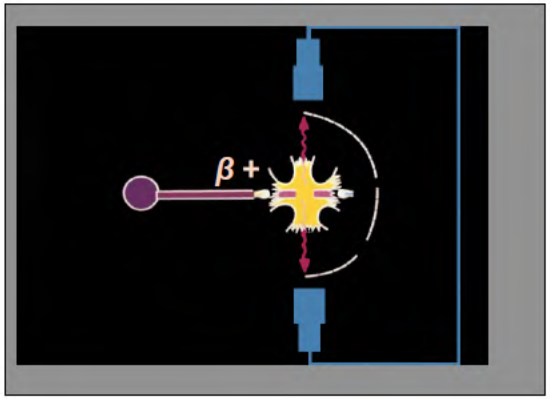
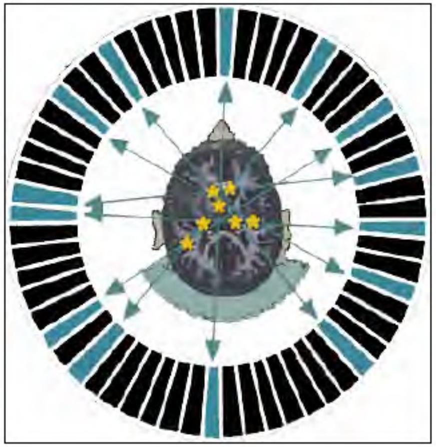
Principles of Neuroimaging

Positron Emission Tomography (PET) Applications





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310-825-0606
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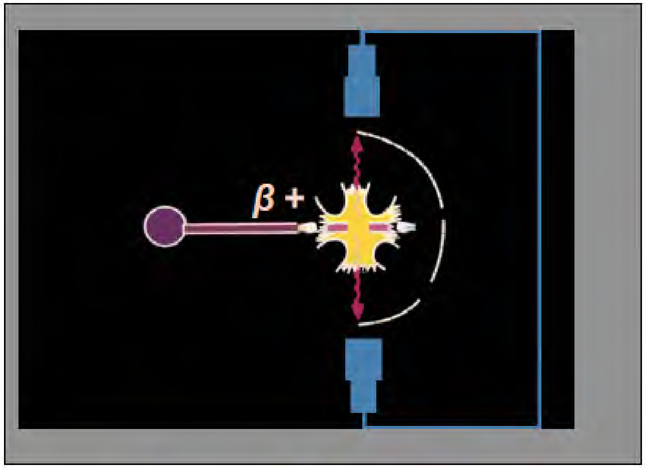
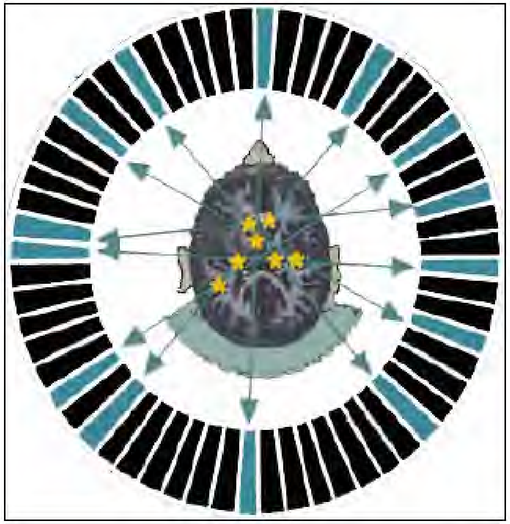
What is Positron Emission Tomography (PET)?

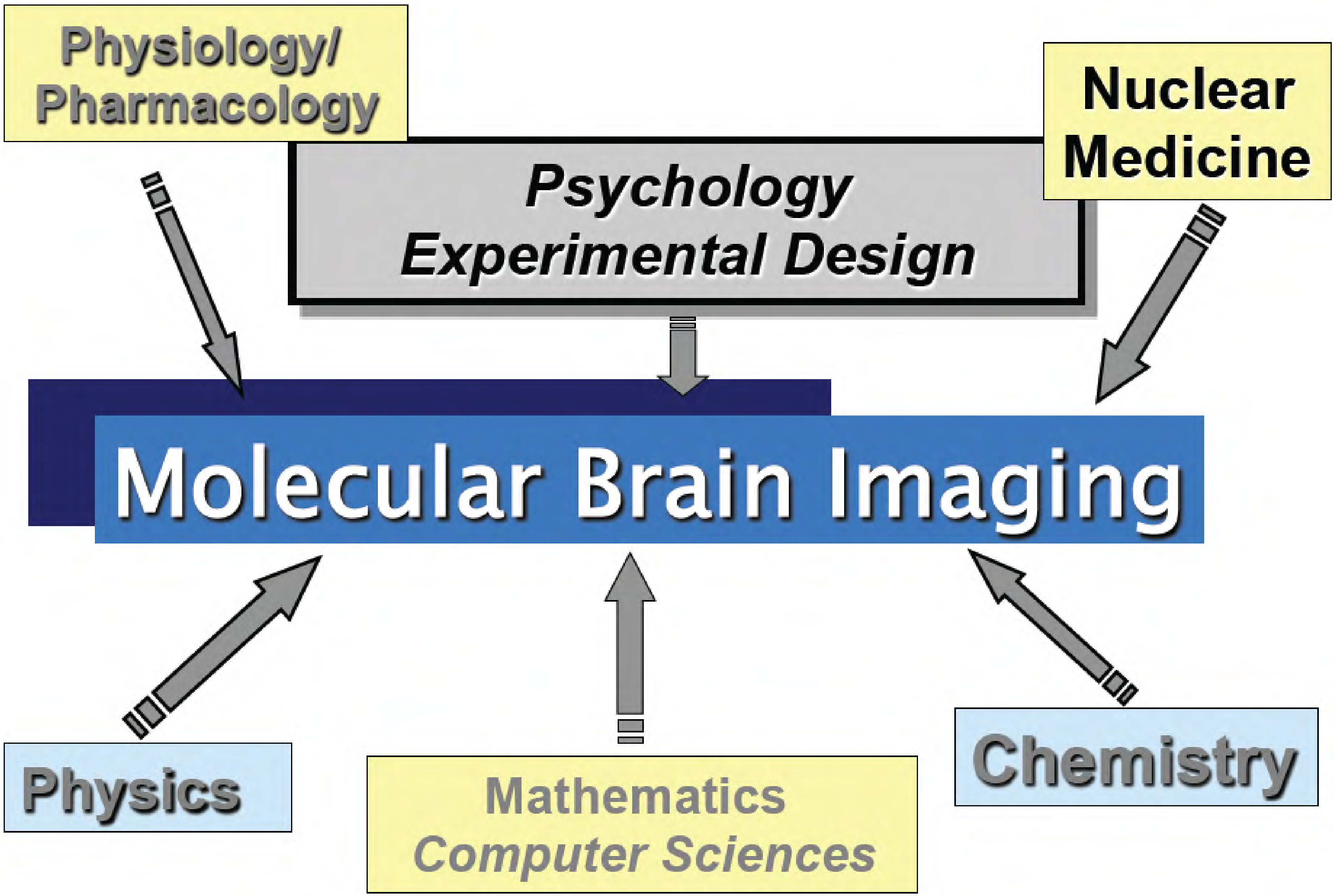
Tomograph is a picture of a slice



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?

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- Indices of regional brain function:

blood flow, glucose metabolism, O_2 *metabolism*

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- Dynamic changes in neurotransmitter function with cognition?

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  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:

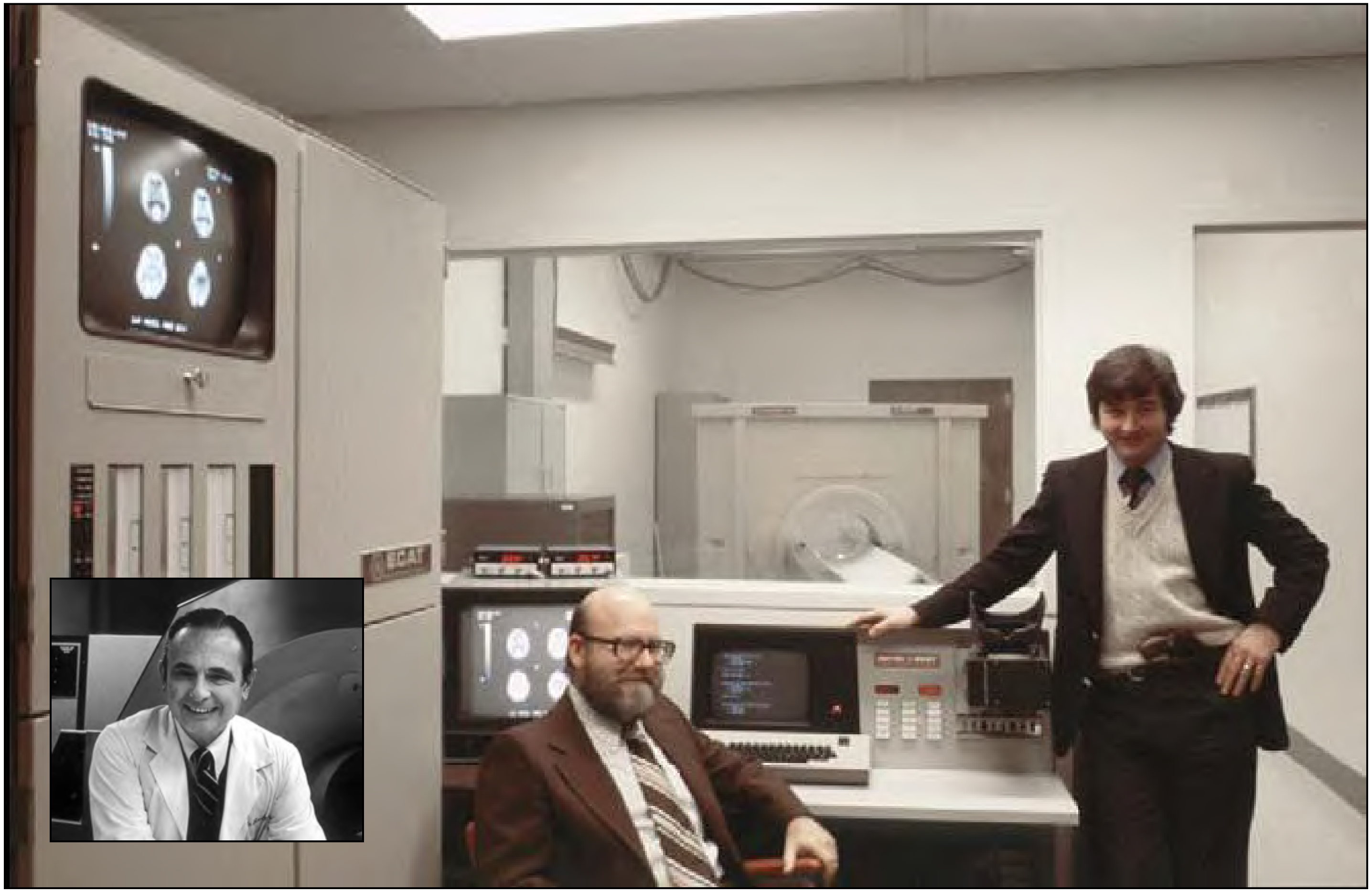
*[I-123]ADAM, [I-123]*β-CIT

Nicotinic Acetylcholine Receptor

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

Development of PET

PET III built in 1974 - Washington University

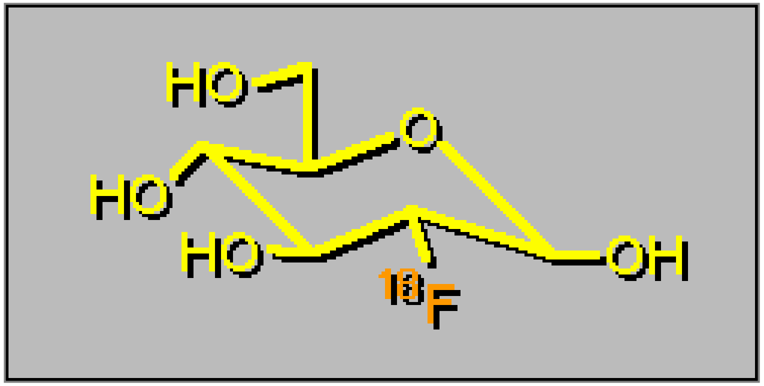


M. Ter-Pogossian **E.** Hoffman M. Phelps

Functional Imaging with PET

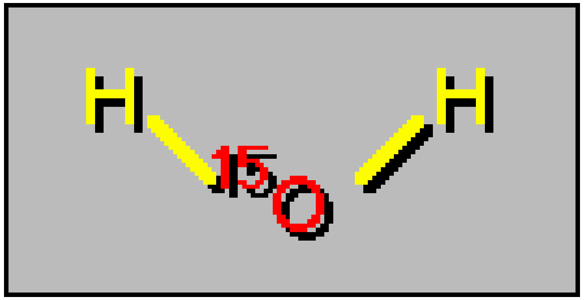
The brain uses glucose and O2 for energy.

Cerebral Glucose Metabolism



[F-18]fluorodeoxyglucose

Cerebral Blood Flow



[O-15]Water

Used less often:

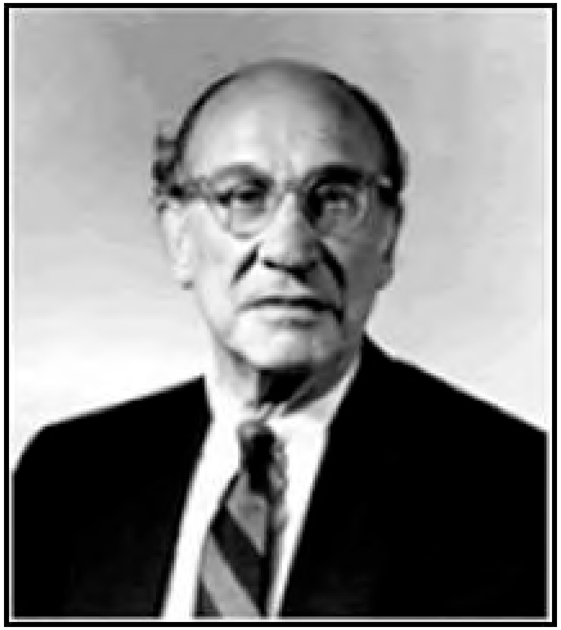
O-15 --*oxygen metabolism*

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

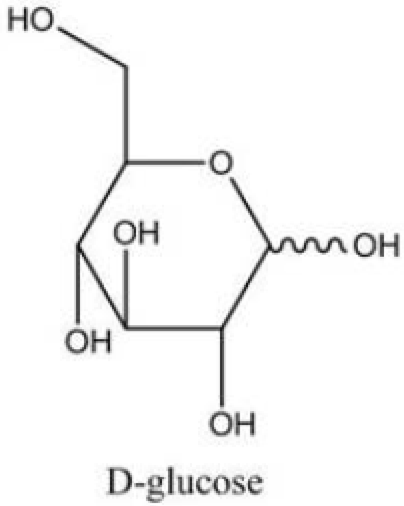
[C-11]acetate – *brain tumors*

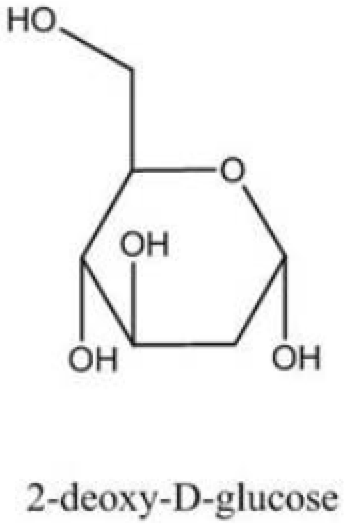
Beginning of Metabolic Mapping

The Deoxyglucose Method



L. Sokoloff

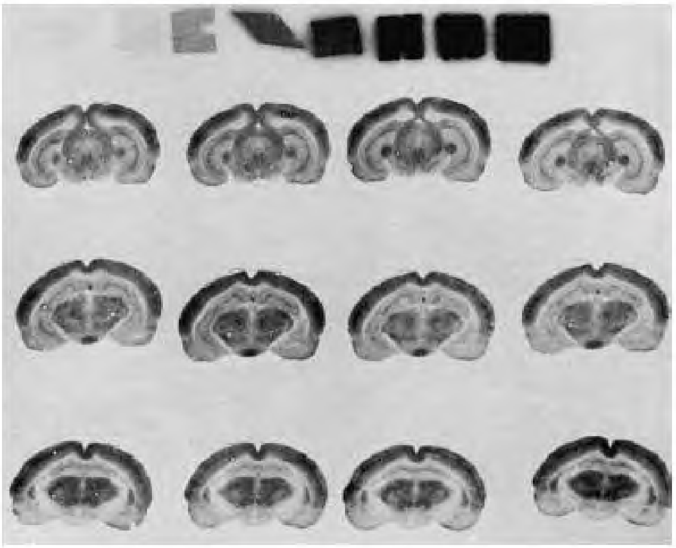




THE [^{14}C]DEOXYGLUCOSE METHOD FOR THE MEASUREMENT OF LOCAL CEREBRAL GLUCOSE UTILIZATION: THEORY, PROCEDURE, AND NORMAL VALUES IN THE CONSCIOUS AND ANESTHETIZED ALBINO RAT

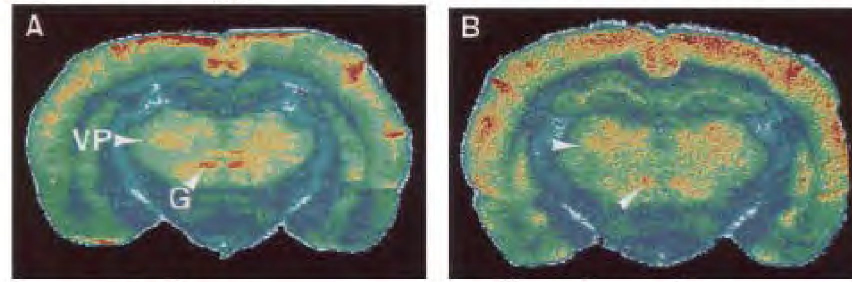
L. Sokoloff, M. Reivich, C. Kennedy, M.H. Des Rosiers, C.S. Patlak, K Pettigrew, O. Sakurada and M. Shinohara.
J. Neurochemistry, 1977

Quantitative Autoradiography Preceded PET

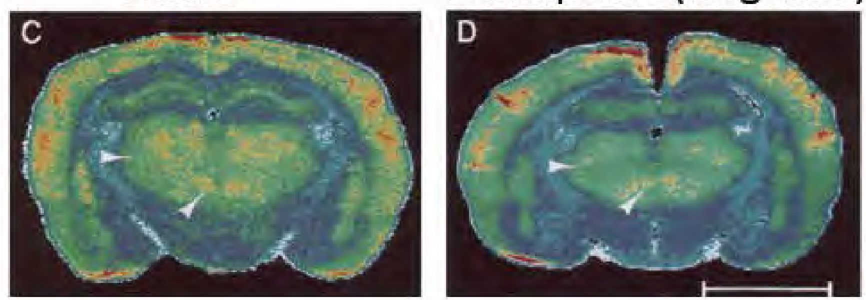


L. Sokoloff et al., 1977

Opioid Agonist Effects in Thalamus



Saline Nalbuphine (κ agonist)



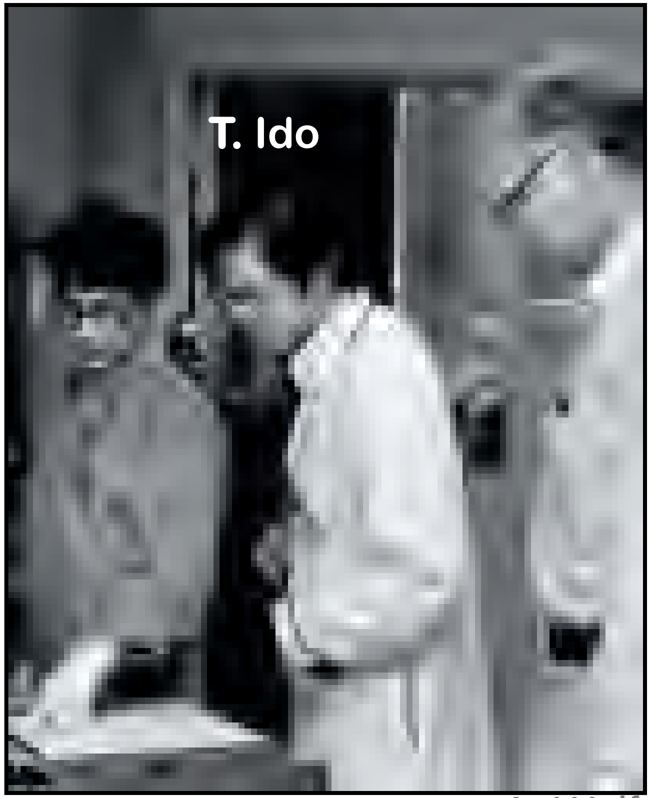
Morphine (μ agonist) Oxymorphone (μ agonist)

V= ventral posterior n.
G = gelatinosus n.

RF Fanelli et al., 1987

Adapting the Deoxyglucose Method for PET

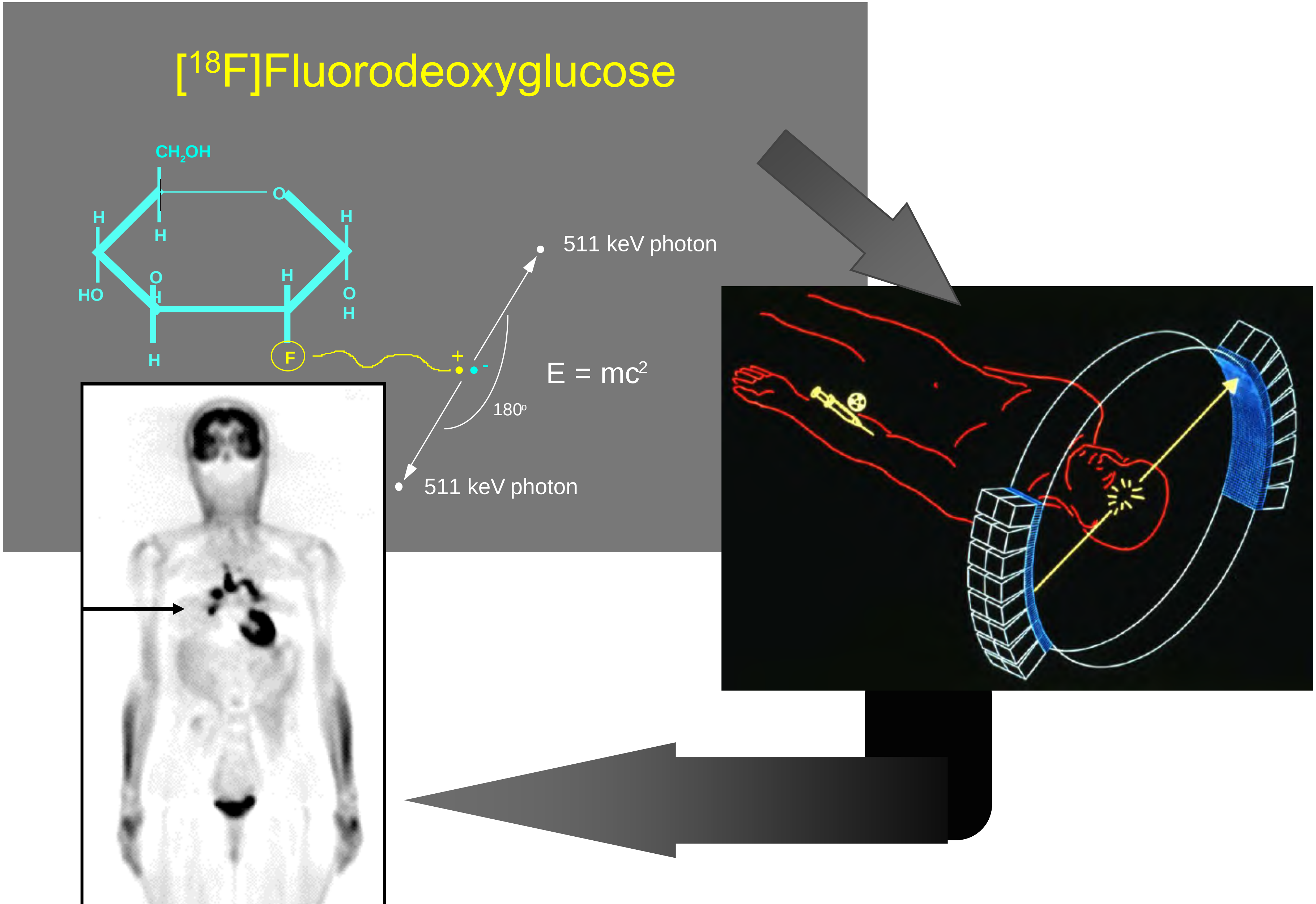
[^{18}F]Fluorodeoxyglucose Synthesis 1976



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



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

Tracer Kinetic Models

a mathematical framework for calculating rates of biological processes with PET

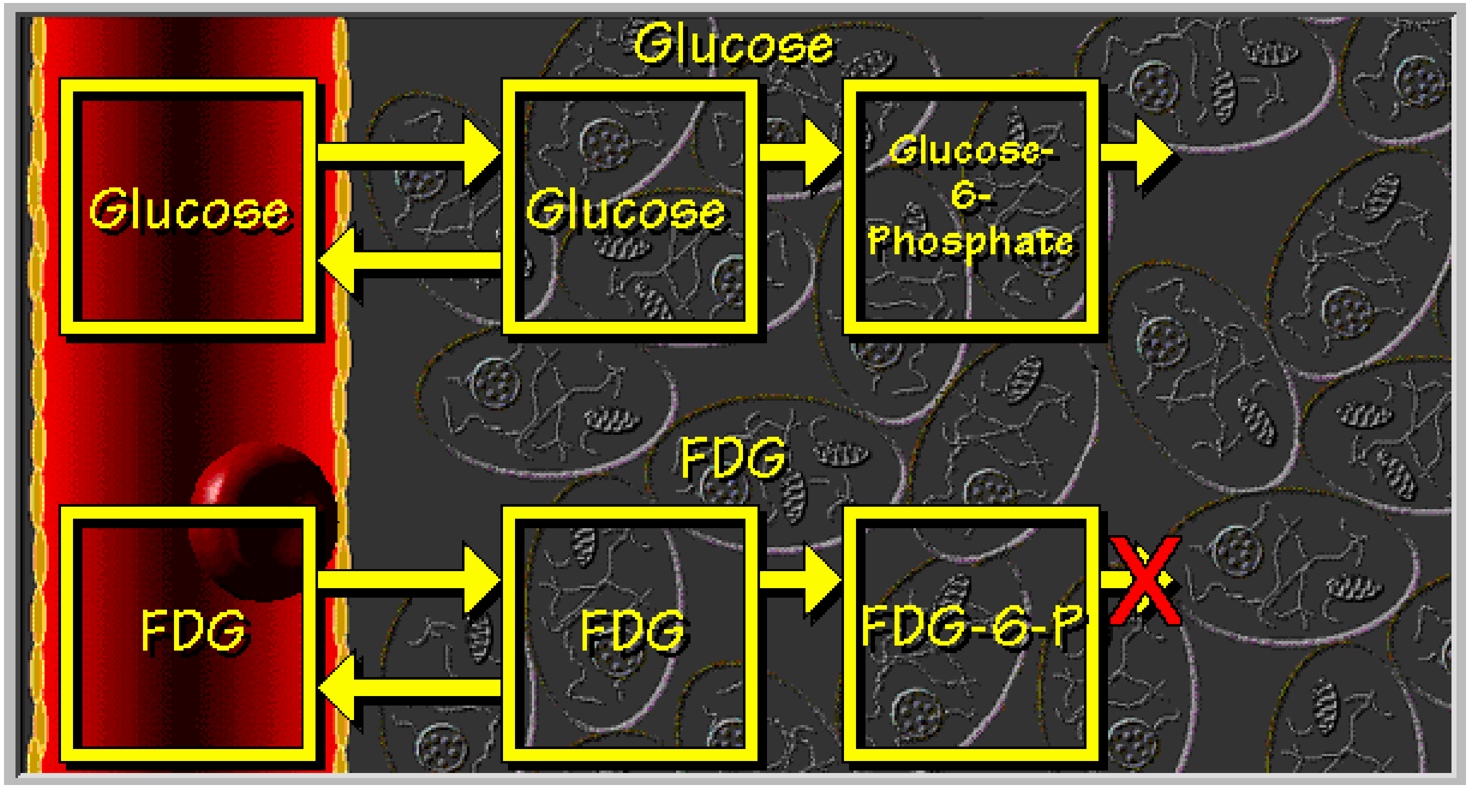
- Compartmental models - most common.
- Simplifications of biological systems.
- Formulated by differential equations describing exchange between compartments.
- Describe biochemical systems
- Require:

  - 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

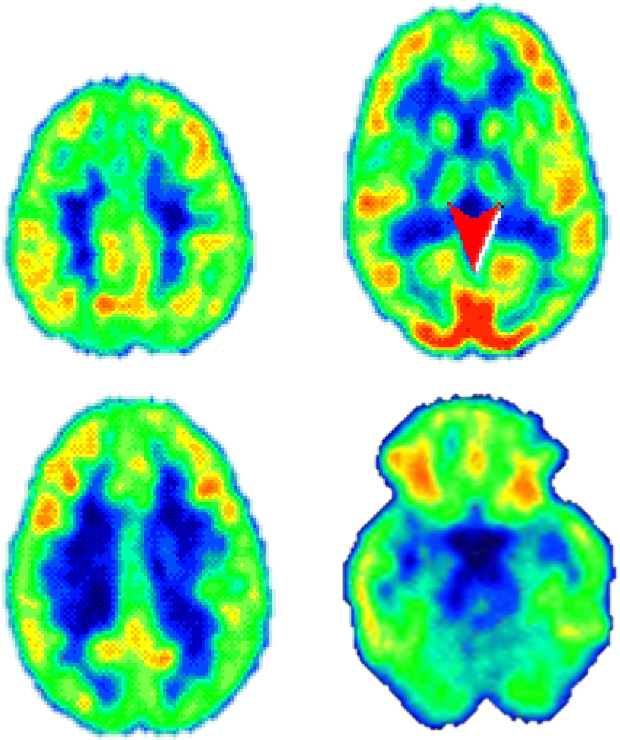
(R$_i$, rate of tracer incorporation)

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

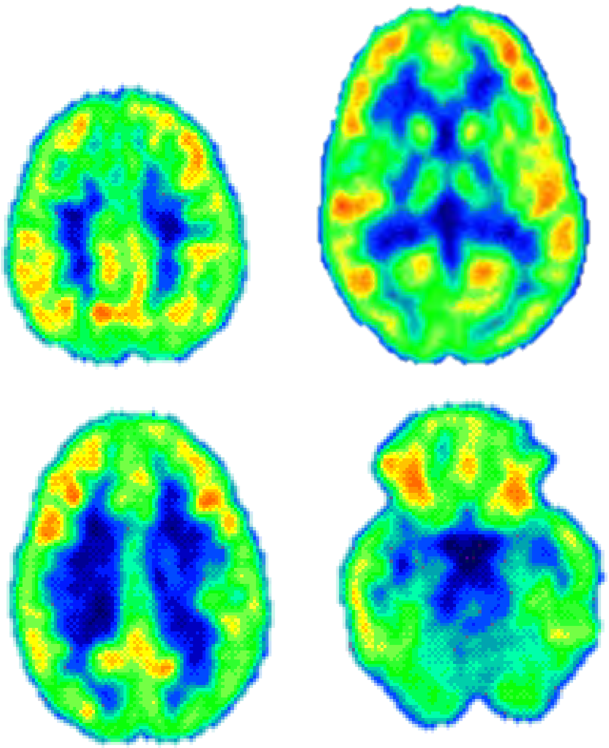
(replacing arterial with venous sampling
as in original Sokoloff 1977 method)

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

Visual Activation (FDG)



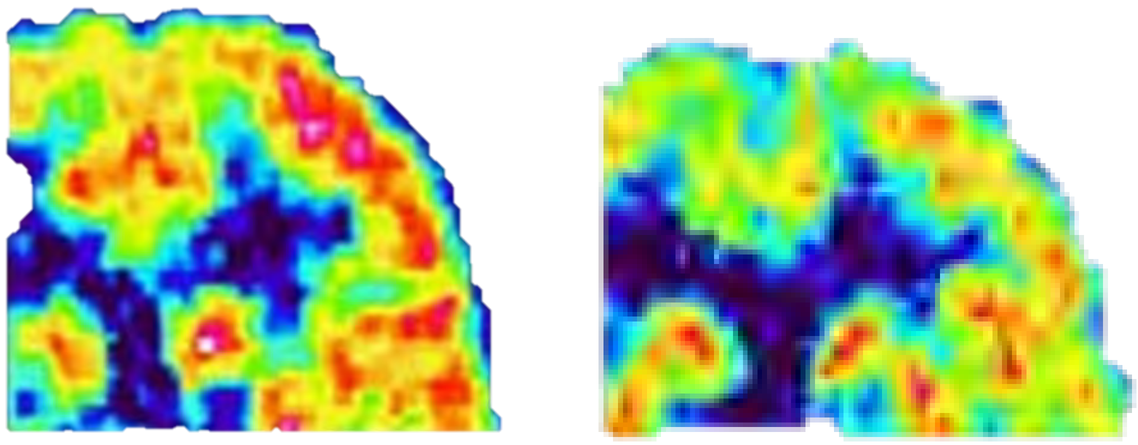
Resting Brain



Viewing a
Complex Scene

FDG PET Shows Disease-Related Dysfunction

Cortical Hypometabolism in Schizophrenia



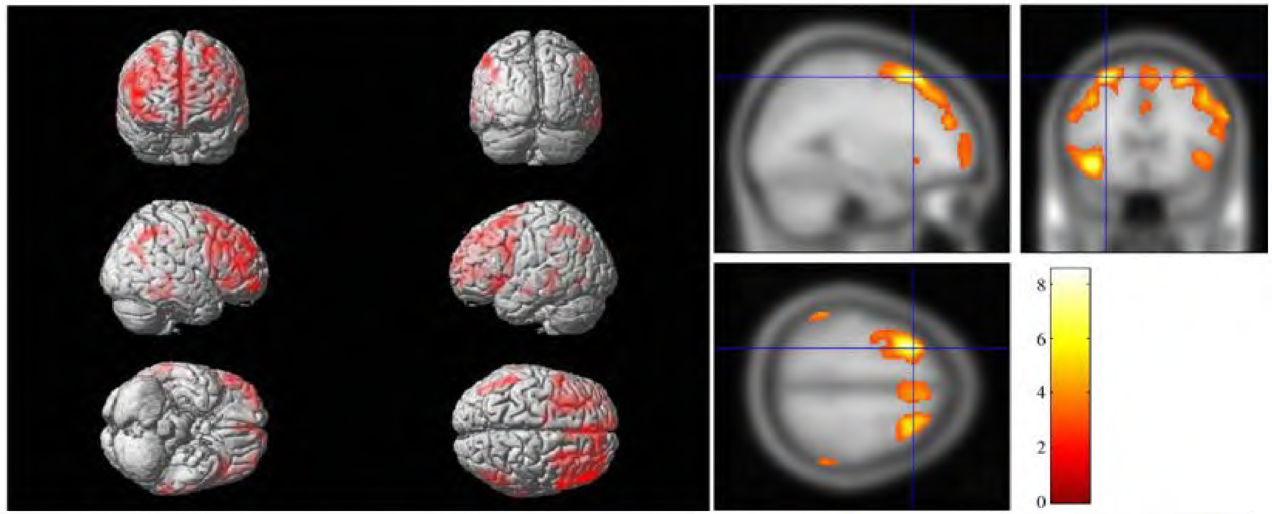
Healthy control   Schizophrenic

altered metabolic relationship between
frontal cortex, striatum & thalamus

[18F]FDG Reveals Cortical Deficit in Glucose Metabolism Bipolar and Unipolar Depression

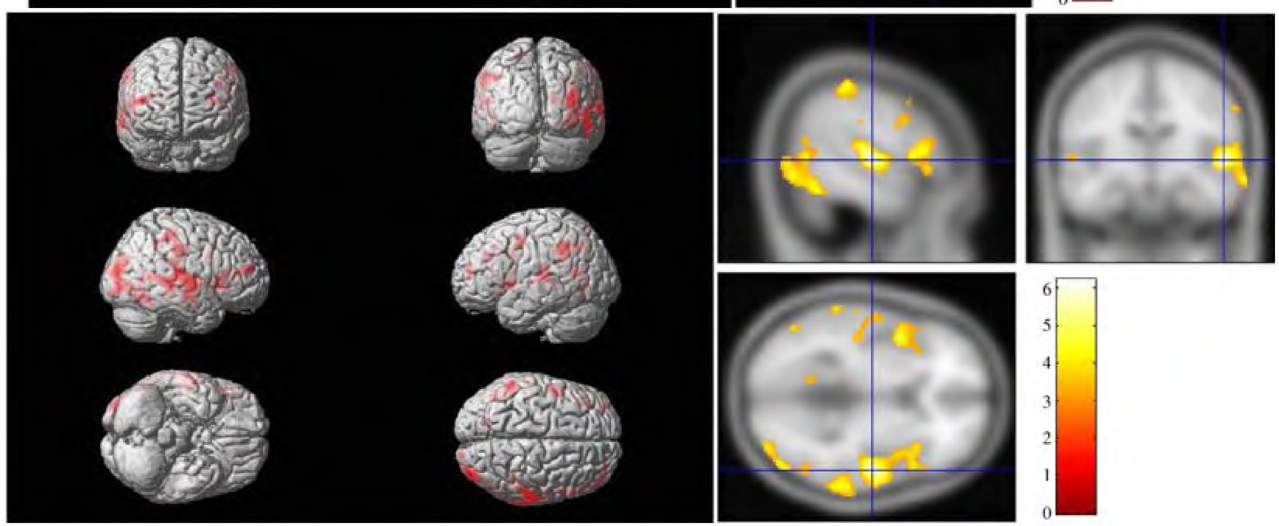
Bipolar Depression

colors indicate areas of lower glucose metabolism vs. control



Unipolar Depression

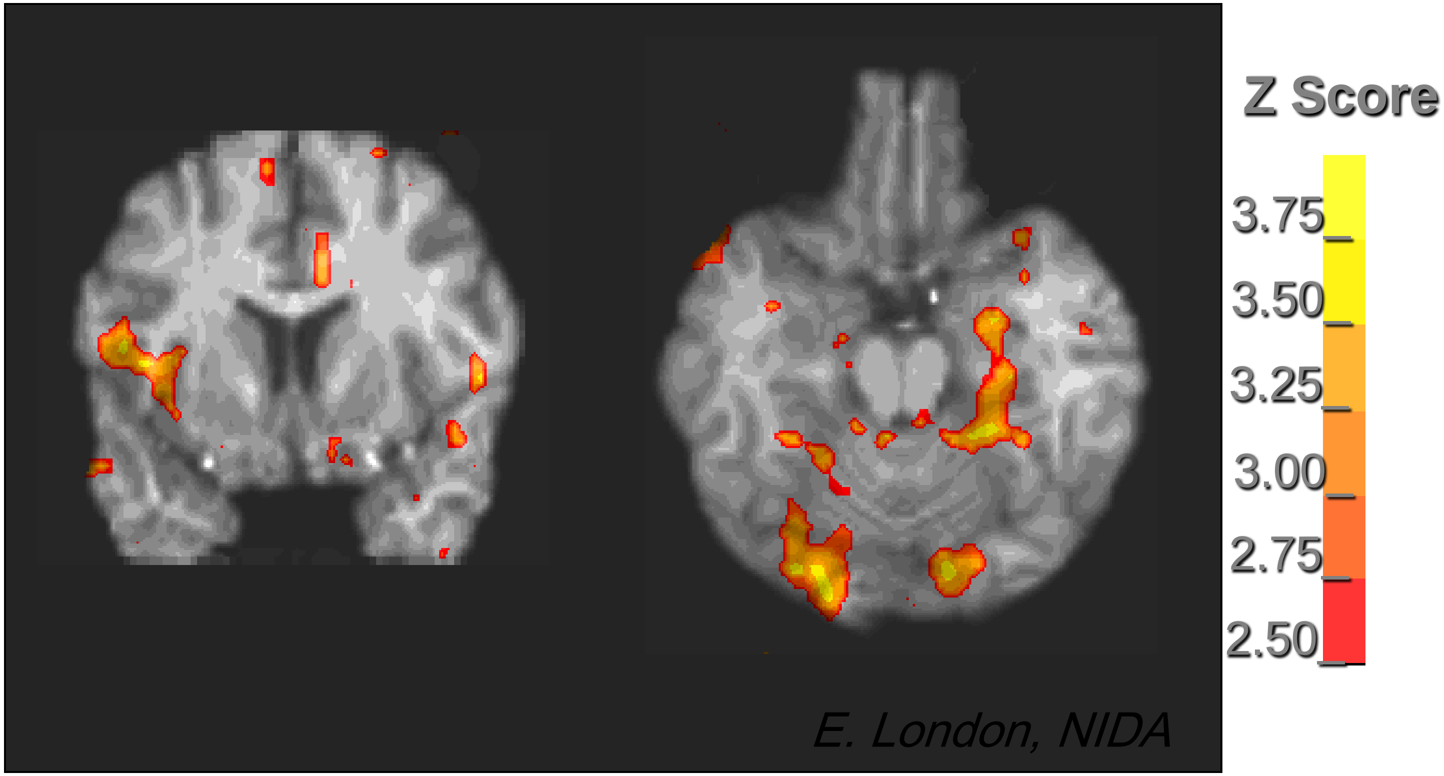
colors indicate areas of lower glucose metabolism vs. control



Hosokawa et al., 2009

FDG PET 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

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:*

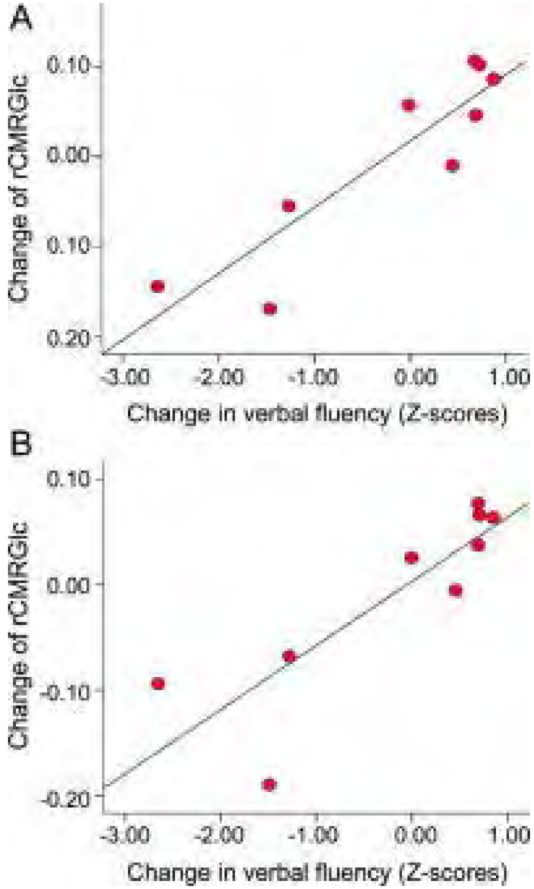
What regions/circuits are affected by a drug treatment?

Better with fMRI?

Yes, for cognitive challenge.
No, for drug challenge if drug affects vasculature directly.

When to use PET Instead of fMRI for Functional Imaging

Frontal FDG-PET activity correlates with cognitive outcome after STN-DBS in Parkinson disease



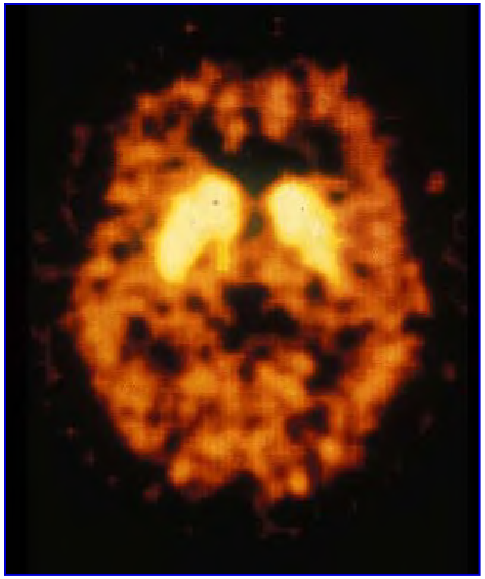
Postoperative changes of verbal fluency correlated with nCMRGlc alterations in the left DLPFC (BA46: $r = 0.90$, $p = 0.001$)

With nCMRGlc in left Broca area (BA 44/45: $r = 0.85$, $p = 0.004$)

E Kalbe et al., Neurology (2009) 72: 42-9

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

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

F = free ligand

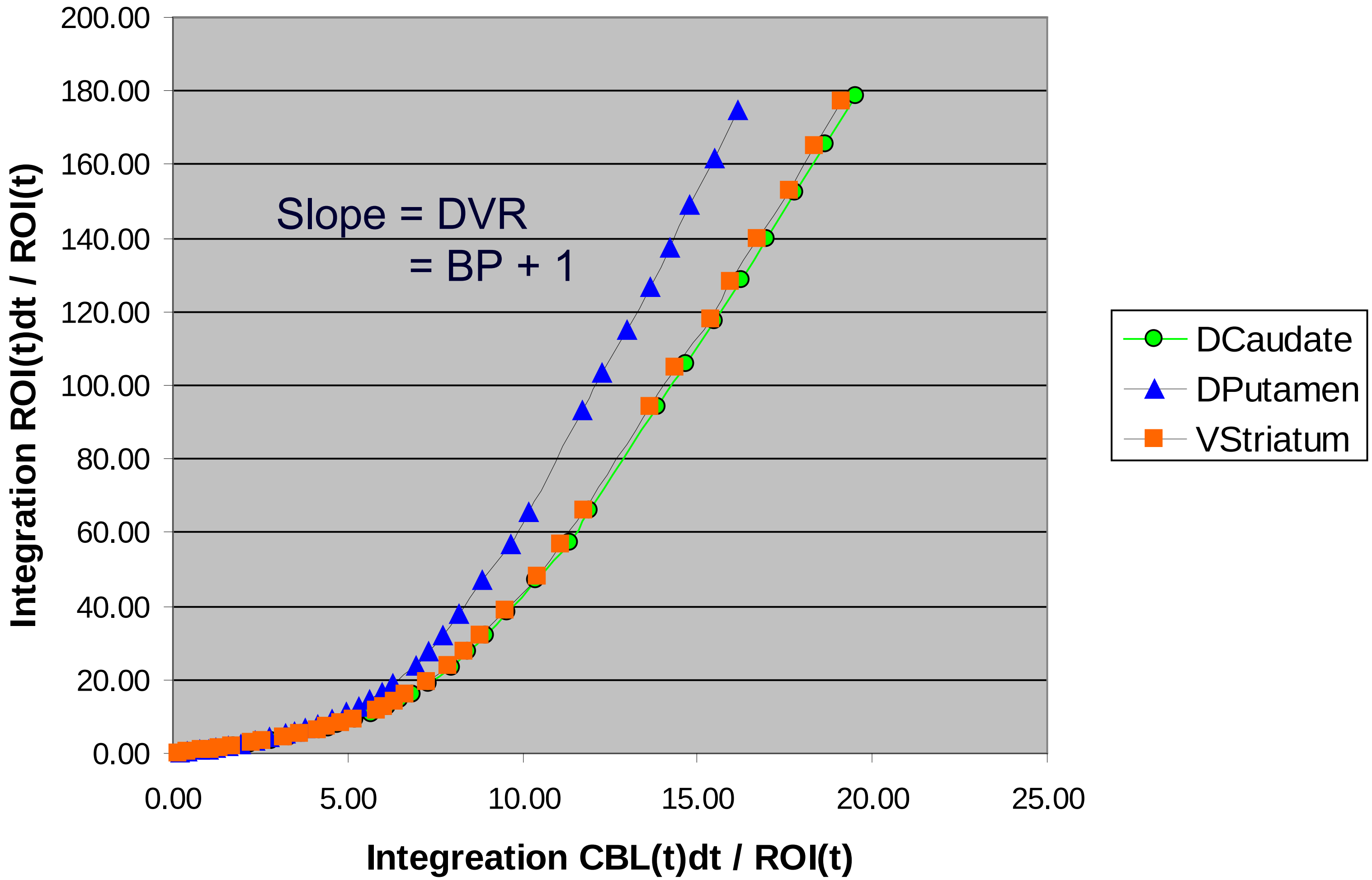
In plasma – Measure free ligand concentration directly (metabolite correction).

In brain – Measure radioactivity after calibration (phantom).

Model distinguishes free from bound radioactivity.

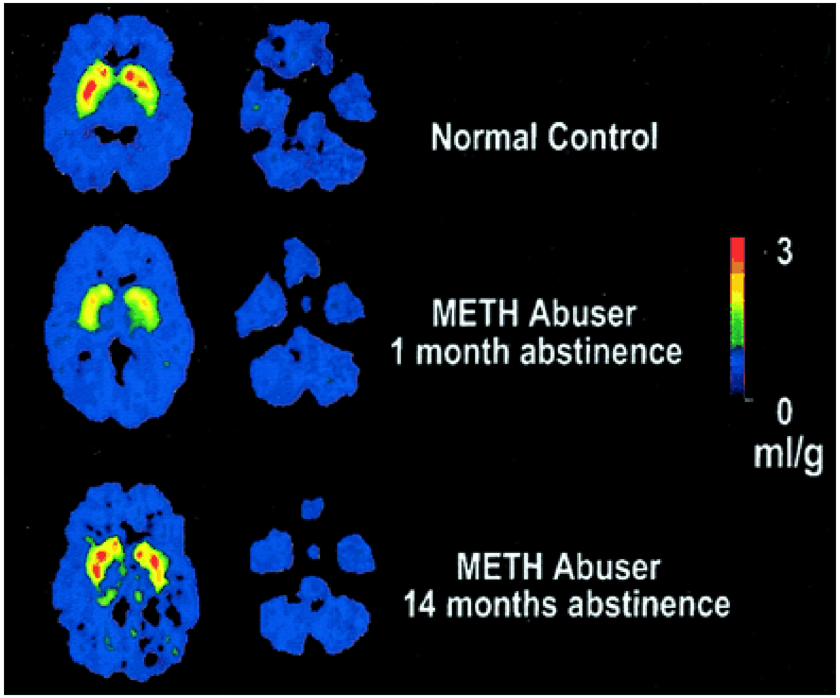
Binding Potential: Receptor Availability

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.

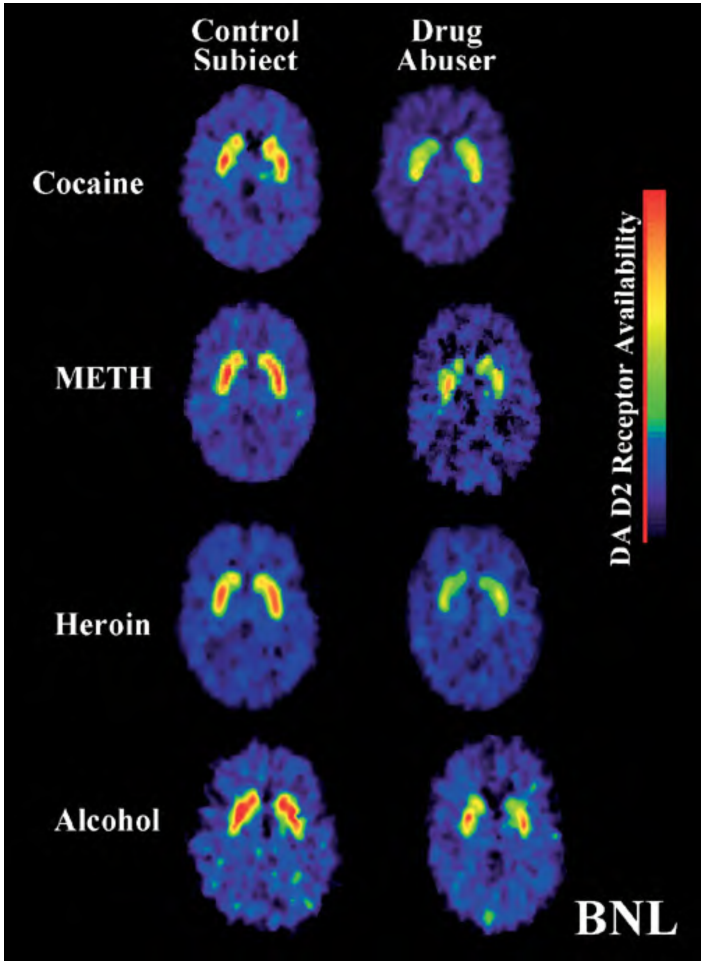


- No differences in K1 between short vs. protracted abstinence.
- Increased binding to DAT in striatum (not cerebellum).
- DAT recovery was negatively correlated with amount and years of METH use.

Abuse severity may limit recovery.

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

Addiction: Low D2-like Receptor Availability



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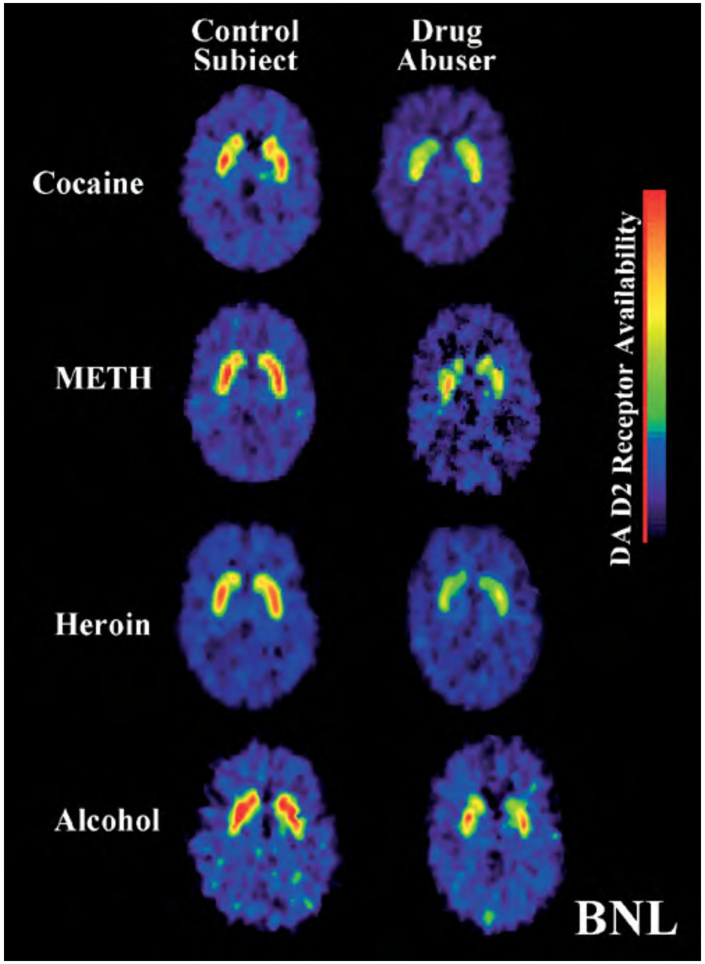
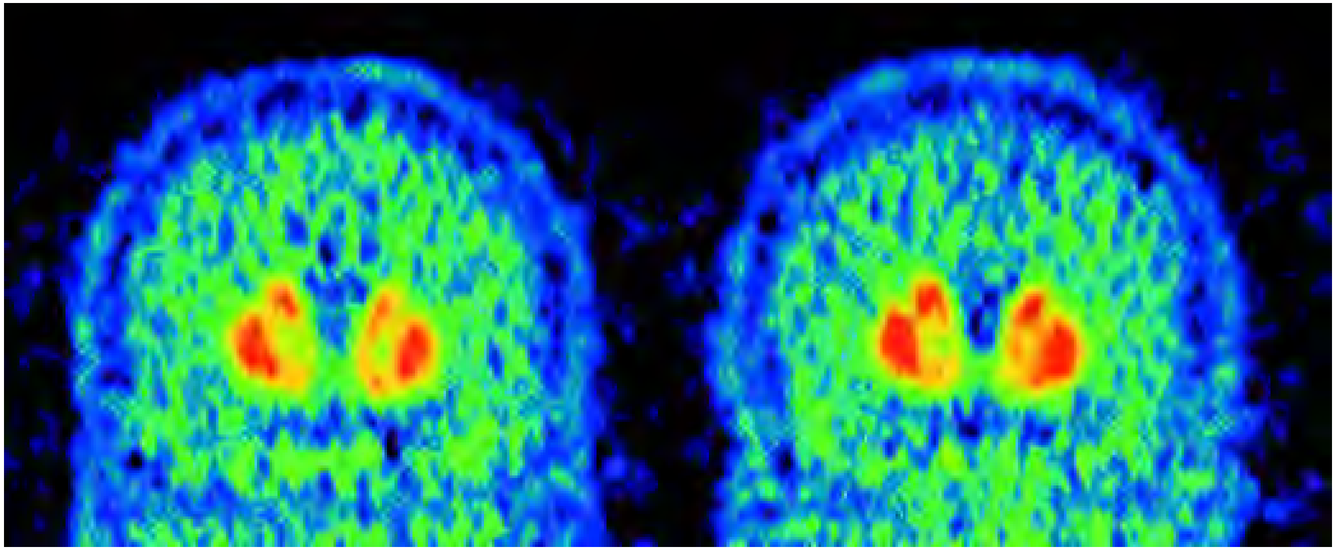


Is it all about receptor density?

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

Effect of Endogenous DA on Binding Potential

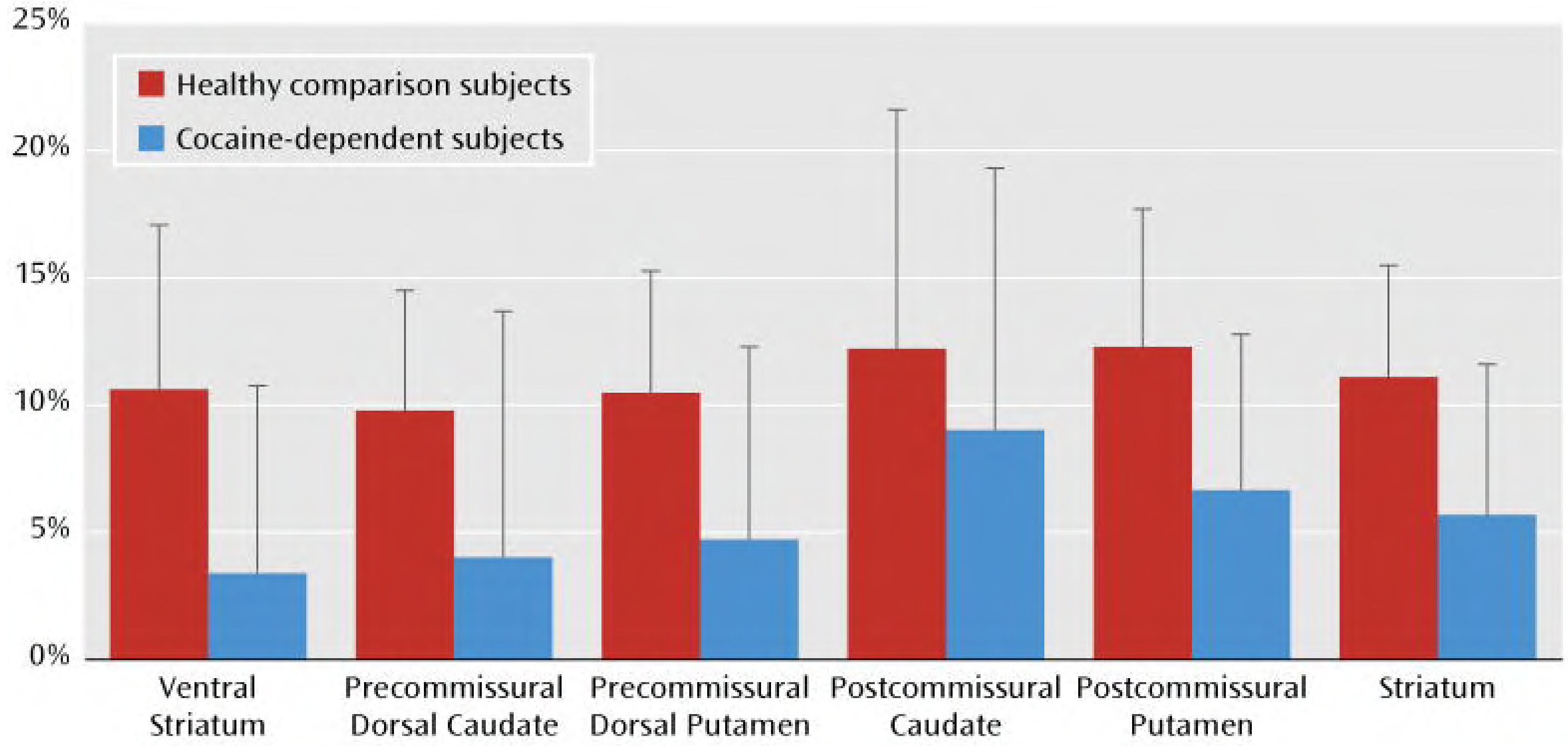


Placebo

α – Methylparatyrosine

Decreased DA synthesis ➡ less competition from endogenous DA ➡ enhanced radiotracer labeling.

To What Extent is BP Affected by Endogenous Dopamine?

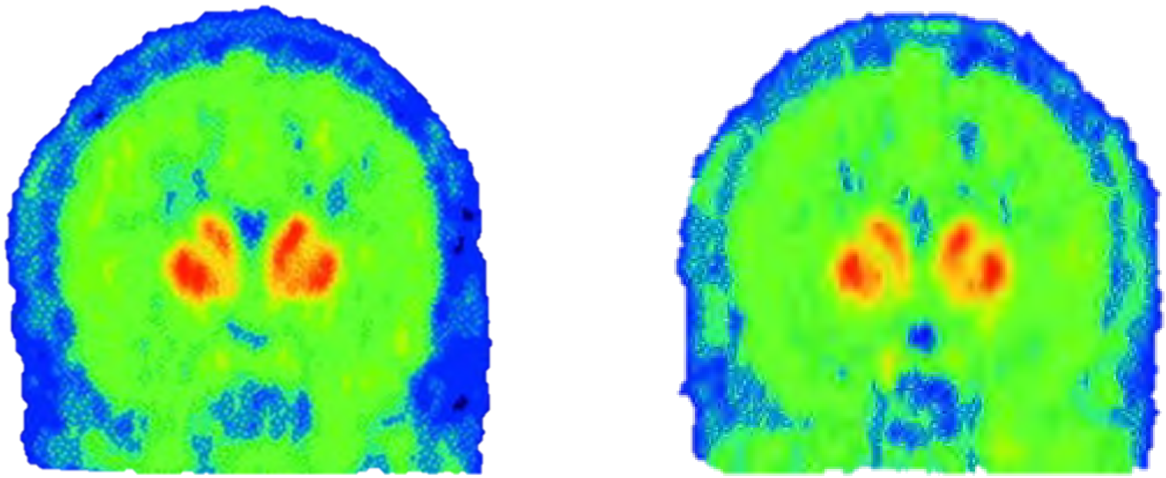


Percent Change in [^{11}C]Raclopride Nondisplaceable BP for Cocaine-Dependent and Healthy Control Subjects After AMPT

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

Neurotransmitter Dynamics

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



placebo methylphenidate

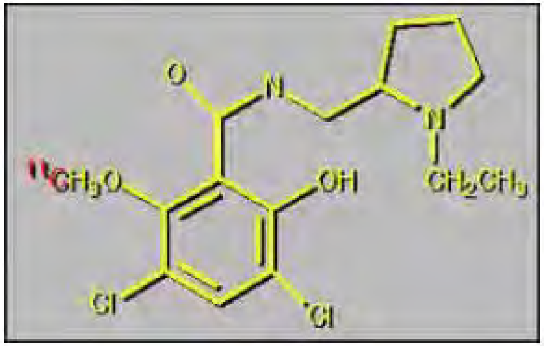
Block DA reuptake → more competition from endogenous DA (depending on release)

→ reduced radiotracer labeling.

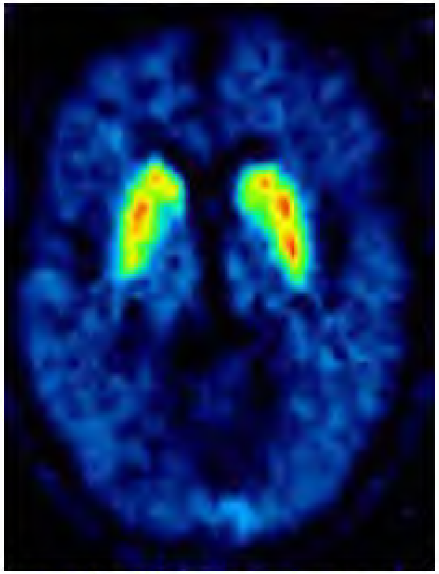
Studies of Cocaine Craving Use Videotapes with Images that Remind the Participant about Cocaine

The Participant Scores Cocaine Craving During PET Scanning

Cocaine-related cues



[11C]Rclopride
--radiotracer for
D2/D3 DA receptors

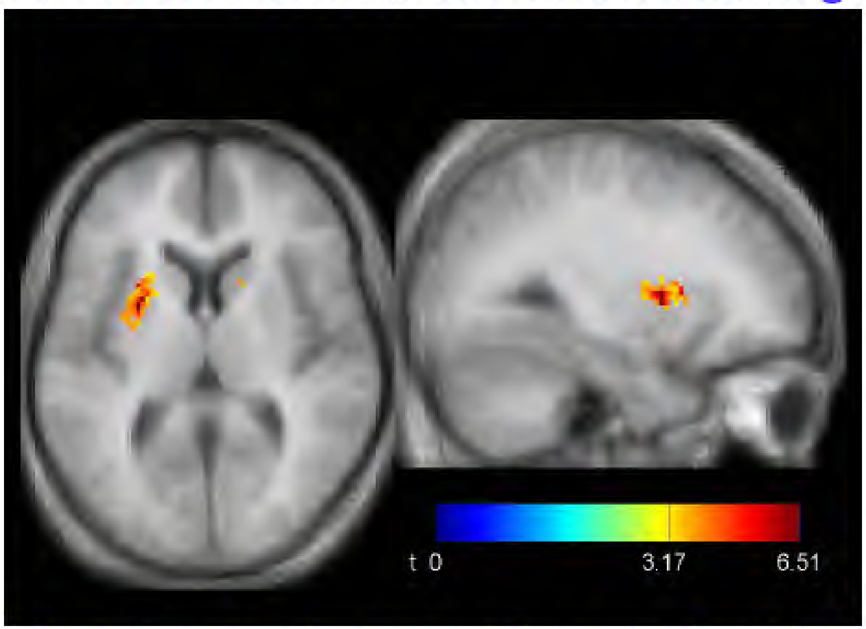


D2/D3 DA receptors
visualized with PET

Cocaine Craving and Dopamine Release

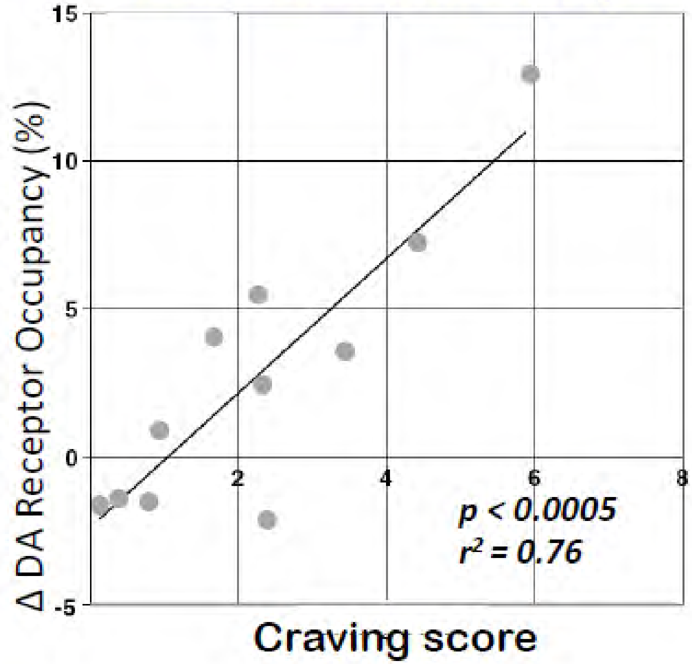
Studies of [^{11}C]Raclopride Binding to D2/D3 DA Receptors

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)

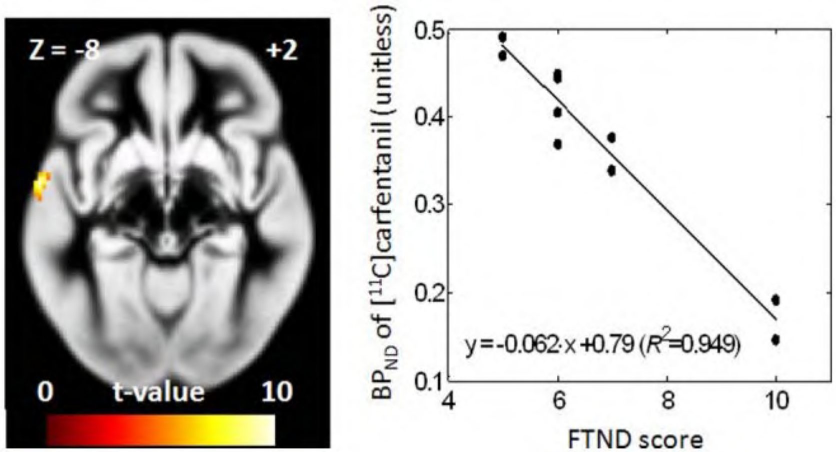
Dopamine release in dorsal striatum is correlated with craving.



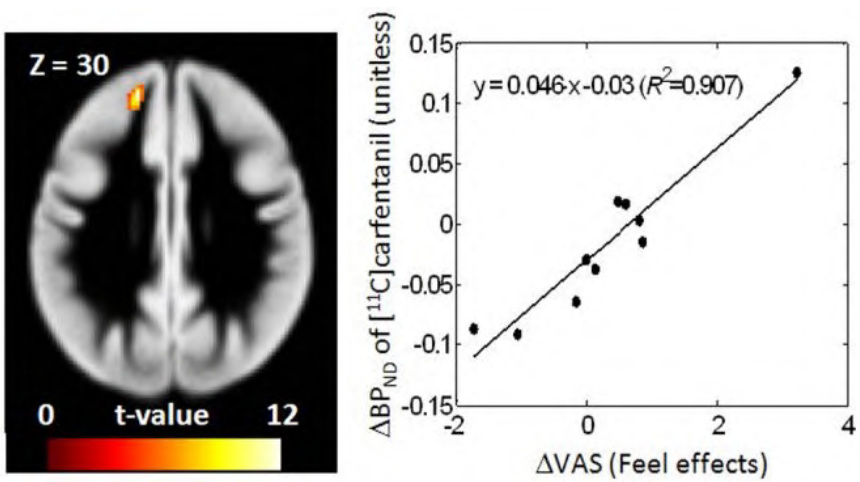
D.F. Wong et al. Neuropsychopharmacology, 2006

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

Mu Opioid Receptor Binding is Correlated with Nicotine Dependence and Reward in Smokers



Baseline mu opioid receptor binding

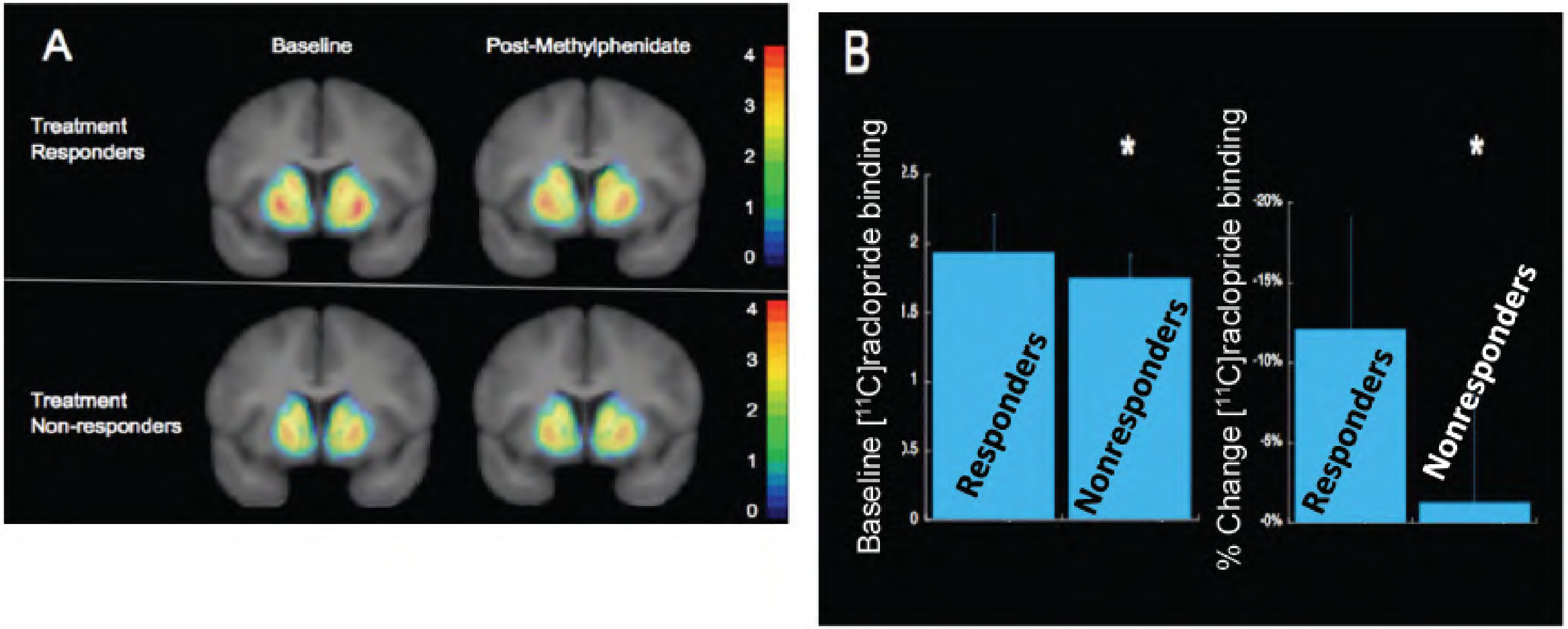


Endorphin release

Kuwabara et al, Plos One , 2014.

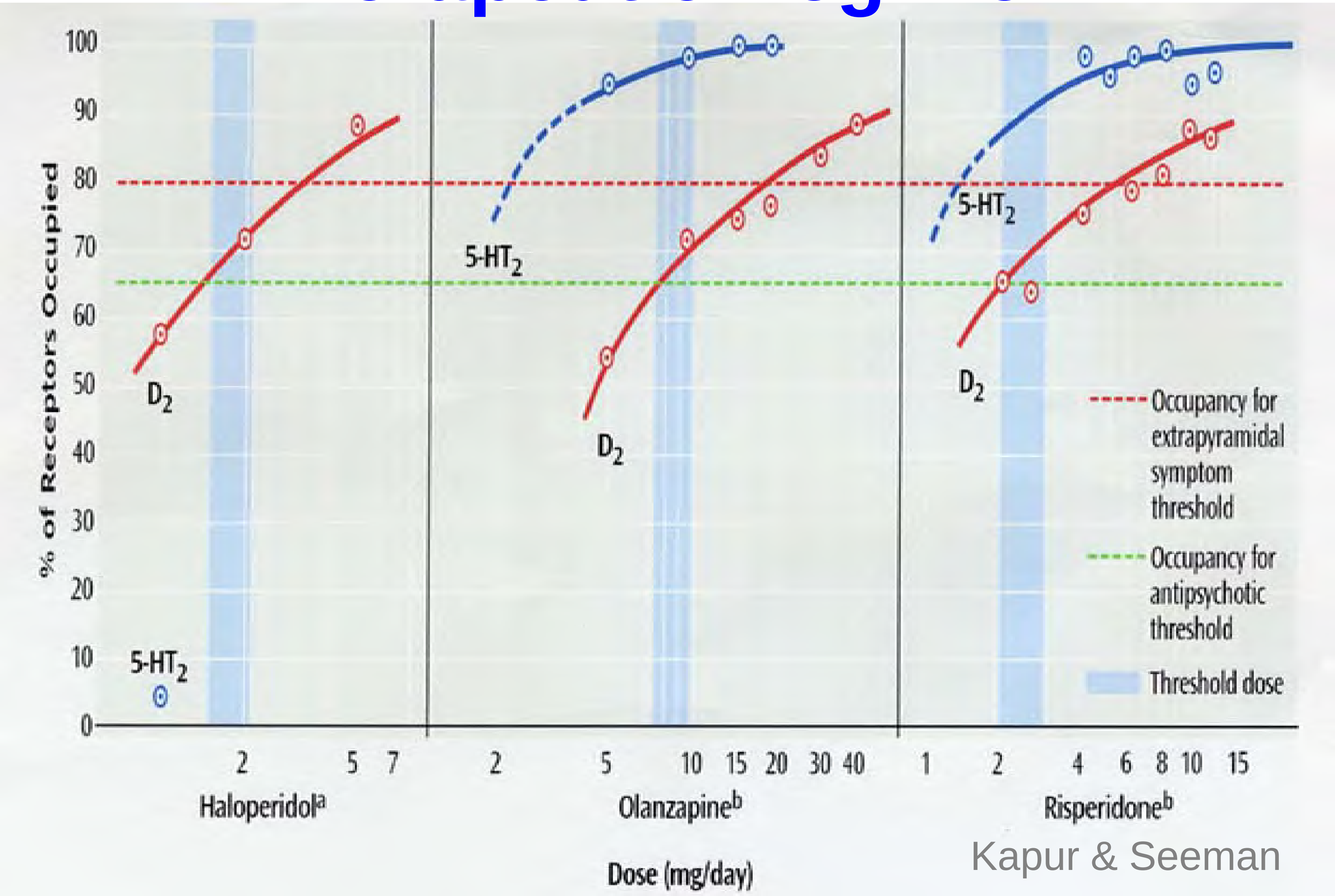
PET to Predict Treatment Outcome

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



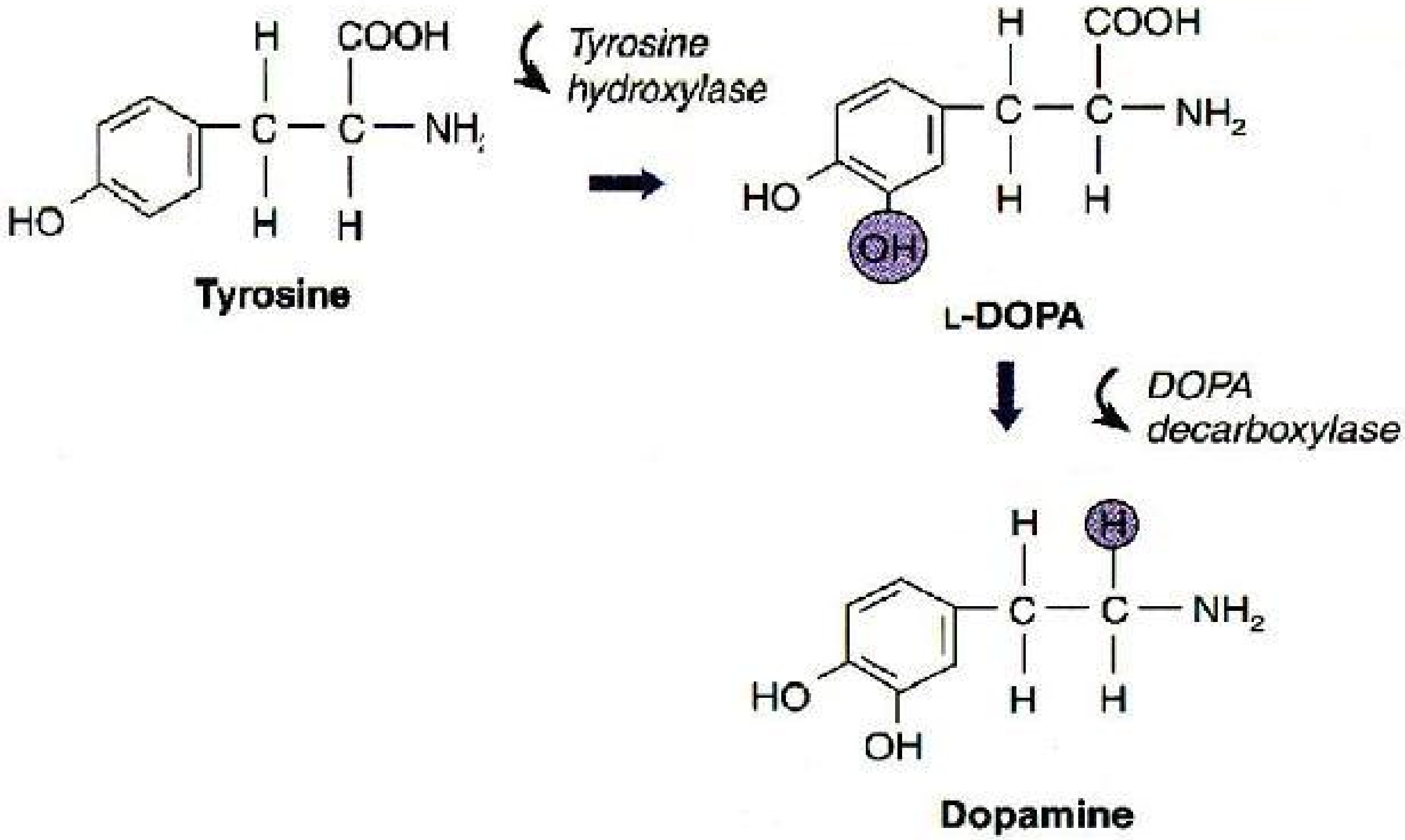
D. Martinez et al., 2011

PET Used to Determine Therapeutic Regimen

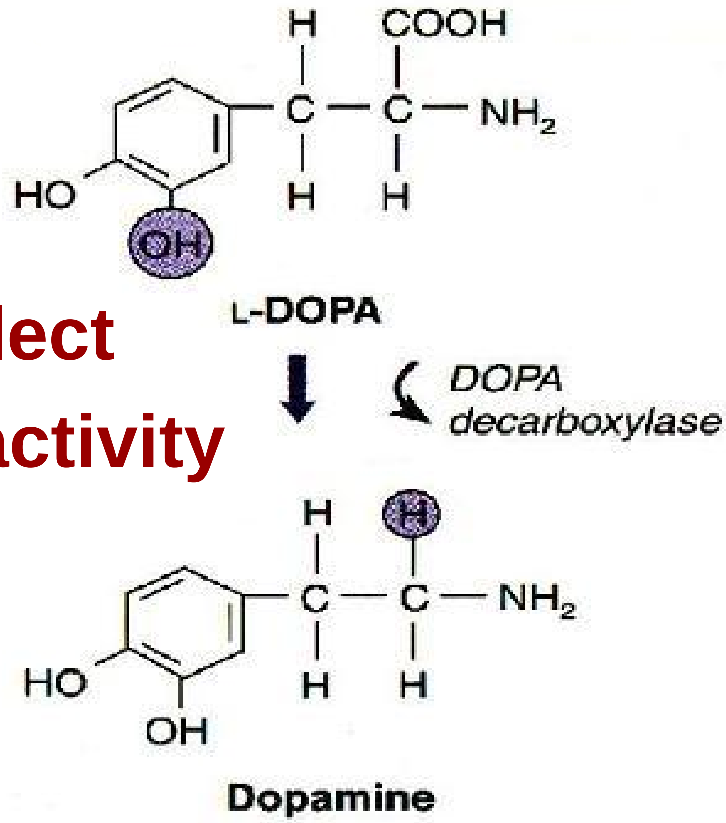


Kapur & Seeman

Dopamine synthesis involves two major enzymatic steps.

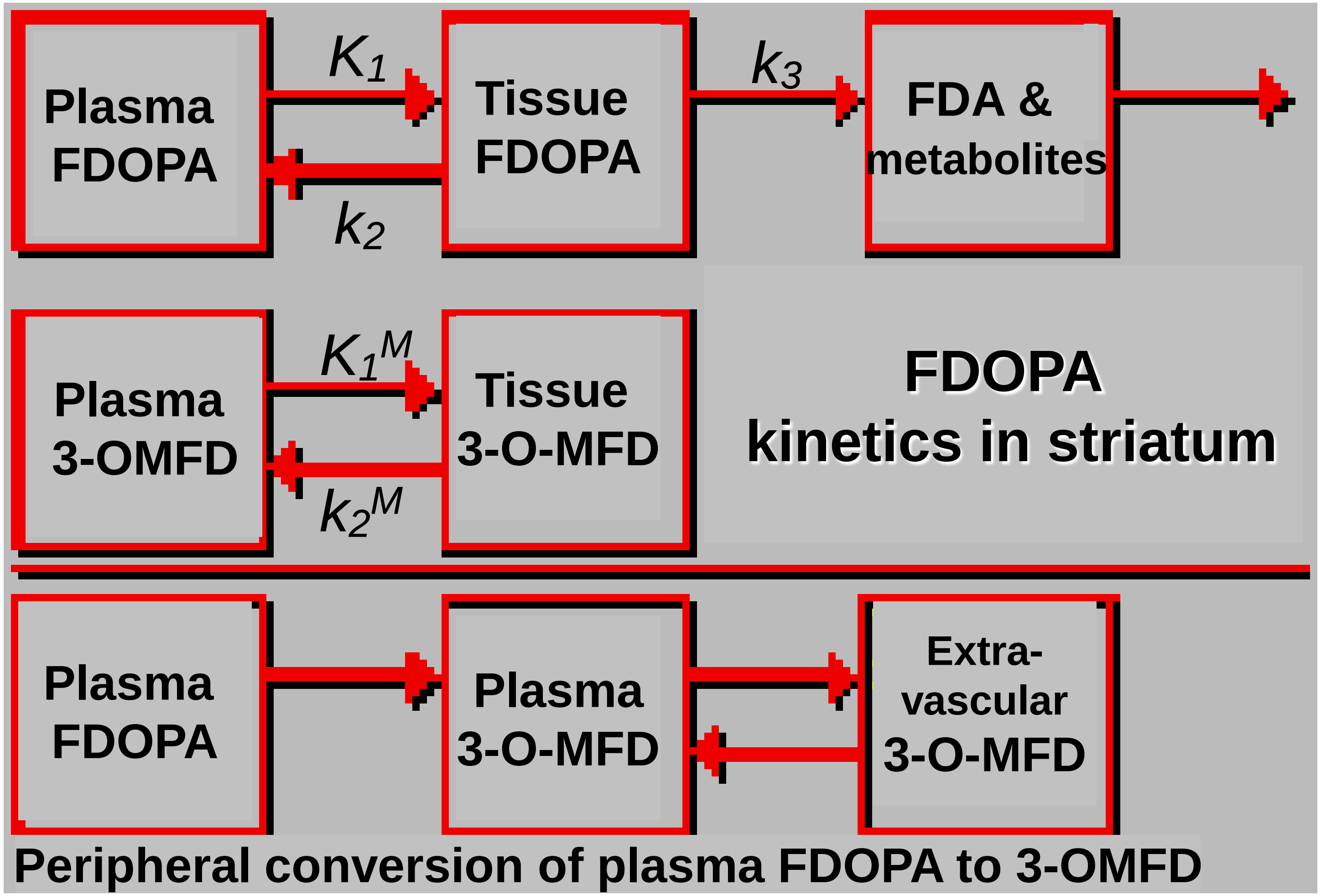


$[^{18}F]$FDOPA is taken up into the presynaptic terminal, and is converted to $[^{18}F]$DA

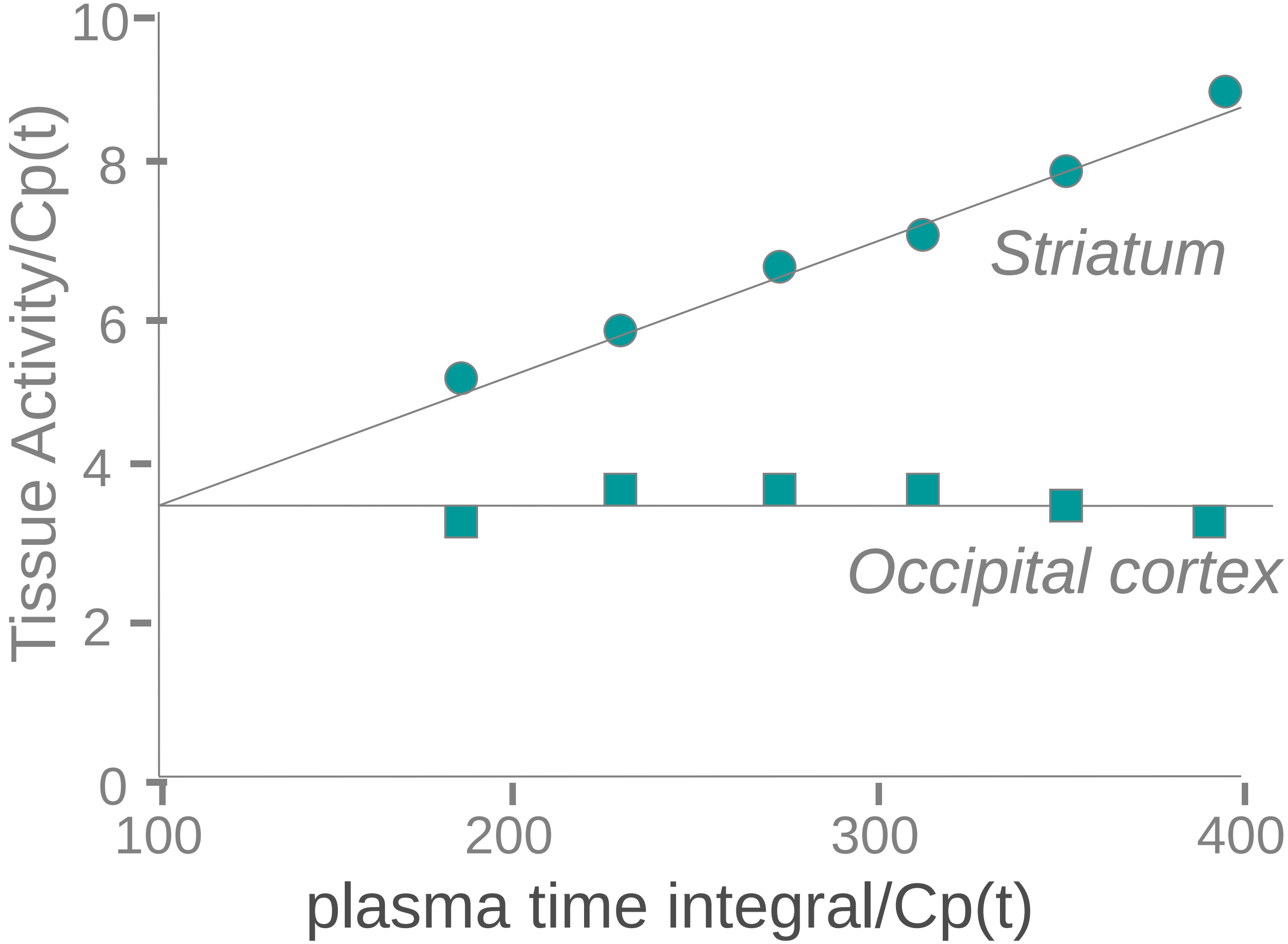


$[^{18}F]$FDOPA data reflect DOPA decarboxylase activity & DA storage.

FDOPA kinetics follows a 5-compartment model



Slope of the Patlak Plot is the estimated FDOPA K_i.

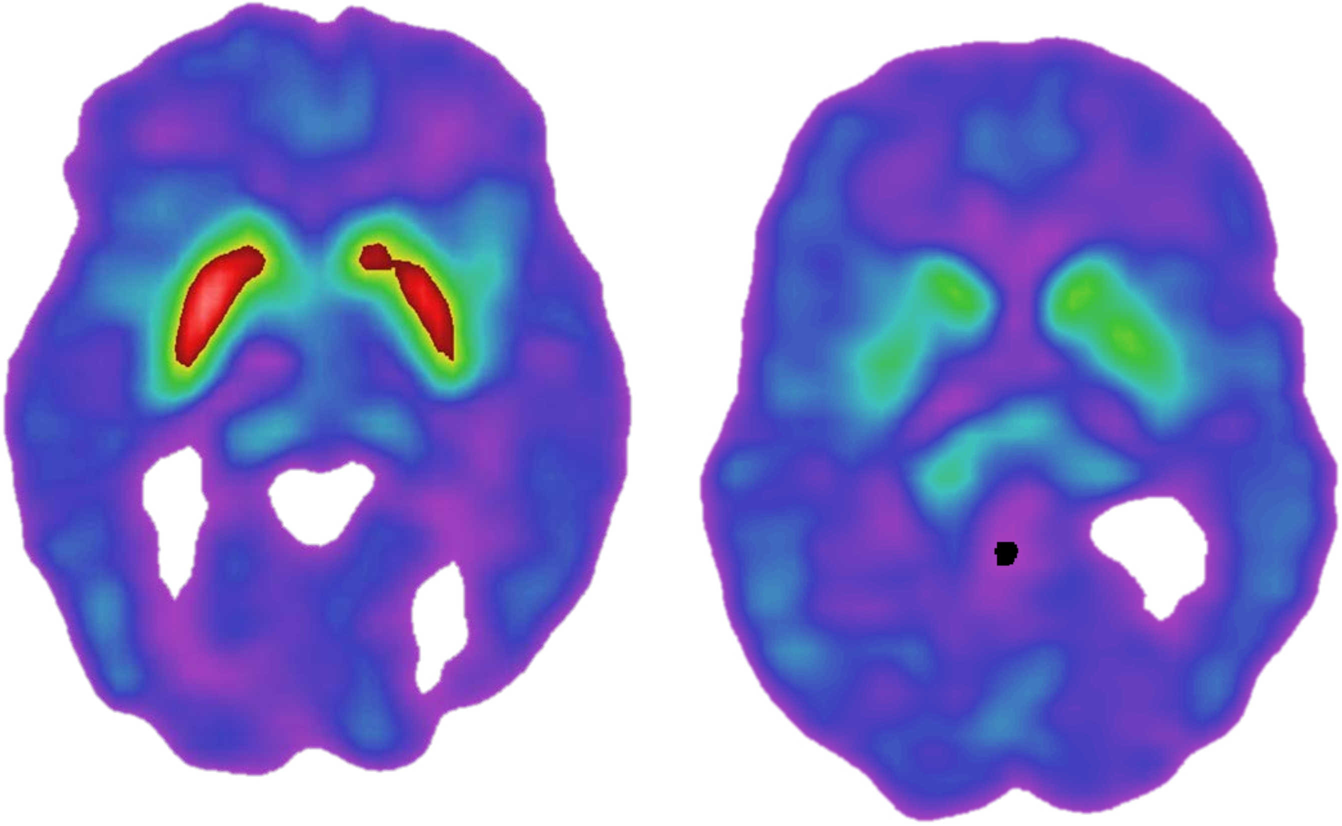


Measurements of Uptake or Influx of FDOPA

- 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

Selective PET Tracers Other than Neurotransmitter and Metabolism Probes

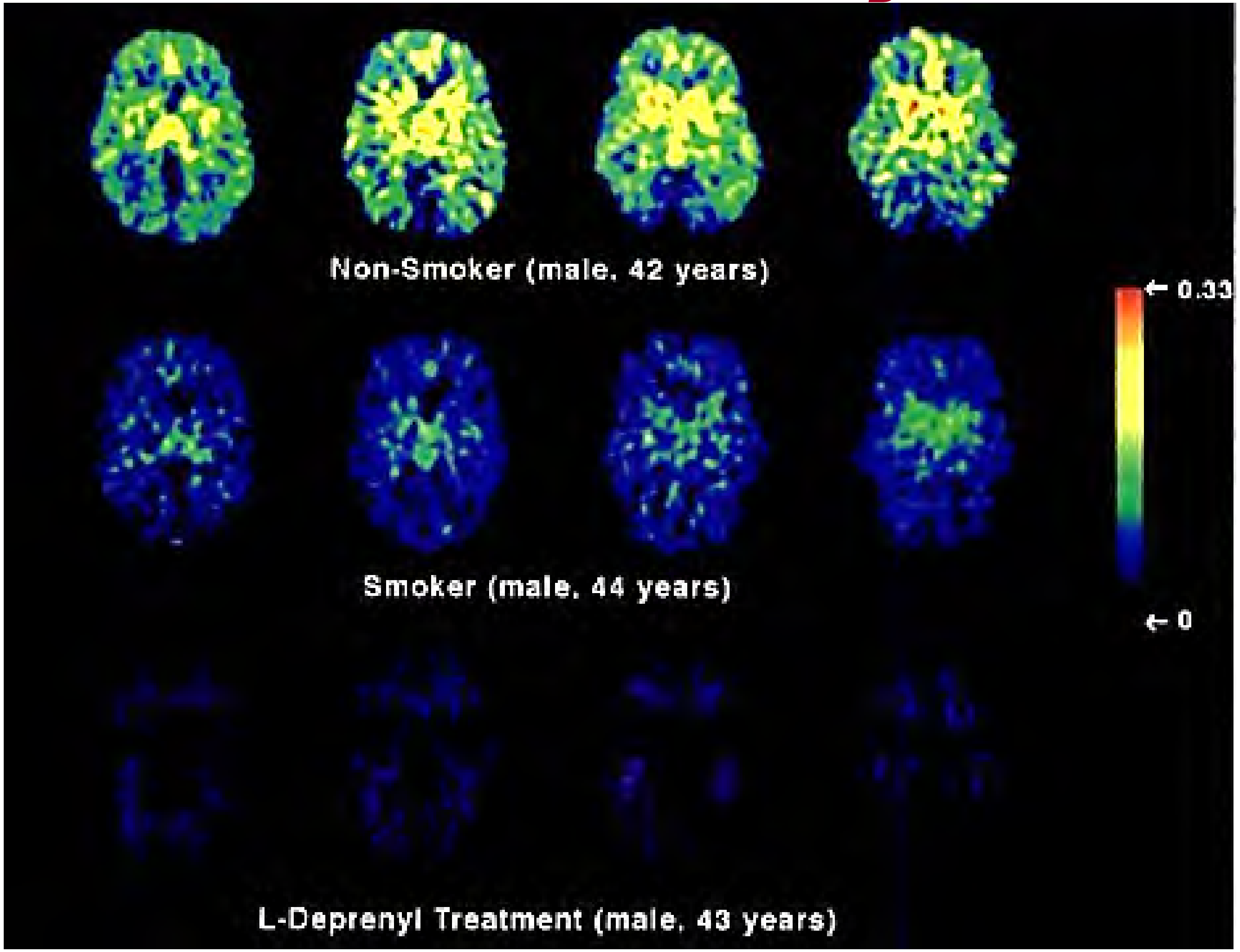
- Enzymes
- Alzheimer probes

(for amyloid protein and neurofibrillary tangles)

- Translocator Protein Ligands

[^{11}C]L-Deprenyl Labels Monoamine Oxidase B

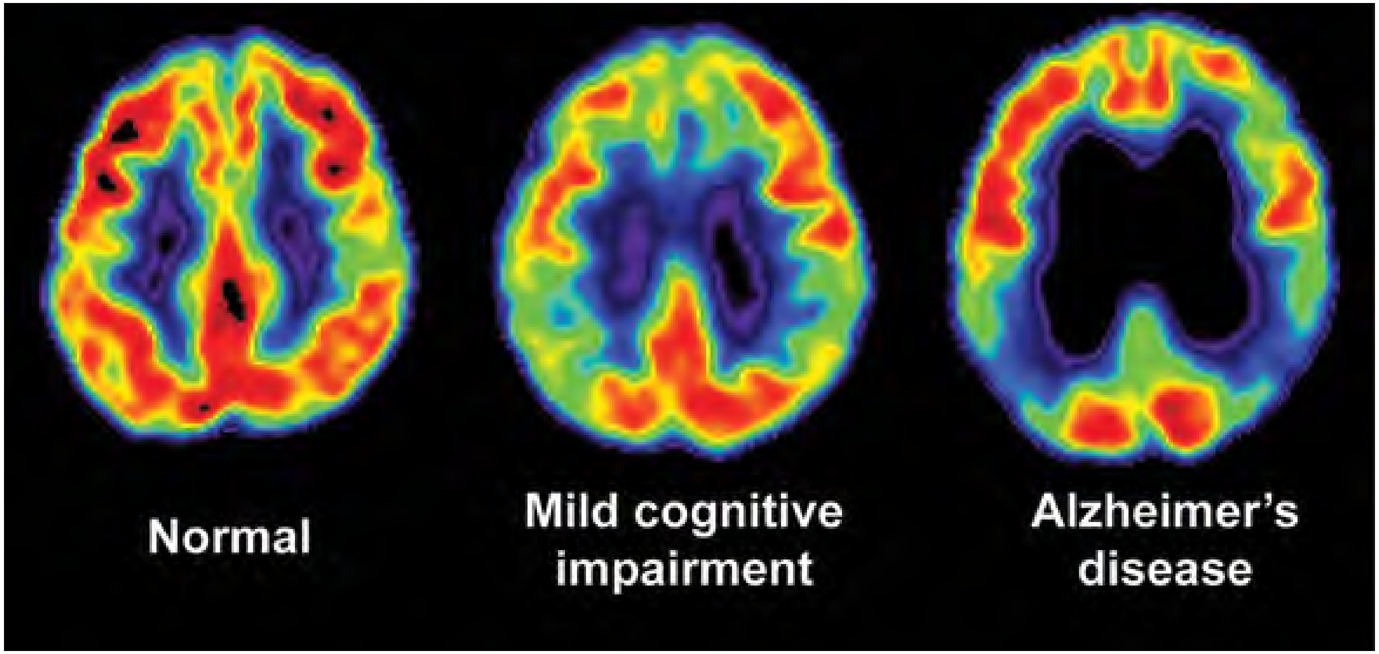
Smokers have low MAO_B activity



Fowler et al., 1996

Alzheimer's Disease

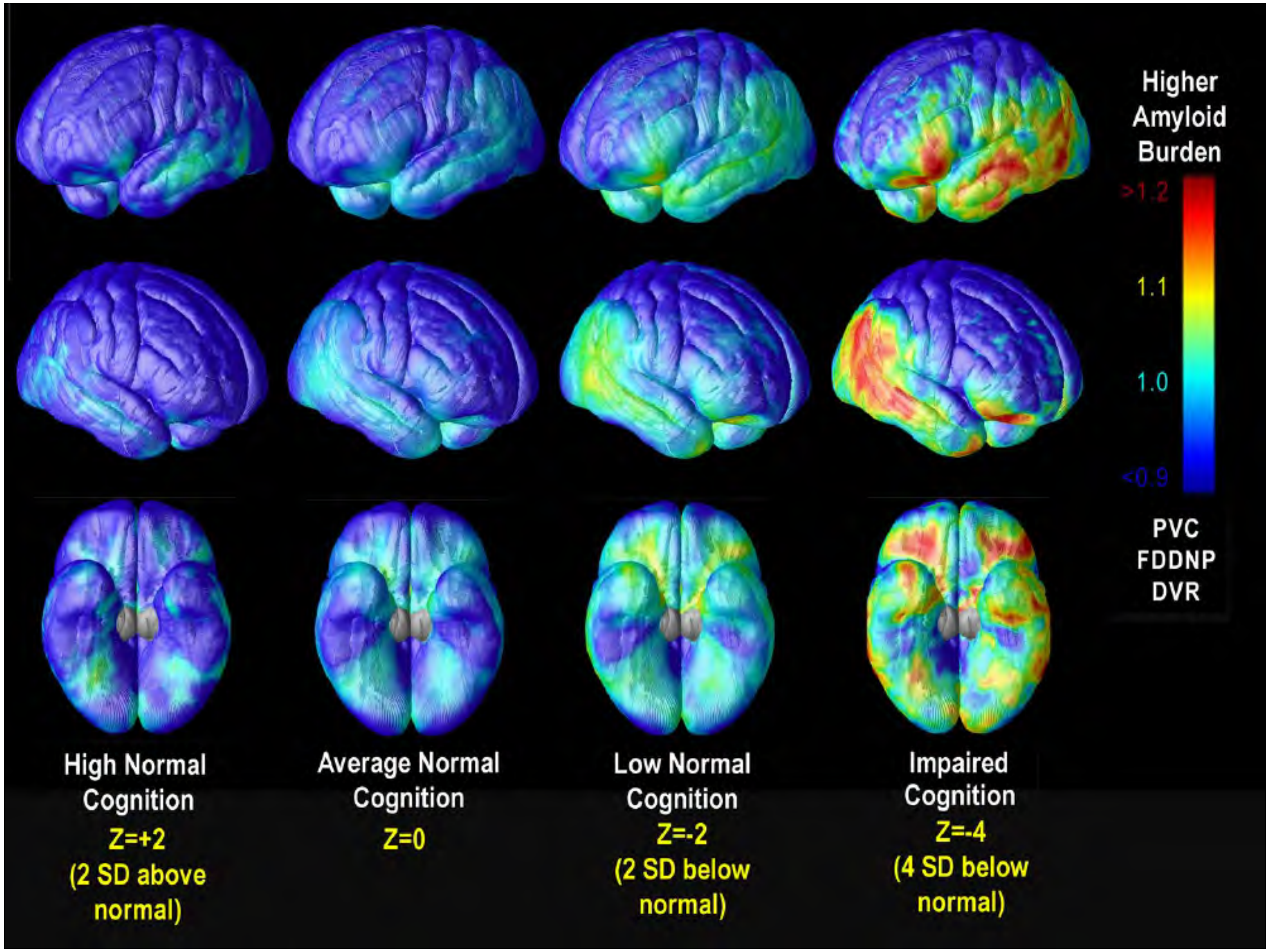
[^{18}F]FDG Shows *Deficits in Temporal-Parietal and Frontal Areas*



Jagust et al., 2010

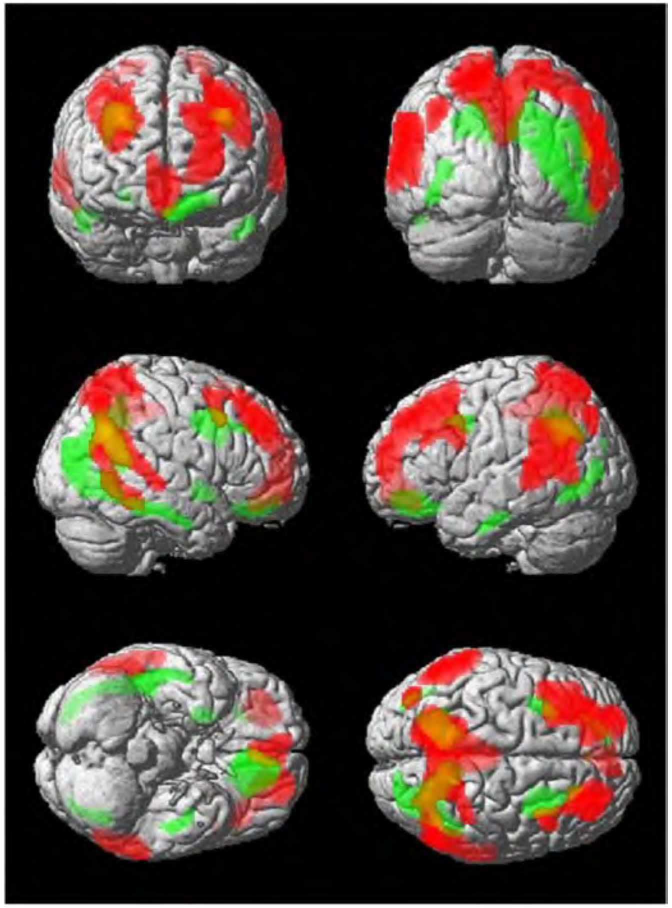
[^{18}F]FDDNP Binding: a Marker for AD Pathology

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



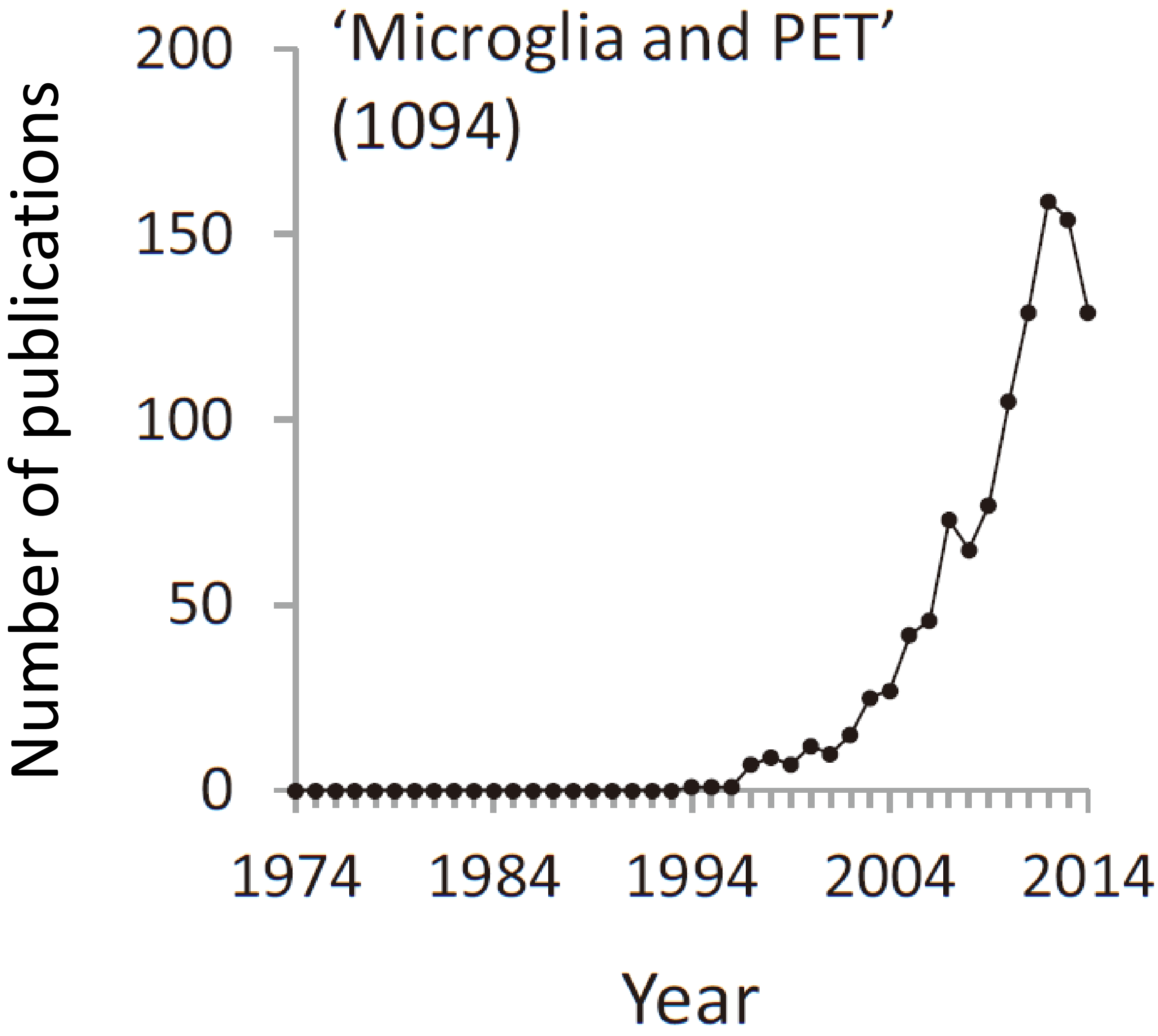
Colors indicate binding in AD subjects minus binding in Control subjects.

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

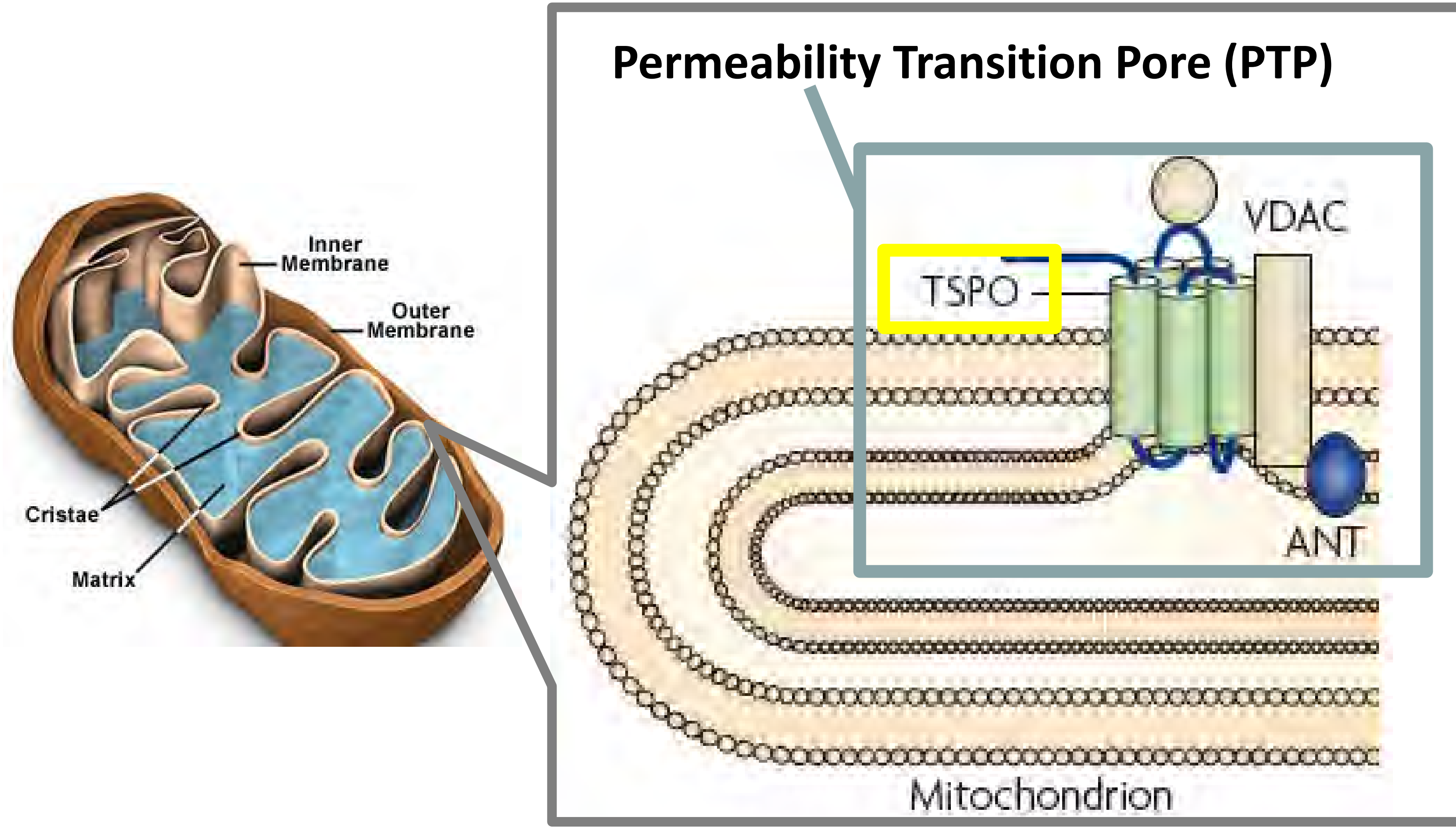
Shin et al., 2010

Hot Topic

ET imaging of Neuroinflammation

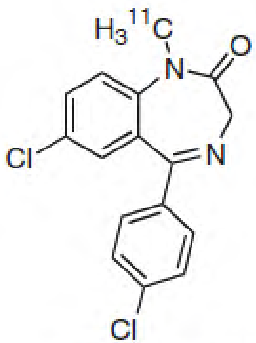


Translocator Protein (TSPO): Target of neuroinflammation PET tracers

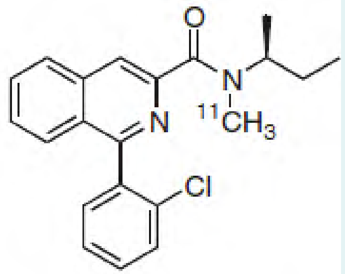


TSPO Ligands

1st generation ligands

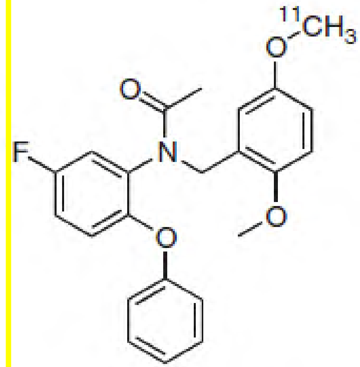


[11C]Ro 5-4864

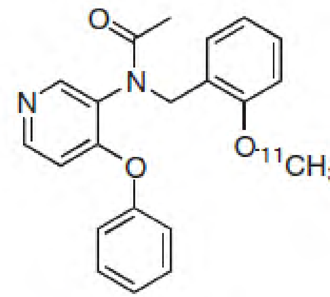


[11C]PK11195

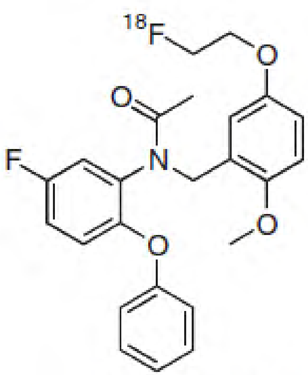
2nd generation ligands



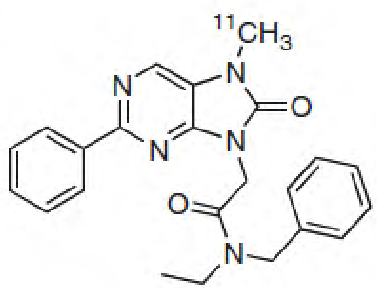
[11C]DAA1106



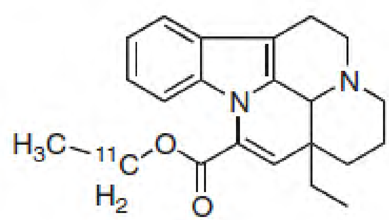
[11C]PBR28



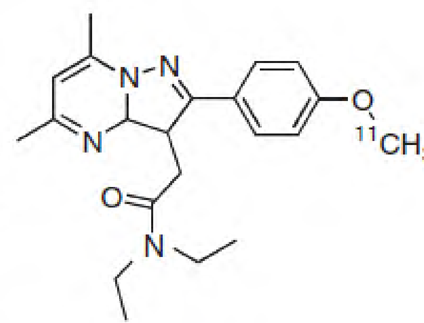
[18F]FEDAA1106



[11C]AC-5216

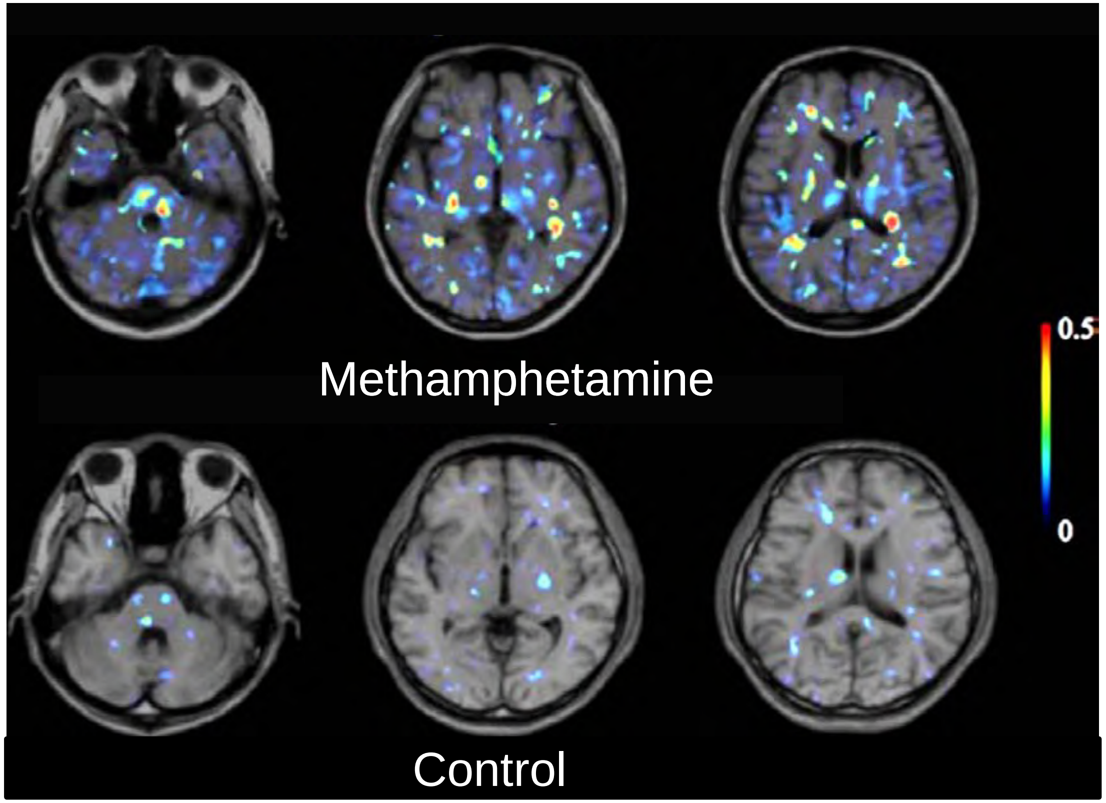


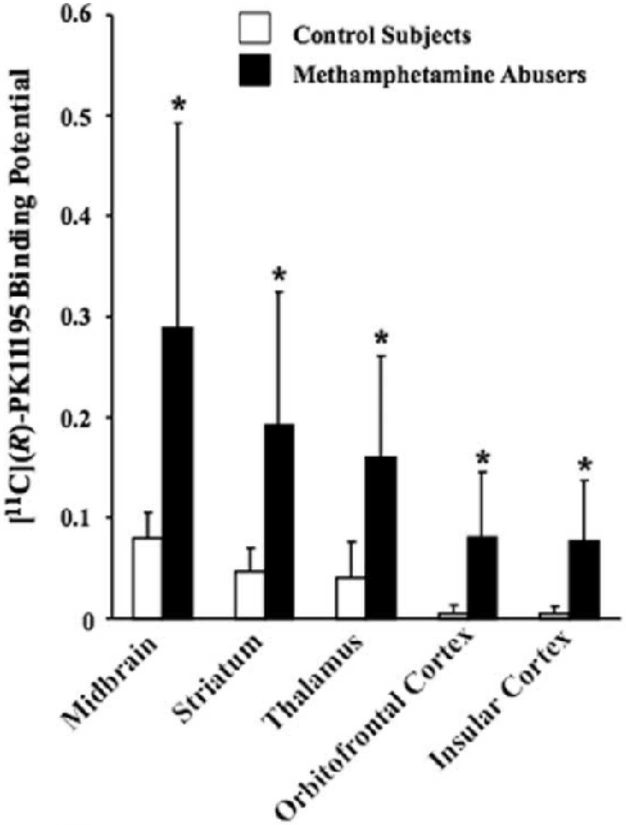
[11C]Vinpocetine



[11C]DPA-713

Neuroinflammation in Methamphetamine Users Measured with [^{11}C](R)-PK11195





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

The RatCAP

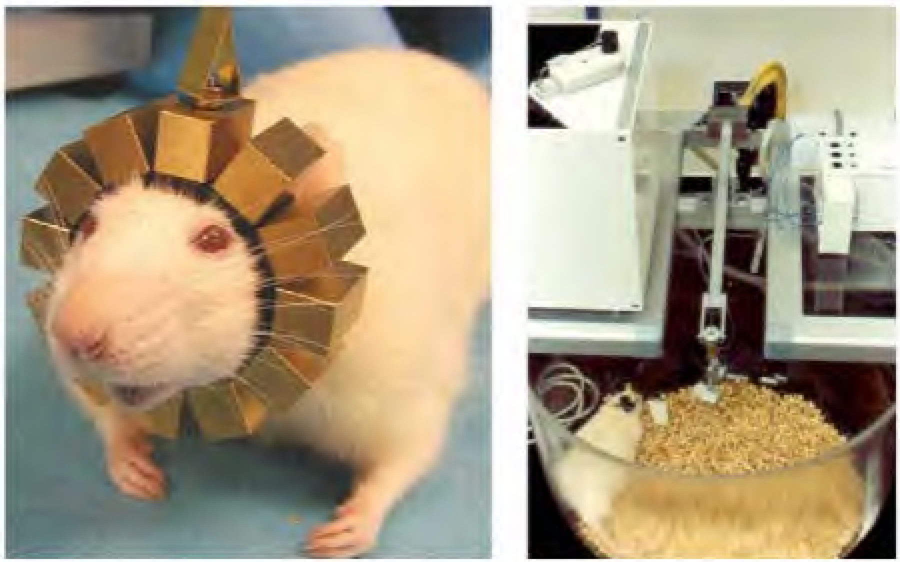
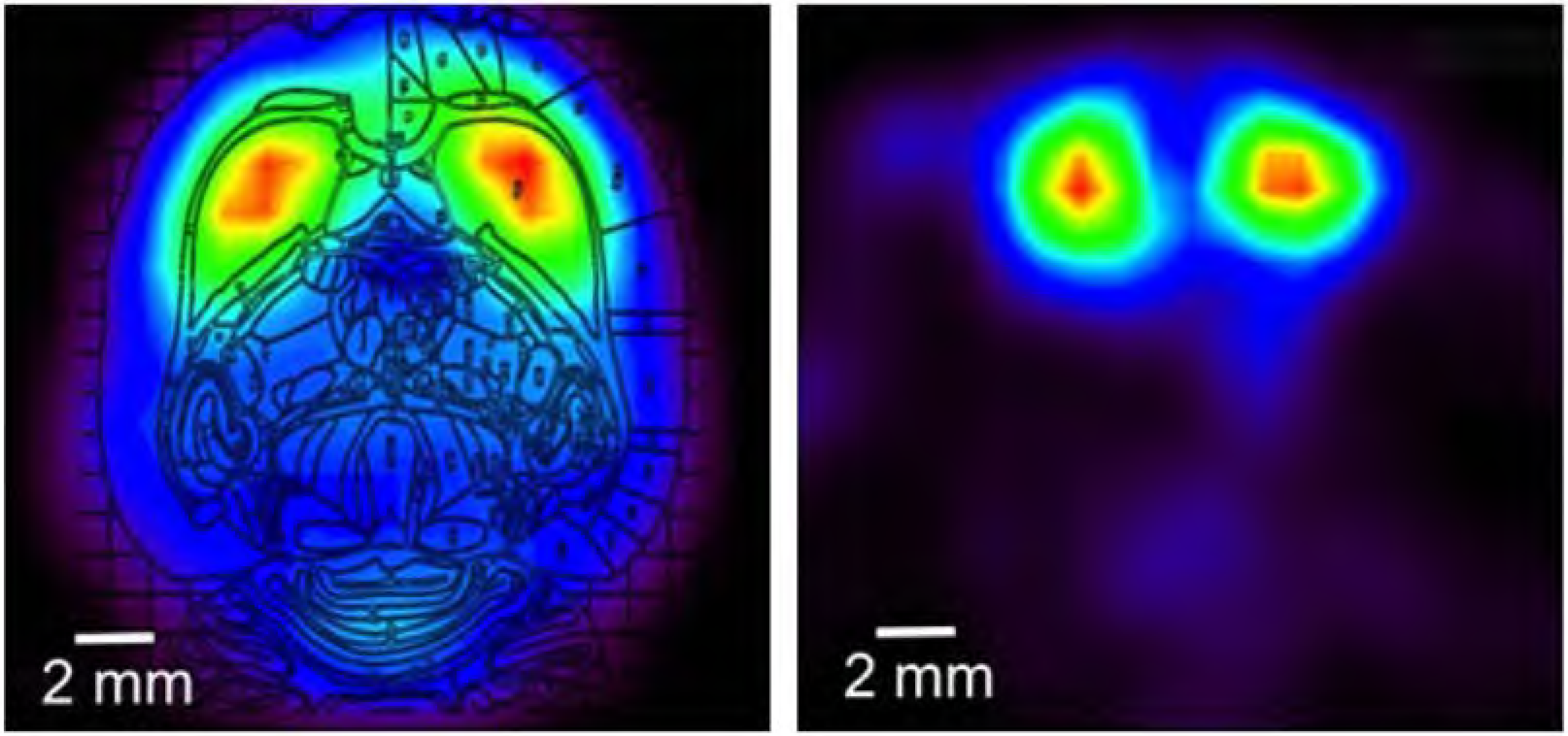


Fig. 1. (a) Mockup of the RatCAP ring on the head of a rat. (b) Ratturn bowl used to support ring and allow freedom of movement.

Fig. 4. Block detectors form a ring connected with a flexible cable that serves as bus for transmitting serial data of the ring and receiving power and control signals.

Dopamine Receptors Measured with the RatCAP



PET scans of a rat's brain made with the RatCAP scanner (horizontal view superimposed on a rat brain atlas figure, left, and a coronal slice, right). The rainbow scale (red = high, violet = low) indicates the level of a radiotracer that binds to receptors for dopamine, which are concentrated in the striatum, a brain region involved in reward and motivation.

+ ENLARGE

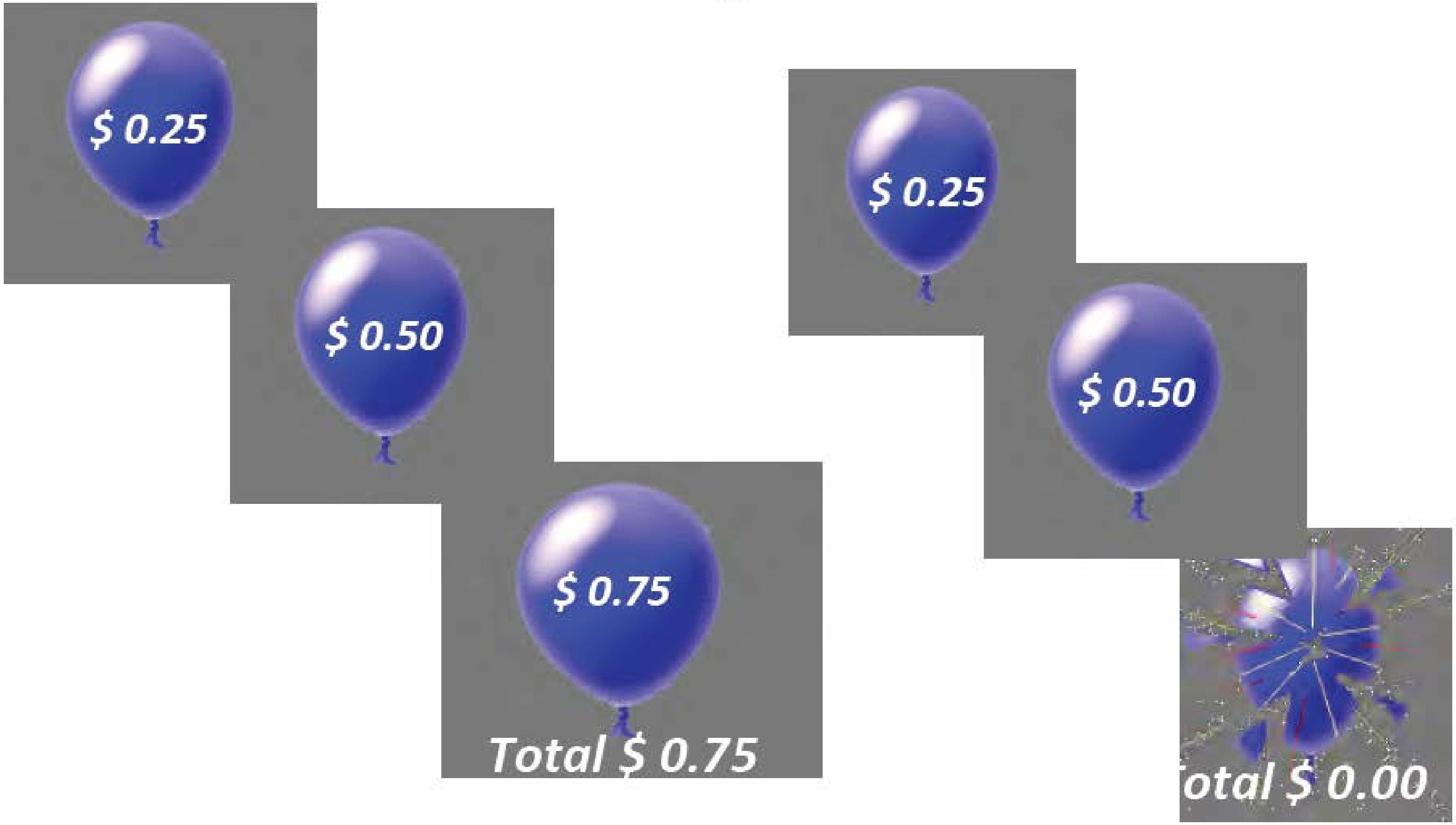
PET fMRI Multimodality Imaging

Striatal D2-type Dopamine Receptors and Complex Decision-Making

The Balloon Analogue Risk Task

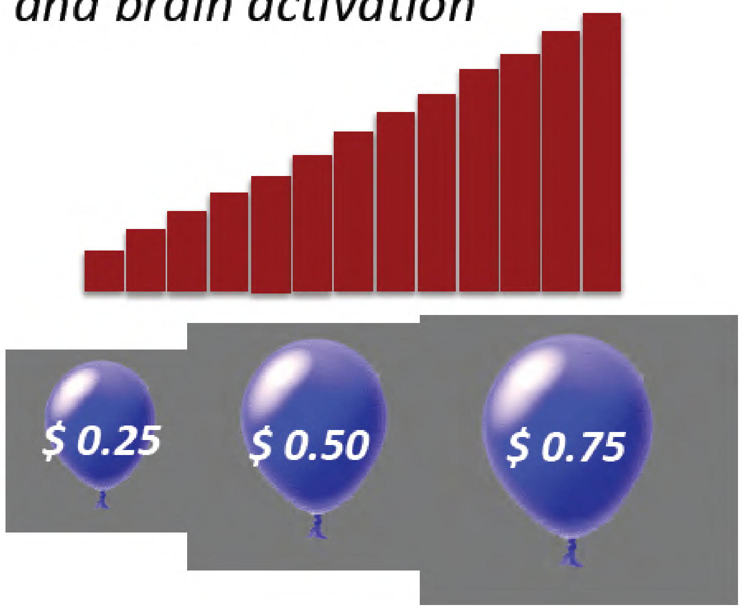
Striatal D2-type Dopamine Receptors and Complex Decision-Making

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

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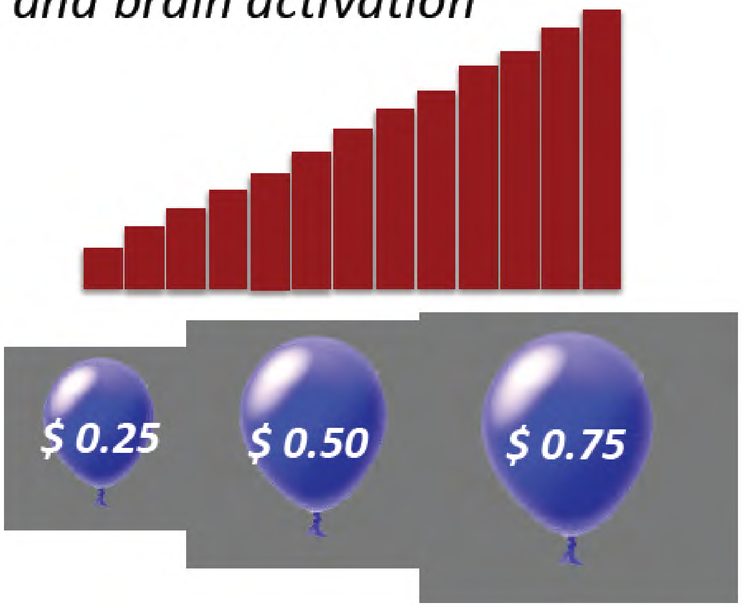
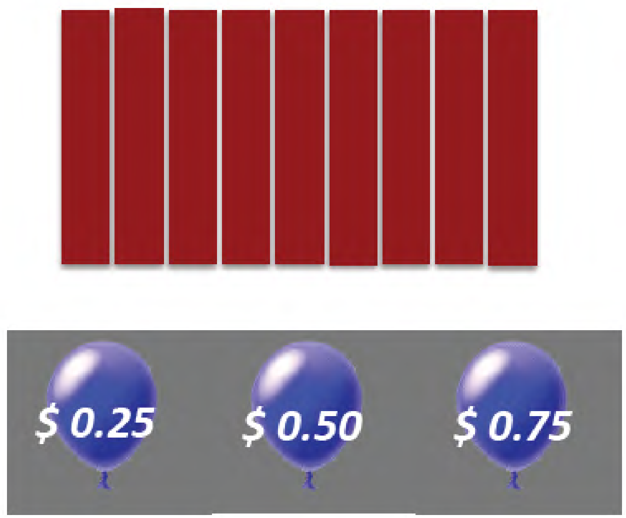
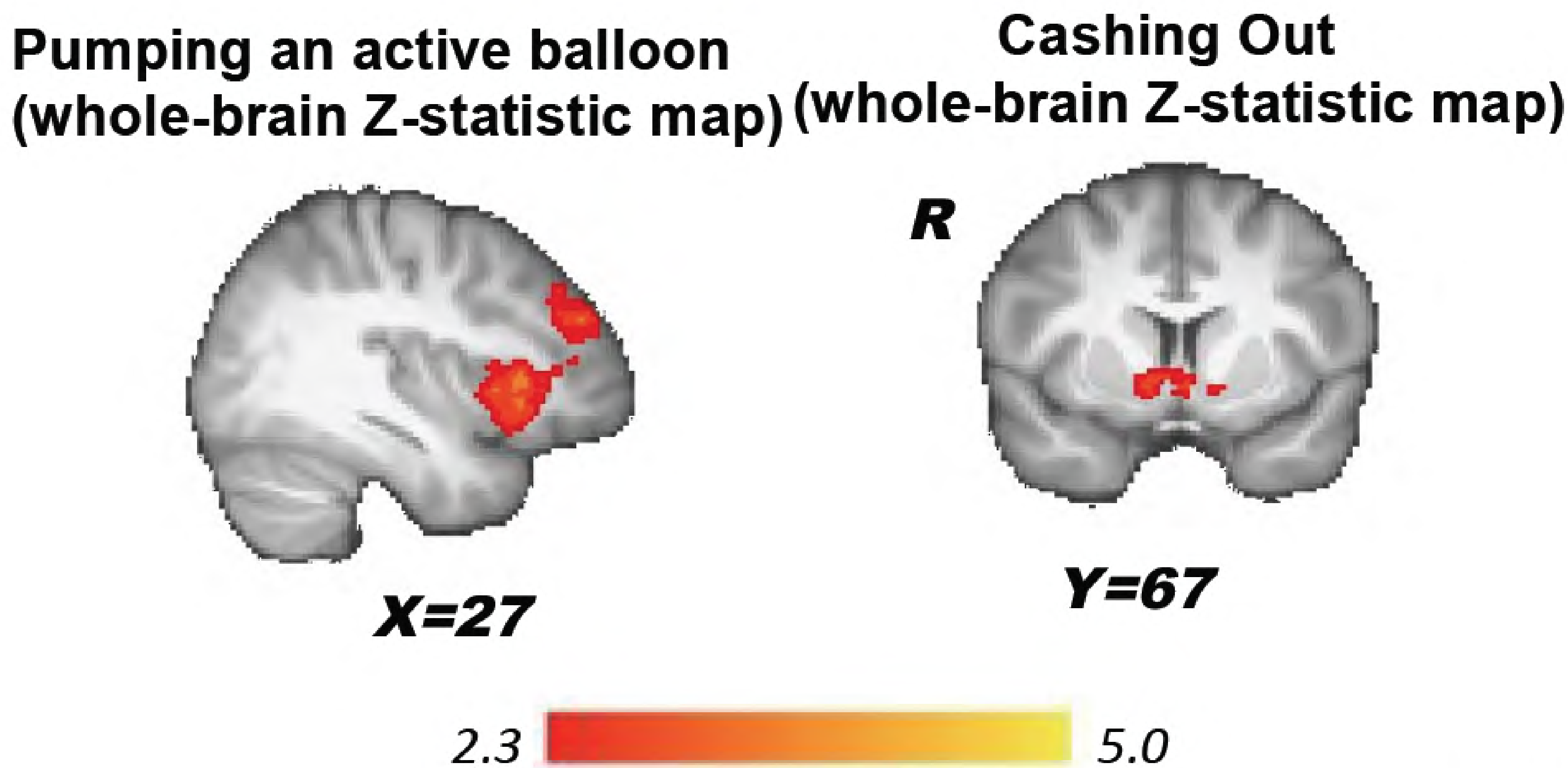


Nonparametric regressors to control for mean activation with each event



Frontostriatal Activity is Modulated by Risk and Reward



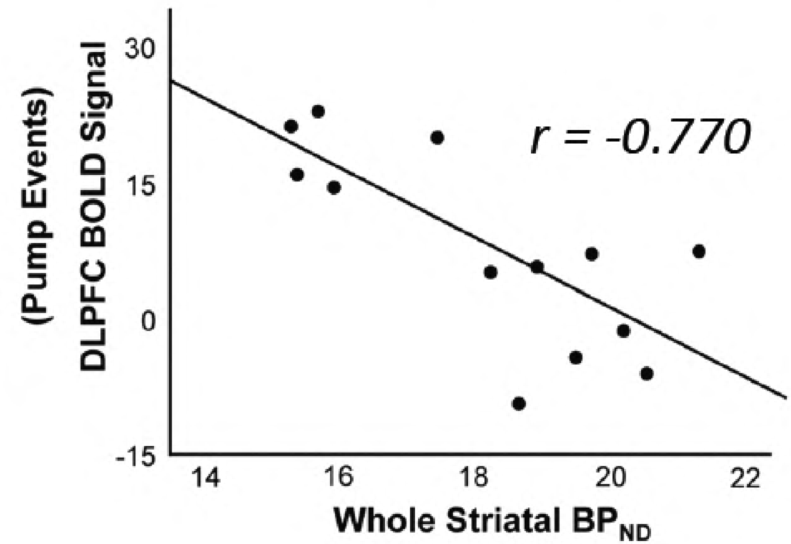
M. Kohno et al., Cerebral Cortex, 2013

Striatal Dopamine Receptors and Risk-Taking

Cortical Activity is Modulated by Risk

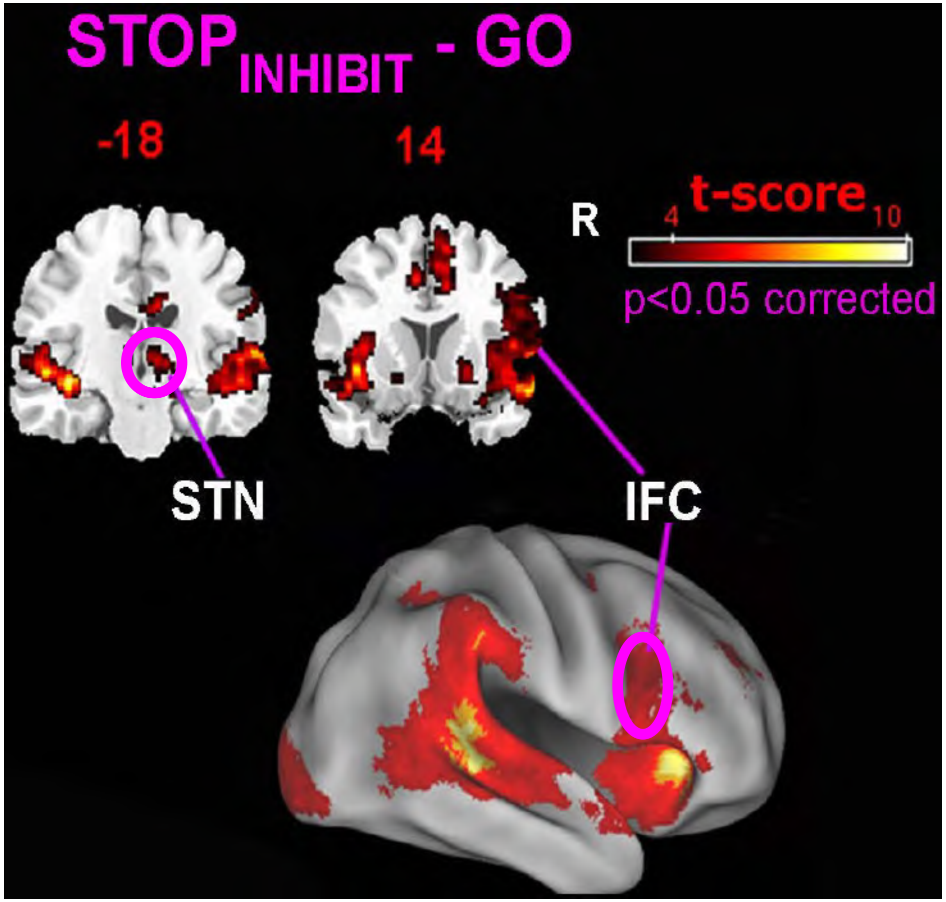
X=27

Modulation is Related to Dopamine Receptors in Striatum



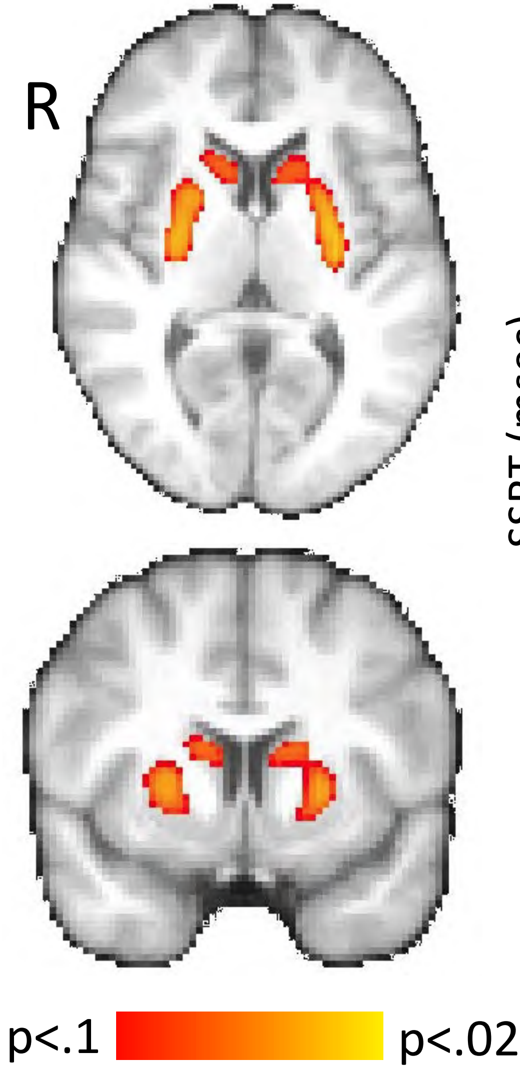
M. Kohno et al., Cerebral Cortex, 2013

Stopping Associated with Activation in PFC-Pre-SMA-Subthalamic Nucleus Network



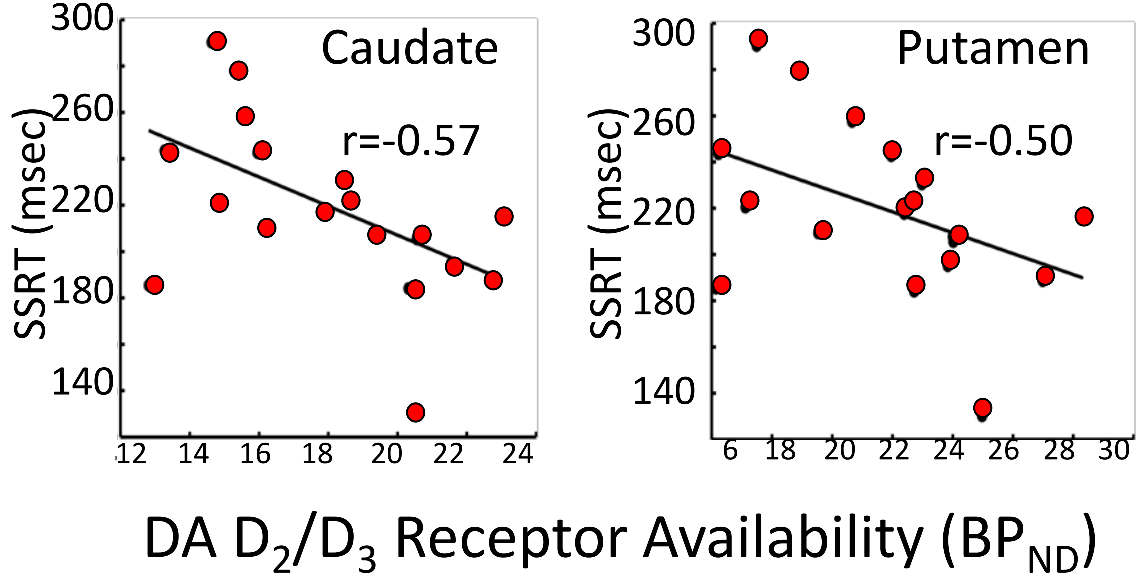
A Aron, R Poldrack: J Neurosci, 2006

DA D2/D3 Receptor Availability is Related to Stopping Ability



[18]F]Fallypride PET

Healthy Control Participants

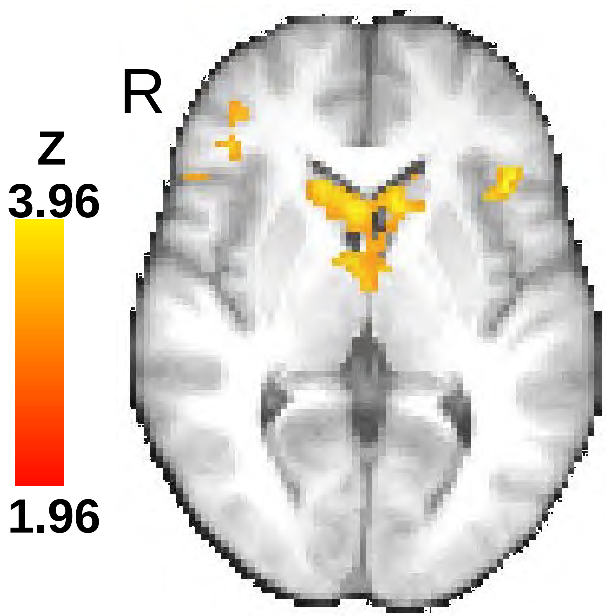


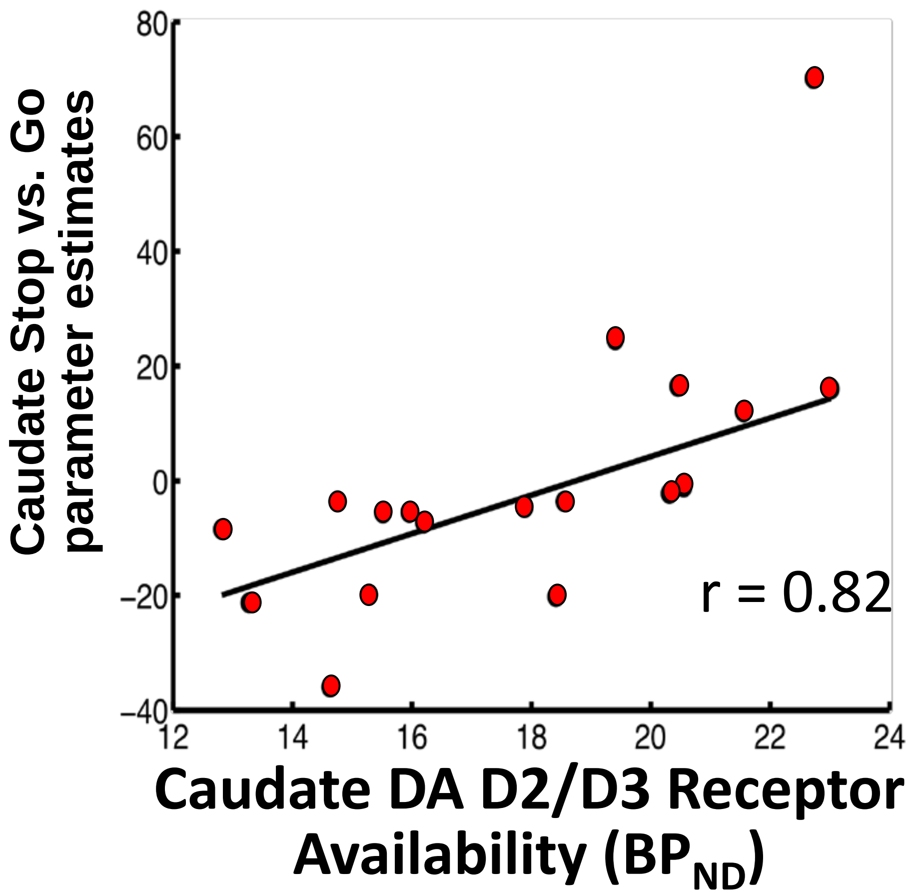
D Ghahremani et al., 2012

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

fMRI - [^{18}F]Fallypride PET

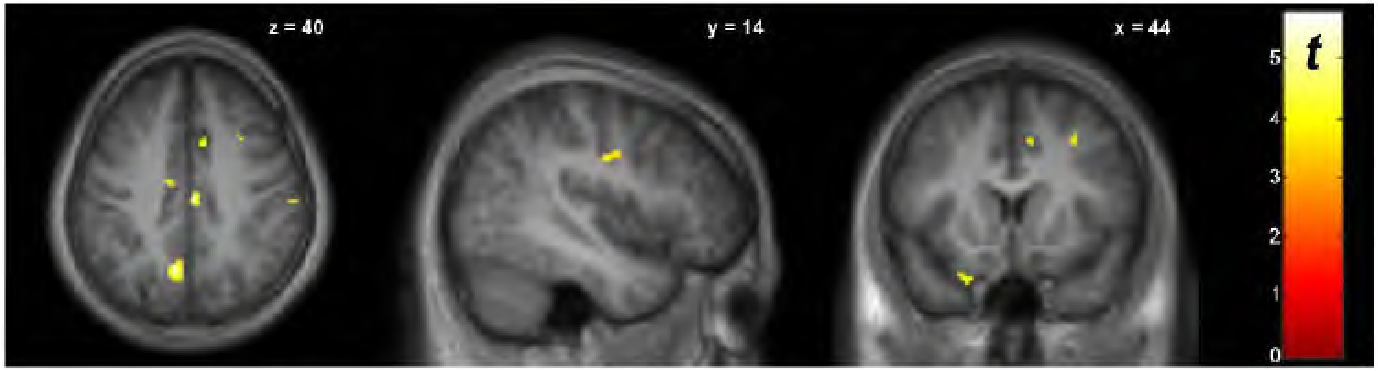
Healthy Control Participants





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.
- When fMRI is not possible – implanted stimulators

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.