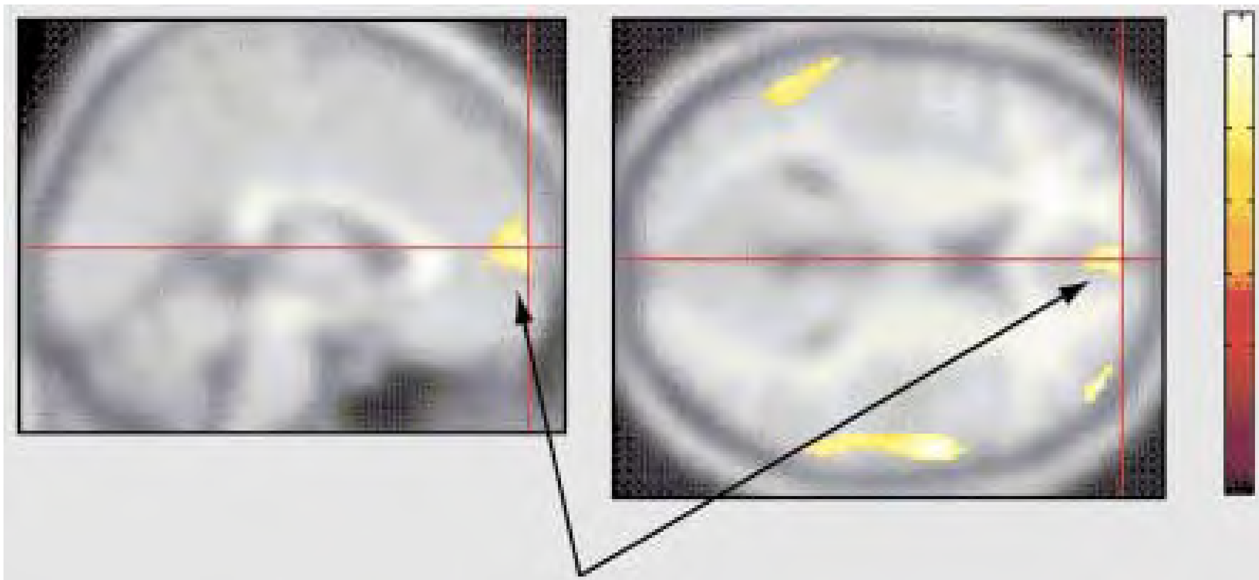
colors indicate areas of lower glucose metabolism vs. control



Hosokawa et al., 2009

FDG PET to Predict Treatment Outcome

Baseline Glucose Metabolism Predicts Response to Paroxetine



Midline PFC and rostral ACC

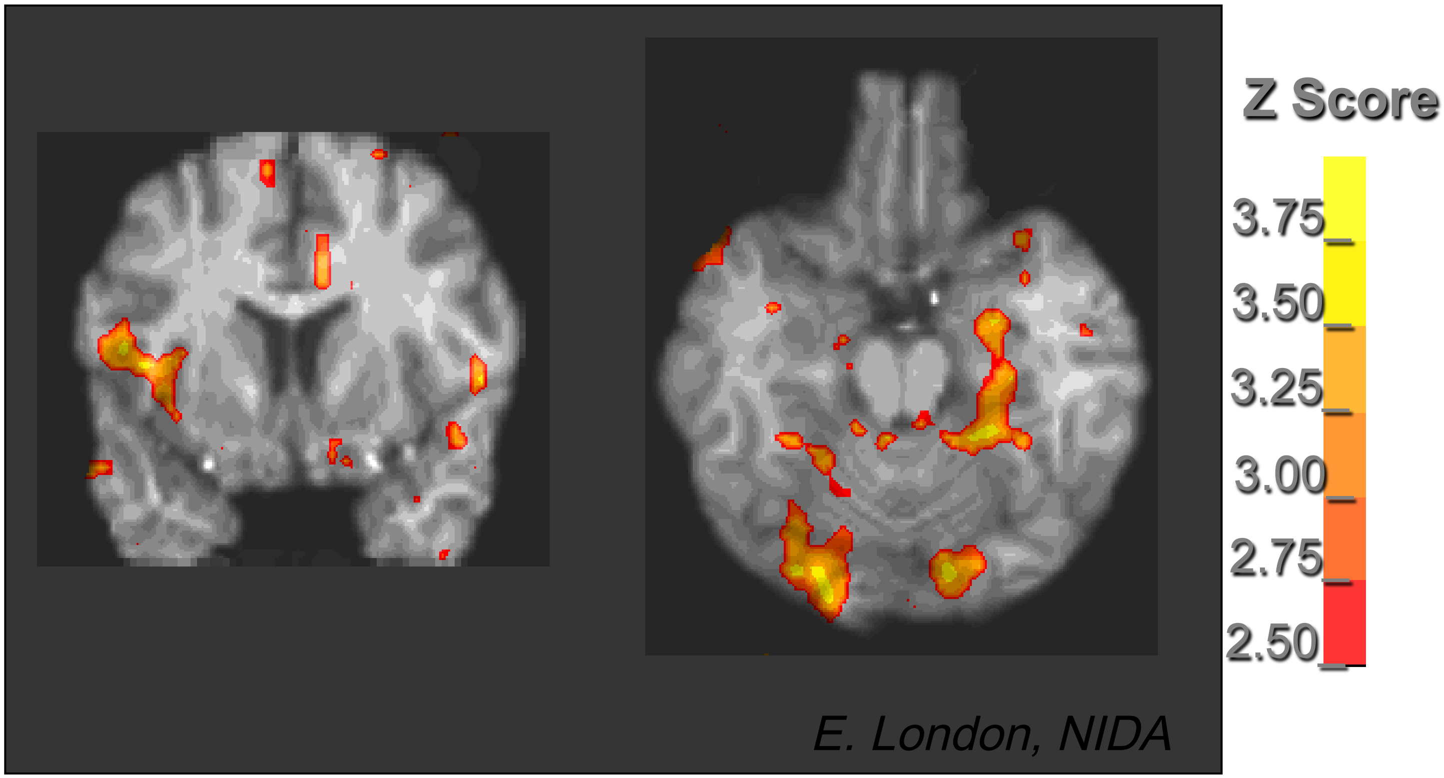
Decline in Hamilton Depression Scale correlated with pretreatment glucose metabolism.

71 patients with major depression, OCD, depression + OCD

S. Saxena et al., 2003

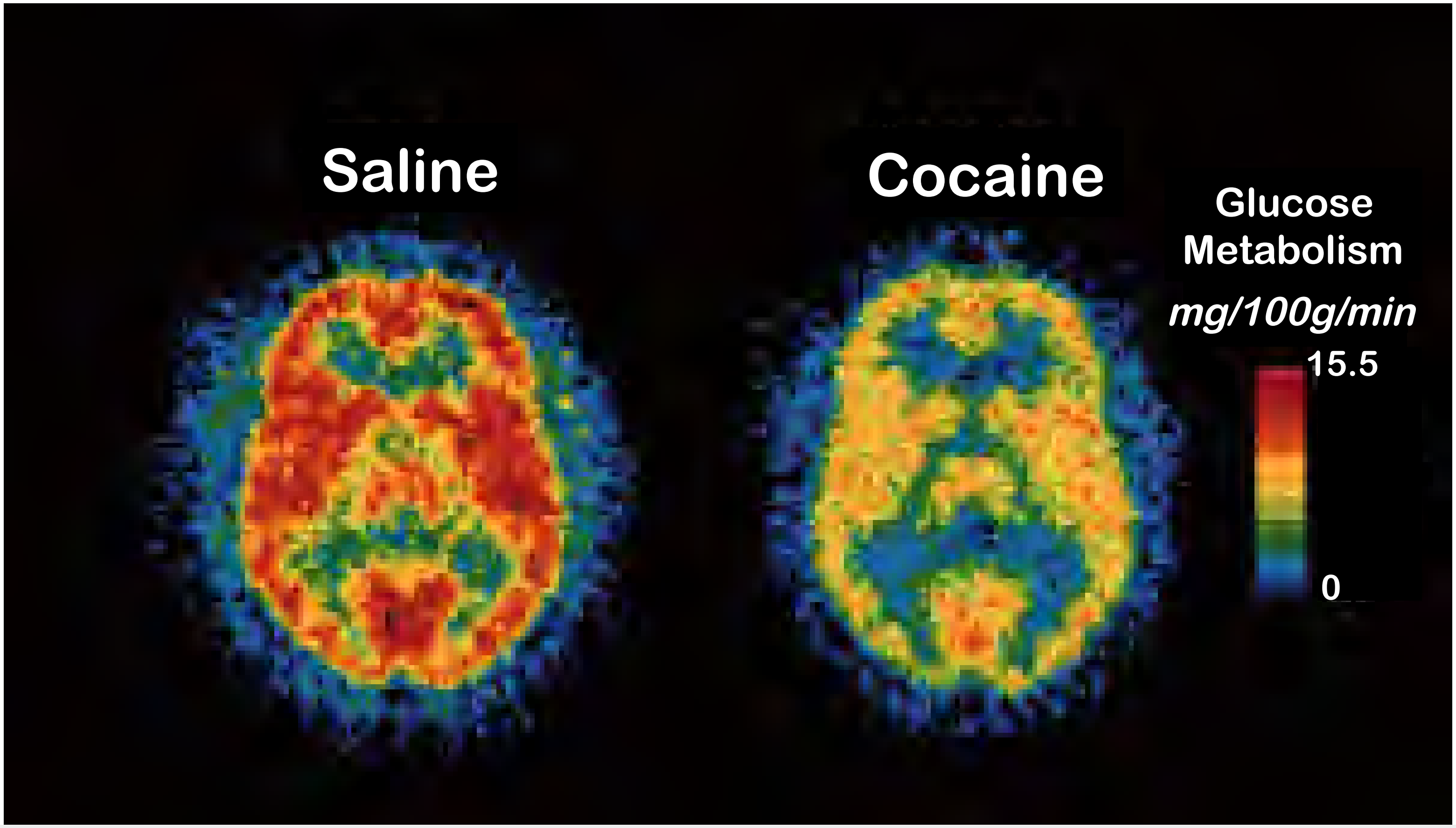
FDG PET Shows Neural Correlates of Behavioral State

Limbic activation accompanies cocaine craving



S. Grant et al. *Proc Nat. Acad. Sci,* 1996
A.-R. Childress et al. *Am. J. Psychiatry,* 1999
C. Kilts et al. *Arch Gen. Psychiatry.,* 2001

Acute Cocaine Administration Reduces Cerebral Glucose Metabolism

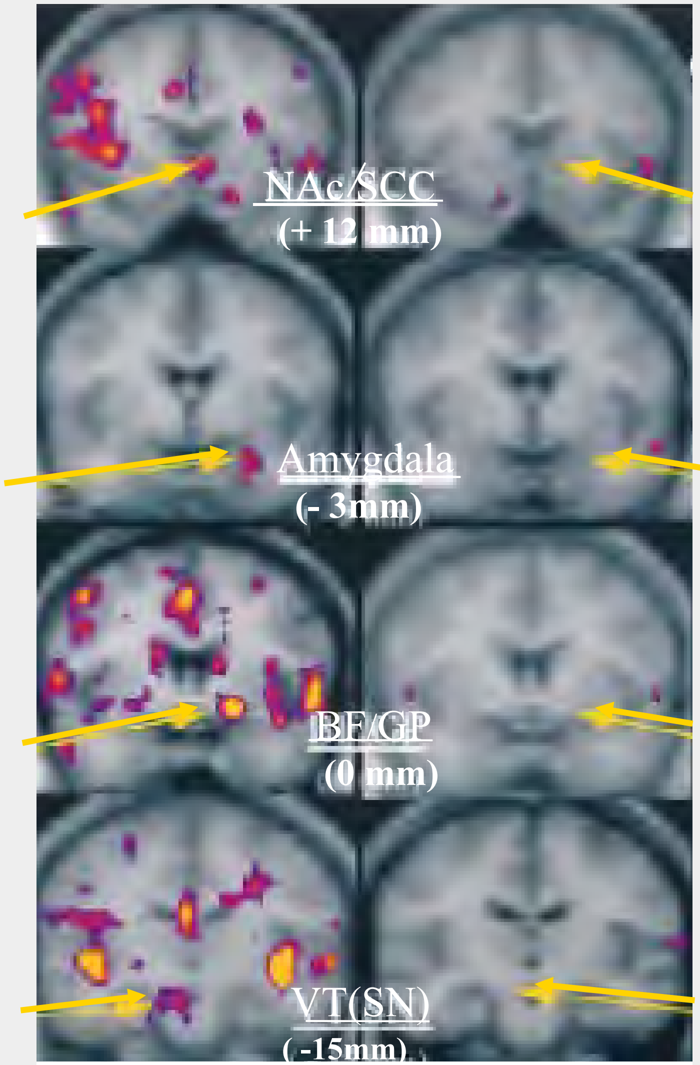


E. London et al. Arch Gen Psychiatry, 1990

Imaging the Acute Effects of Cocaine

Rapid Time Resolution (fMRI)

cocaine



saline

H.C. Breiter et al. Neuron, 1997

Questions about Circuitry Asked with PET

[F-18]FDG and [O-15]water

- *Studies at rest:*

What circuitry contributes to dysphoric mood?

To pathology of OCD?

To Cognitive decline in Alzheimer's disease?

- *Activation Studies:*

What circuitry is involved in a certain cognitive function?

- *Drug challenge studies:*

What regions/circuits are affected by a drug treatment?

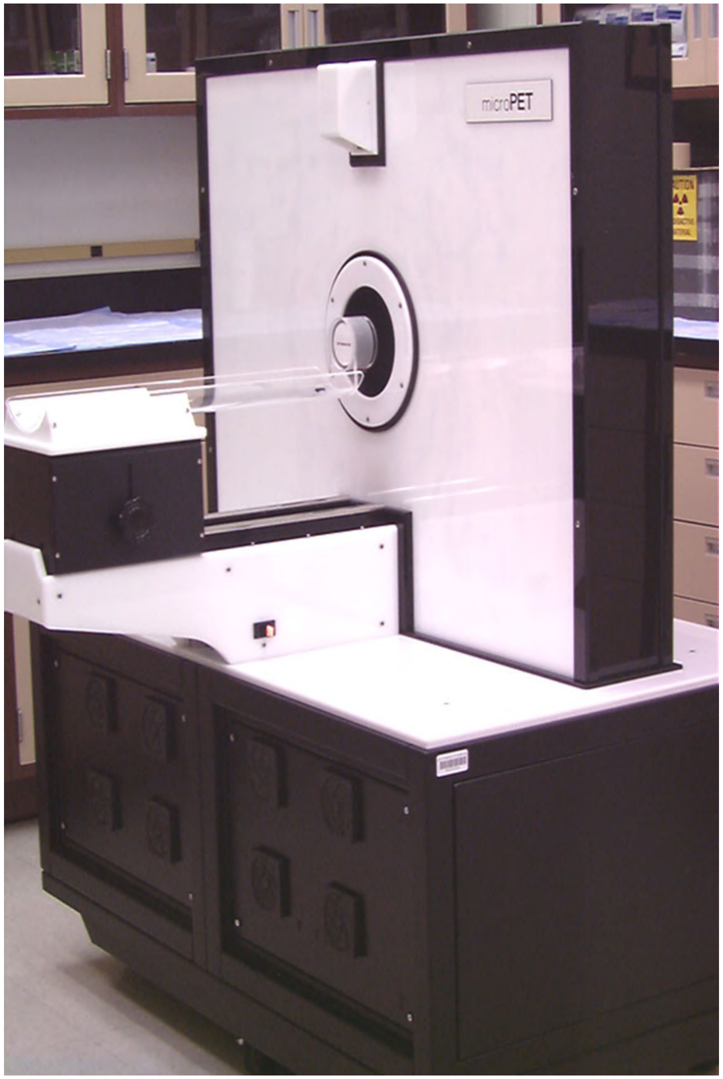
Better with fMRI?

Yes, for cognitive challenge.

No, for drug challenge if drug affects vasculature directly.

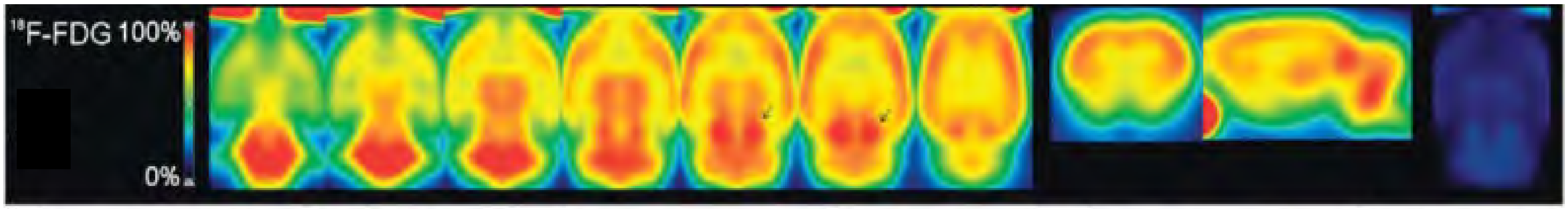
Animal Models
MicroPET

- 30 detector modules (8x8)
- 1920 individual LSO elements
- ring diameter 17.2 cm
- 10 cm transaxial FOV
- 1.8 cm axial FOV
- volume resolution ~ 6 μL
- sensitivity: 210 cps/μCi



Small Animal PET Data Analyzed by SPM

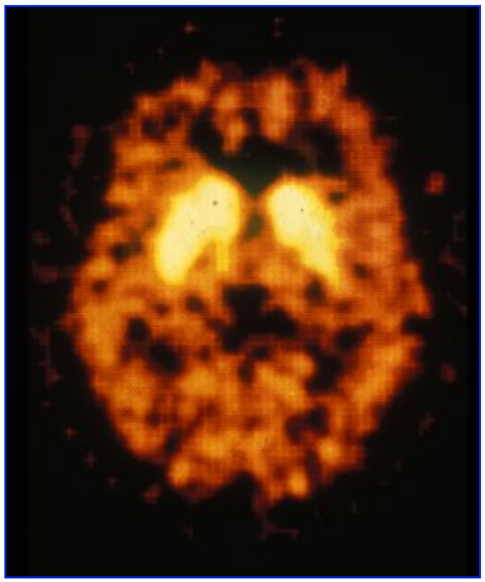
Functional FDG template constructed in Paxinos standard space



Casteels et al., 2006

First Dopamine PET Scan 1983

D2/D3 Receptors visualized with [11C]N-Methylspiperone



H. Wagner D. Wong

H.N. Wagner, H.D. Burns, R.F. Dannals, D.F. Wong et al. Science, 1983

Receptor/Transporter Probes

Questions about neurotransmitters

- How is dopaminergic (serotonergic, etc.) function different in the disease state?
  - *Does a neurotransmitter parameter relate to severity of disease?*
- Does a drug reach the intended receptor target?
- In disease, is the presynaptic element working?
  - *How does a challenge that interacts with the presynaptic element (e.g., amphetamine) affect synaptic transmitter dynamics?*

  How do such questions relate to function (mood, cognition)?

Radiolabeled Receptor Ligand

Depends on specific binding
high affinity, low capacity
(Nonspecific binding is low affinity, high capacity)

Generally -- Radioactivity in early scans depends on blood flow (distribution).
Radioactivity in later scans due to specific binding.
Unbound radioactivity and nonspecific binding have shorter residence in tissue.

Dopamine-Related PET Probes

Postsynaptic receptors:

D2/D3 striatal: [C-11]NMSP, [C-11]raclopride
D2/D3 striatal and extrastriatal: [F-18]fallypride, [C-11]FLB-457

D3: [C-11]PHNO

D1: [C-11]SCH23390, [C-11]NNC-112

Transporters:

[C-11]methylphenidate, [C-11]cocaine

Enzymes: [C-11]deprenyl, [C-11]clorgyline

Neurotransmitter Turnover: [F-18]fluoroDOPA

Non-Dopamine PET Probes

Monoamines in General

Vescicular monoamine transporter: [^{11}C]DihydroTBZ

Monoamine oxidase A: [^{11}C]Clorgyline

Monoamine oxidase B: [^{11}C]Pargyline and [^{11}C]L-deprenyl (Selegiline)

Serotonergic System

5-HT$_{1A}$ receptor: [^{11}C]WAY-100635, [^{18}F]MPPF

5-HT transporter: [^{11}C]McN5625, [^{11}C]DASB

Cholinergic Systems

Nicotinic acetylcholine receptors: [^{18}F]A-85380

Muscarinic acetylcholine receptors: [^{18}F]FP-TZTP

Acetylcholinesterase: MP4A Butyrylcholinesterase: MP4B

Metabotropic Glutamate Receptors

mGluR1: [^{18}F]MK-1312

mGluR5: [^{11}C]ABP688, 18F]F-PEB

Others: *Benzodiazepine receptors*

Selective Radiotracers in PET

- static neurochemical measures
- neurotransmitter dynamics

Receptor Binding

$$B = Bmax\ X\ F/\ K_D + F$$

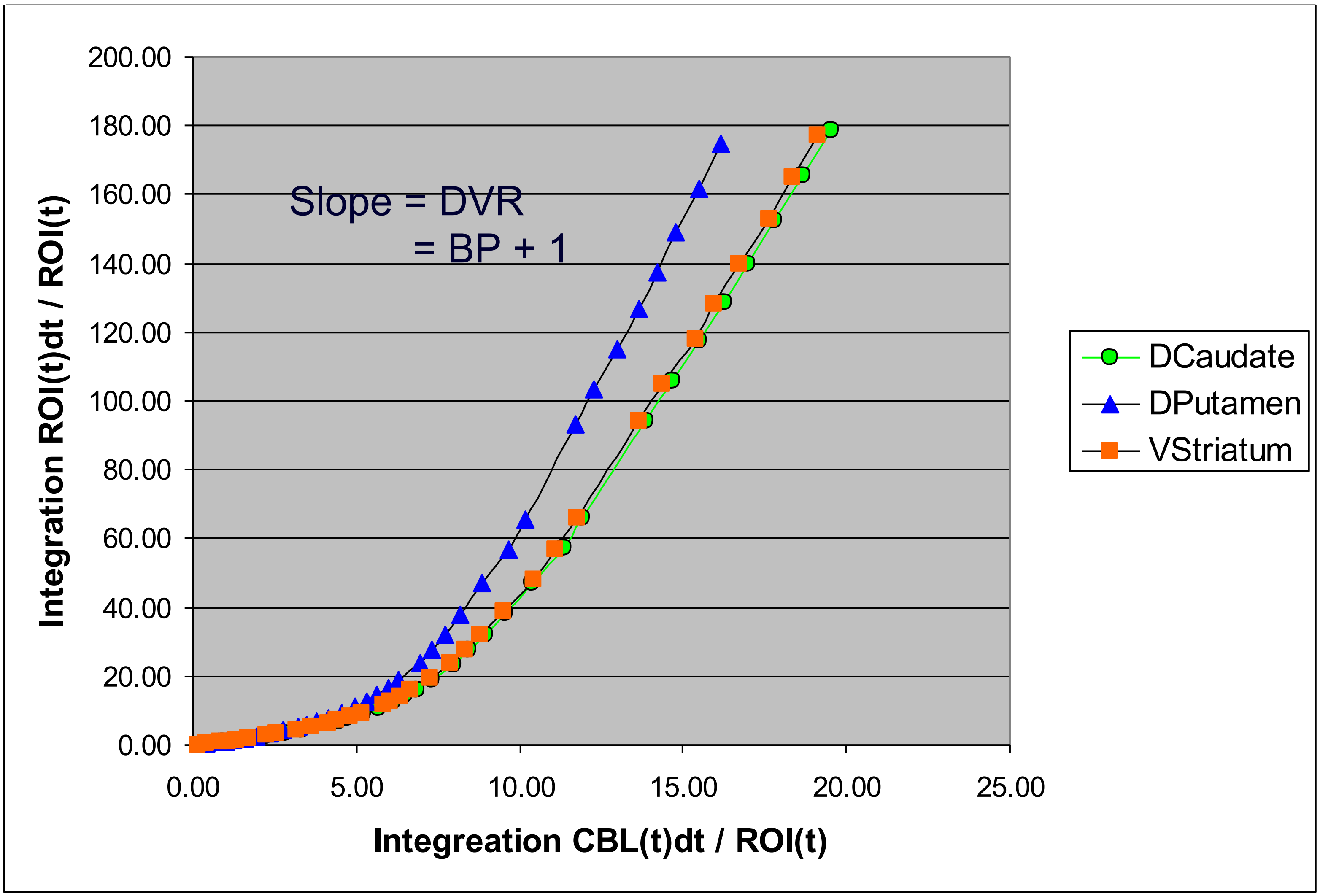
F = free ligand

In plasma – Measure free ligand concentration directly (metabolite correction).

In brain – Measure radioactivity after calibration (phantom).
Model distinguishes free from bound radioactivity.

Binding Potential: Receptor Availability

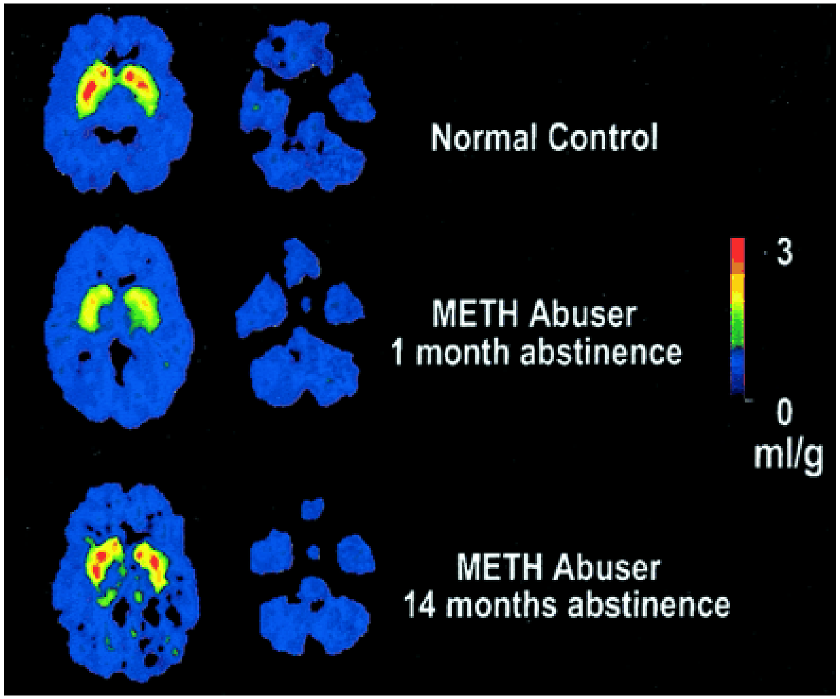
The Logan Method



Static Measure:

[^{11}C]*d-threo*-Methylphenidate in Methamphetamine Abusers

The transfer constant of [^{11}C]d-threo-methylphenidate from plasma to brain (K_1) and the distribution volumes (DV) were calculated by tracer-kinetic modeling.

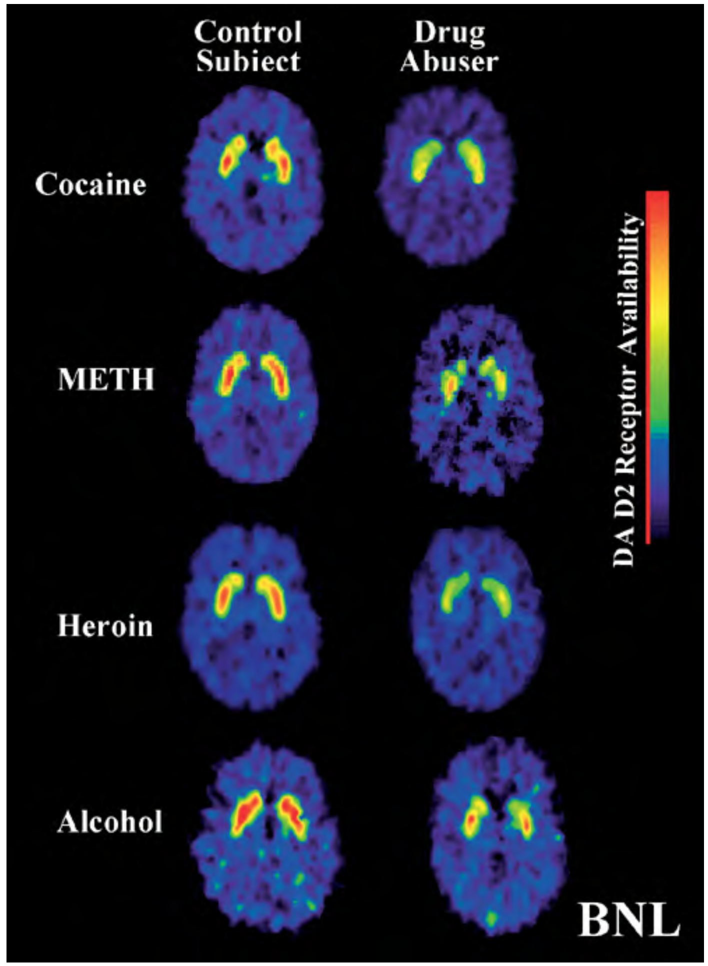


- No differences in K1 between short vs. protracted abstinence.
- Increased binding to DAT in striatum (not cerebellum).
- DAT recovery was negatively correlated with amount and years of METH use.

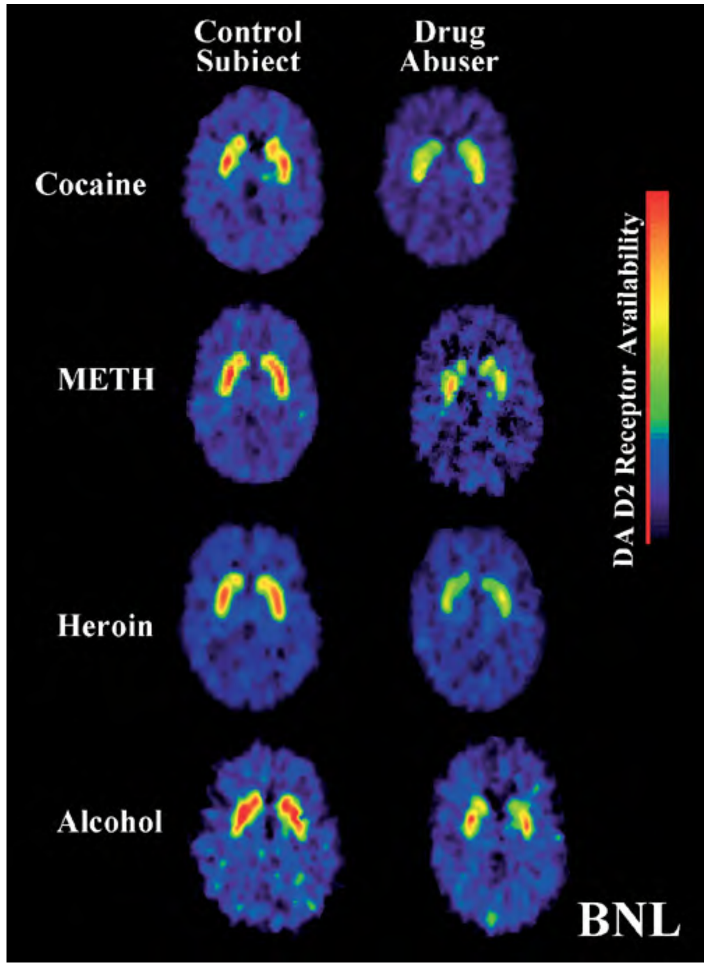
Abuse severity may limit recovery.

ND Volkow et al. J. Neurosci 2001; 21:9414

Addiction: Low D2-like Receptor Availability



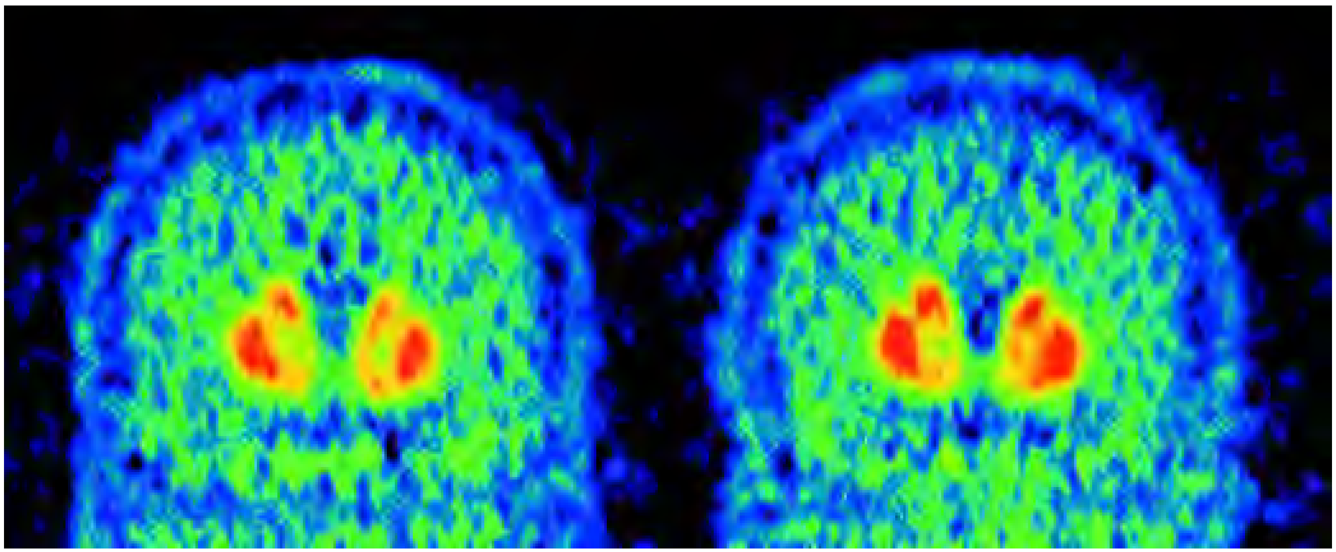
Addiction: Low D2-like Receptor Availability



Is it all about receptor density?

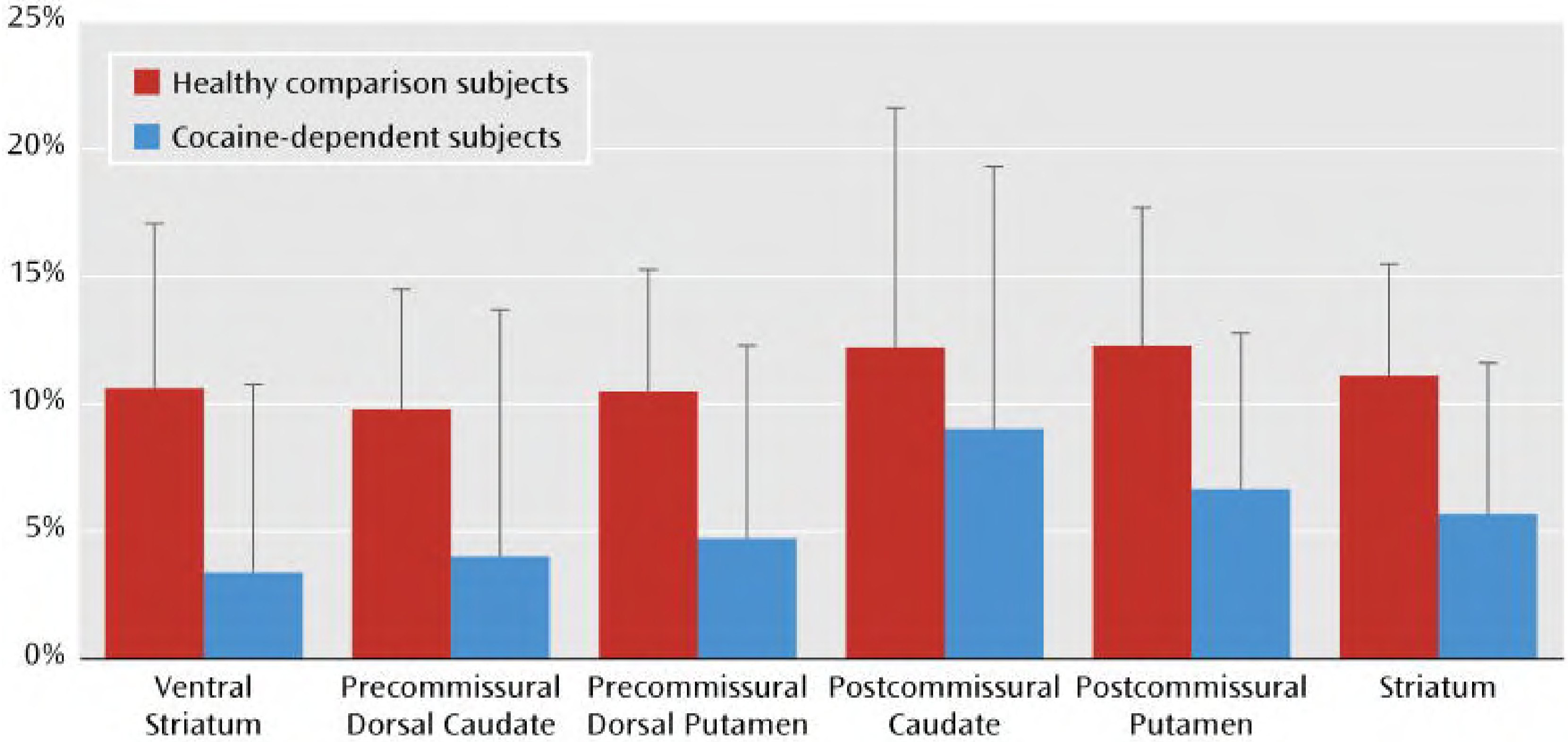
$[^{11}C]$Raclopride in the Striatum:

Effect of Endogenous DA on Binding Potential



Placebo α - Methylparatyrosine

To What Extent is BP Affected by Endogenous Dopamine?

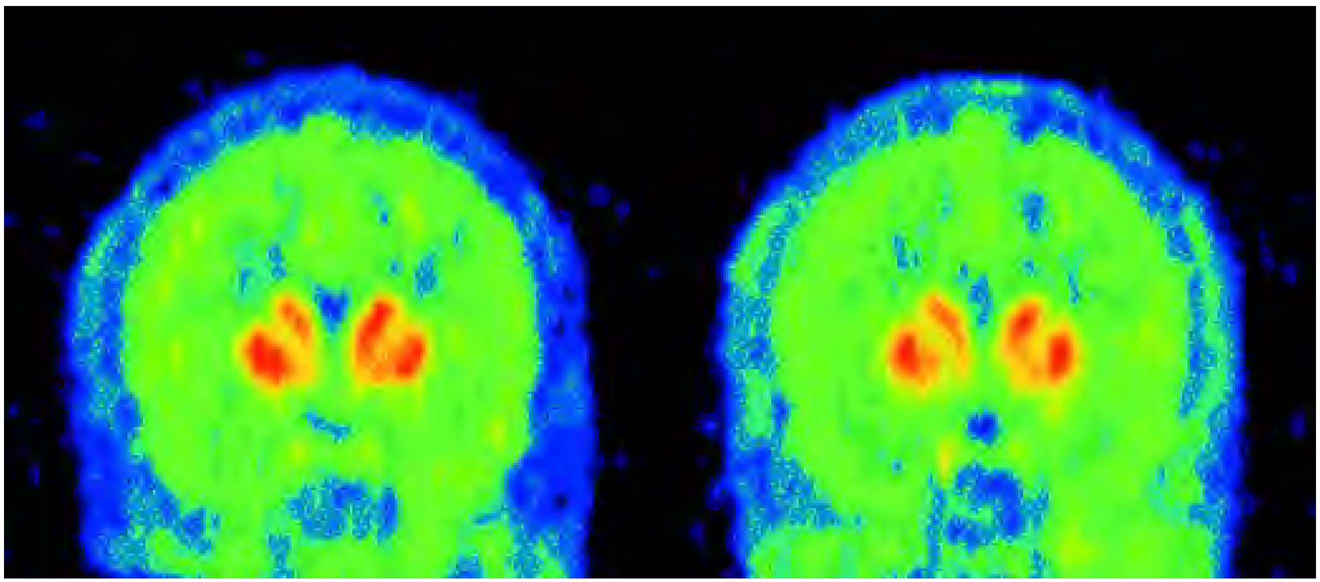


Percent Change in [^{11}C]Raclopride Nondisplaceable BP for Cocaine-Dependent and Healthy Control Subjects After AMPT

D. Martinez et al., Am. J. Psychiatry, 2009

Neurotransmitter Dynamics

[^{11}C]raclopride in the Striatum: Measuring changes in Intrasynaptic DA

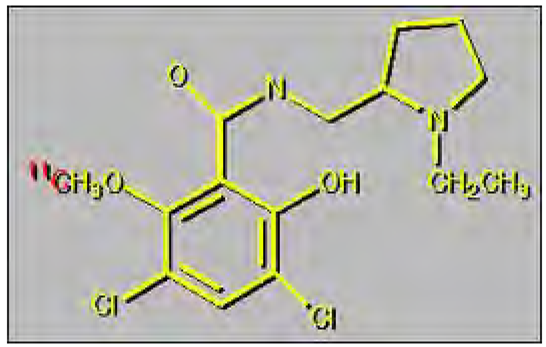


placebo   methylphenidate

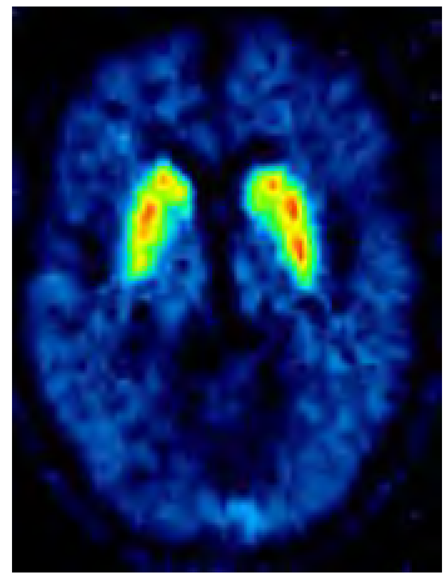
Studies of Cocaine Craving Use Videotapes with Images that Remind the Participant about Cocaine

The Participant Scores Cocaine Craving During PET Scanning

Cocaine-related cues



$[^{11}C]$Rclopride
--radiotracer for
D2/D3 DA receptors

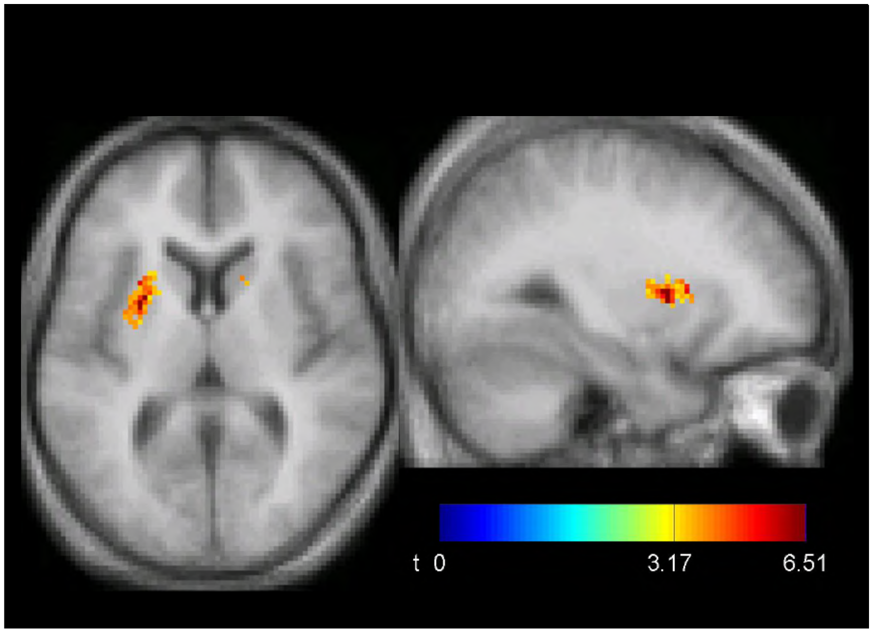


D2/D3 DA receptors
visualized with PET

Cocaine Craving and Dopamine Release

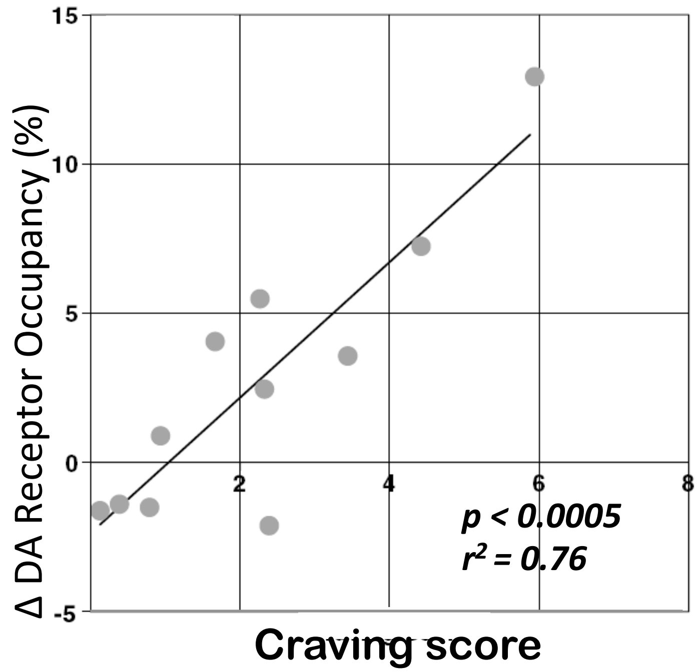
Studies of [^{11}C]Raclopride Binding to D2/D3 DA Receptors

The maps below show striatal regions where DA release was related to craving.



Participants who craved the most had the most DA release
(largest change in DA receptor occupancy)

Dopamine release in dorsal striatum is correlated with craving.

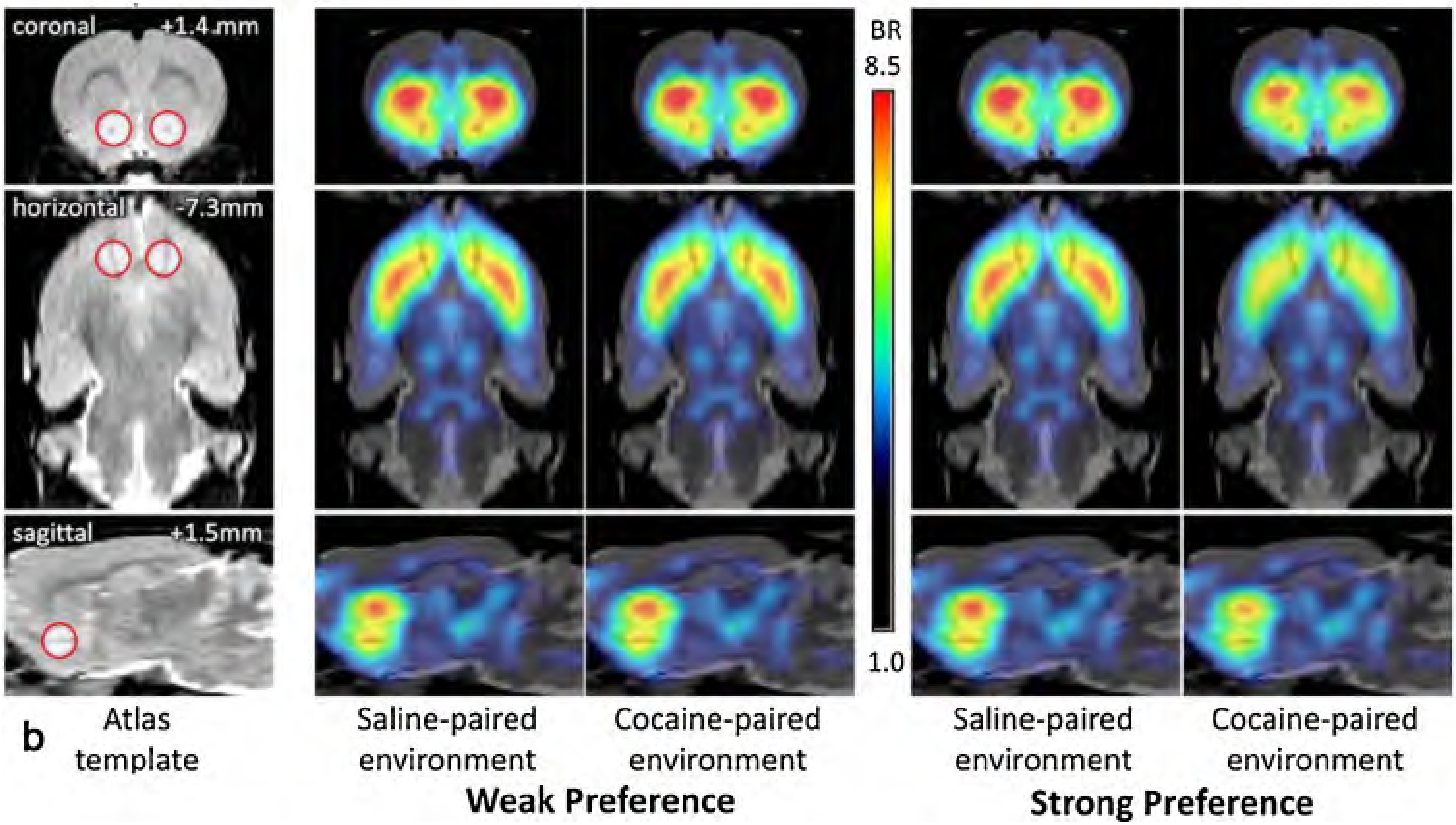


D.F. Wong et al. Neuropsychopharmacology, 2006

N.D. Volkow et al., J. Neurosci., 2006

Cocaine Preference and Environmental Influence on D2/D3 Receptor Availability

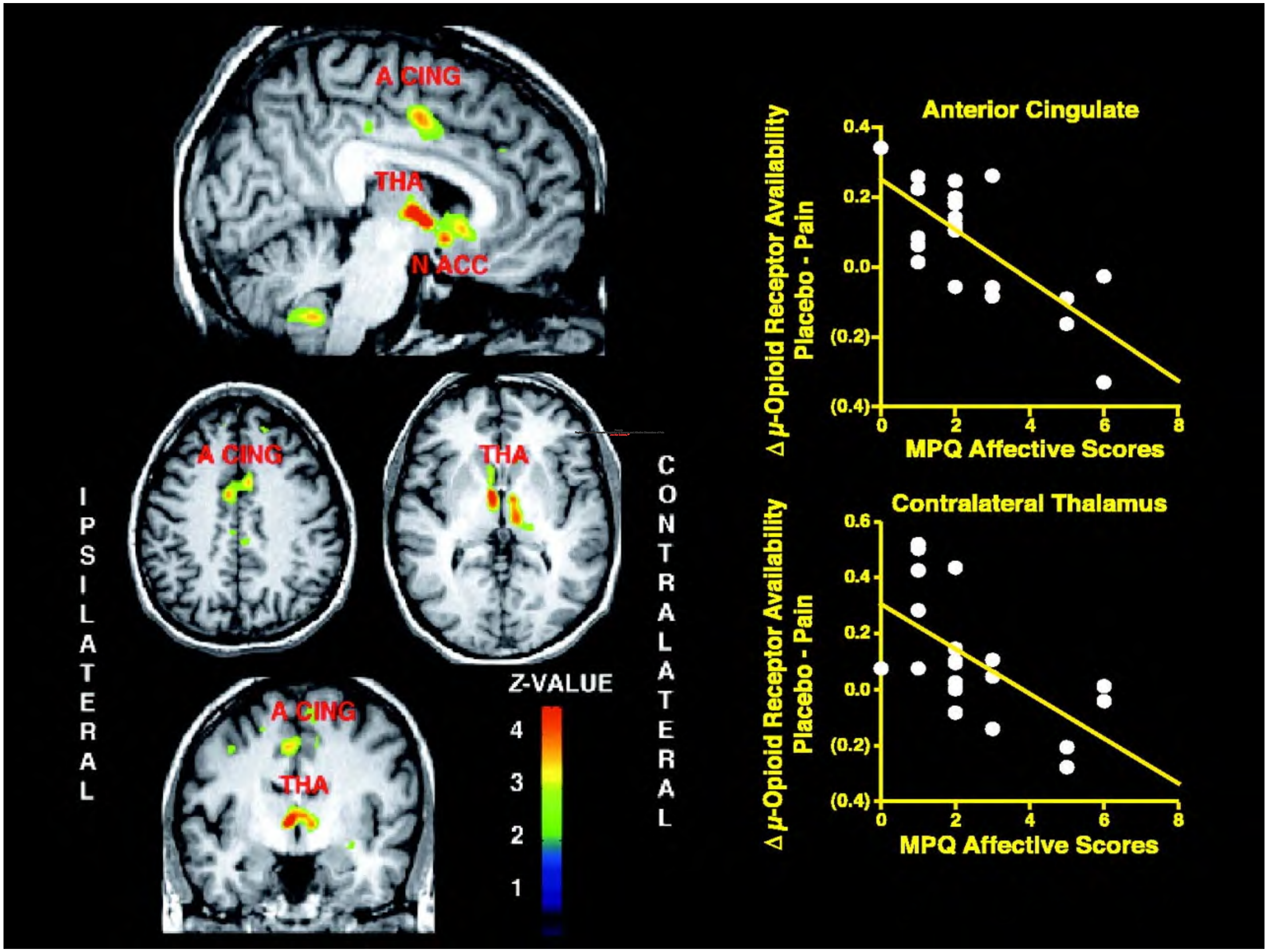
In freely-moving rats, exposure to environmental cues associated with cocaine decreased striatal [^{11}C]raclopride binding.



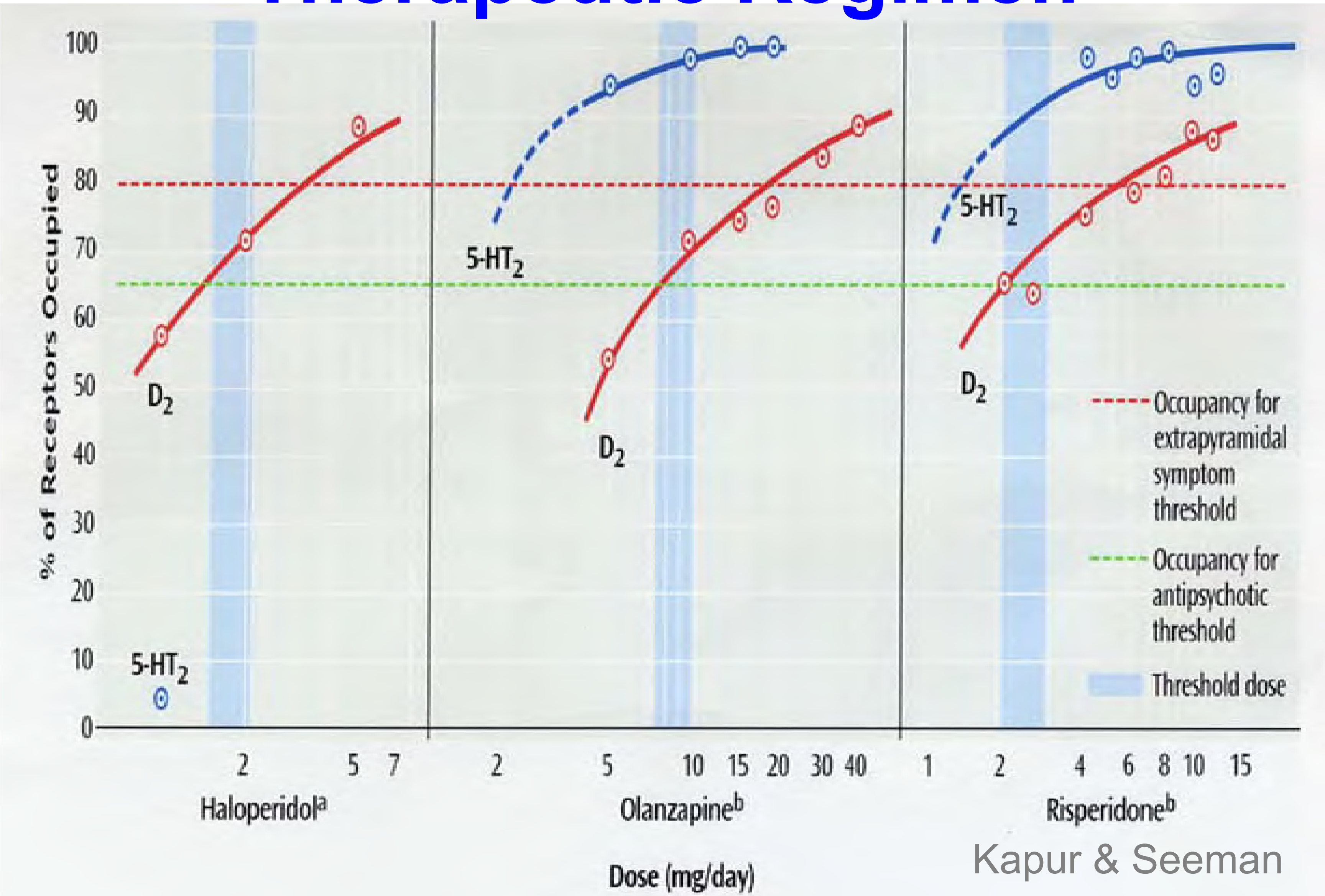
Schiffer et al., 2009

Neurotransmitter Dynamics:
Endogenous Opioid Release

Negative correlations of MPQ sensory scores with μ-opioid system activation

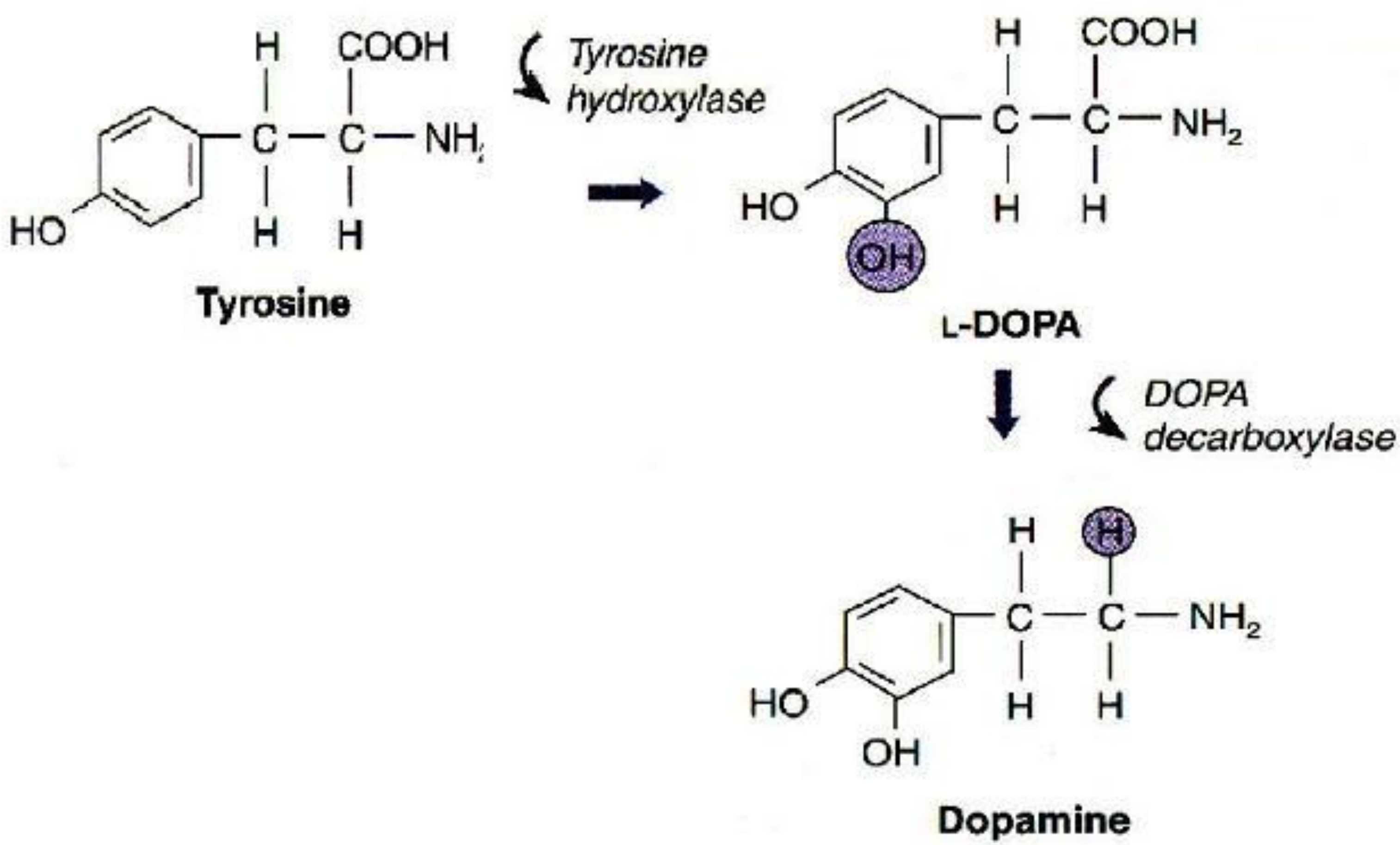


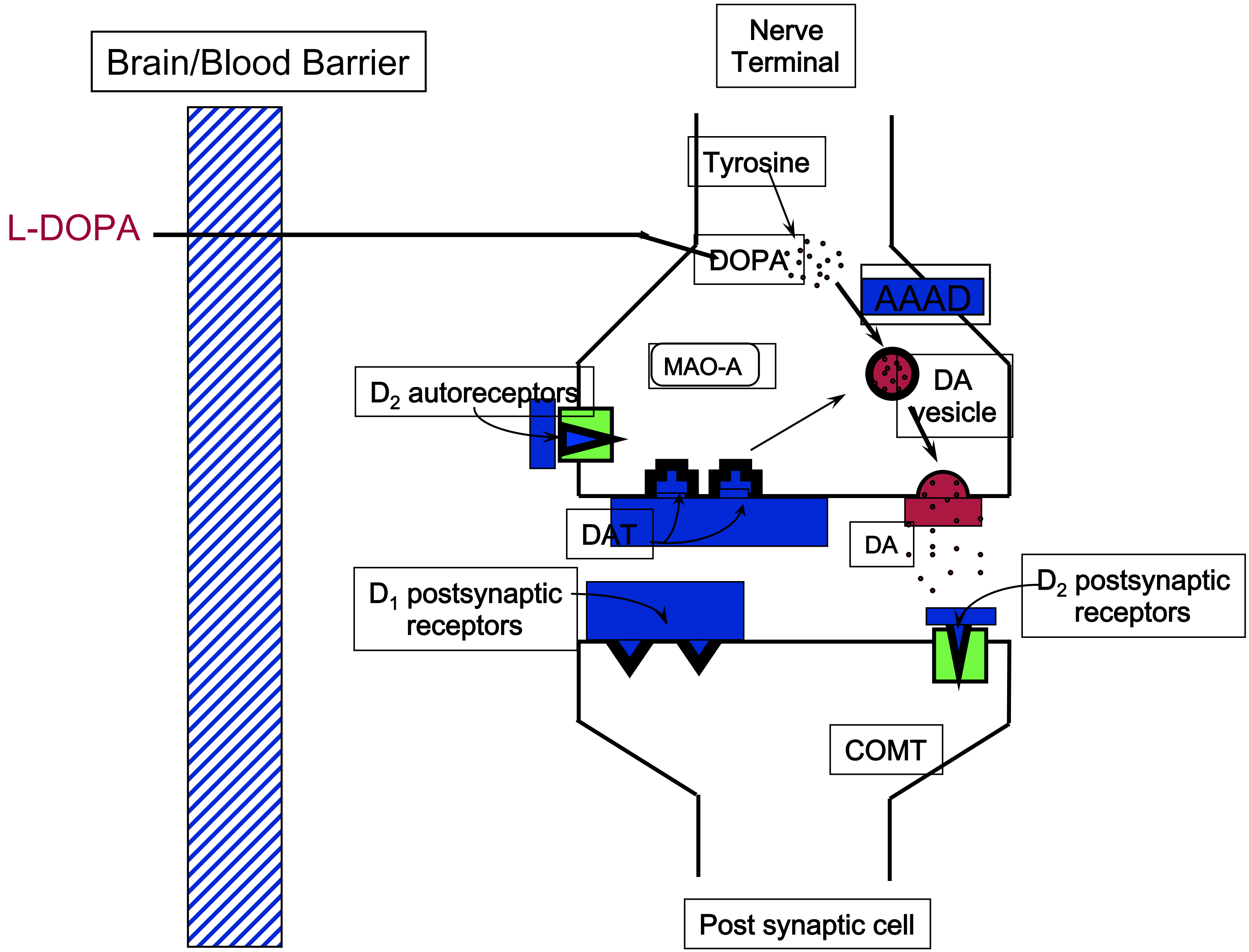
PET Used to Determine Therapeutic Regimen



Kapur & Seeman

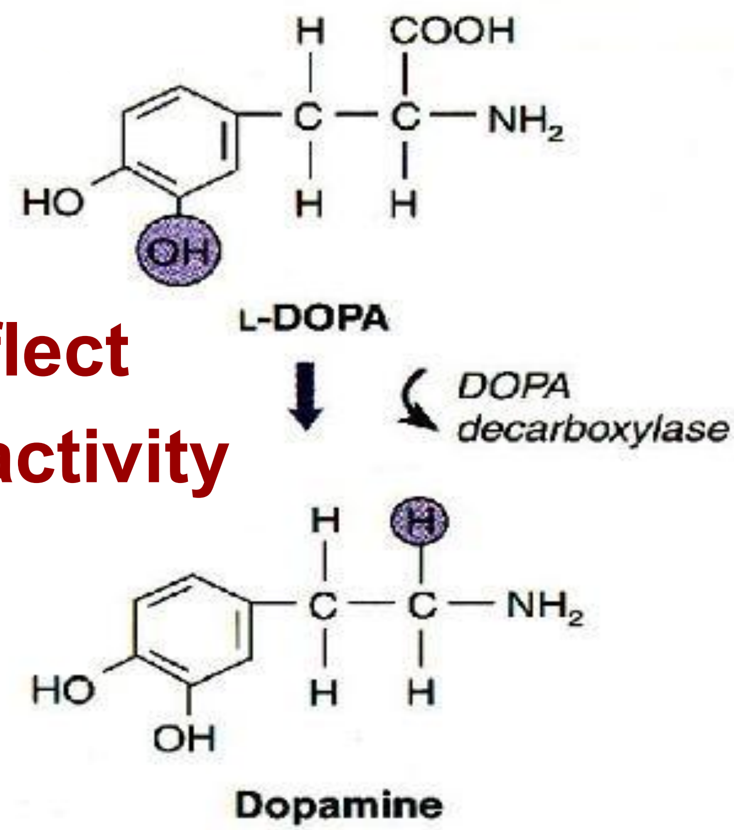
Dopamine synthesis involves two major enzymatic steps.





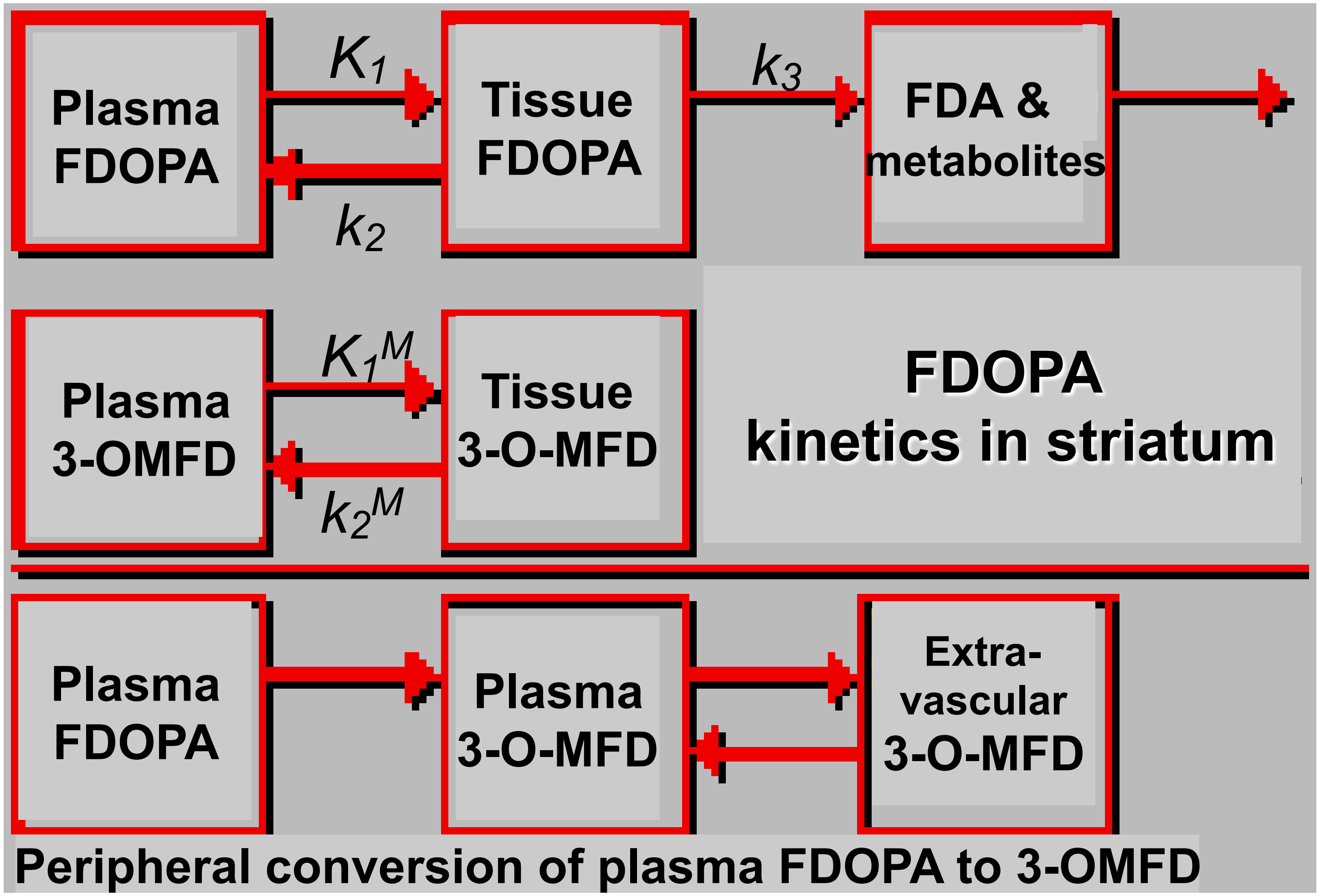
Brain/Blood Barrier
Nerve Terminal
Tyrosine
L-DOPA
DOPA
AAAD
MAO-A
D_2 autoreceptors
DA vesicle
DAT
DA
D_1 postsynaptic receptors
D_2 postsynaptic receptors
COMT
Post synaptic cell

[^{18}F]FDOPA is taken up into the presynaptic terminal, and is converted to [^{18}F]DA

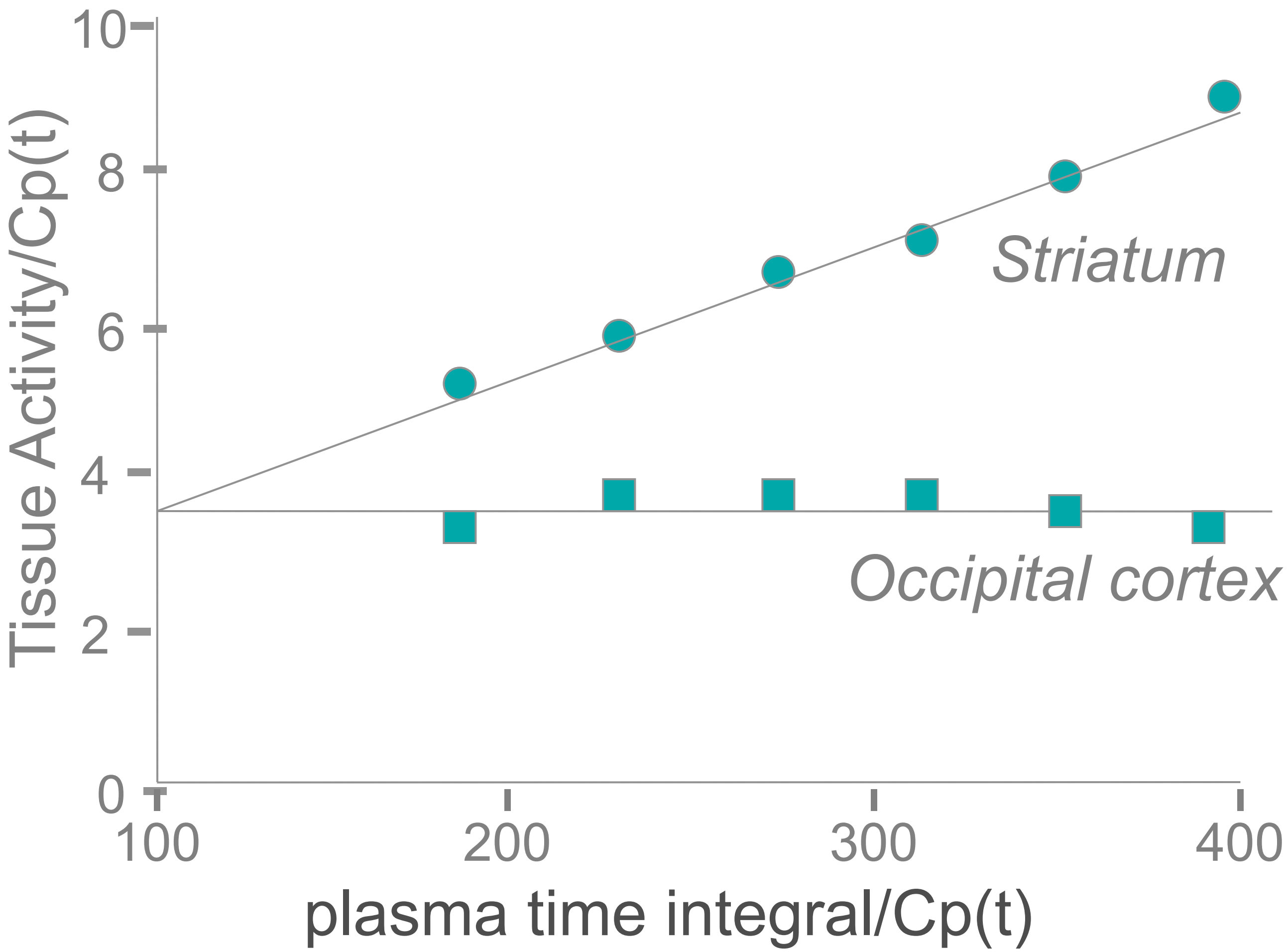


[^{18}F]FDOPA data reflect DOPA decarboxylase activity & DA storage.

FDOPA kinetics follows a 5-compartment model



Slope of the Patlak Plot is the estimated FDOPA K_i.

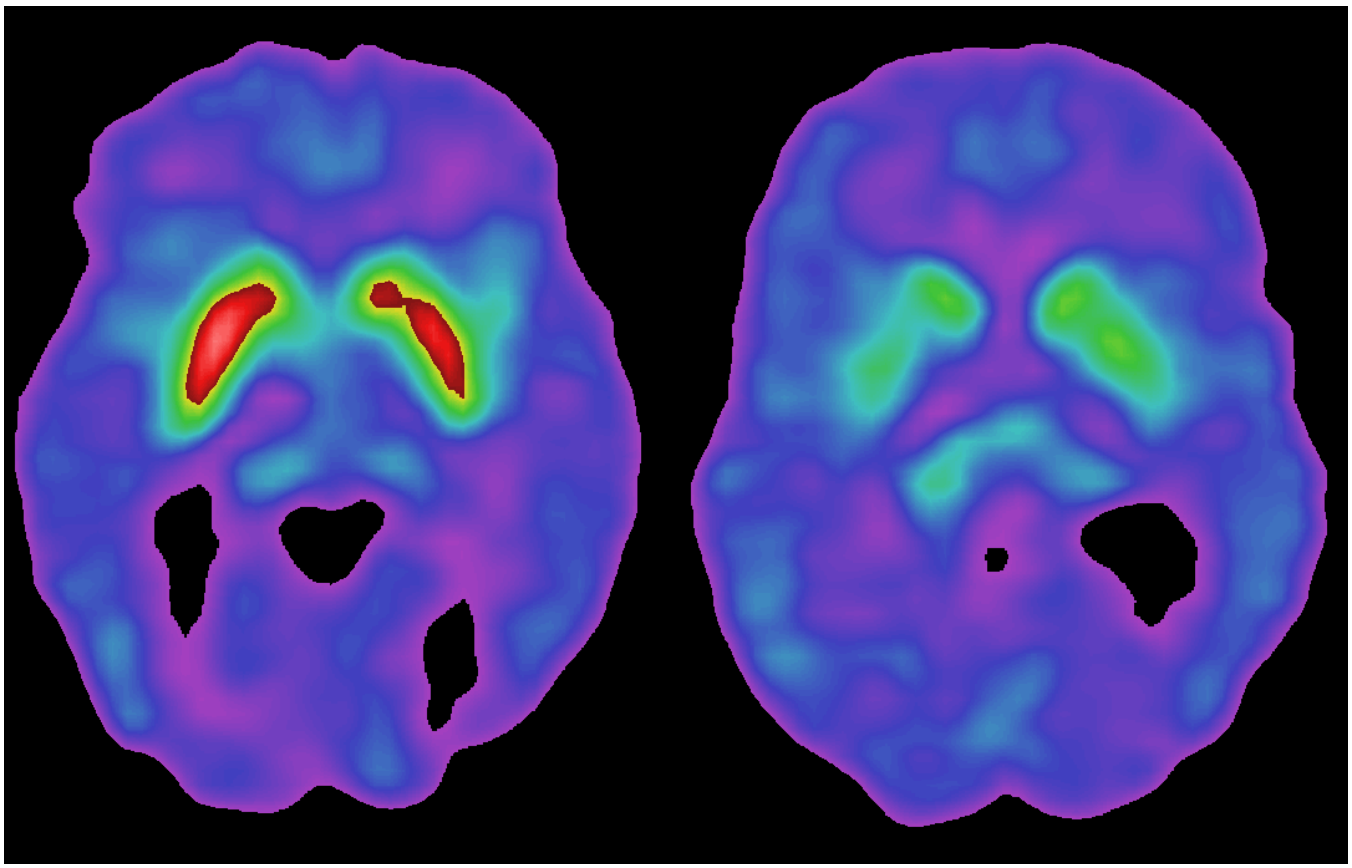


Measurements of Uptake or Influx of FDOPA

• ratio of specific /nonspecific uptake
(region of interest ^{18}F - occipital ^{18}F)/ occipital ^{18}F

• Determination of ^{18}F-FDOPA influx constant (K_1 or K_i) calculated with a multiple time graphical analysis method

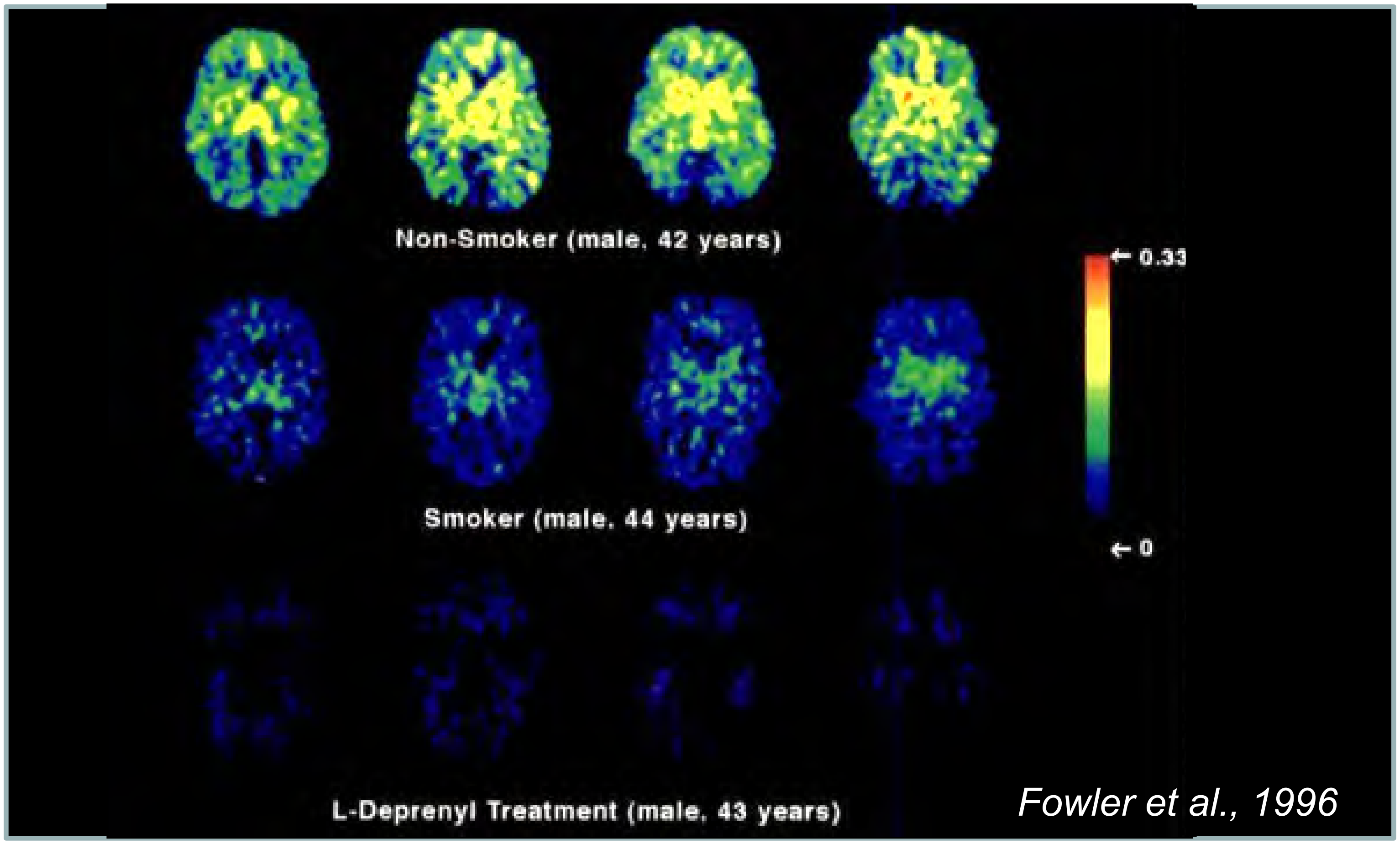
Loss of Nigrostriatal Innervation
[F-18]Fluorodopa and PET



Healthy Control   Parkinson's Disease

[[11]C]L-Deprenyl Labels Monoamine Oxidase B

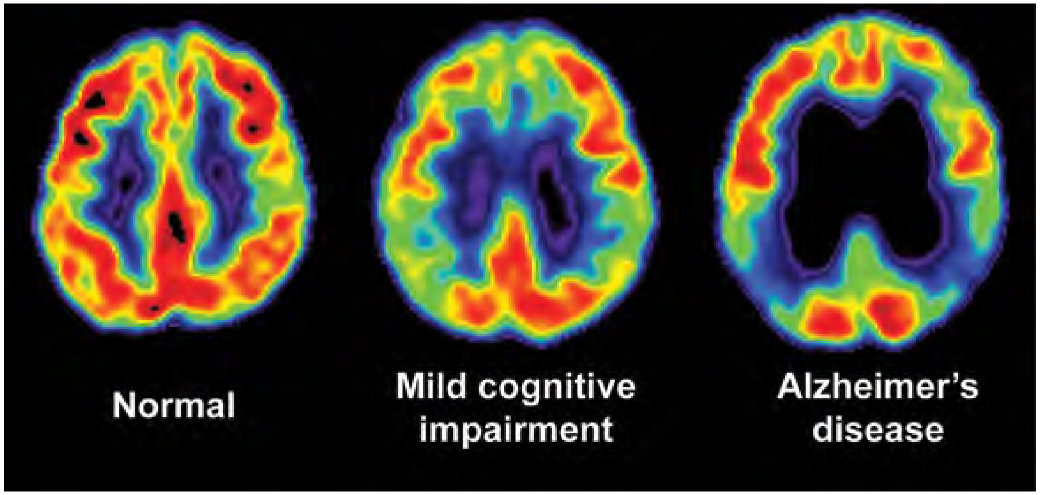
Smokers have low MAO_B activity



Castagnoli & Murugesan 2004 identified an MAO-B inhibitor in tobacco leaf extracts as 2,3,6-trimethyl-1,4-naphthoquinone (TMN), also in cigarette smoke.

Alzheimer’s Disease

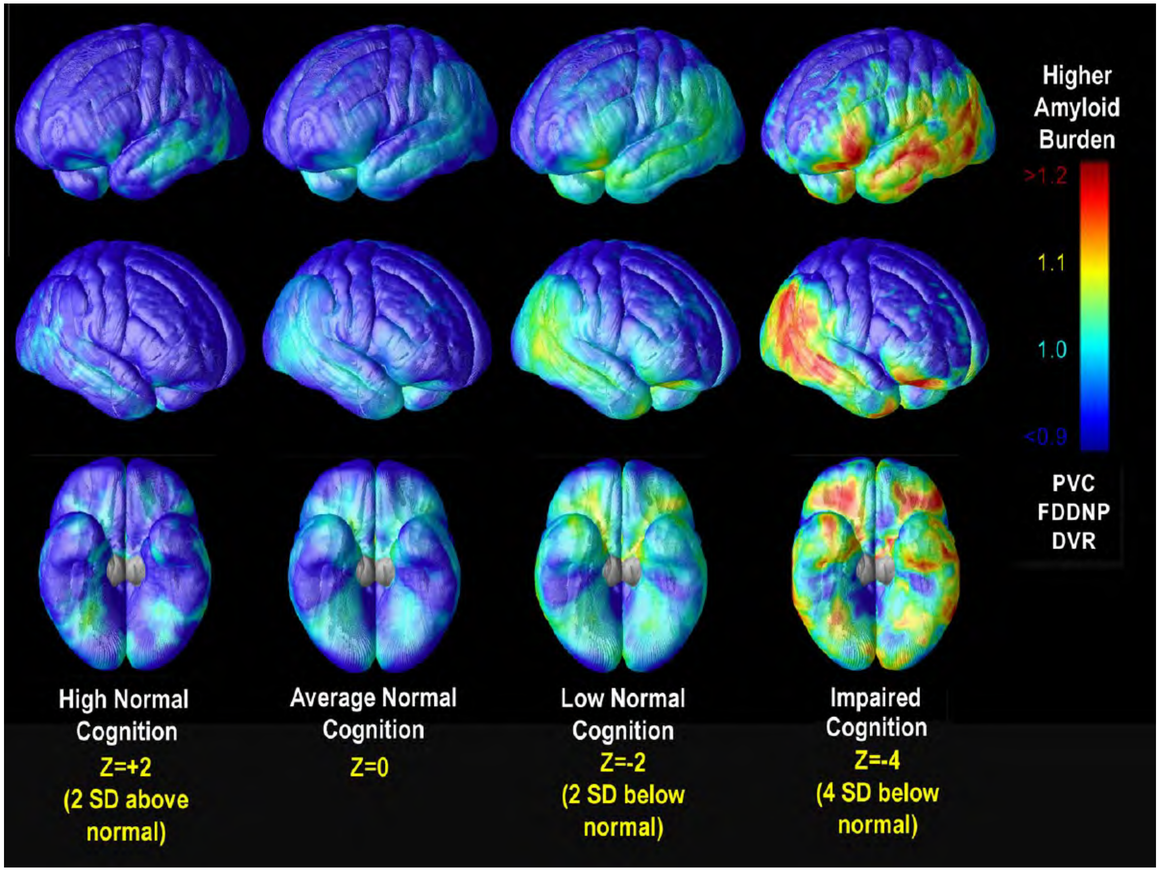
[^{18}F]FDG Shows *Deficits in Temporal-Parietal and Frontal Areas*



Jagust et al., 2010

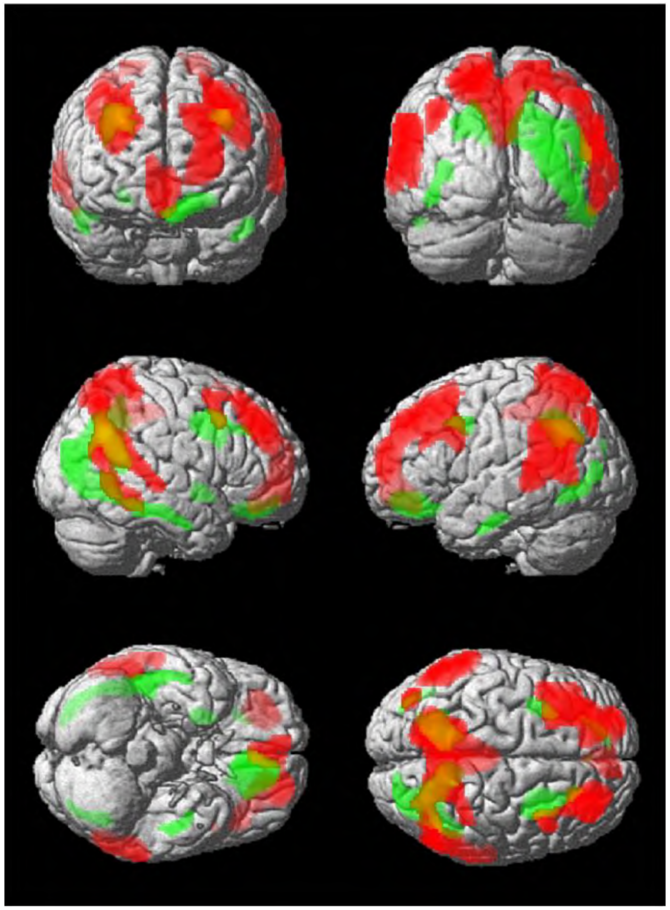
$[^{18}F]$FDDNP Binding: a Marker for AD Pathology

FDDNP binds to neurofibrillary tangles and amyloid plaques.
Binding is negatively related to cognitive performance.



Braskie et al., 2010

$[^{11}C]$PIB and $[^{18}F]$FDDNP



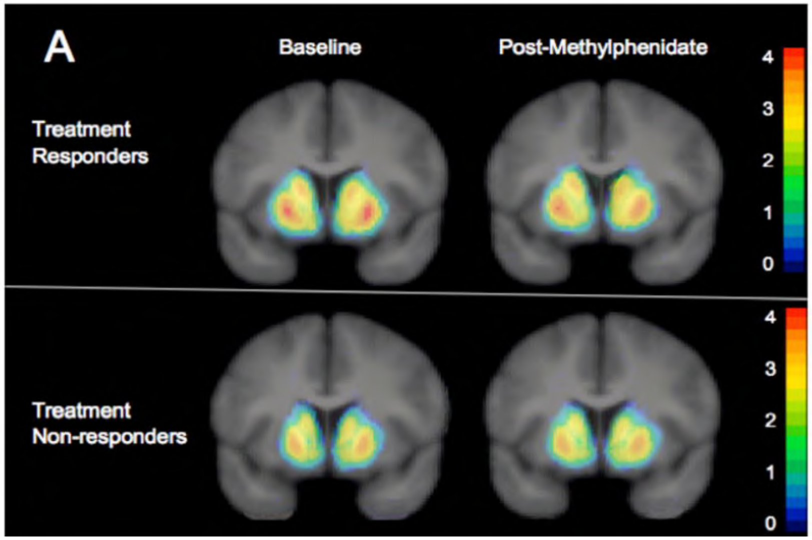
Colors indicate binding in AD subjects minus binding in Control subjects.

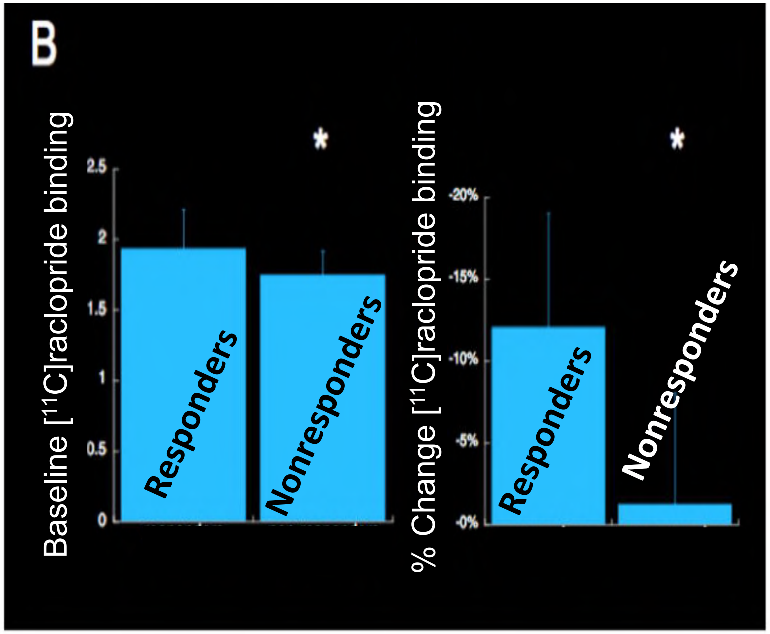
- $[^{11}C]$Pittsburgh Compound B (PIB) labels amyloid plaque deposition (red).
- $[^{18}F]$FDDNP labels plaques and tangles -- binding in regions of high tangle accumulation (green).

Shin et al., 2010

PET to Predict Treatment Outcome

D2/3 Receptor Binding Measured with [^{11}C]raclopride
Dopamine Release Assessed with Methylphenidate

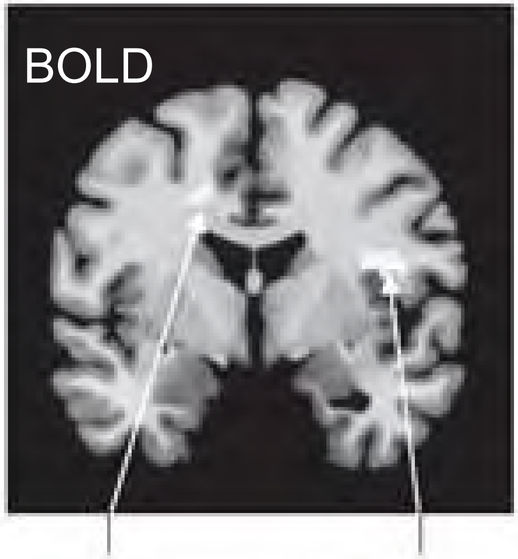


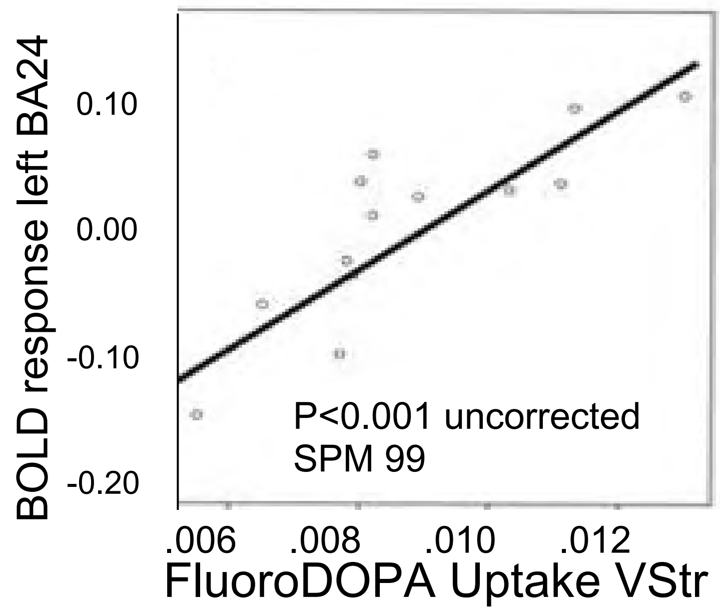


D. Martinez et al., 2011

PET fMRI Multimodality Imaging

Striatal DA Transmission Interacts with Central Processing of Rewarding Stimuli





FDOPA net influx in bilateral VST
is correlated with BOLD response in left ACC
elicited by positive vs. negative stimuli.

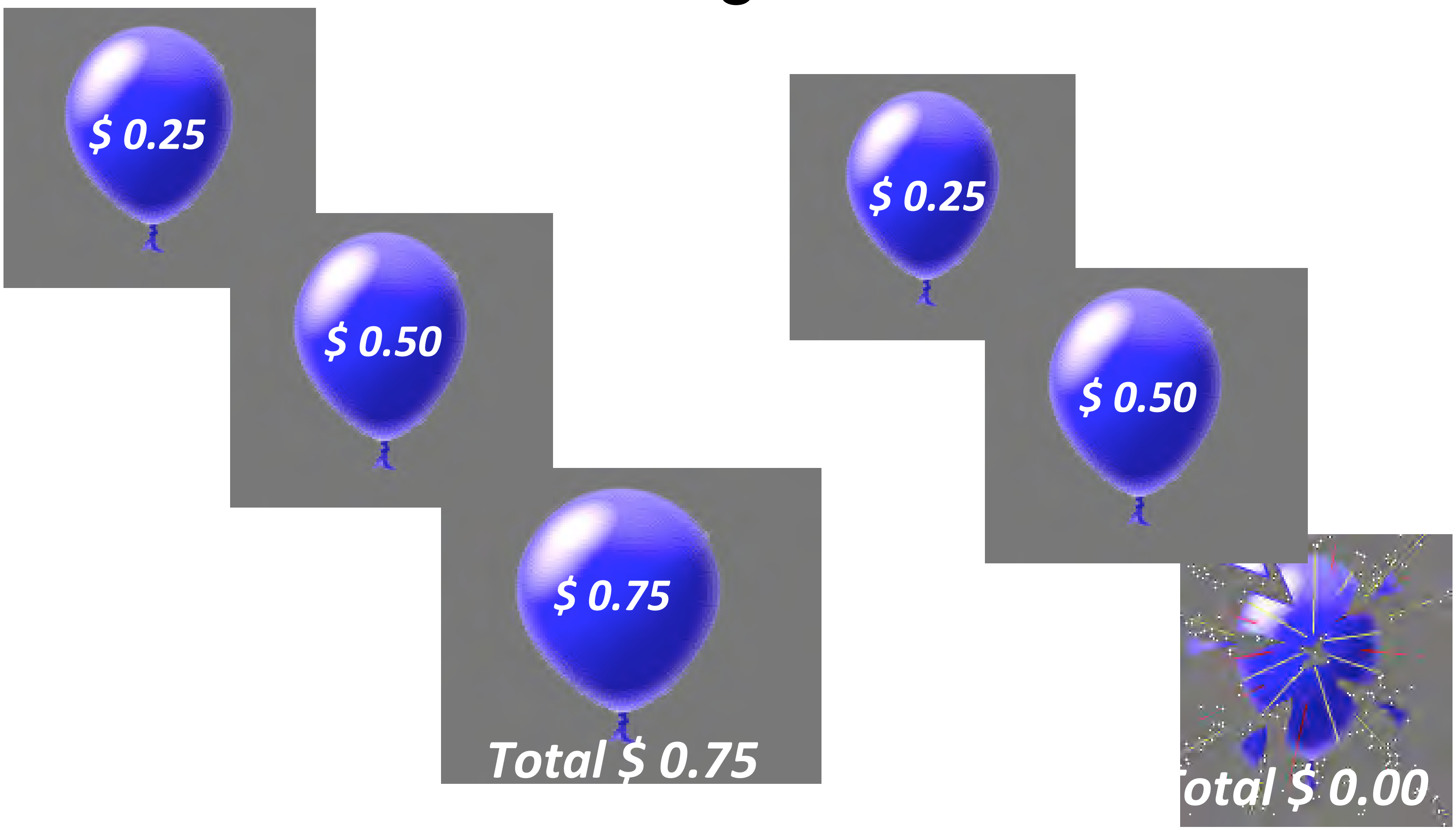
T. Seissmeier et al.,
Eur. J. Neurosci. 2006; 24, 305.

Striatal D2-type Dopamine Receptors and Complex Decision-Making

The Balloon Analogue Risk Task

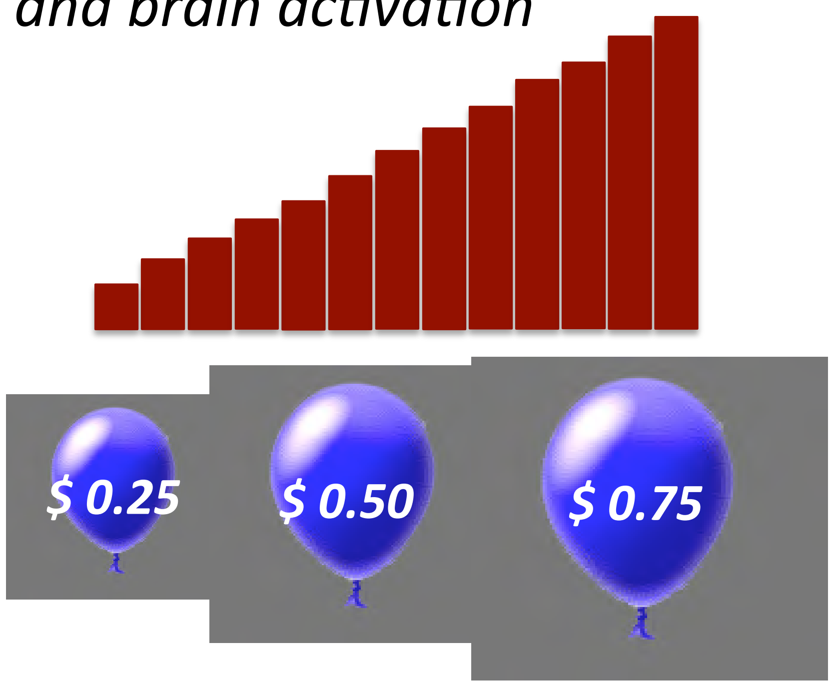
Striatal D2-type Dopamine Receptors and Complex Decision-Making

The Balloon Analogue Risk Task



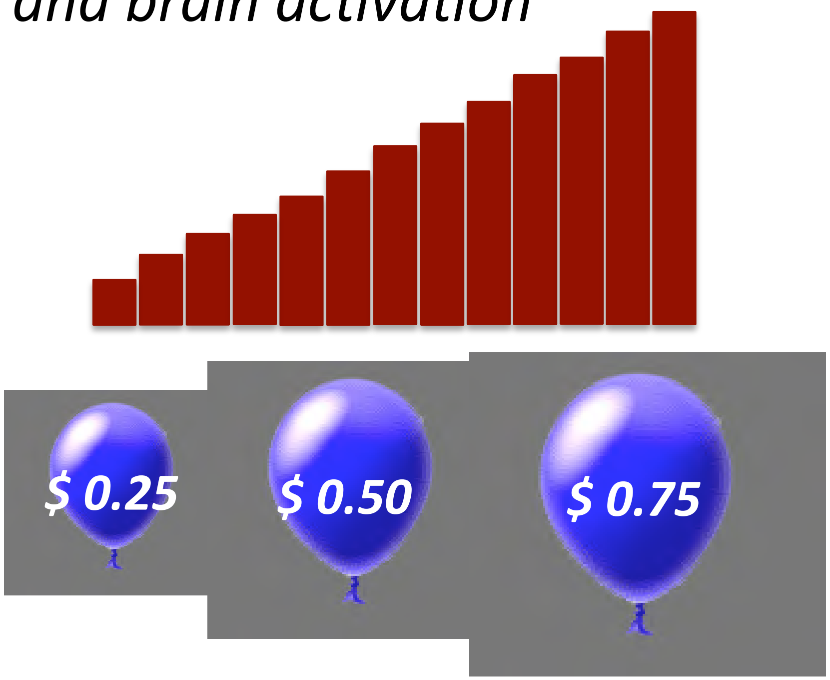
Parametric Modulation of Activation by Pump Number

Parametric analysis to test linear relationship between pump number and brain activation

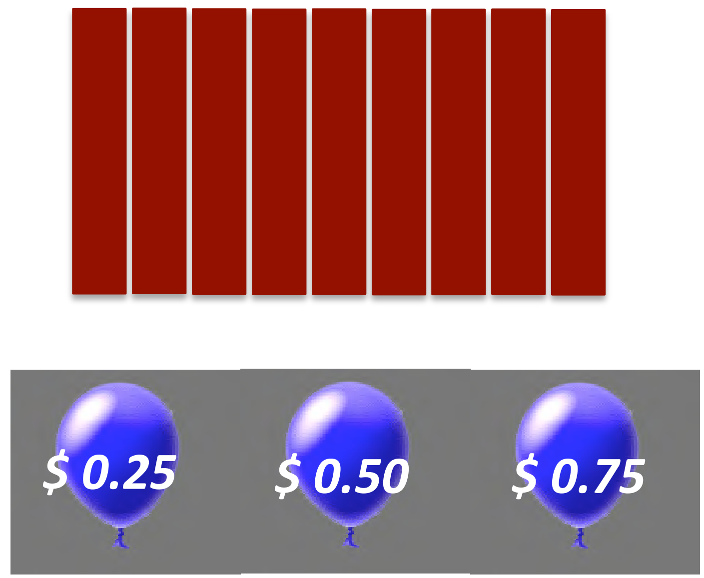


Parametric Modulation of Activation by Pump Number

Parametric analysis to test linear relationship between pump number and brain activation



Nonparametric regressors to control for mean activation with each event

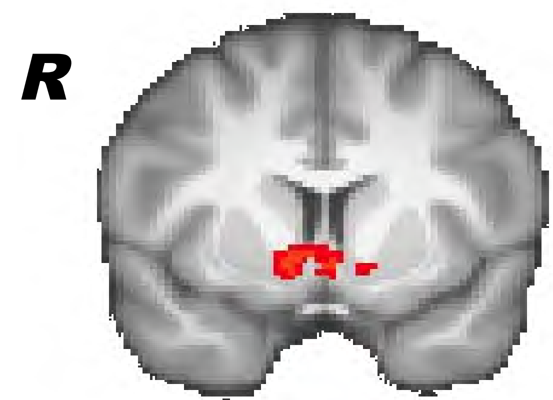


Frontostriatal Activity is Modulated by Risk and Reward

Pumping an active balloon (whole-brain Z-statistic map)

X=27

Cashing Out (whole-brain Z-statistic map)



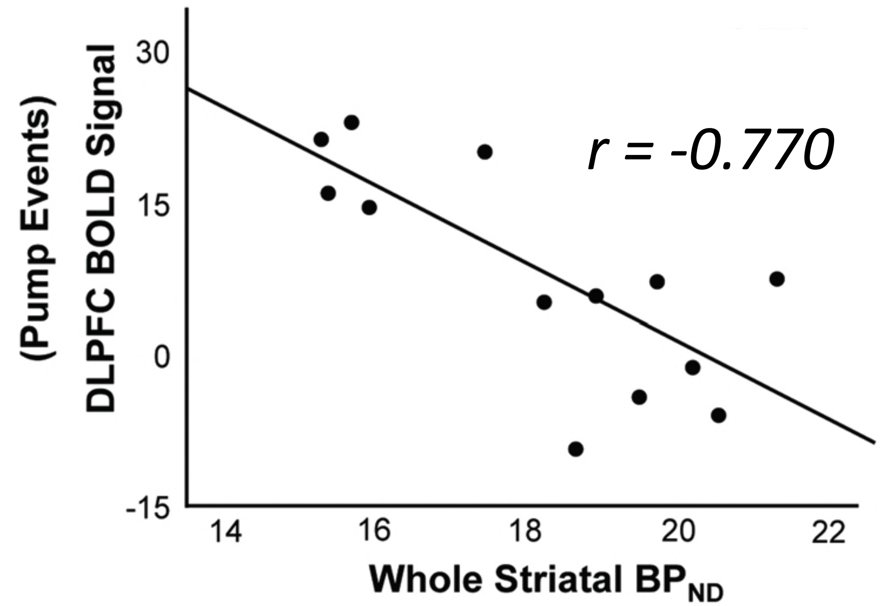
Y=67

M. Kohno et al., Cerebral Cortex, 2013

Striatal Dopamine Receptors and Risk-Taking

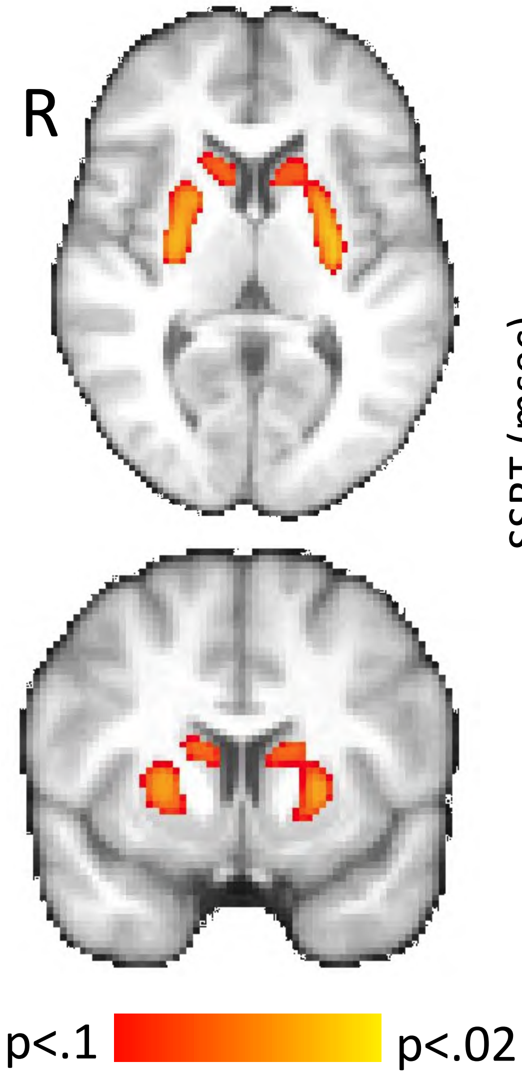
Cortical Activity is Modulated by Risk

Modulation is Related to Dopamine Receptors in Striatum



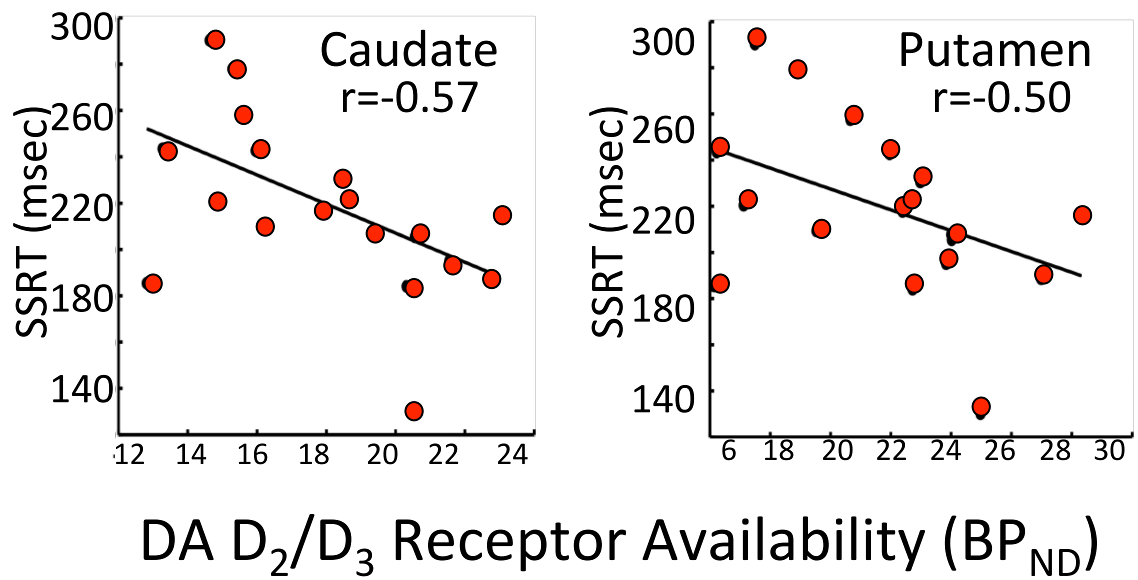
M. Kohno et al., Cerebral Cortex, 2013

DA D2/D3 Receptor Availability is Related to Stopping Ability



[18F]Fallypride PET

Healthy Control Participants

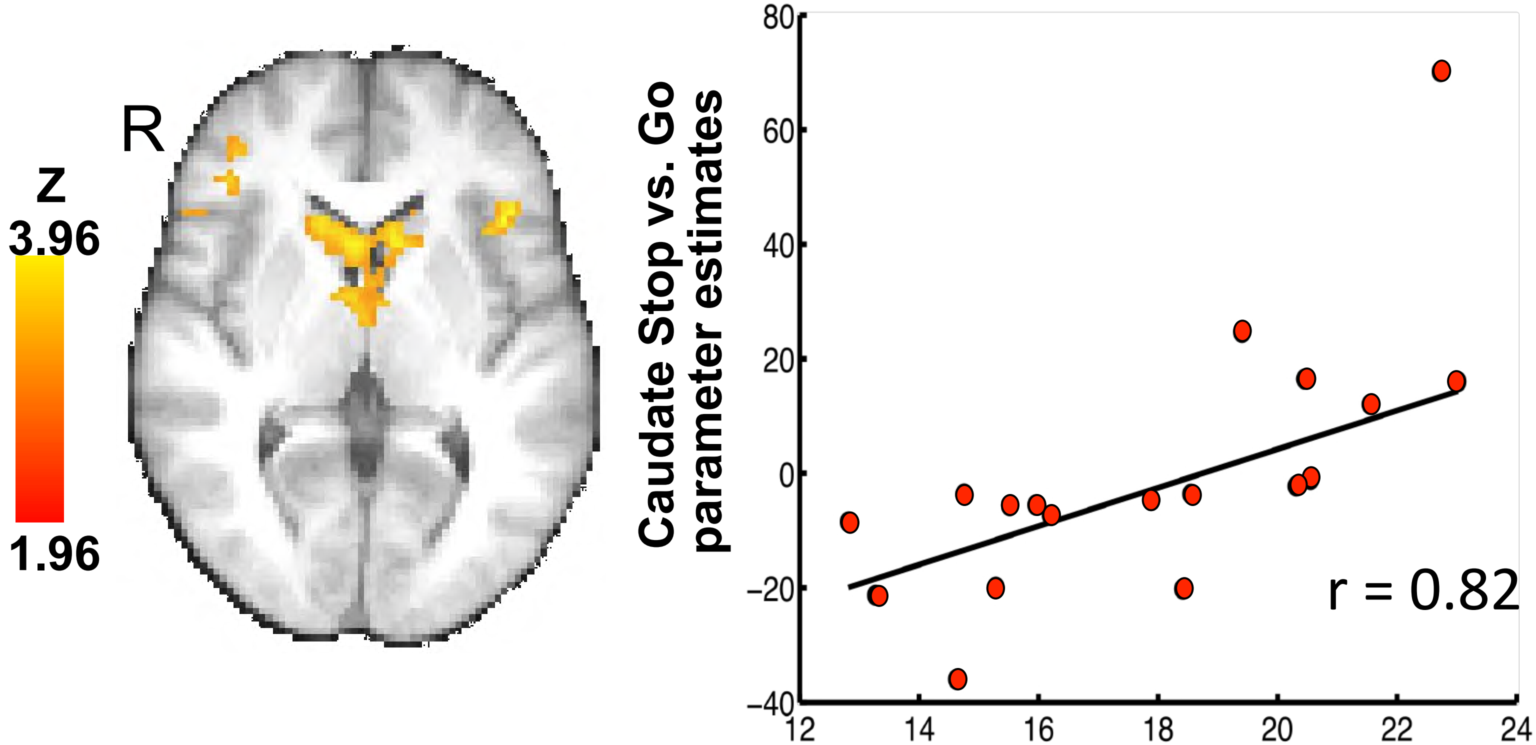


D Ghahremani et al., 2012

Caudate DA D2/D3 Receptor Availability is Related to Fronto-striatal fMRI Response during Inhibition

fMRI - [^{18}F]Fallypride PET

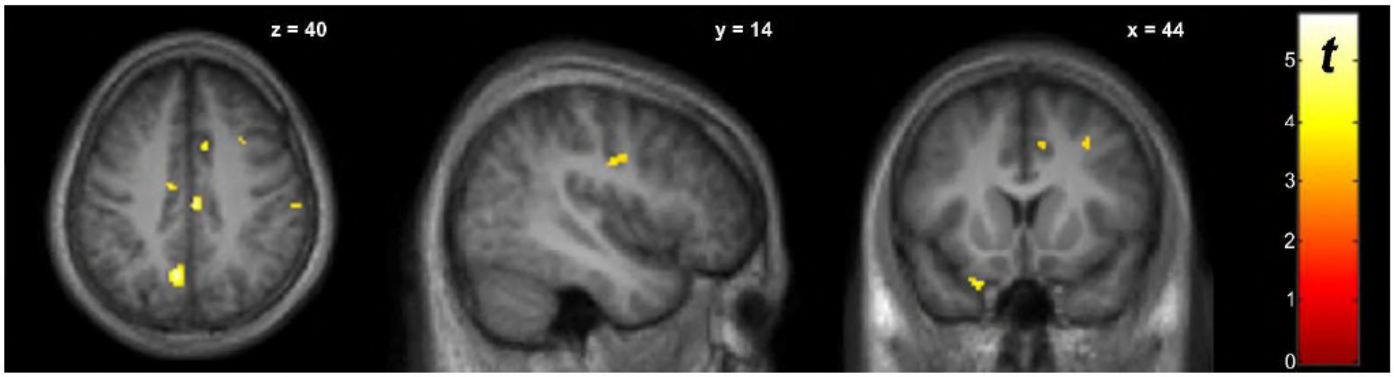
Healthy Control Participants



Caudate DA D2/D3 Receptor Availability (BP_{ND})

D Ghahremani et al., 2012

Cortical DA release during inhibition on the SST



Whole-brain voxel-wise paired t-test comparing BPND between baseline "Go" and SST scan conditions (n = 9). The "hot" colorscale indicates voxels where BPND, BL was significantly higher than BPND, SS (increased DA during SST). Display threshold $p < 0.005$, uncorrected, $k > 10$.

DS Albrecht et al., Synapse, 2014

Why do PET instead of another technique?

Molecular resolution

Specific biochemical processes (metabolic, enzymatic)

Neurotransmitter function

Pharmacological agents interacting *in situ*

Advantages of PET over fMRI:

For functional imaging:

When blood flow is not a marker for neuronal activity (e.g., when a drug has direct effects on microvasculature)

- Deoxyglucose method (FDG) – insensitive to changes in blood flow.

For assay of specific neurotransmitter systems:

- Can label tracers with C-11, F-18 -- *Chemical flexibility.*
- High sensitivity
  Assay of receptor binding requires ability to detect nM or pM concentrations.

Advantages of fMRI over PET:

Time resolution:

PET has a 10-minute window for repeat measurements with [O-15]water.

fMRI has temporal resolution beyond tens of milliseconds

Spatial resolution:

~2 mm for hi-res scanner (HRRT)

No need for ionizing radiation with fMRI.

Summary

Molecular neuroimaging with PET:

- Functional studies avoiding confound of direct vascular effects
- Neurotransmitter-specific probes
- Also enzymes and other metabolic markers
- Static and dynamic measures
- Animal studies possible
- Can be paired with fMRI – in multi-modality imaging.