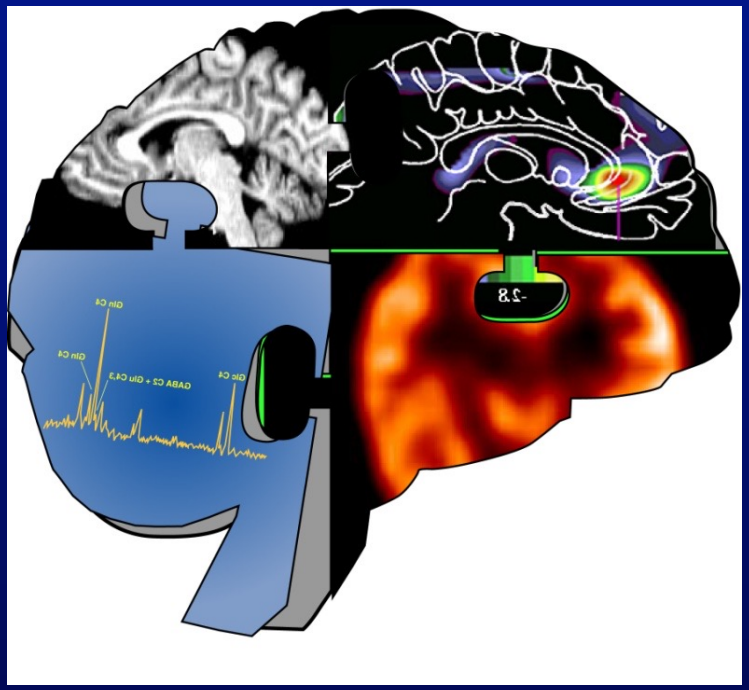
Positron Emission Tomography:
Tool to Study Pharmacokinetics and to Facilitate Drug Development



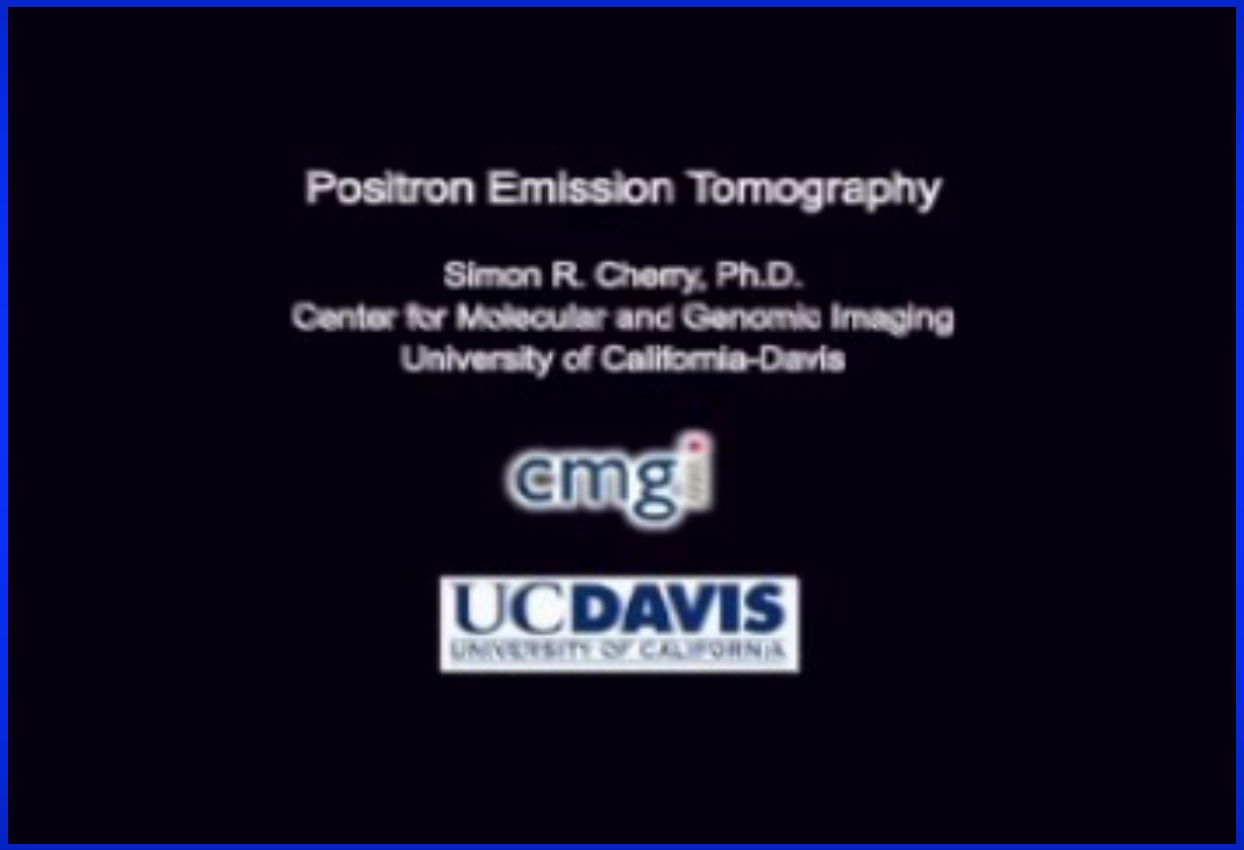
Robert B. Innis, MD, PhD
Molecular Imaging Branch
National Institute Mental Health

Outline of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling of plasma concentration and tissue uptake can measure receptor density
4. Study drug distribution: block distribution to periphery and increase distribution to brain
5. Study drug metabolism: inhibit defluorination

Imaging Receptors with PET

Positron Emission Tomography



PET vs. MRI

	PET	MRI
Spatial Resolution	2 – 6 mm	<< 1 mm
Sensitivity	10^{-12} M	10^{-4} M
Temporal Resolution	minutes	<1 sec

Radionuclide (^{11}C): high sensitivity

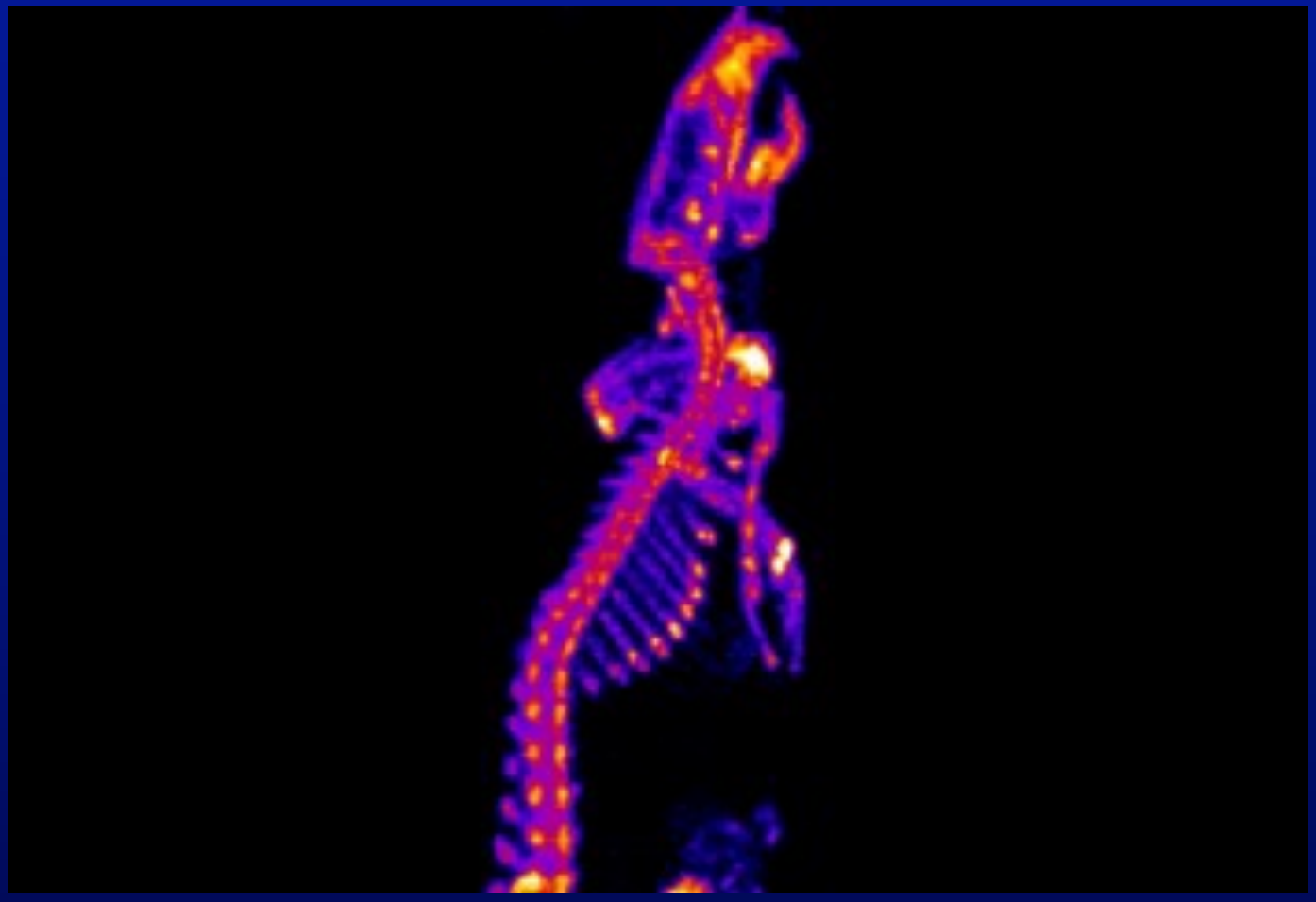
Ligand (raclopride): high selectivity

Radioligand [^{11}C]raclopride: high sensitivity & selectivity

Radioligand = Drug + Radioactivity

1. **Drug administered at tracer doses**
   a) No pharm effects
   b) Labels <1% receptors
   c) Labeled subset reflects entire population
2. **Radioligand disposed like all drugs**
   a) Metabolism & distribution
3. **Radiation exposure**

NIH Rodent PET Camera
^{18}F bone uptake rat

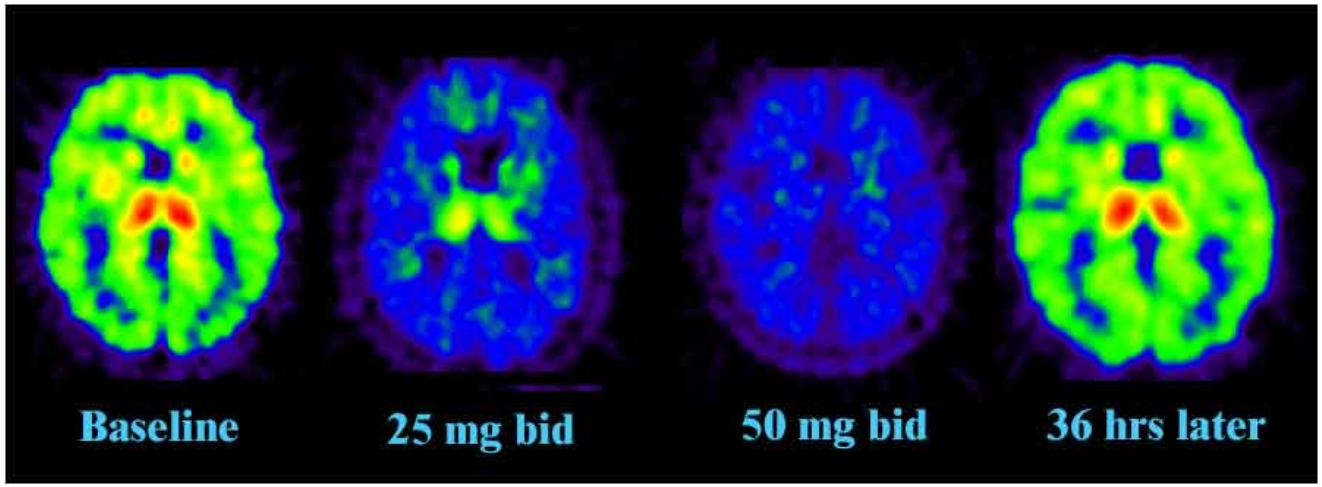


Developed By: Mike Green & Jurgen Seidel

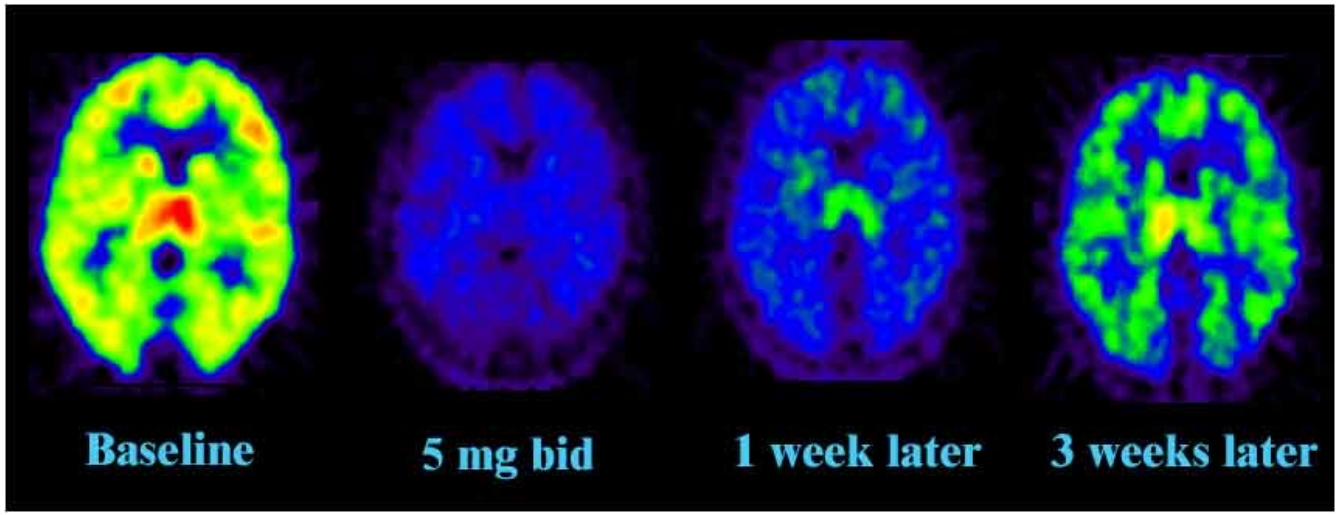
PET: Tool in Therapeutic Drug Development

- Determine dose and dosing interval
- Identify homogeneous group
- Biomarker for drug efficacy

Lazabemide blocks [^{11}C]deprenyl binding to monoamine-oxidase-B (MAO-B)



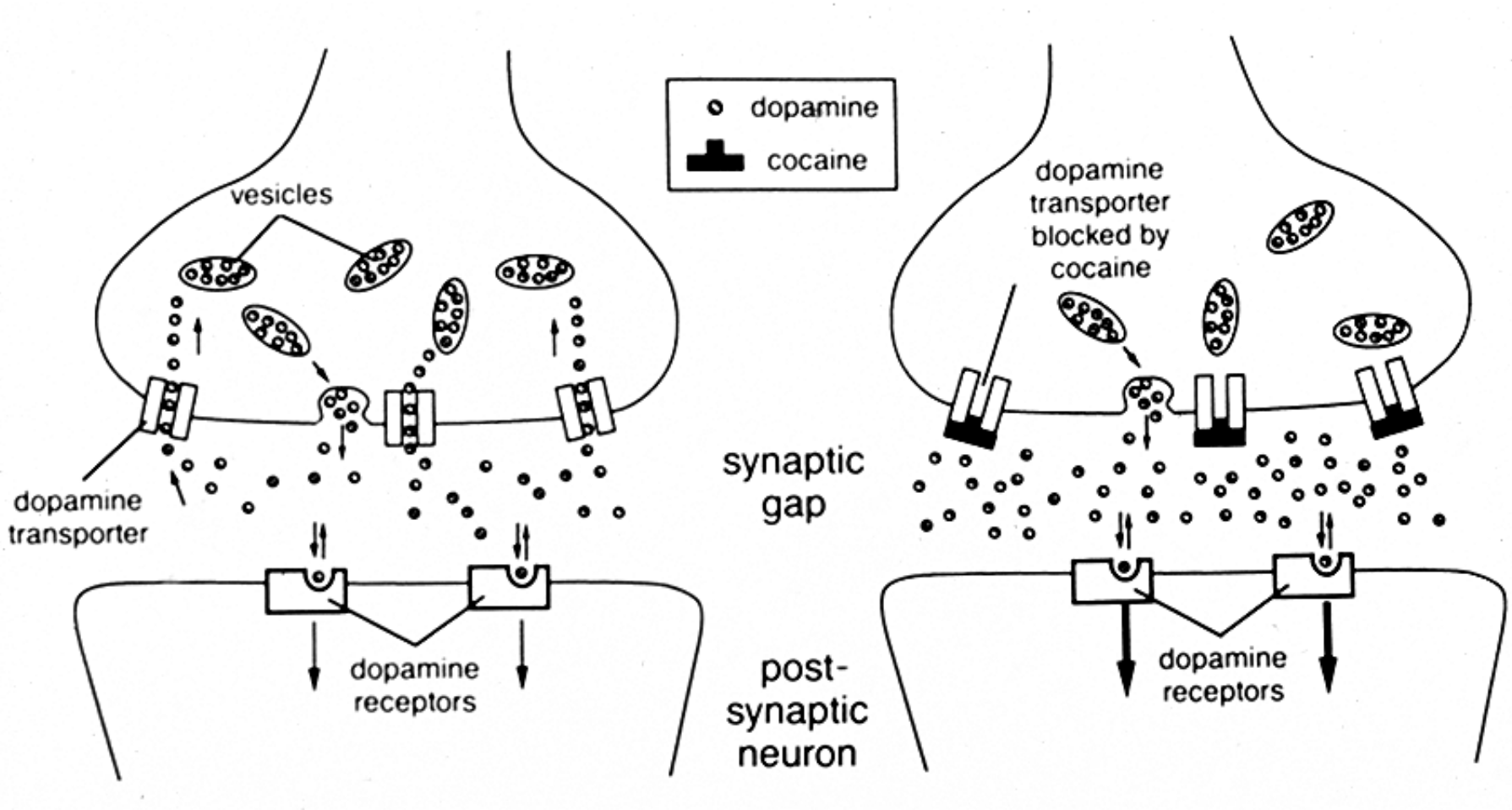
Selegilene is more potent and longer acting than lazabemide



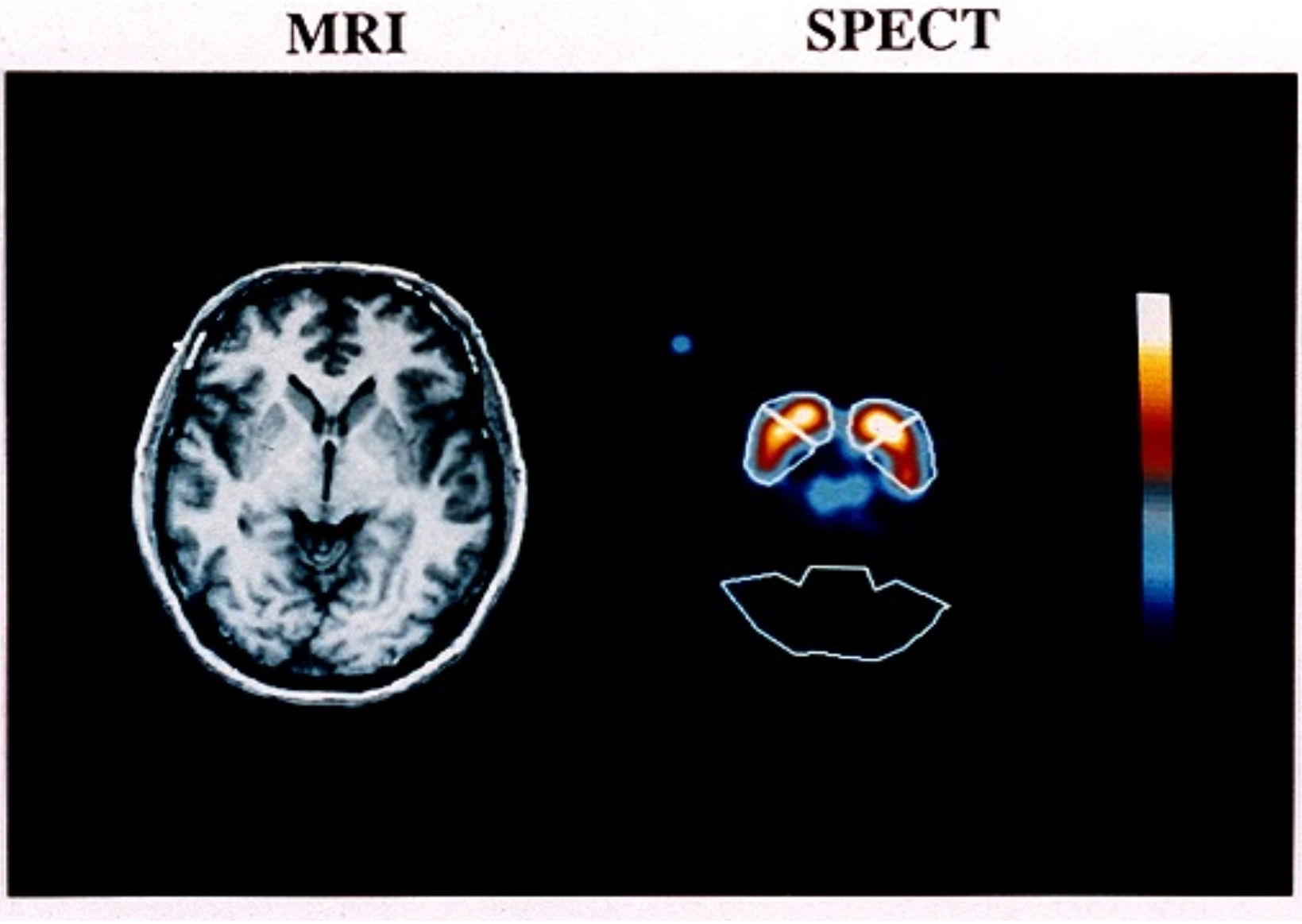
PET: Tool in Therapeutic Drug Development

- Determine dose and dosing interval
- Identify homogeneous group
- Biomarker for drug efficacy

Dopamine Transporter: Located on DA Terminals Removes DA from Synapse

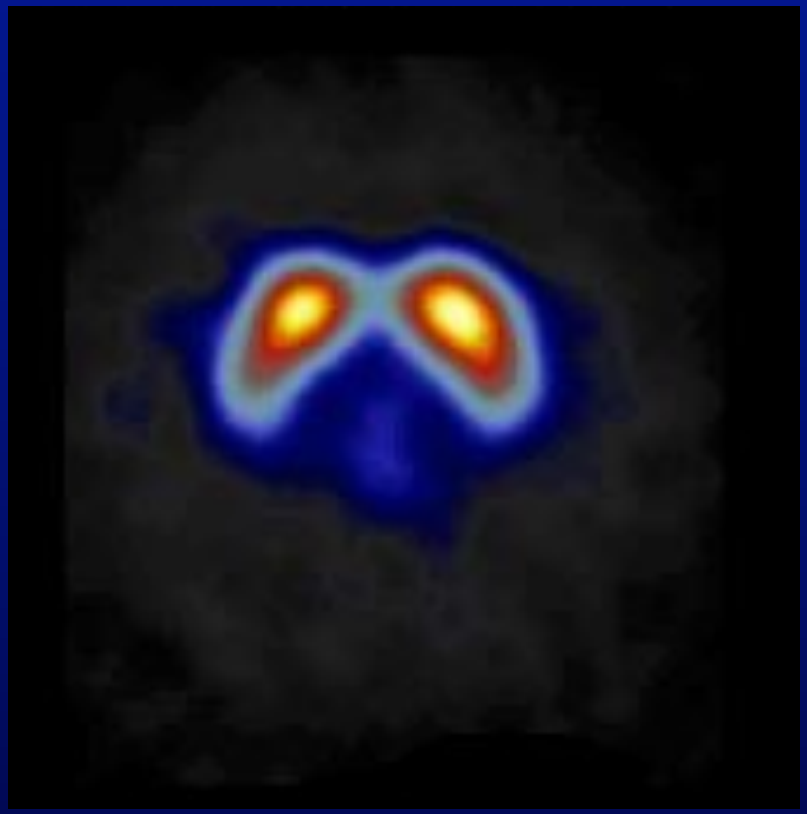


SPECT Imaging of Dopamine Transporter in Caudate and Putamen of Human Brain

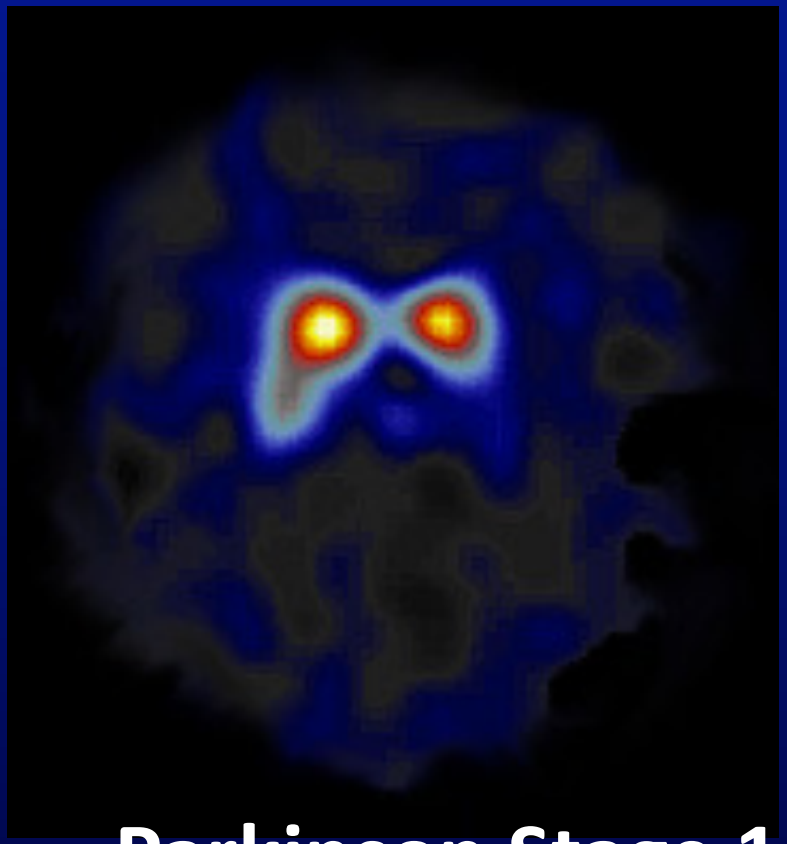


Dopamine Transporter SPECT in Parkinson's Disease:

Decreased, asymmetrical,
loss in putamen > caudate



Healthy

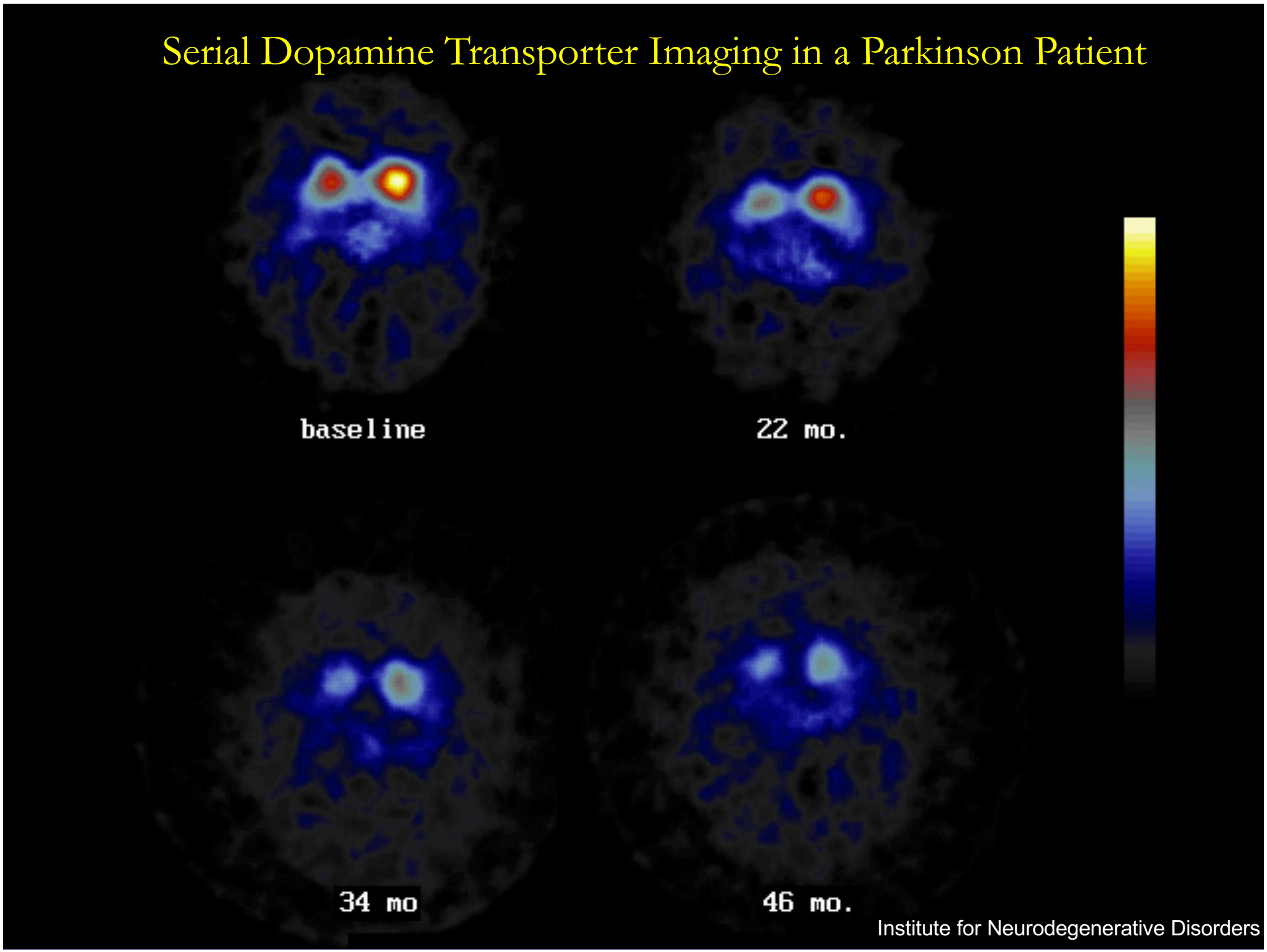


Parkinson Stage 1

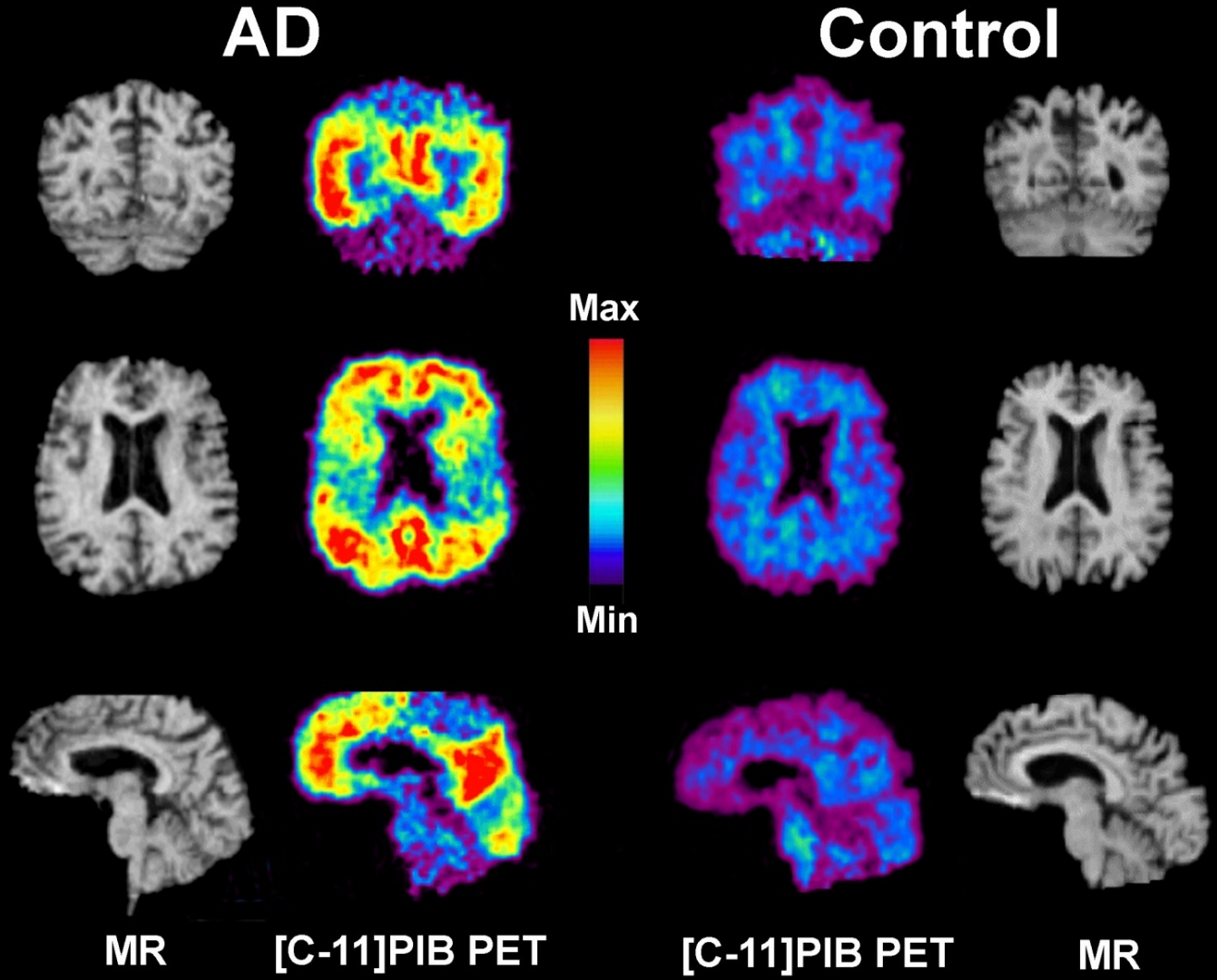
PET: Tool in Therapeutic Drug Development

- Determine dose and dosing interval
- Identify homogeneous group
- Biomarker for drug efficacy

Serial Dopamine Transporter Imaging in a Parkinson Patient



PET Imaging of Amyloid: Biomarker for Alzheimer's Disease

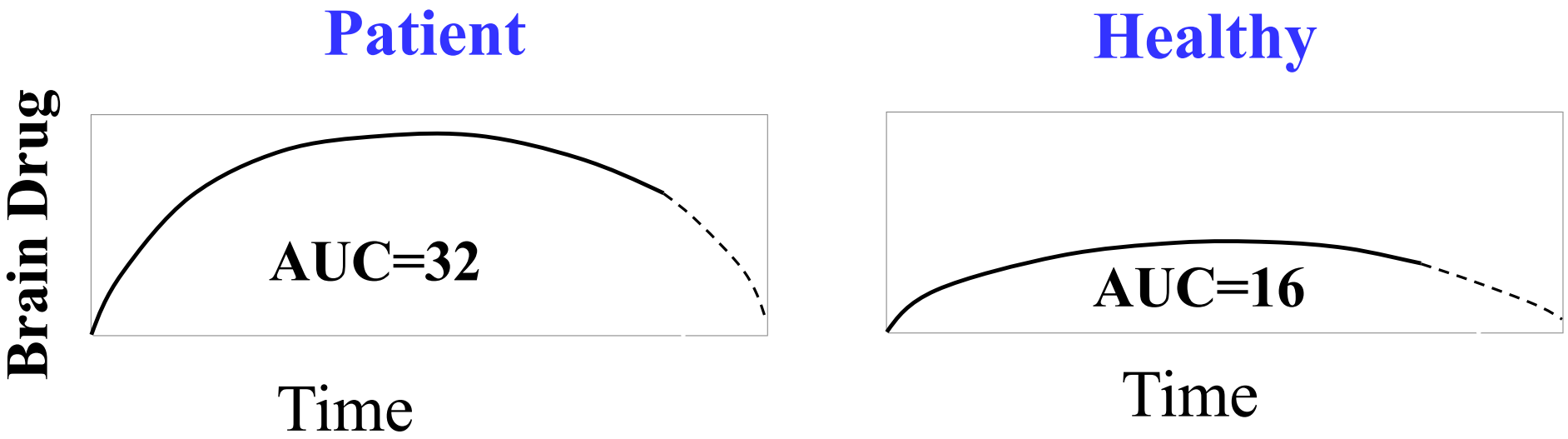


University of Pittsburgh
PET Amyloid Imaging Group

Outline of Talk

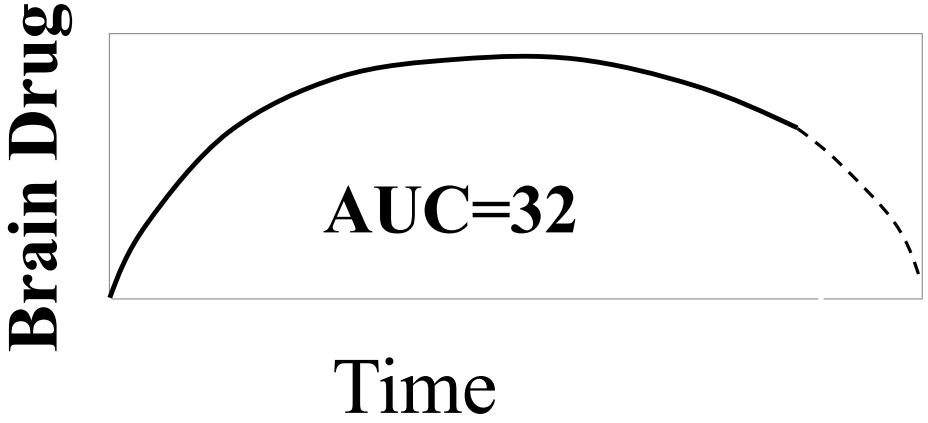
1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling: plasma concentration and tissue uptake
4. Study drug distribution: “peripheral” benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination

Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine

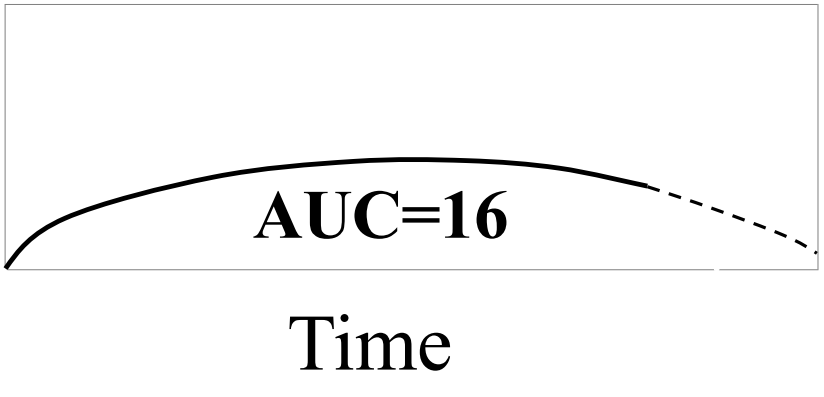


Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine

Patient

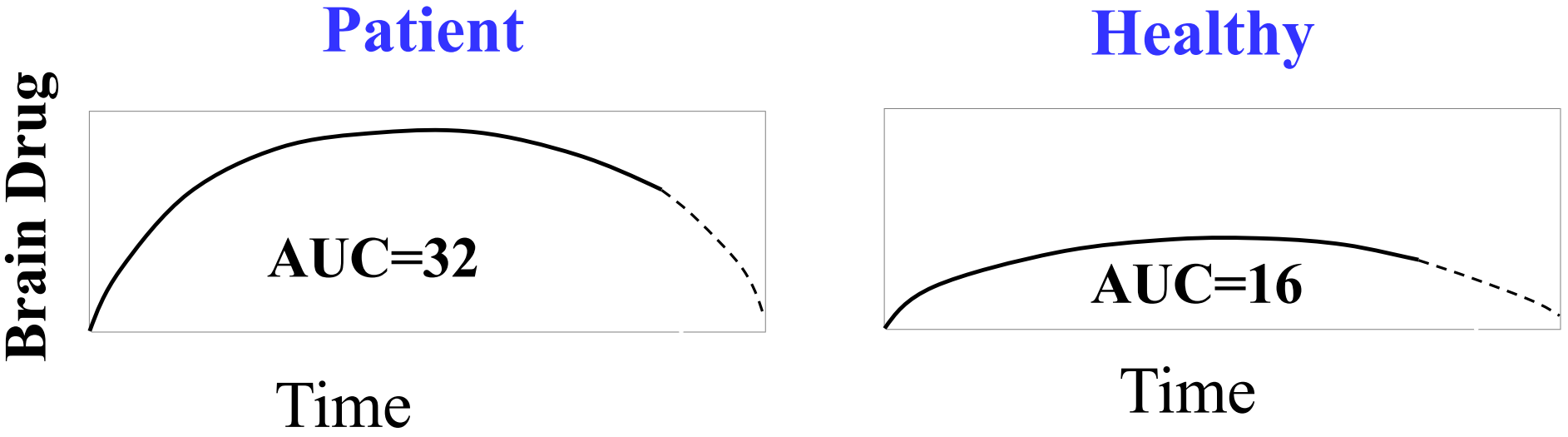


Healthy



	Patient	Healthy
Inject Activity	20 mCi	10 mCi

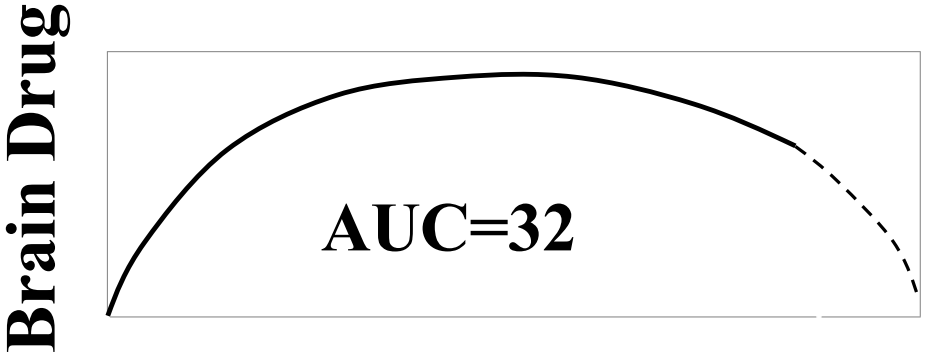
Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine



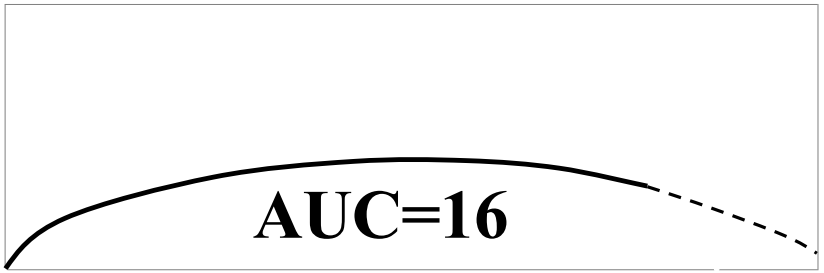
	Patient	Healthy
Inject Activity	20 mCi	20 mCi

Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine

Patient



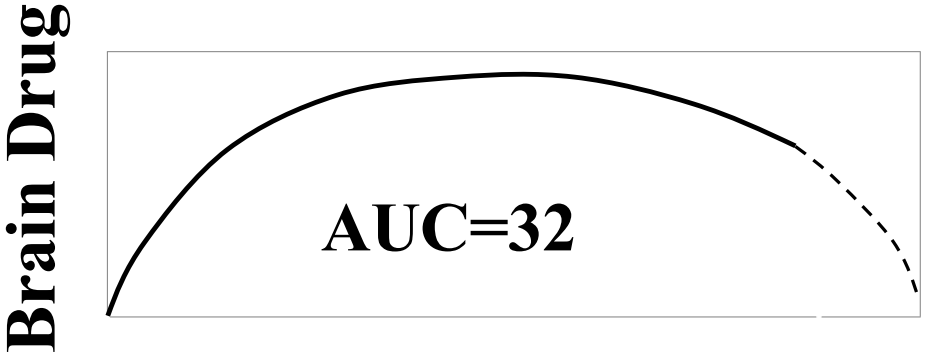
Healthy



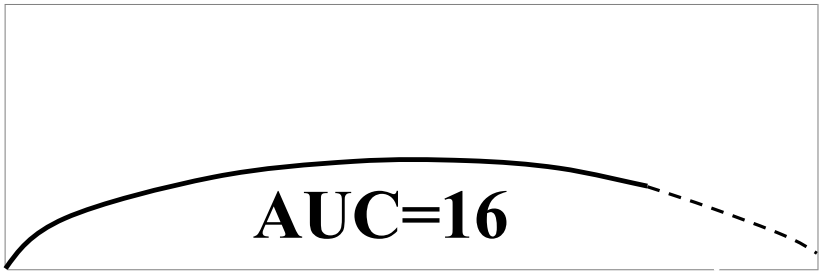
	Patient	Healthy
Inject Activity	20 mCi	20 mCi
Weight	50 kg	100 kg

Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine

Patient



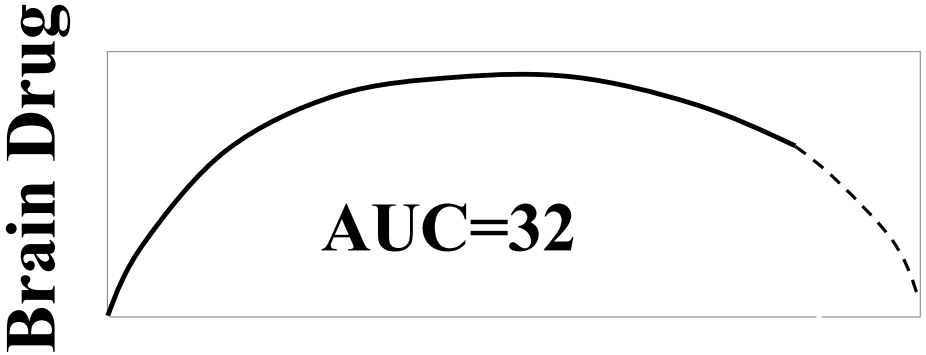
Healthy



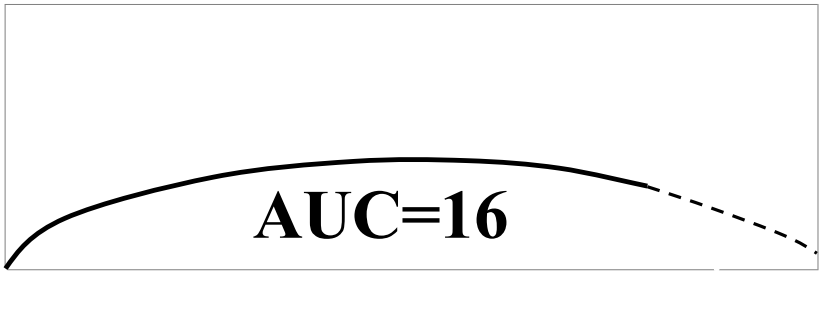
	Patient	Healthy
Inject Activity	20 mCi	20 mCi
Weight	100 kg	100 kg

Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters

Patient



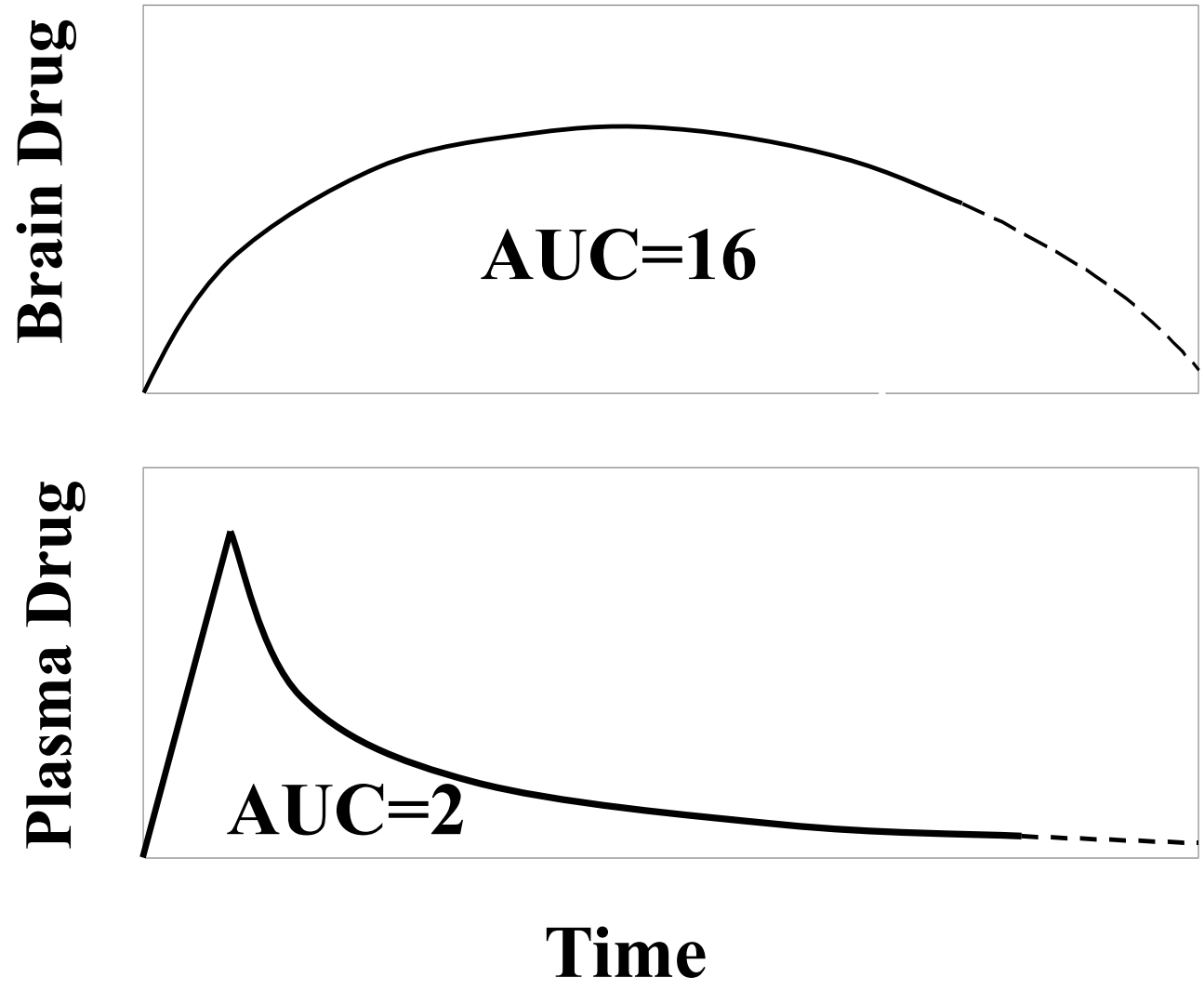
Healthy



	Patient	Healthy
Inject Activity	20 mCi	20 mCi
Weight	100 kg	100 kg
Liver disease	Yes	No

Binding Potential (BP): Receptor Density * Affinity

BP equals uptake in brain relative to how much drug is delivered via arterial plasma.



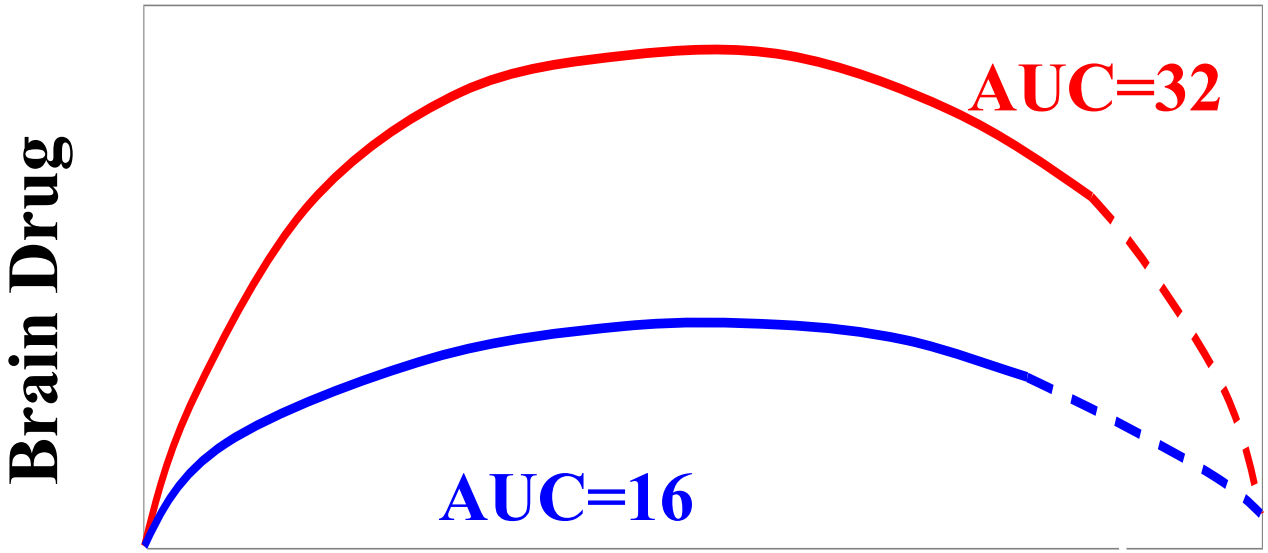
$$BP = \frac{\text{Area Brain Curve}}{\text{Area Plasma Curve}}$$

$$BP = \frac{16}{2} = 8$$

Binding Potential: Independent of Injected Dose*

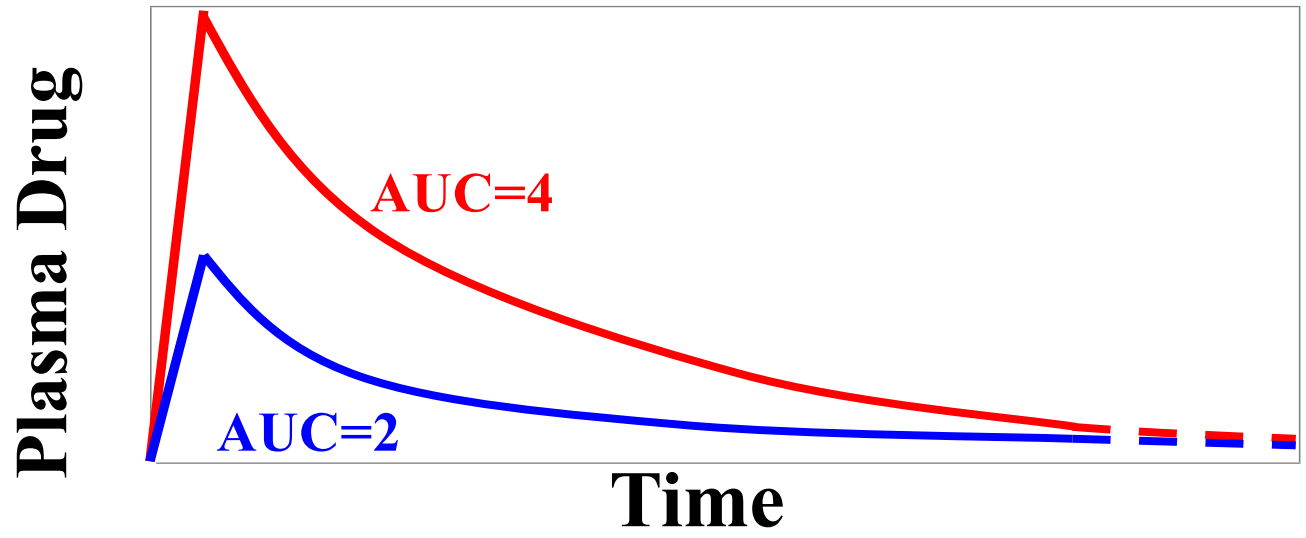
Double Plasma Input =>Double Brain Response

***If ligand does not saturate receptors - i.e., if tracer doses used**



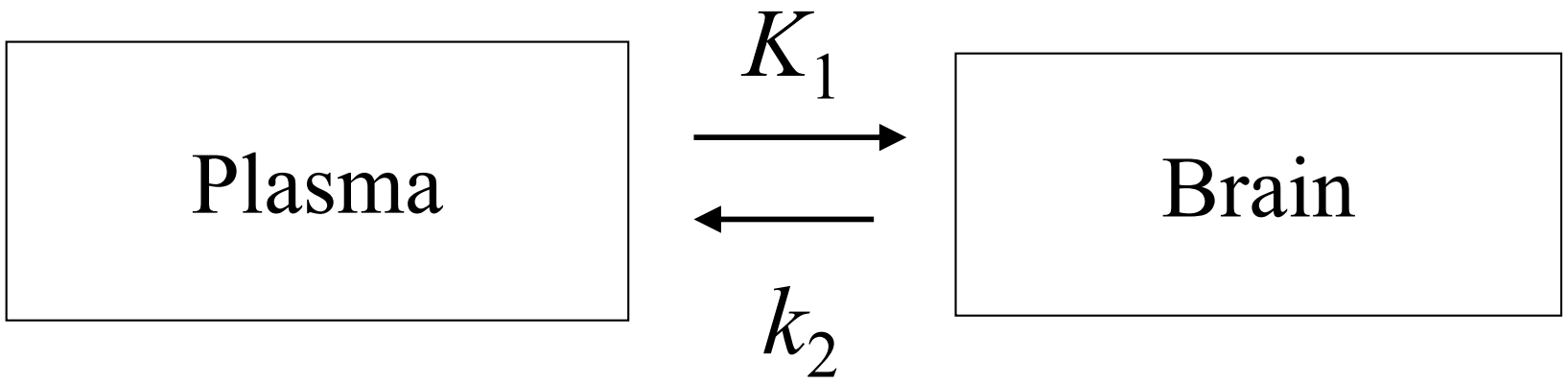
$$\text{BP 1st Time} = \frac{16}{2} = 8$$

$$\text{BP 2nd Time} = \frac{32}{4} = 8$$



BP can be calculated from the Area Under Curve (math integral) as well as rate constants (math differential).

From curves of plasma and brain radioactivity over time, estimate rate constants of entry and removal to/from tissue.



$$BP = \frac{K_1}{k_2}$$

Tissue uptake is proportional to density of receptors and the affinity of the drug

Binding Potential

$$BP = \frac{B_{max}}{K_D} = B_{max} \times \frac{1}{K_D} = B_{max} \times \text{affinity}$$

B_{max} = receptor density

K_D = dissociation binding constant

$\frac{1}{K_D}$ = binding affinity drug

SUMMARY PET KINETICS

- Organ uptake is proportional to receptor density and affinity of drug
- Binding Potential (BP) = density X affinity
- "Drug Exposure" to tissue is AUC of:

  plasma concentration *vs.* time
- "Response" (uptake) of tissue is AUC of:

  tissue concentration *vs.* time

$$BP = \frac{\text{Response}}{\text{Exposure}} = \frac{AUC_{\text{tissue}}}{AUC_{\text{plasma}}}$$

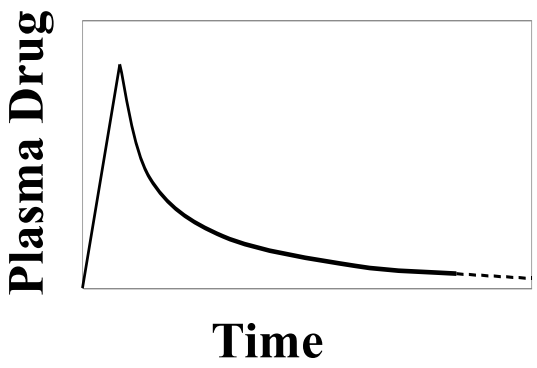
- BP also equals ratio of rate constants of entry and removal to/from tissue

$$BP = \frac{K_1}{k_2}$$

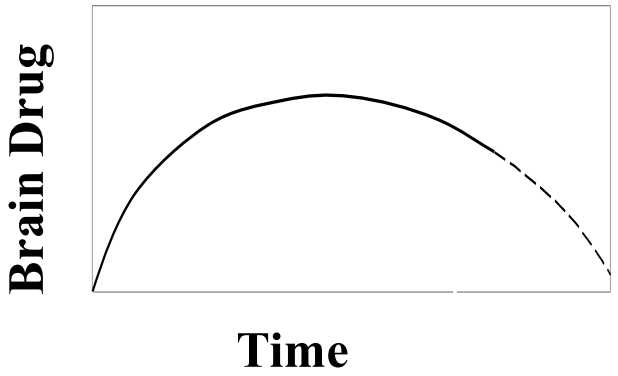
Major Point of PET Pharmacokinetics (in words)

- Plasma pharmacokinetics provides a limited view of what's happening to drug in plasma.
- PET provides a limited view of what's happening to drug in tissue.
- **Concurrent measurement of drug in plasma and of drug in tissue allows quantitation of the target of drug action – *i.e.*, receptor.**

Pharmacokinetics: Drug in plasma & **Pharmacodynamics: Drug acts at receptor** → **Receptor Density**



&



→ **Receptor Density**

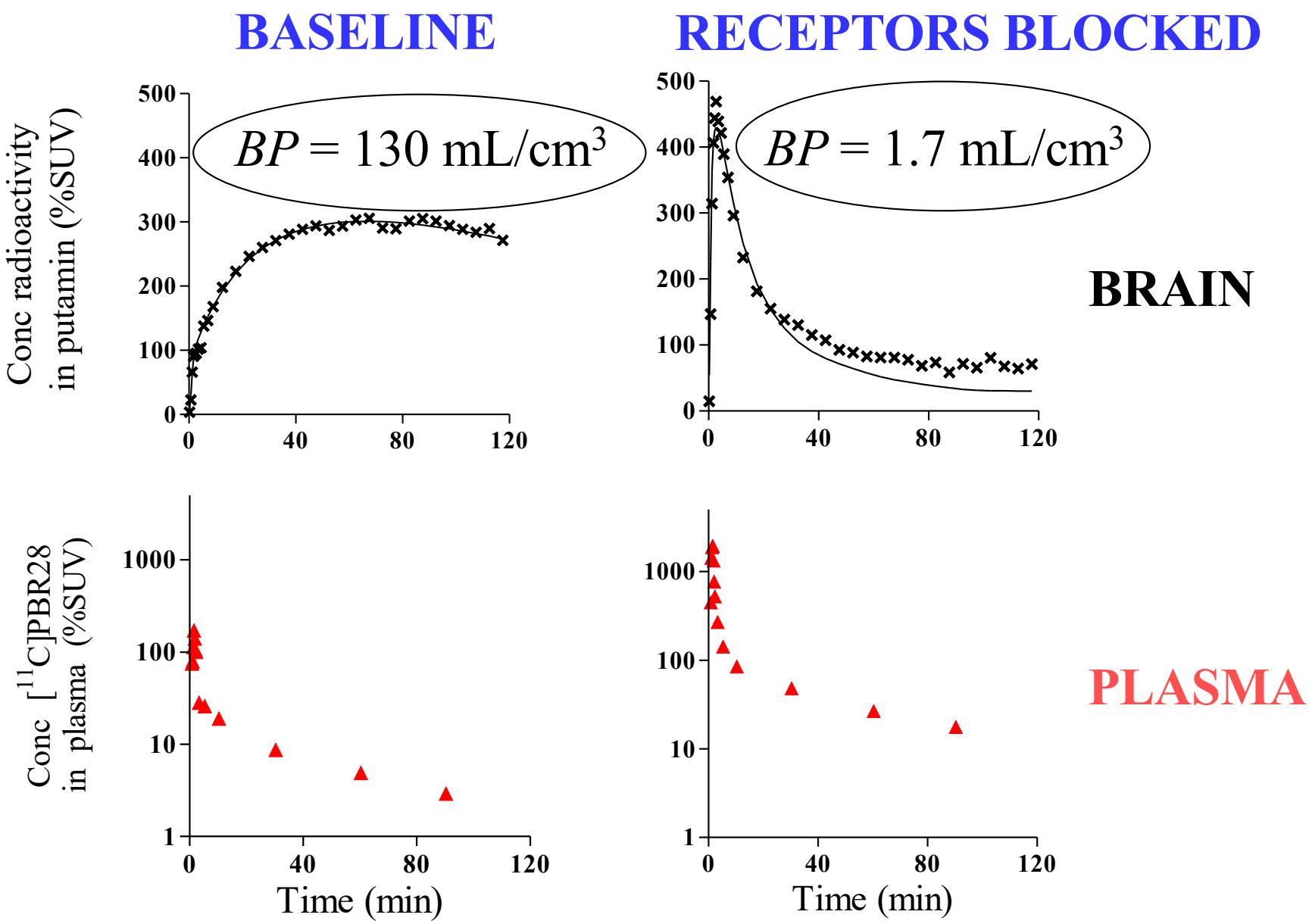
Outline of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling: plasma concentration and tissue uptake
4. Study drug distribution: “peripheral” benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination

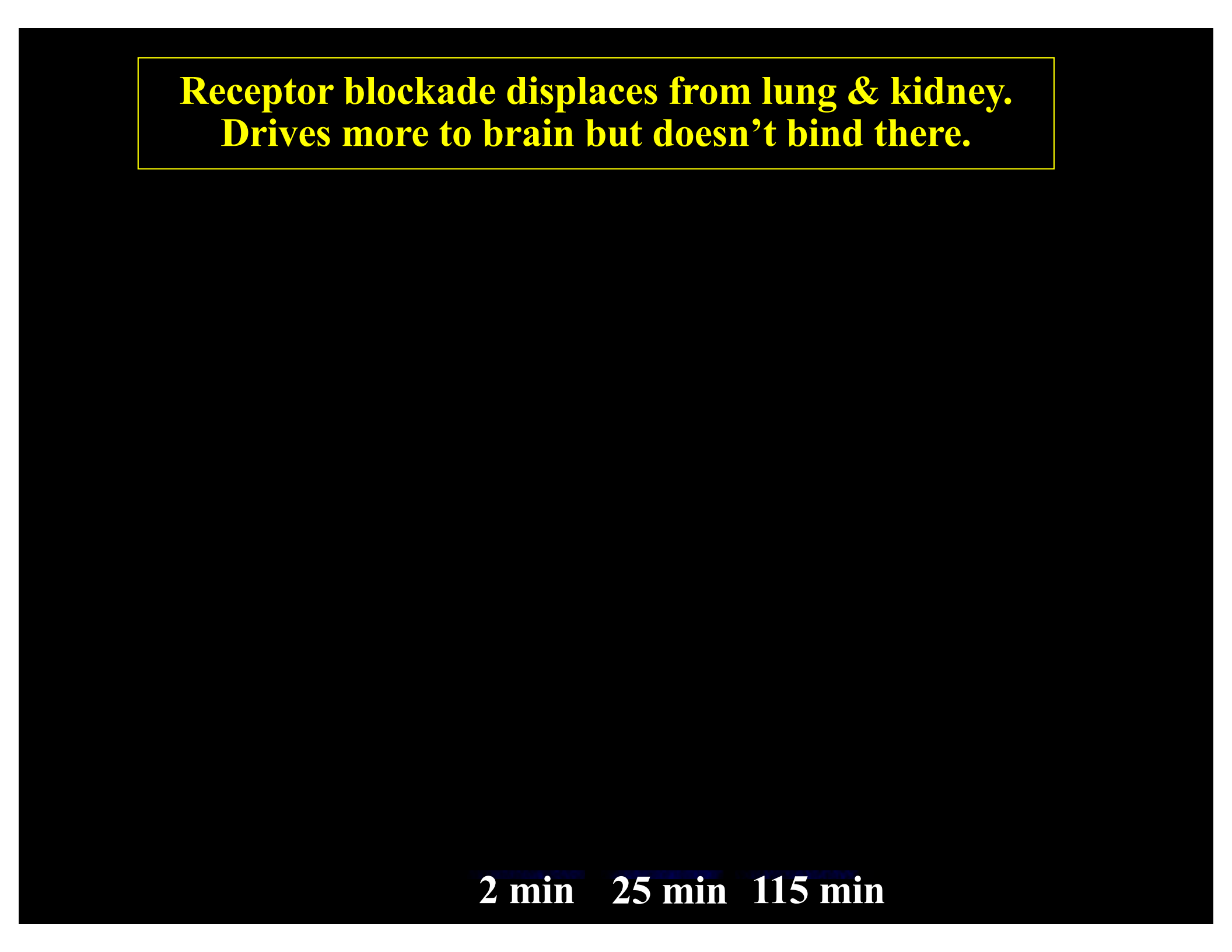
Translocator Protein (18 kDa)
a.k.a. "peripheral benzodiazepine receptor"

1. Mitochondrial protein highly expressed in macrophages and activated microglia
2. Exists in periphery and brain
3. Multiple potential functions: steroid synthesis, nucleotide transport
4. Distinct from typical benzodiazepine $GABA_A$ receptor in brain
5. Marker for cellular inflammation

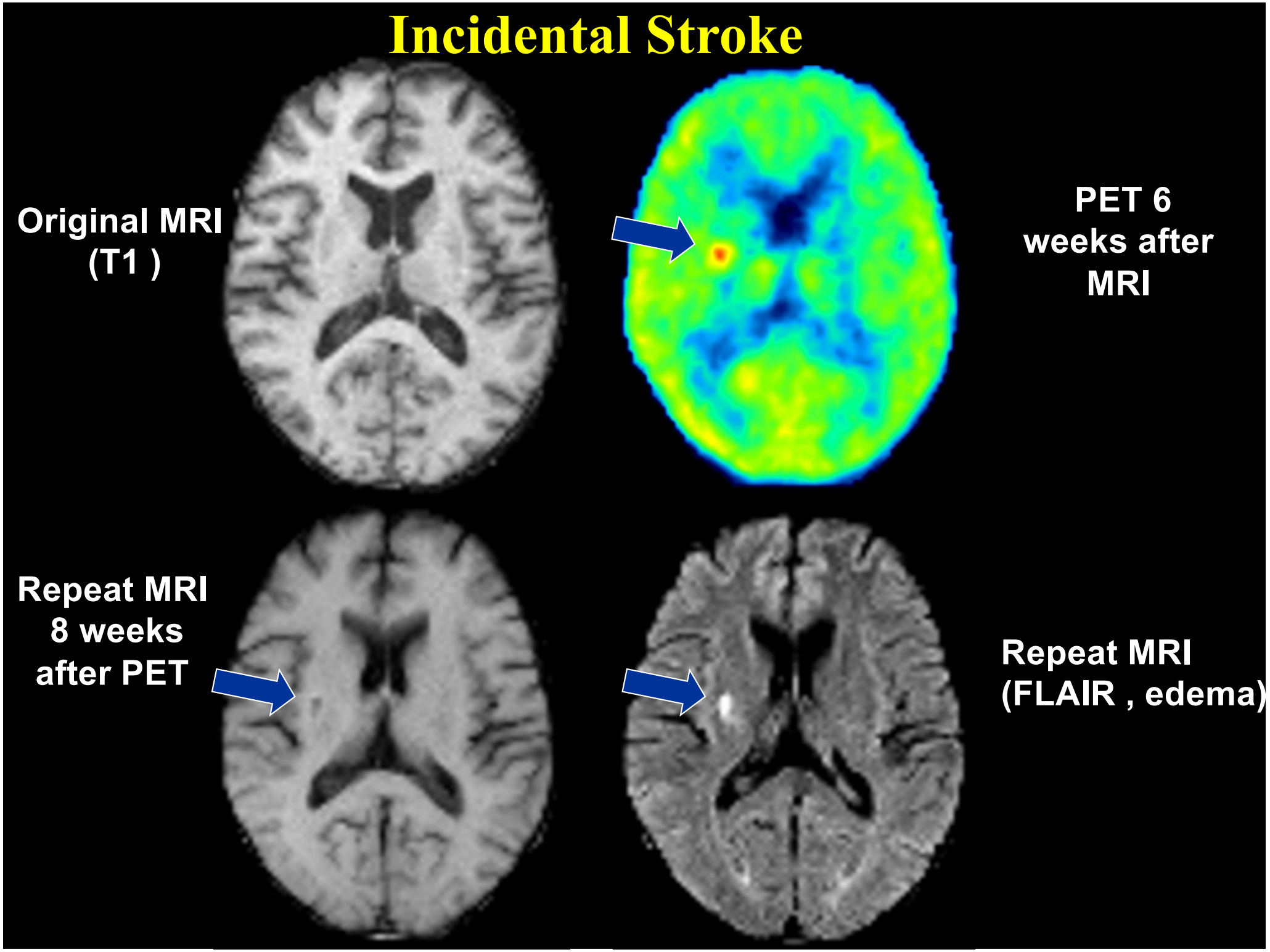
Receptor Blockade [^{11}C]PBR28 in Monkey Brain: more radioligand in plasma and brain



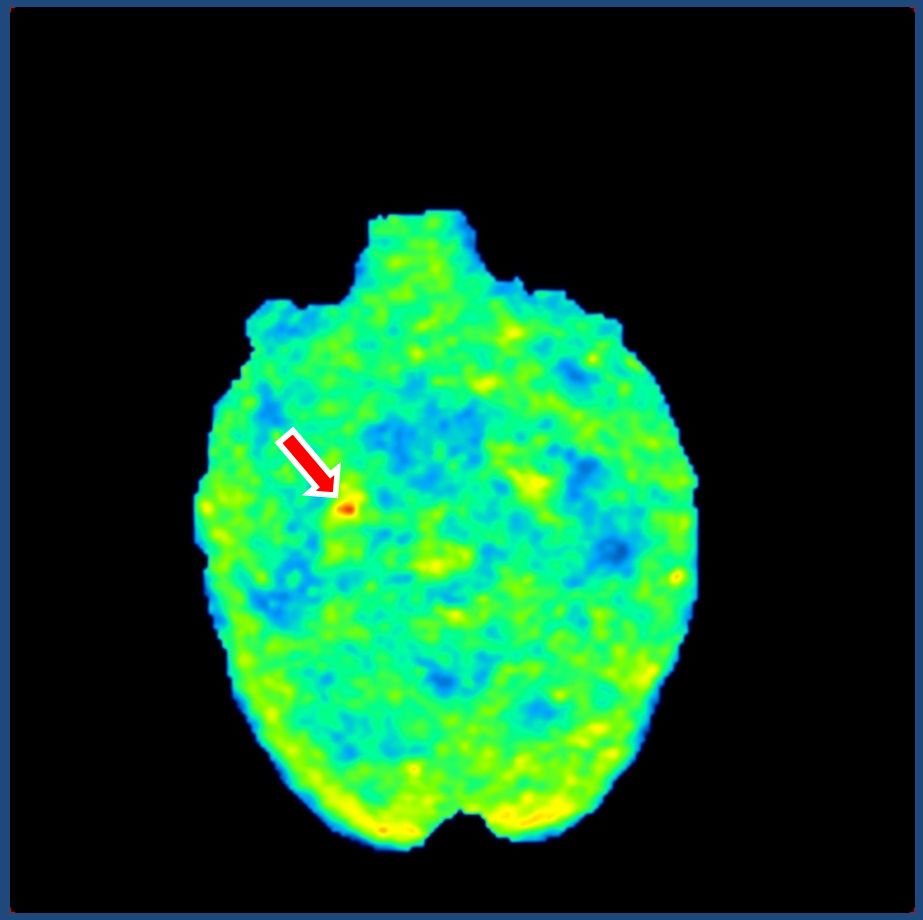
Receptor blockade displaces from lung & kidney.
Drives more to brain but doesn't bind there.

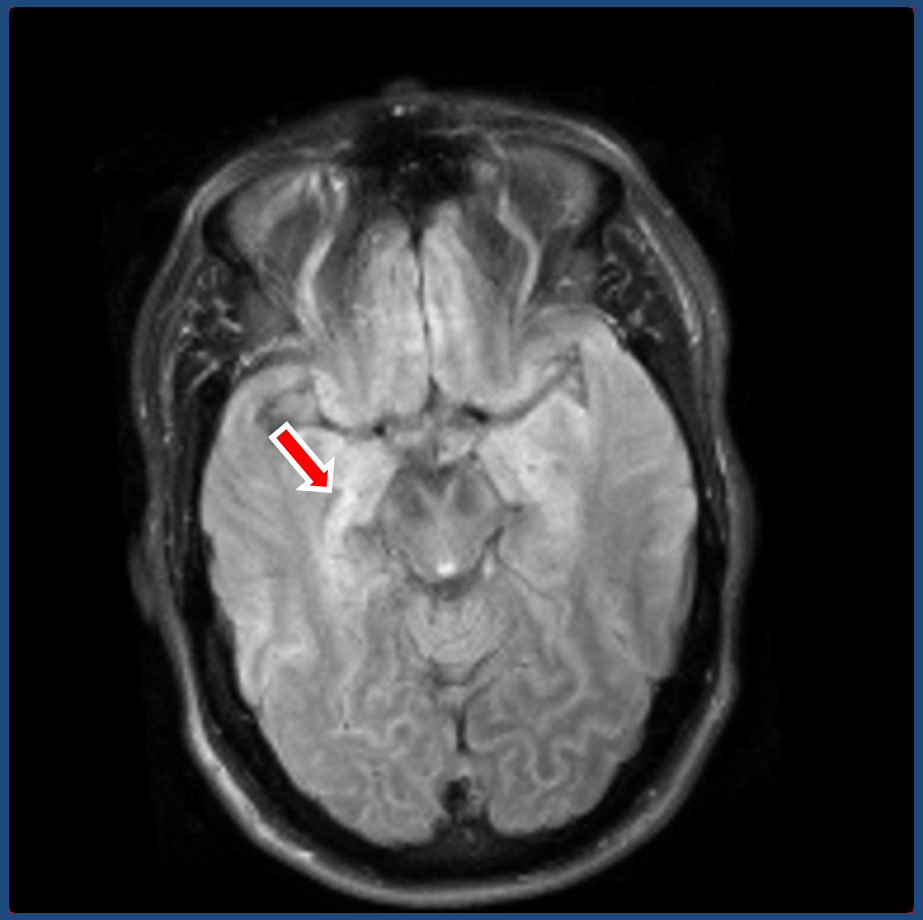


Incidental Stroke



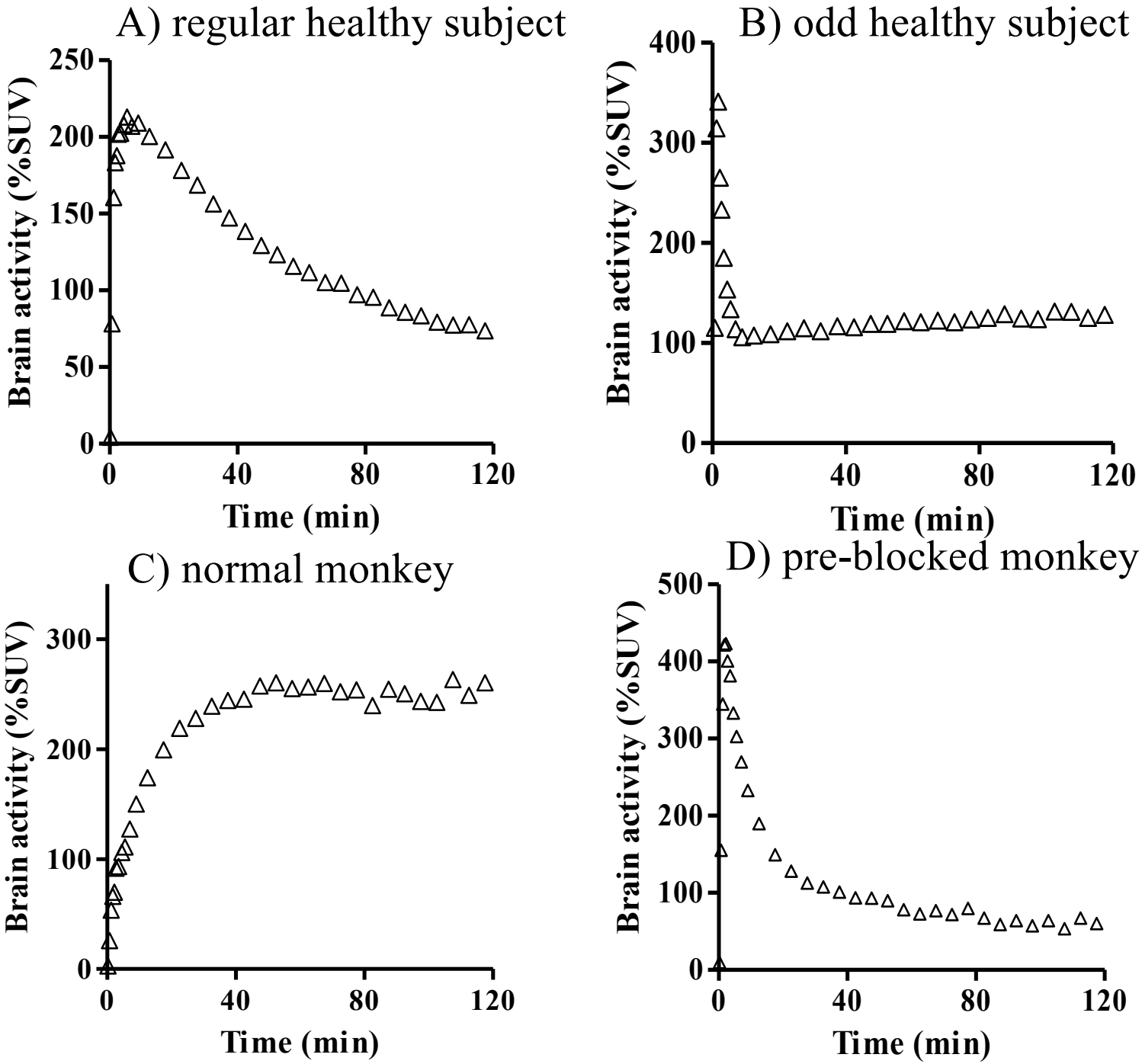
TSPO identifies epileptogenic focus in 15 of 16 patients.





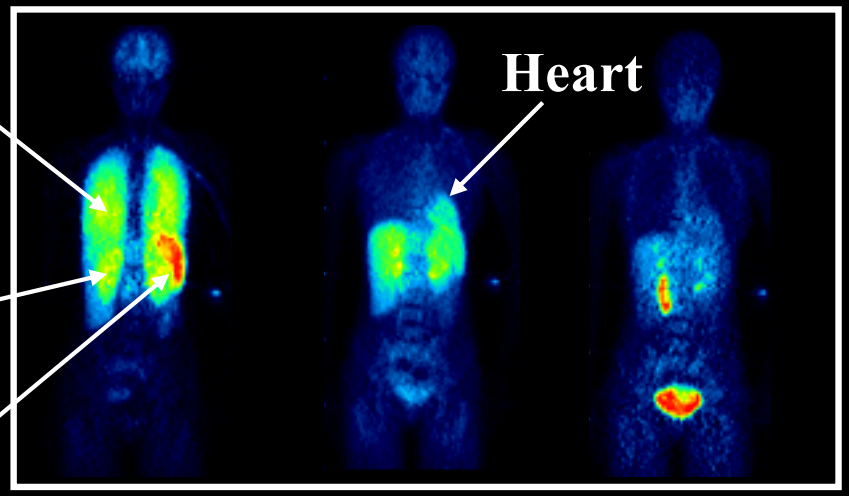
Hirvonen et al., *JNM*, 2012

Human with low uptake is similar to monkey with receptor blockade



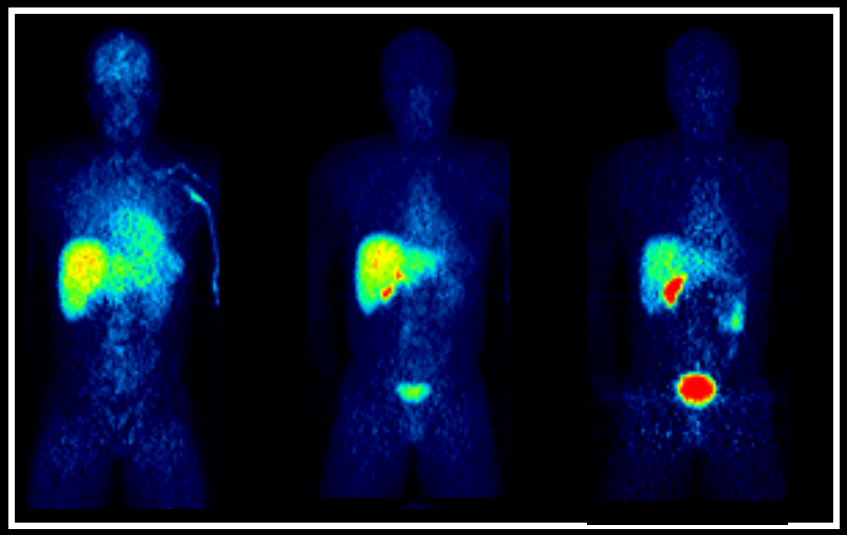
No Binding to [^{11}C]PBR28 in Brain and Periphery

Normal Binding



2 min 26 min **103 min**

No Binding
(~10% subjects)



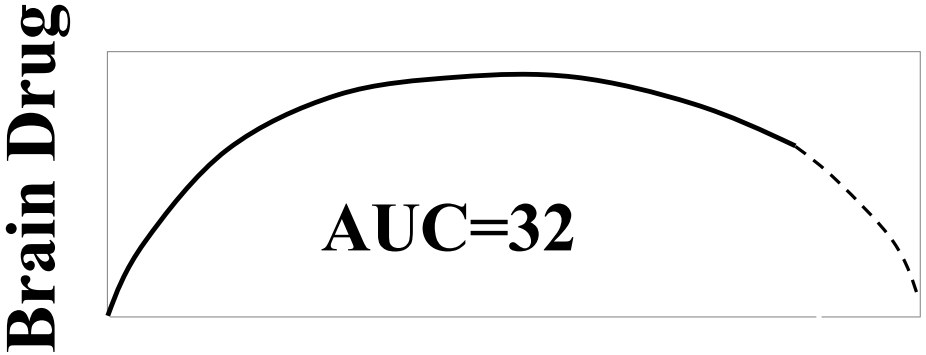
TSPO rs6971 polymorphism causes differential affinity for PBR28

- Ala to Thr substitution
- Allelic frequency ~ 30%.
  - Prevalence of homozygotes ~ 9%
- Codominant expression
  - HAB - high affinity binding
  - LAB - low affinity binding
  - MAB - reduced binding (mixed affinity states)

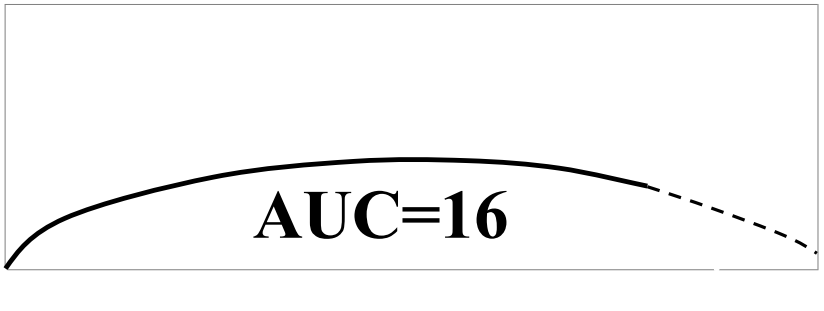
Owen, JCBFM 2012

Brain Uptake of [^{18}F]Fluoxetine: Measures Density of Serotonin Transporters

Patient

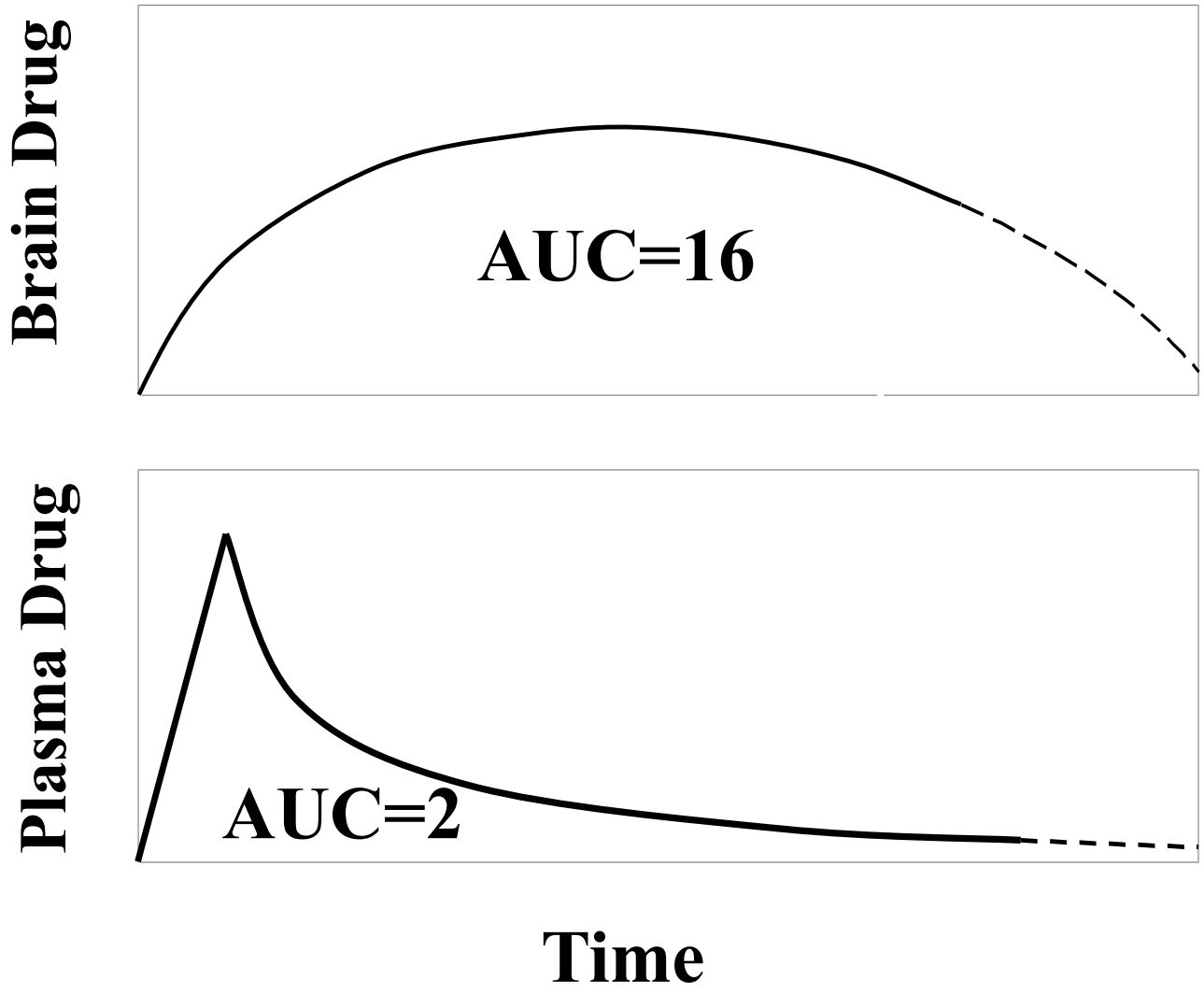


Healthy



	Patient	Healthy
Inject Activity	20 mCi	20 mCi
Weight	100 kg	100 kg
Liver disease	Yes	No

Binding Potential (BP): Receptor Density * Affinity



$$BP = \frac{\text{Area Brain Curve}}{\text{Area Plasma Curve}}$$

$$BP = \frac{16}{2} = 8$$

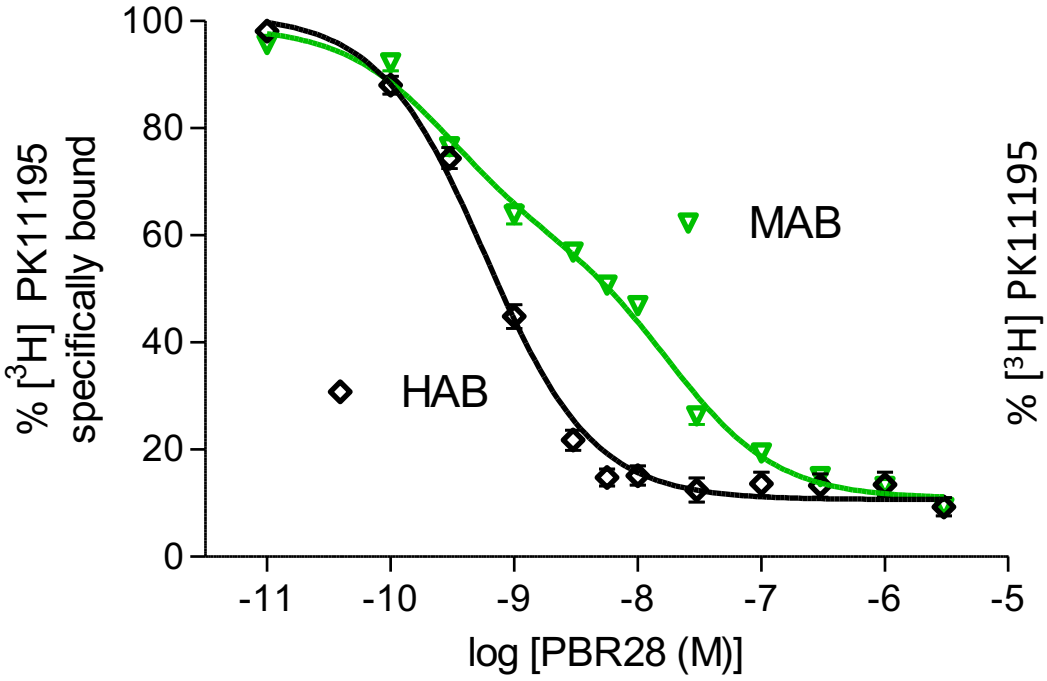
Experimental Design: Effect of TSPO genotype on PBR28 binding

- PET study
  - 27 healthy volunteers
  - In vitro binding: Leukocyte displacement assay
  - In vivo binding: [^{11}C]PBR28 PET imaging

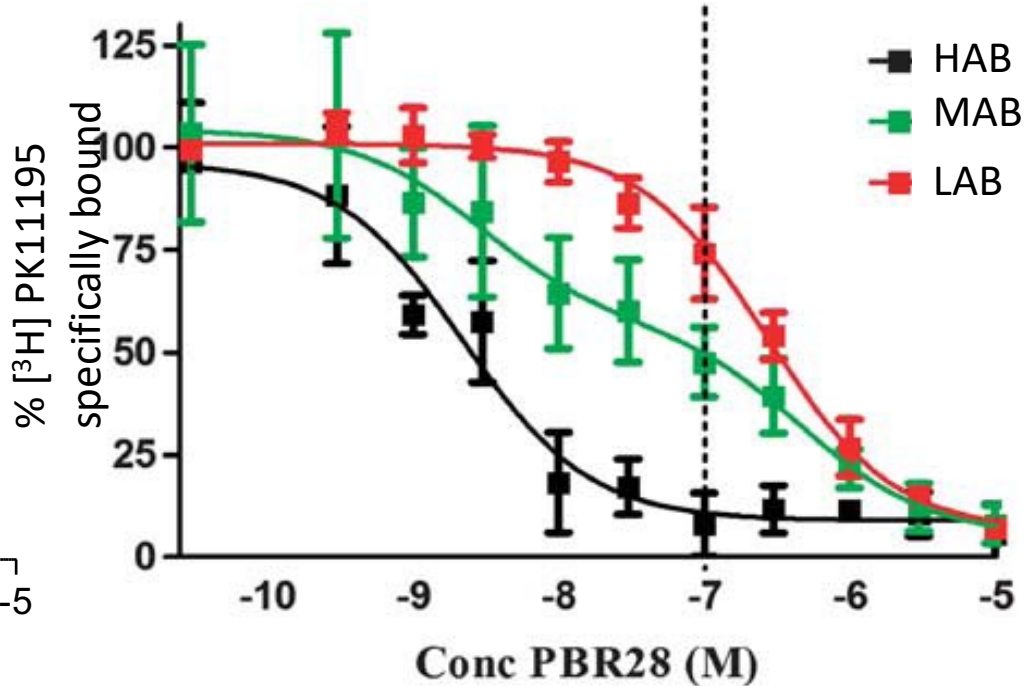
- Post-mortem study
  - 47 healthy controls, 45 schizophrenia patients
  - Specific [^{3}H]PBR28 binding in prefrontal cortex
  - Comparison with and without genotype correction

Kreisl, JCBFM 2013

PET Study: Both TSPO genotype and leukocyte binding assay determine affinity status



Kreisl, JCBFM 2013



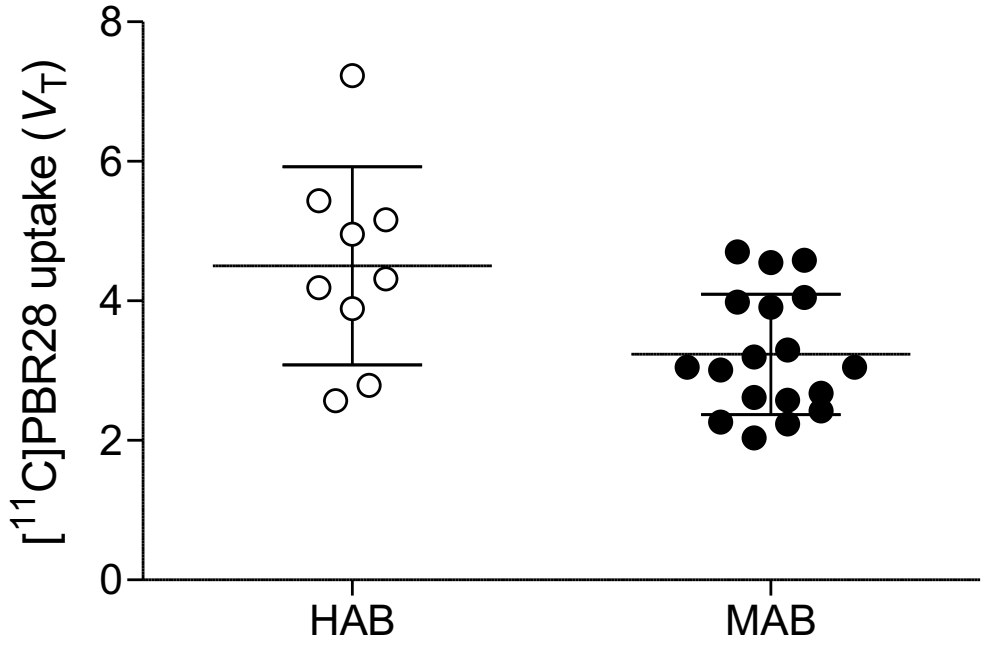
Owen, JCBFM 2012

100% agreement between binding assay results and genotype

One-site fit = HAB

Two-site fit = MAB

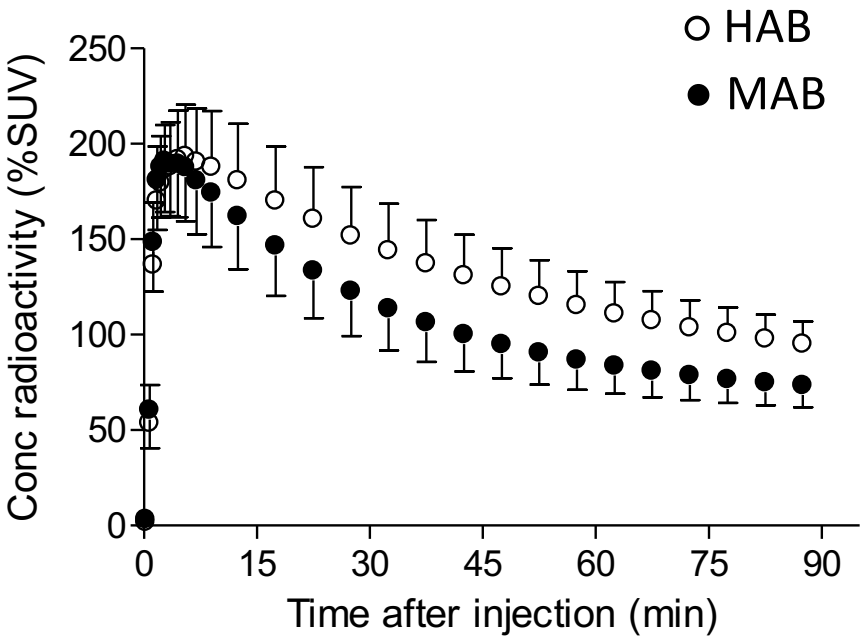
PET Study: [^{11}C]PBR28 binding is 1.4-fold higher in high affinity binders than mixed affinity binders

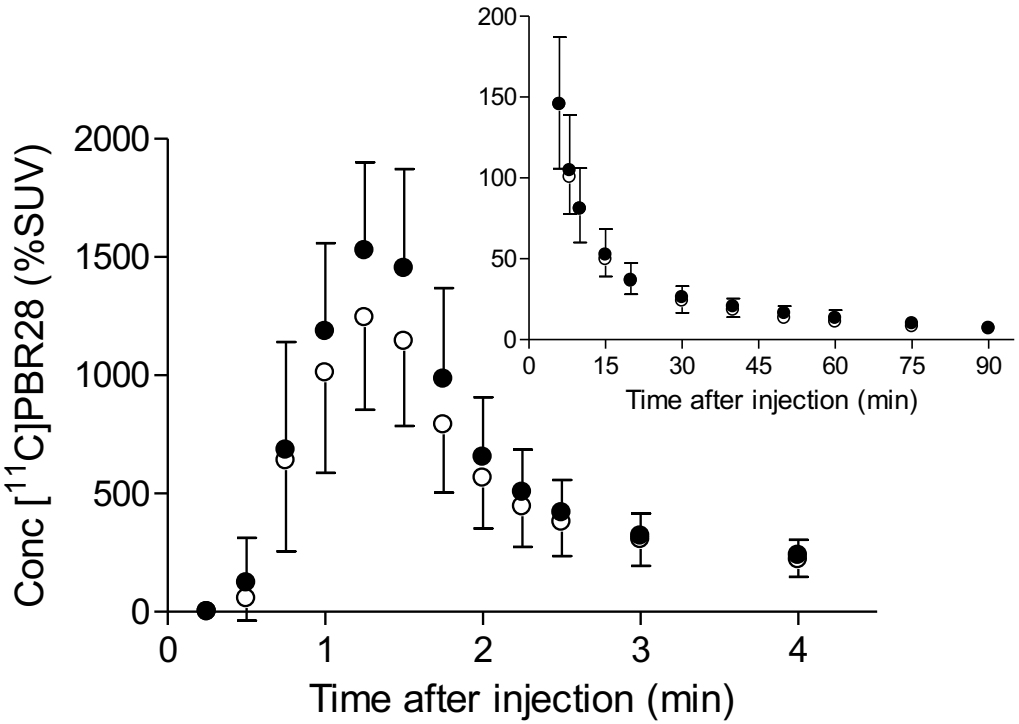


Mean HAB = 4.5 mL • cm^{-3}
Mean MAB = 3.2 mL • cm^{-3}

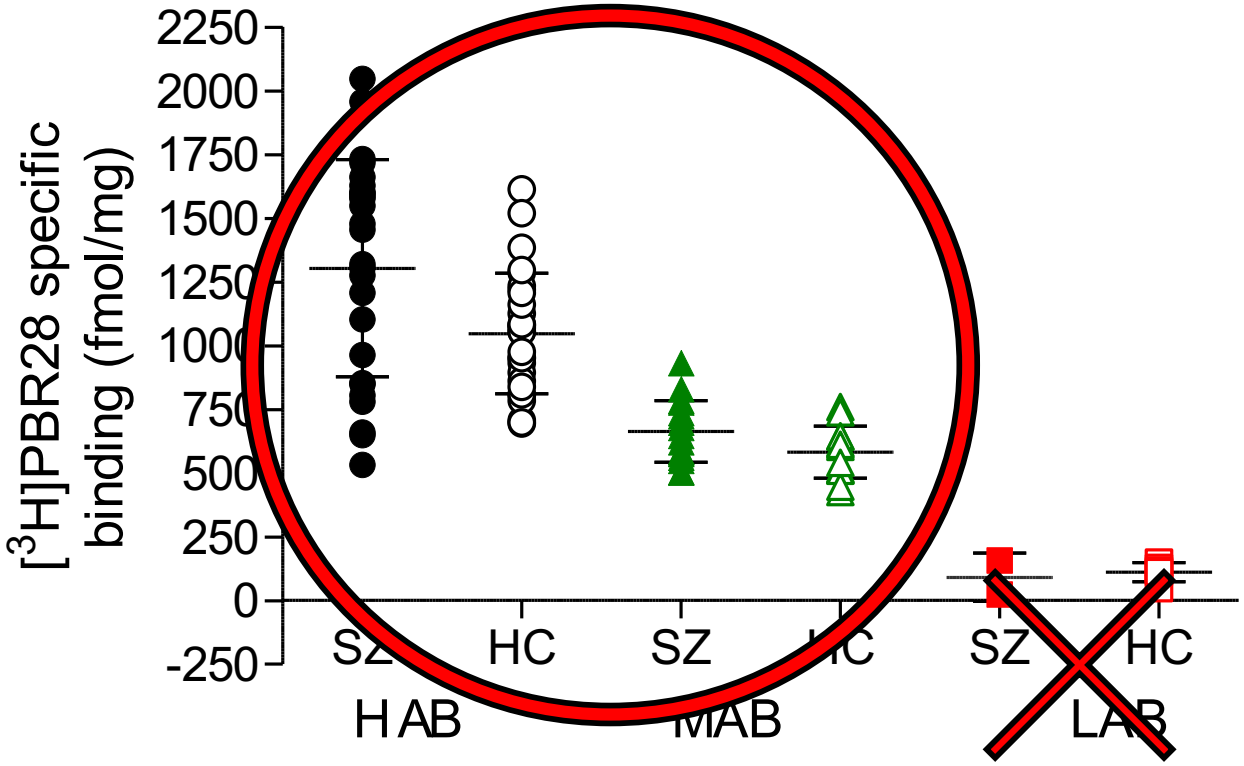
Expect less than 2-fold difference because [^{11}C]PBR28 uptake represents specific and nonspecific binding

PET Study: Greater brain uptake in HH subjects with similar plasma concentration as HL subjects



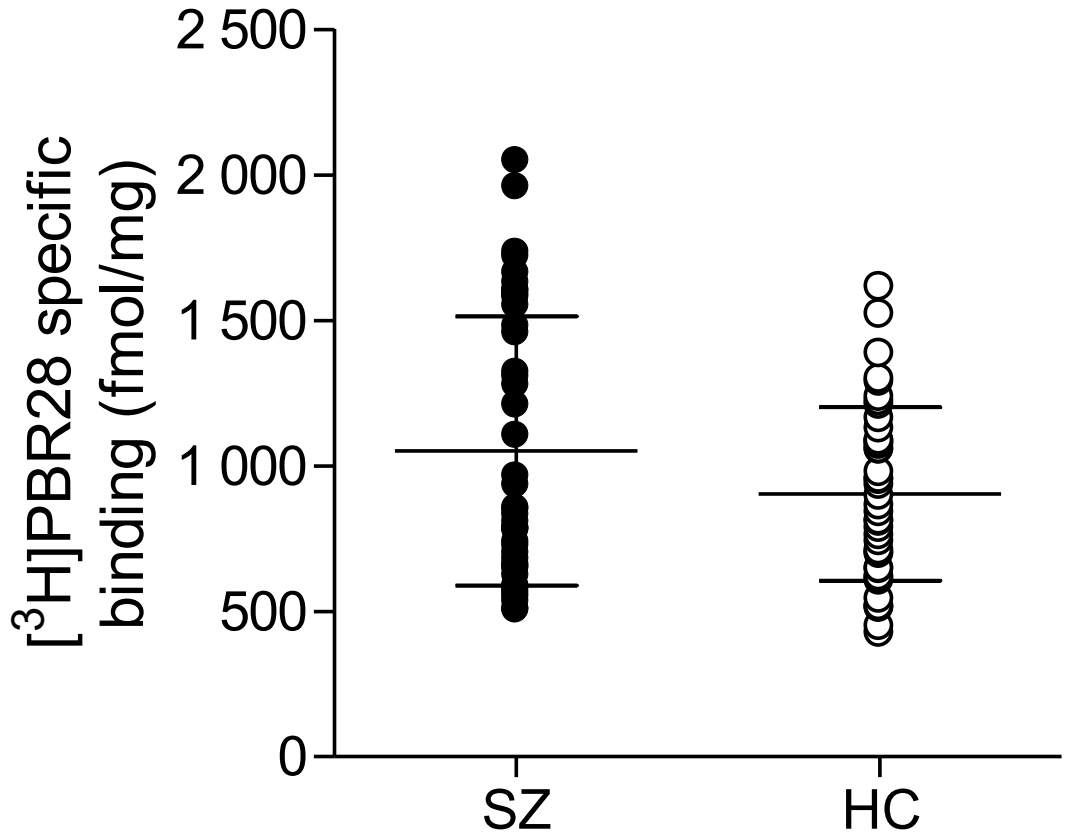


Post-mortem study: High and mixed affinity binders also seen in schizophrenia patients



Kreisl, JCBFM, 2013

Correcting for TSPO genotype increases sensitivity to detect difference between schizophrenia and controls



Without genotype as covariate p = 0.085

With genotype as covariate p = 0.011

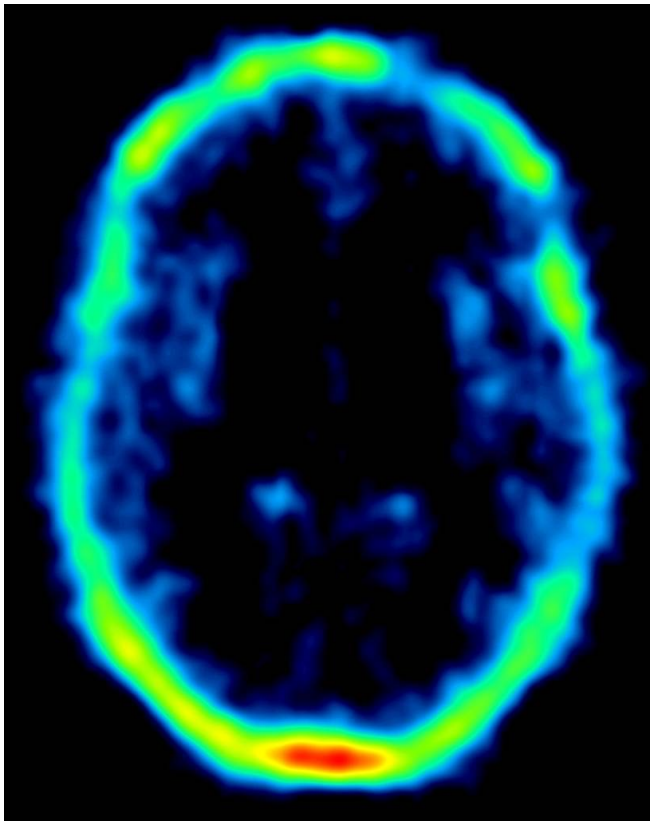
Summary

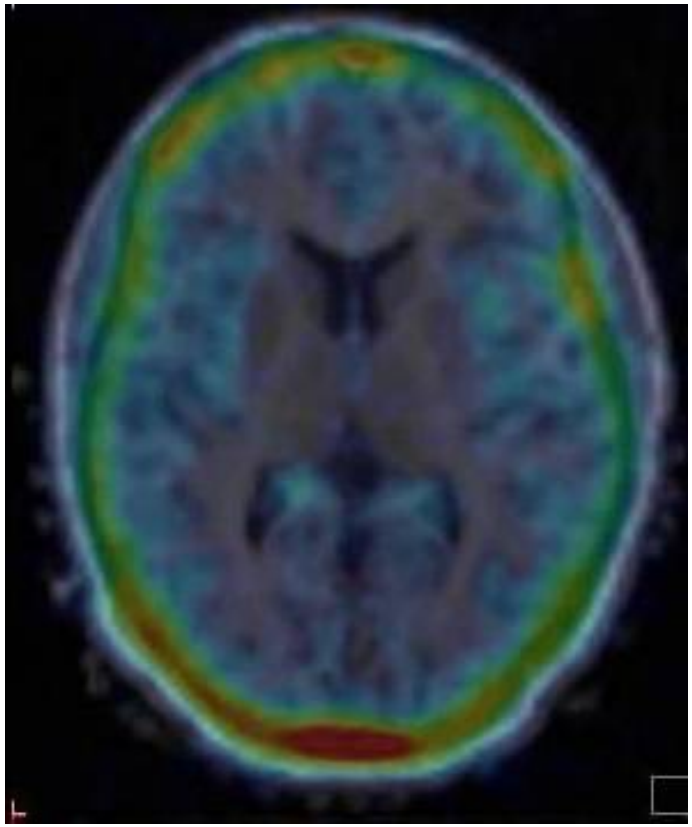
- PBR28 PET study:
  - Leukocyte binding assay predicts TSPO genotype
  - TSPO genotype influences [^{11}C]PBR28 total binding
- PBR28 Post-mortem study:
  - TSPO genotype influences specific binding
  - Genotype correction increases ability to measure difference in schizophrenia and controls
- Correcting for TSPO genotype expected to improve clinical use of [^{11}C]PBR28

Outline of Talk

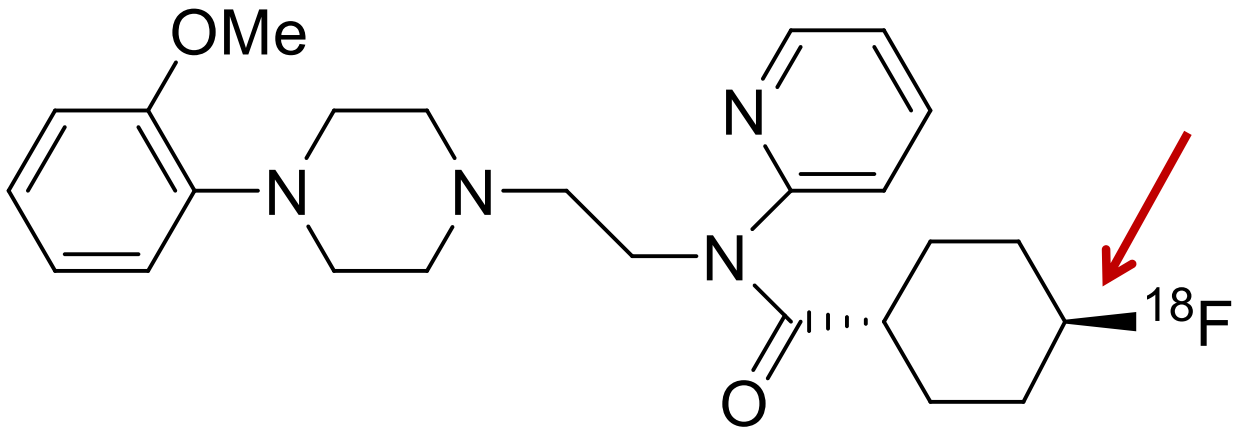
1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling: plasma concentration and tissue uptake
4. Study drug distribution: “peripheral” benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination

[^{18}F]FCWAY: Defluorination
Bone uptake: human skull at 2 h



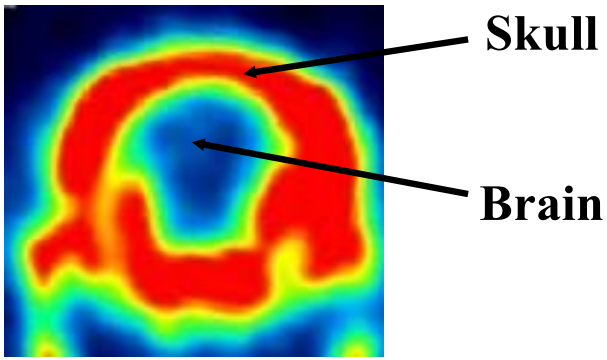


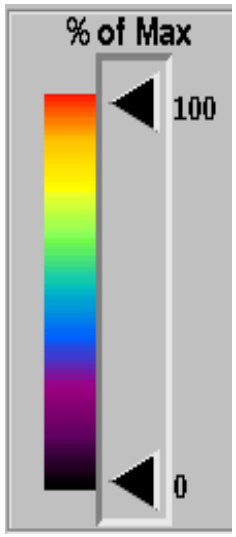
[^{18}F]FCWAY: Defluorination
^{18}F-fluoride ion accumulates in bone



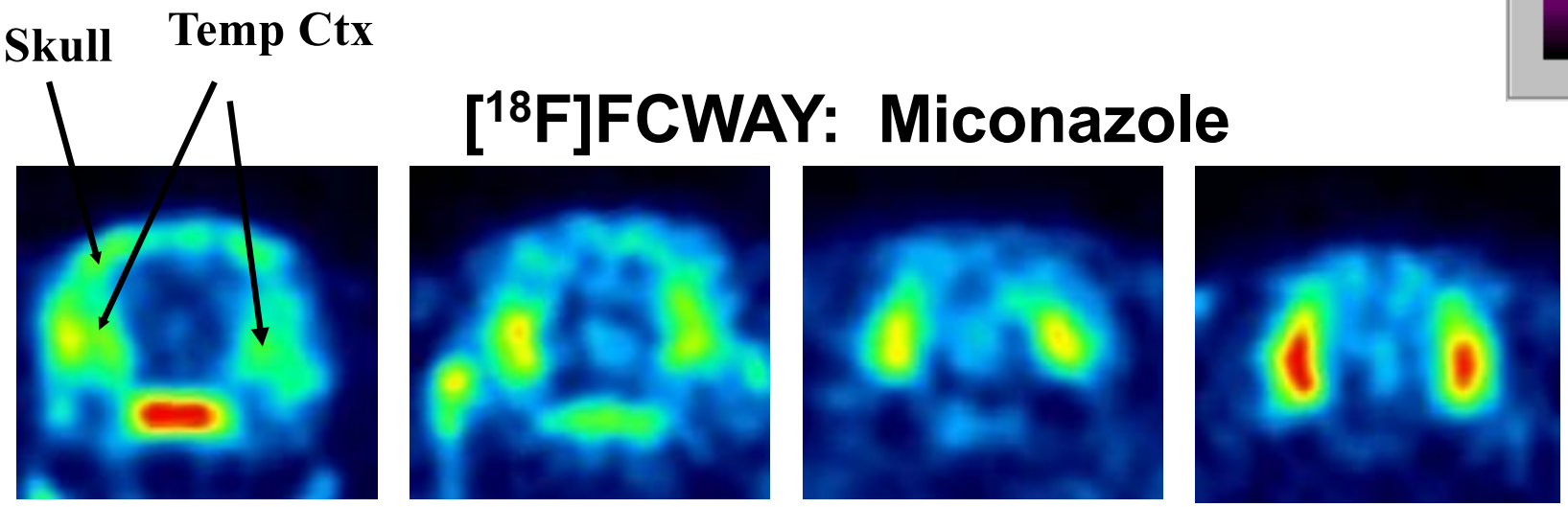
Miconazole Inhibits Defluorination & Bone Uptake

[^{18}F]Fluoride



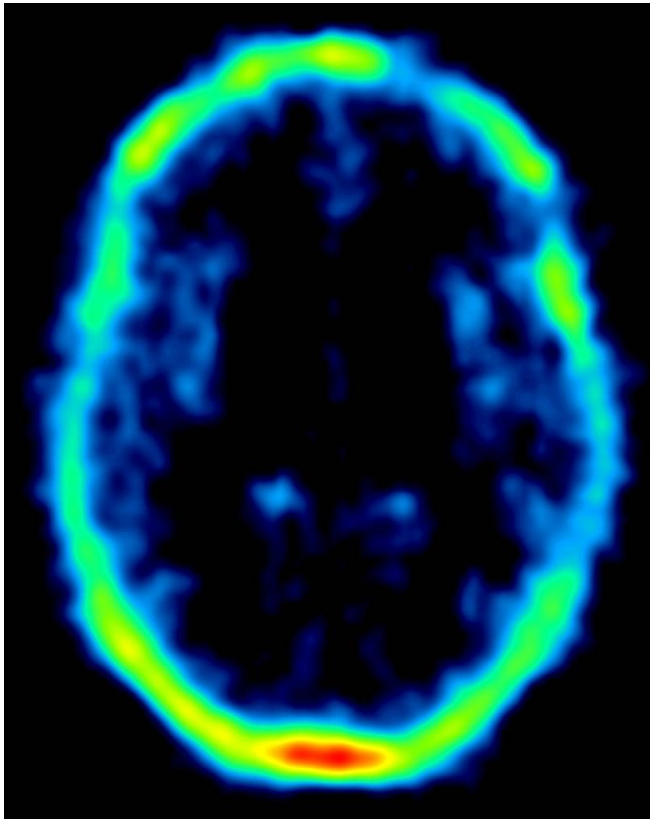


[^{18}F]FCWAY: Miconazole

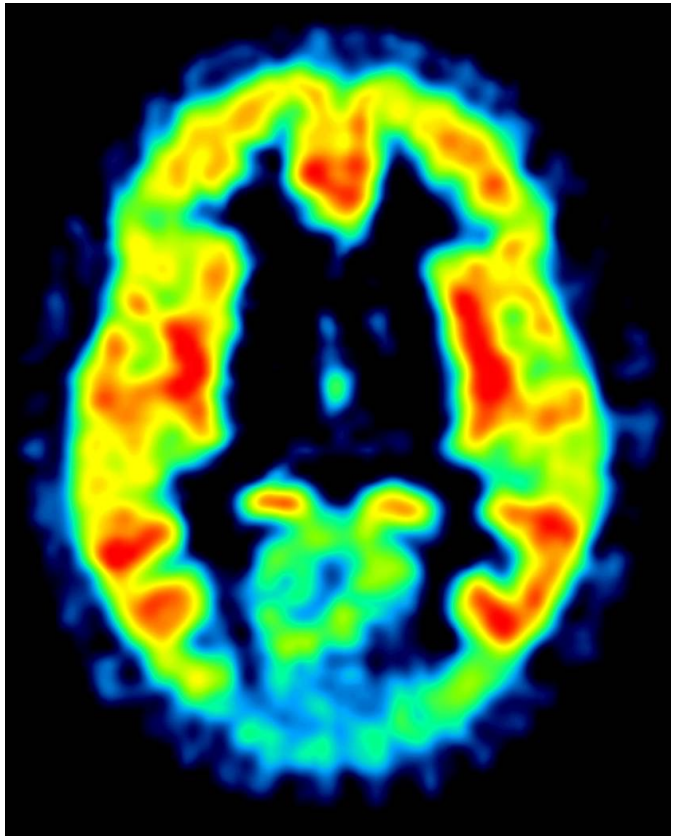


Baseline | 15 mg/kg | 30 mg/kg | 60 mg/kg

Disulfiram: Decreases Skull Activity & Increases Brain Uptake



Baseline

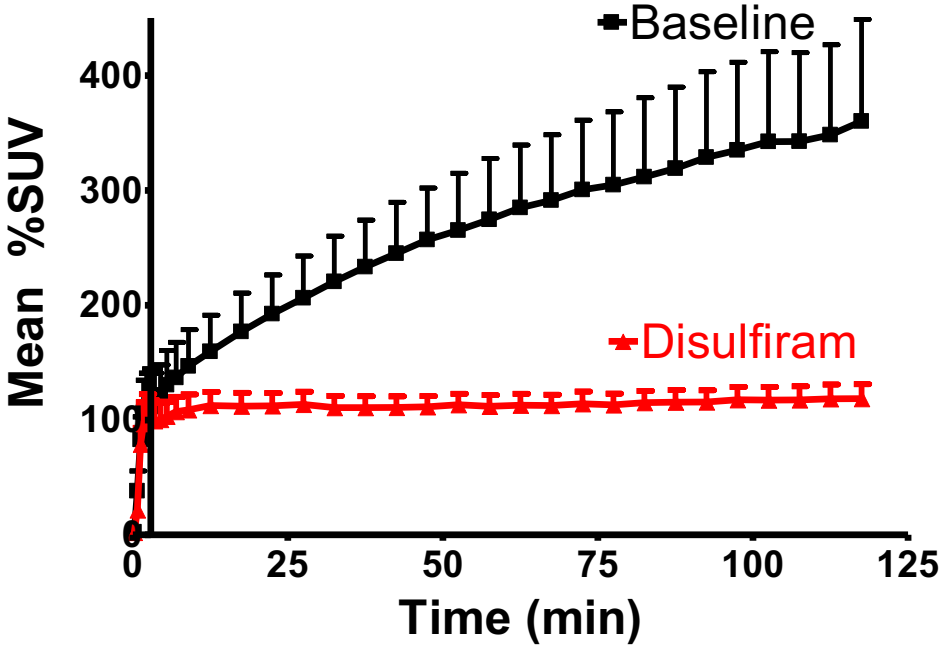


Disulfiram

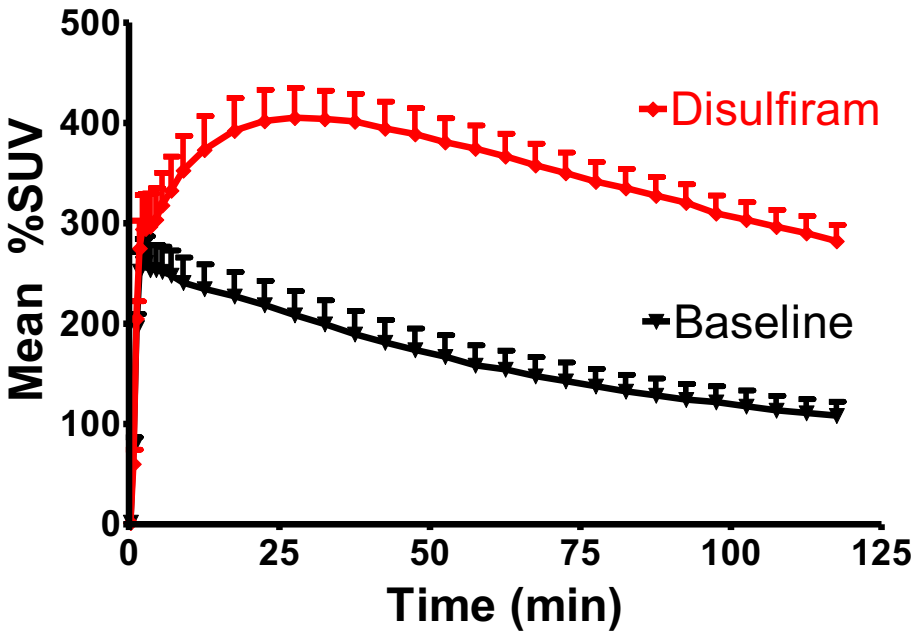
Images at 2 h in same subject. Disulfiram 500 mg PO prior night

Disulfiram: Decreases skull uptake of fluoride & Increases brain uptake of [^{18}F]FCWAY

Skull

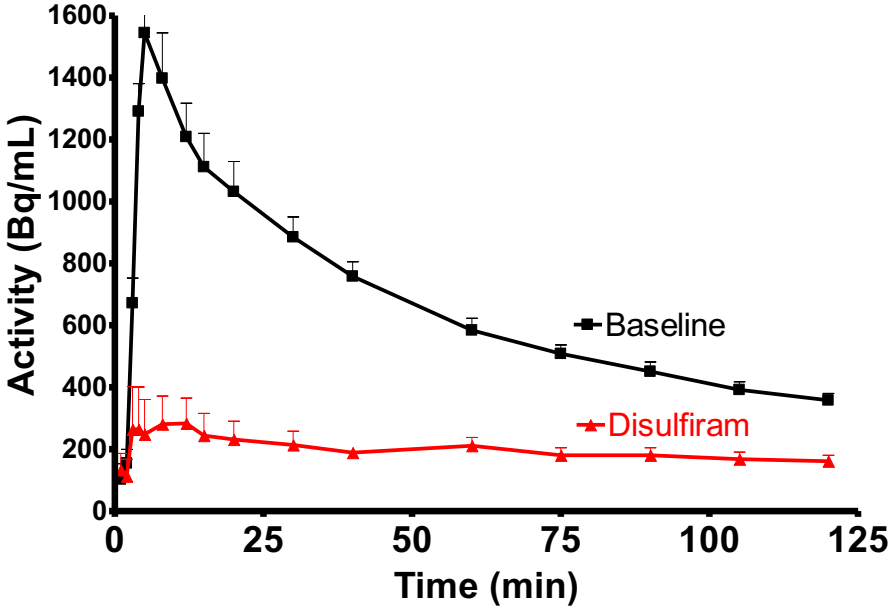


Temporal Cortex

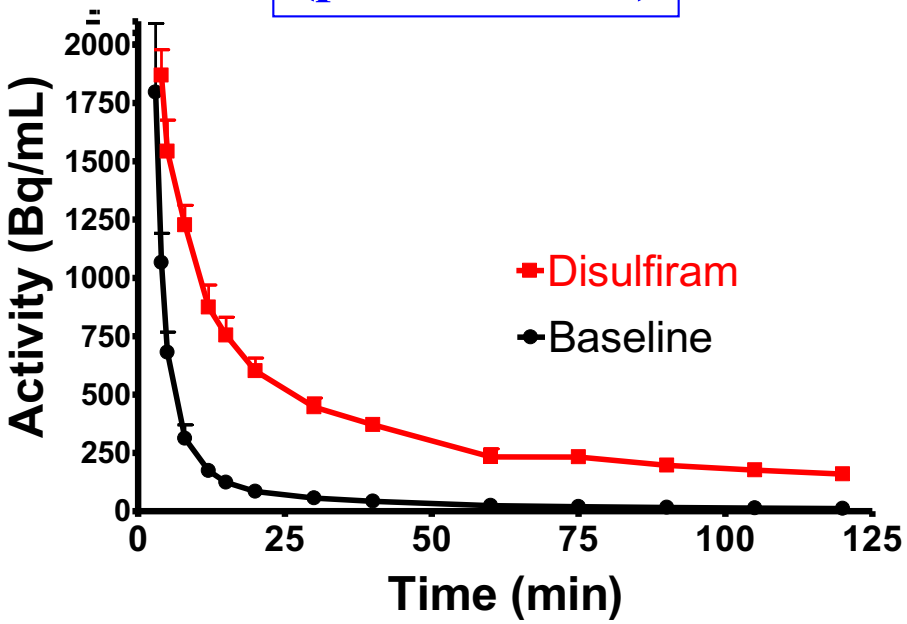


Disulfiram: Decreases plasma fluoride & Increases plasma radiotracer [^{18}F]FCWAY

[^{18}F]fluoride



[^{18}F]FCWAY (parent tracer)



Summary

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling of plasma concentration and tissue uptake can measure receptor density
4. Study drug distribution: block distribution to periphery and increase distribution to brain
5. Study drug metabolism: inhibit defluorination

Self-Assessment Quiz: True or False?

- Imaging with positron emission tomography (PET) involves the injection of a radioactively labeled drug that emits a particle called a positron.
- PET shows the location of radioactivity in a cross section (or tomograph) of the body.
- PET can be used to quantify the density of specific proteins in the body.
- Compartmental modeling of PET data typically uses measurements over time of 1) PET images of the target tissue and 2) concentrations of unchanged parent radioligand in plasma.