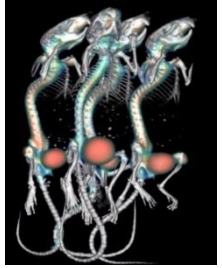
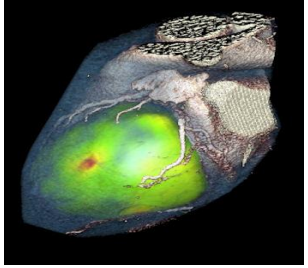
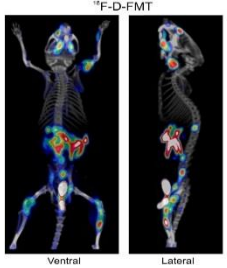

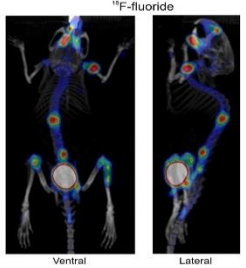

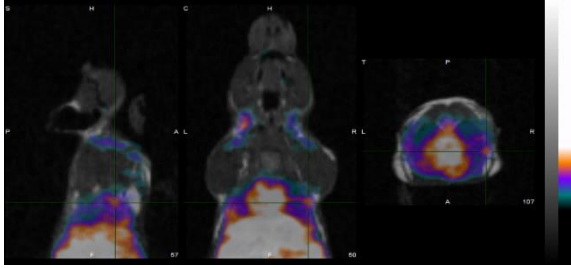

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Preclinical Imaging in Small Laboratory Animals

Instrumentation and Application

Neuroimaging I:

Targeting specific brain receptors

Sebastian Eigner, M.Sc.

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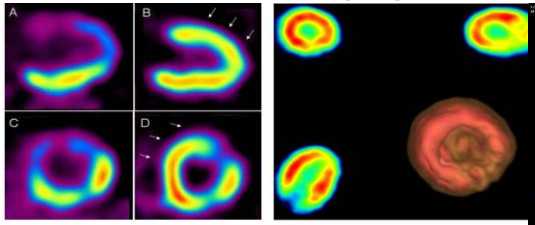
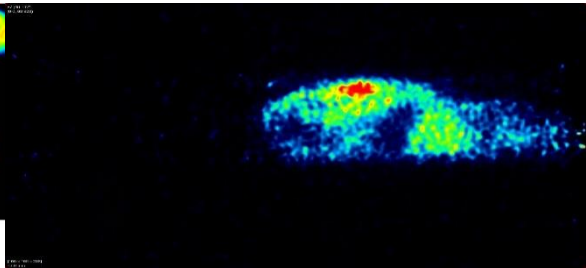
INVESTICE DO VAŠÍ BUDOUCNOSTI

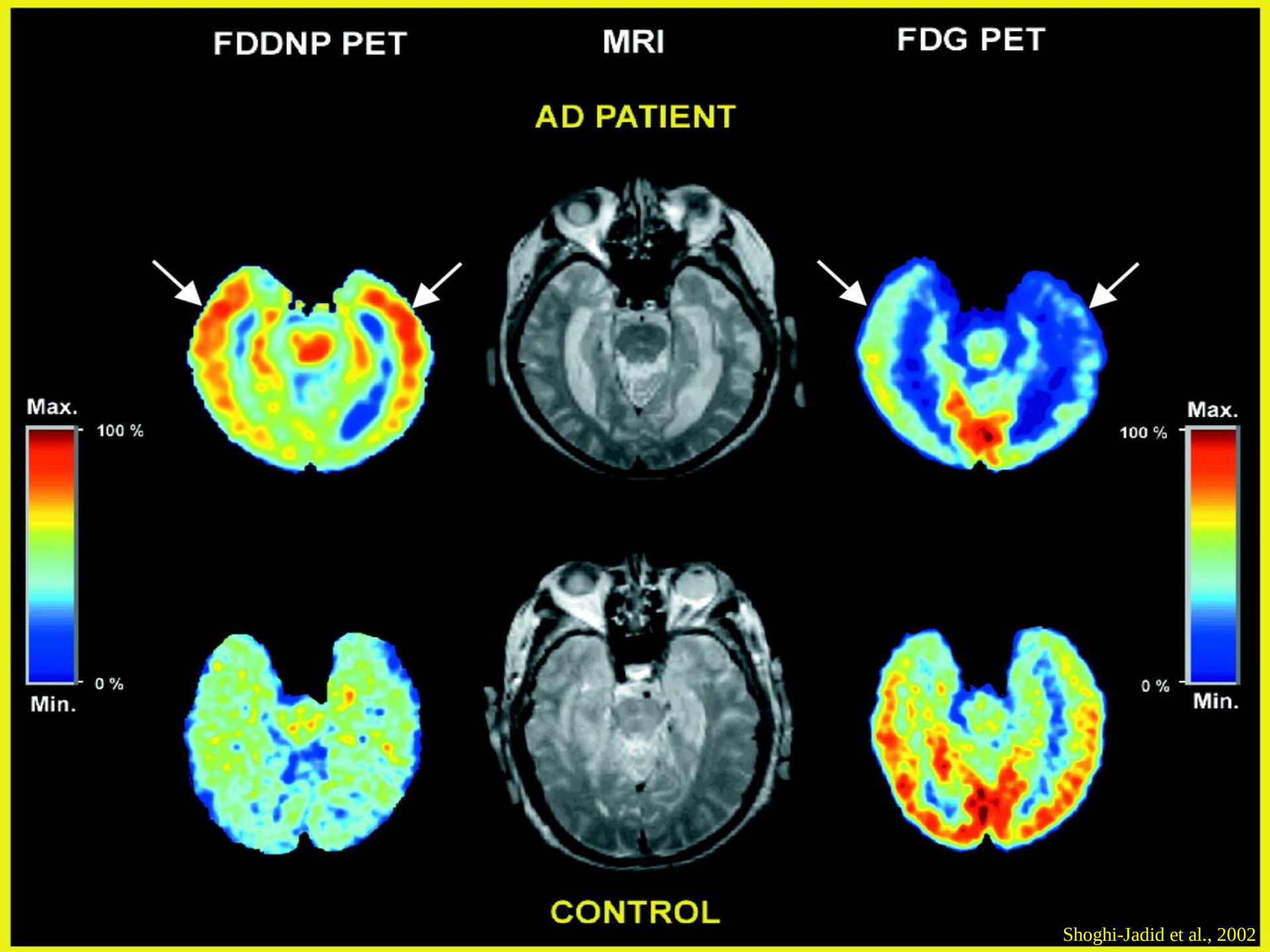
2007-13
OP Výzkum a vývoj pro inovace



^{18}F-FDG – human heart ^{A}

^{18}F-FDG –rat heart ^{B}





Shoghi-Jadid et al., 2002

Neuroimaging

Obtaining evidence from the brain

- Lesion studies – stroke, trauma (PET, SPECT, CT, MRI)
- Cerebral blood flow (PET, SPECT, CT, MRI)
- Neurotransmitter Imaging (PET, SPECT, fMRI)
- Neuro-Receptor Imaging (PET, SPECT)
- Dissease specific Imaging (Multimodal)

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Neuroimaging

"The Big 10"

- Infarction
- Hemorrhage
- Infection
- Tumor
- Trauma
- Dementia
- MS
- Epilepsy
- Cranial neuropathy
- Orbits / Ophtho dx

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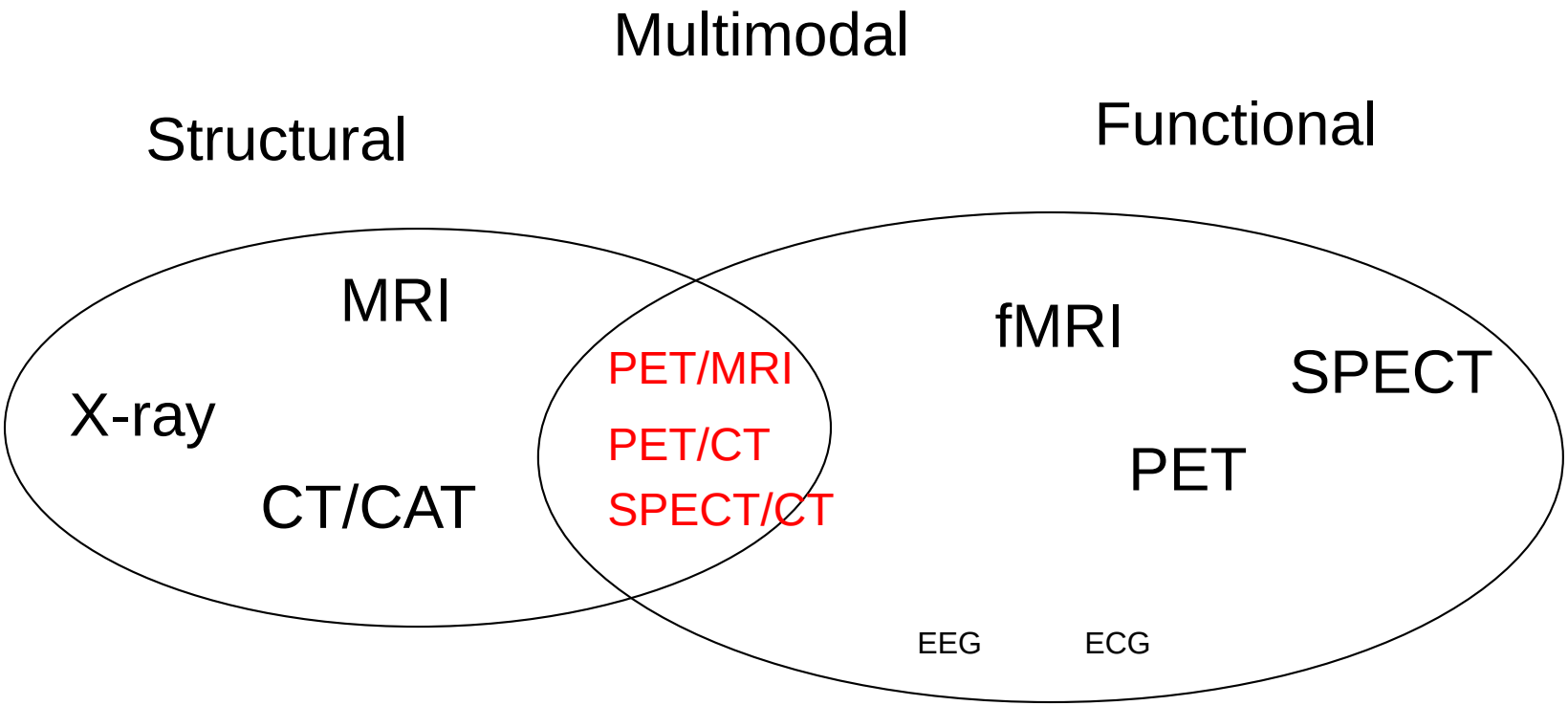
Neuroimaging

Imaging Approaches



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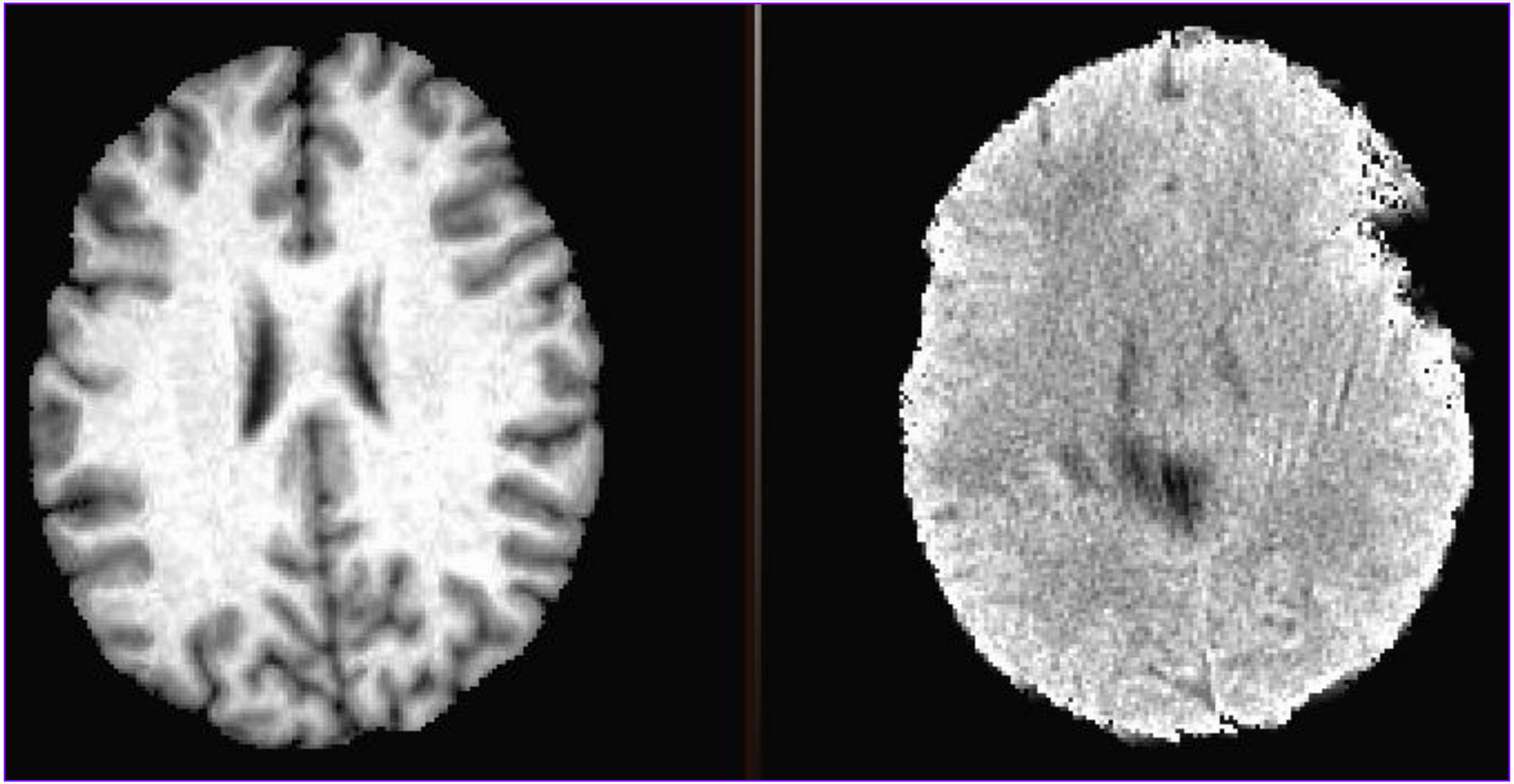
Anatomical Brain Imaging



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Anatomical Brain Imaging

CT

CT Signs in Early MCA Ischemia

Hyperdense MCA

Insular Ribbon

Lentiform Nucleus

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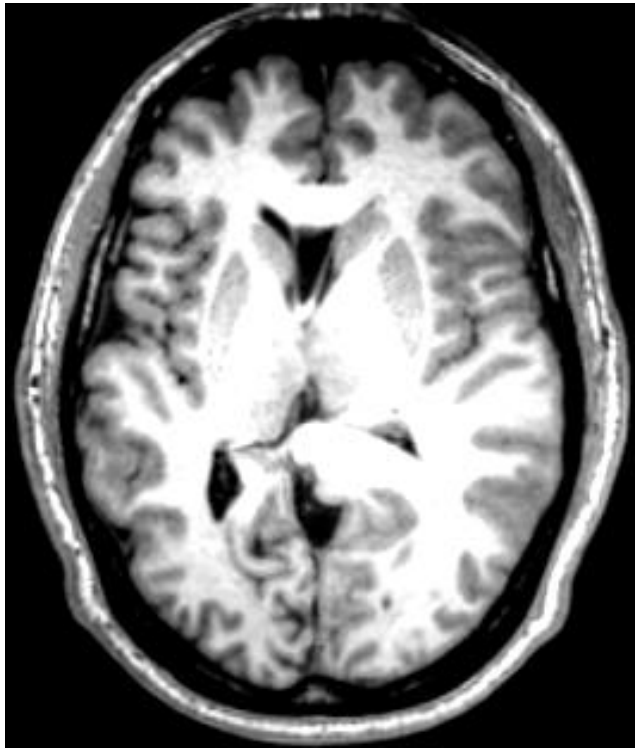
Anatomical Brain Imaging

Structural MRI



- Essential in clinical care
- Radiologists perform qualitative “lightbox” reads
- Most psychiatric and neurological disorders are invisible to reading radiologists

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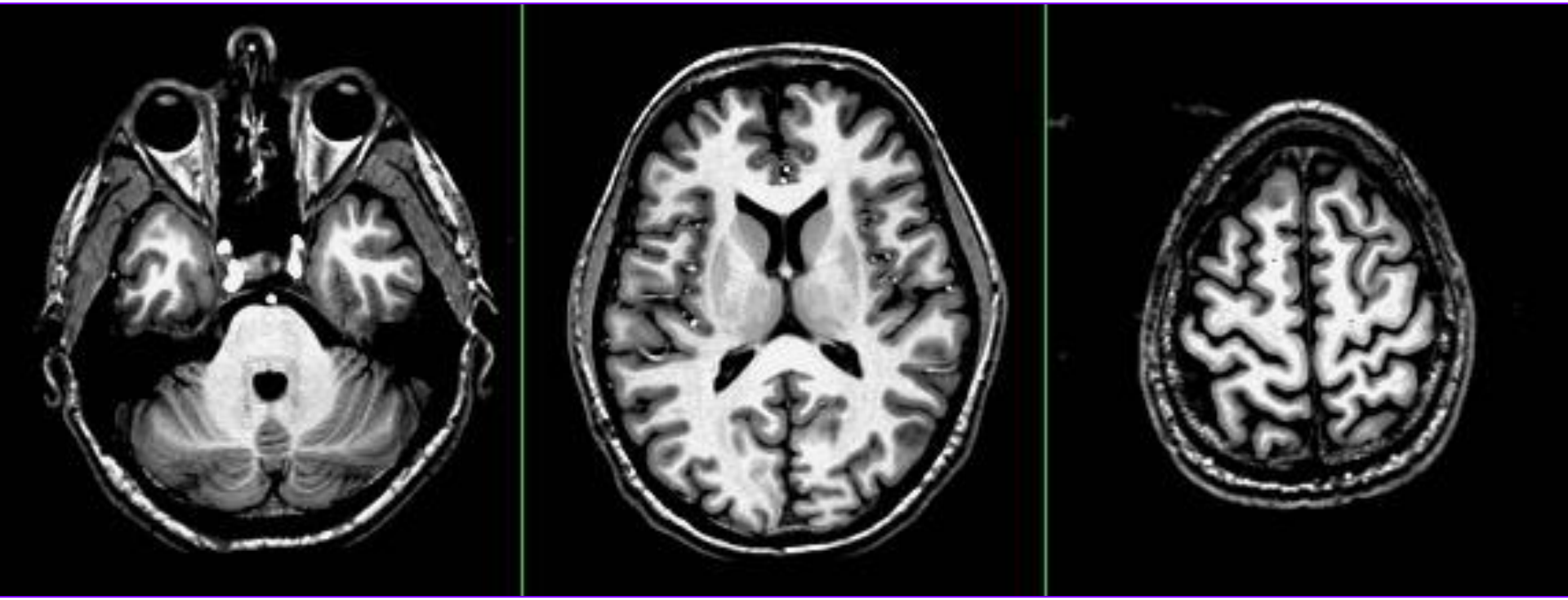
Anatomical Brain Imaging

T1 MRI

designed (timing of radio pulses and data readout) to produce ***contrast*** between gray matter, white matter, and CSF



Spatial resolution: ca. 1 $mm^{3,}$ Acquisition time for whole head is 5-10 minutes

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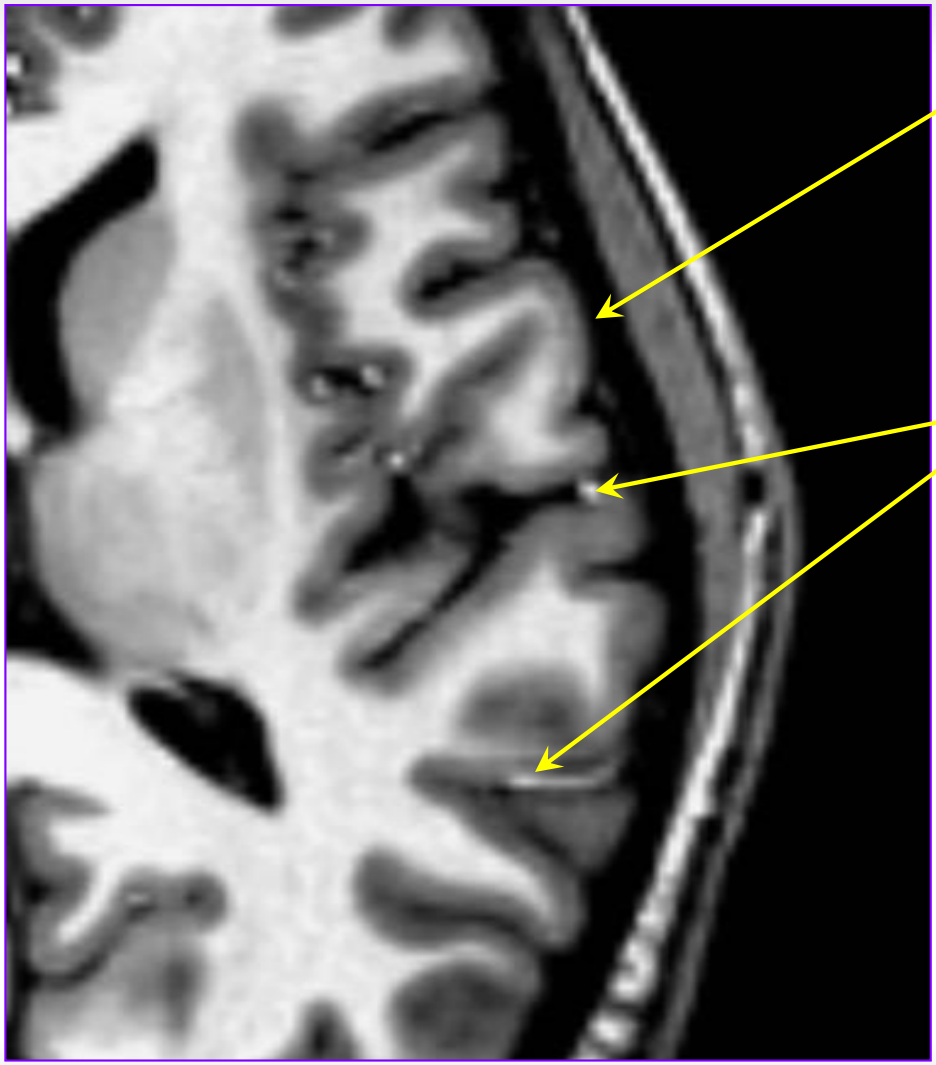
Anatomical Brain Imaging

T1 MRI – Image Zoom



- Can follow GM cortex fairly well
  - Can measure thickness of cortex and try to quantify vs age and/or disease and/or genes
- Bright spots and lines: arterial inflow artifact
  - Leads to idea of MRA = Magnetic Resonance Angiography = acquire images to make arteries stand out even more
- Higher spatial resolution is possible
  - At the cost of scan time

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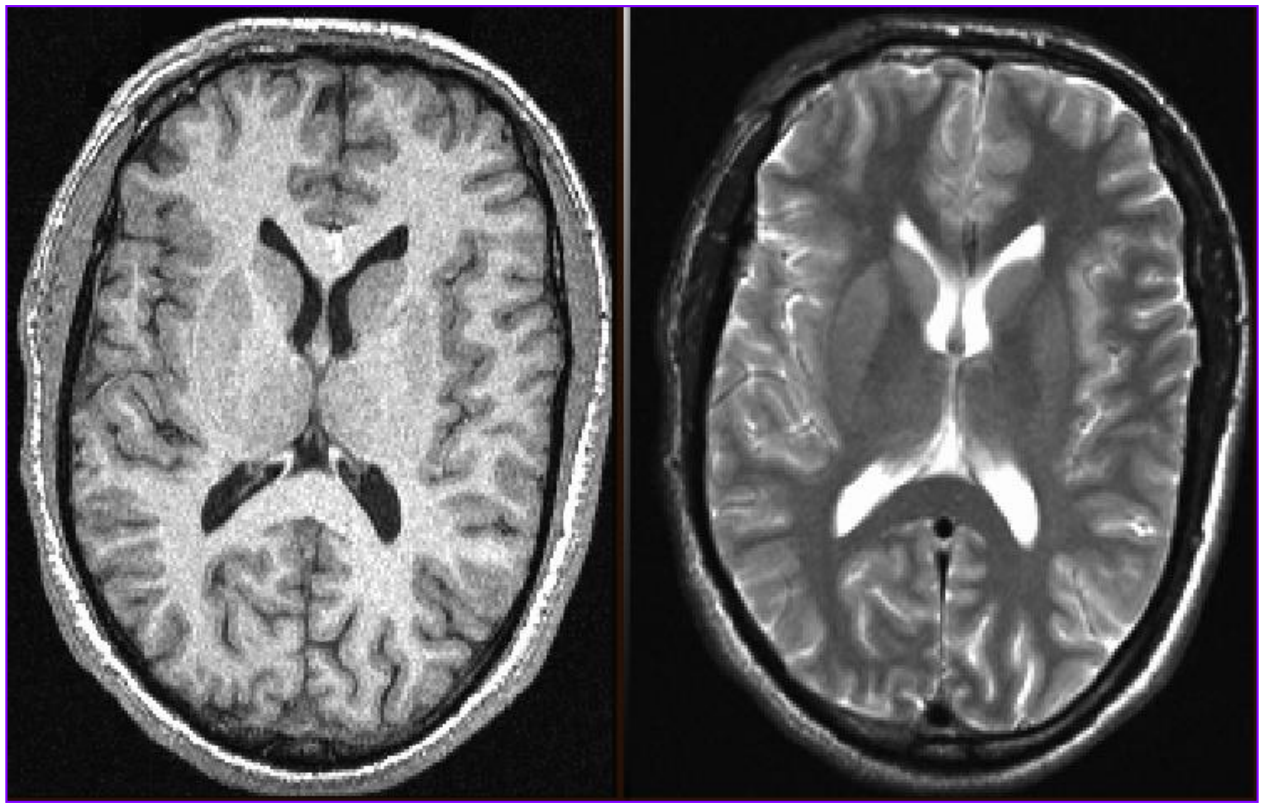
Anatomical Brain Imaging

T2 MRI

Often better than T1-weighting in detecting tumors and infarcts (usually radiologists look at both types of scans)



T1 weighted T2 weighted

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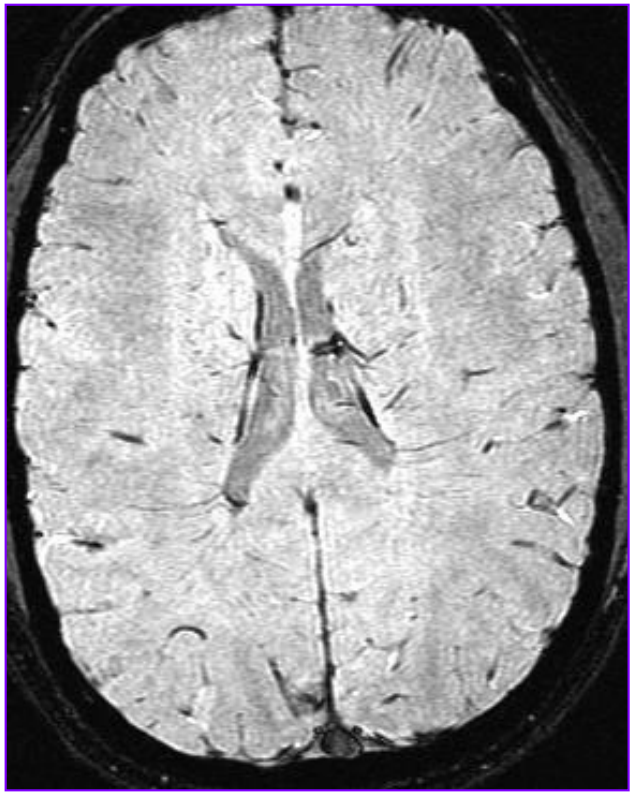
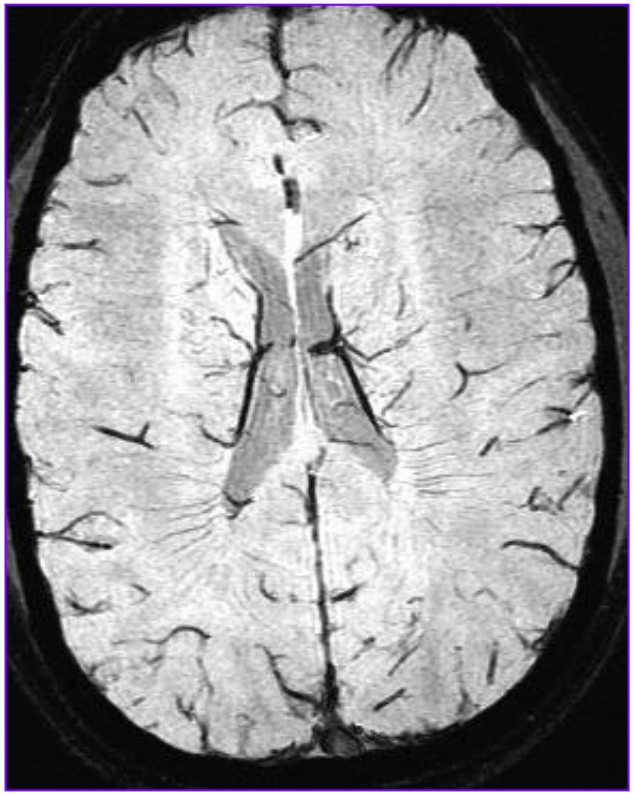
Anatomical Brain Imaging

T2* MRI

Designed to make venous blood (with lots of deoxy-hemoglobin) darker than normal tissue = *venography*



Output image



minIP ± 1 slice

minIP ± 2 slices

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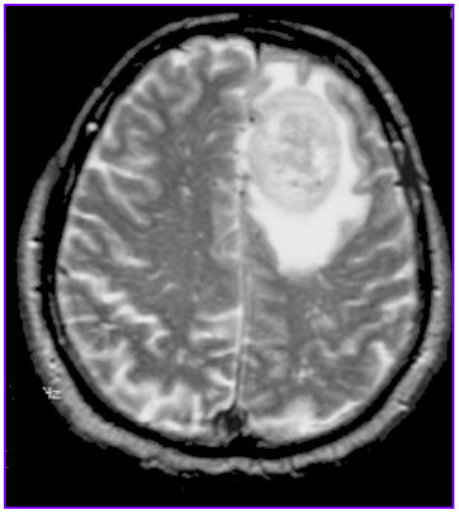
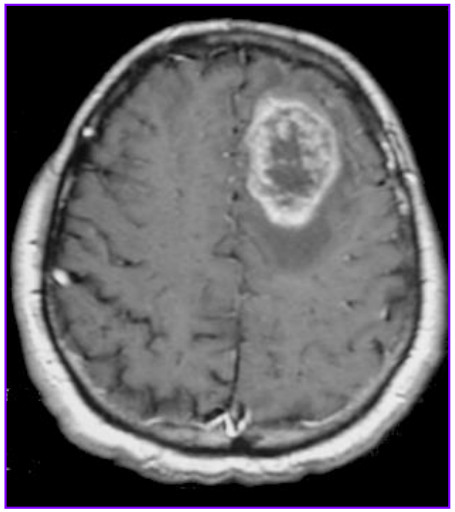
Anatomical Brain Imaging

Contrast enhanced MRI

Tumor

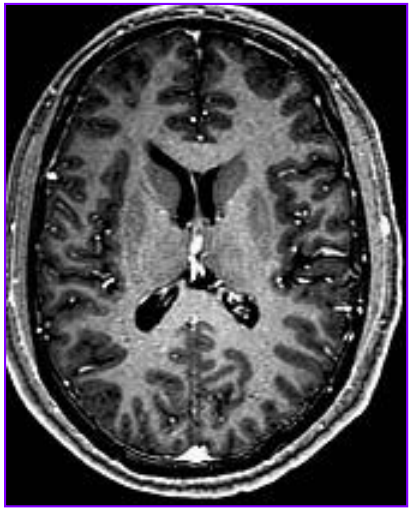


T2-weighted

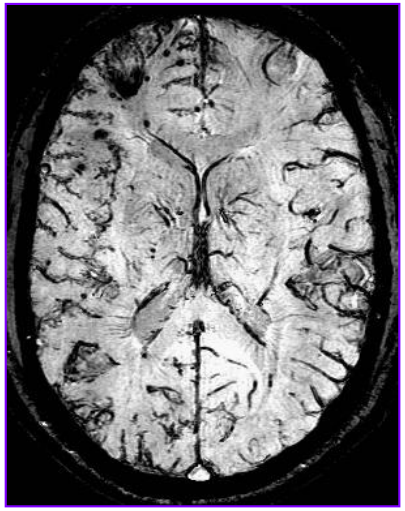


post-contrast T1-weighted

Seizure Patient



Gd-enhanced
T1-weighted



Gd-enhanced
T2*-weighted

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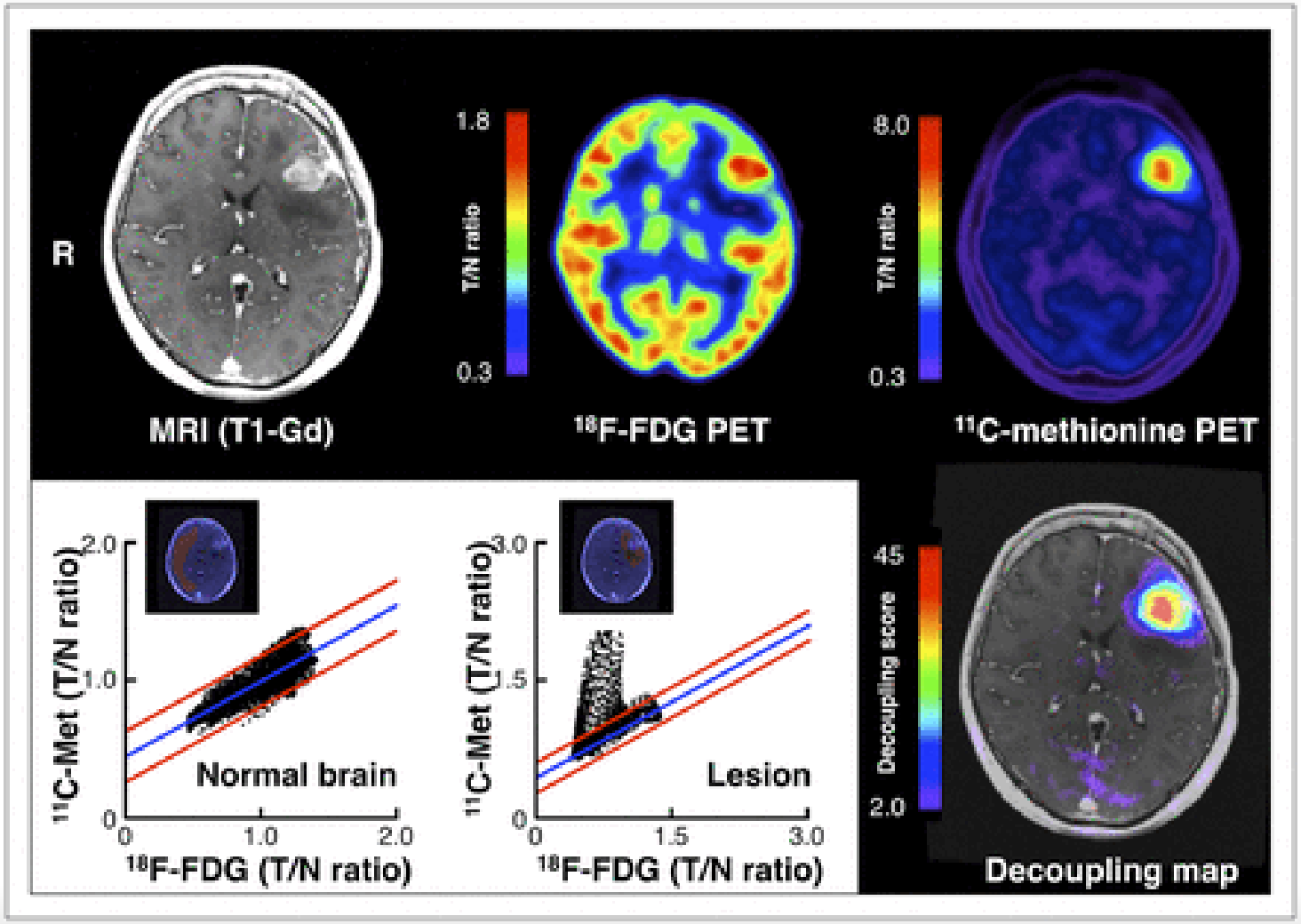
Functional Brain Imaging



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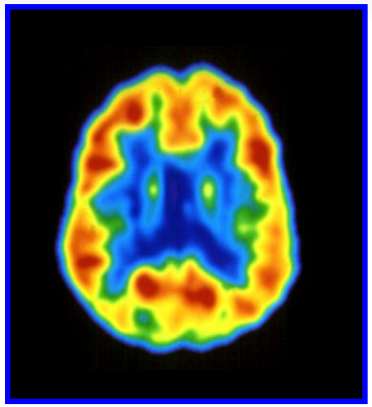
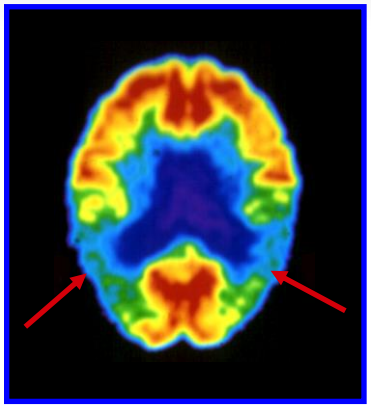
Functional Brain Imaging

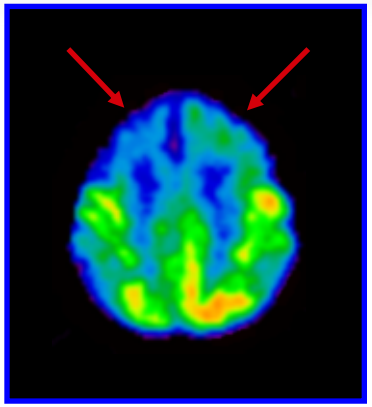
Energy Metabolism ^{18}F-FDG



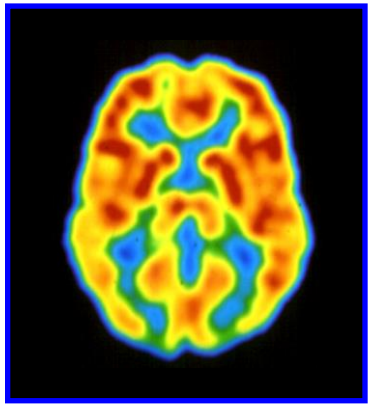
Normal



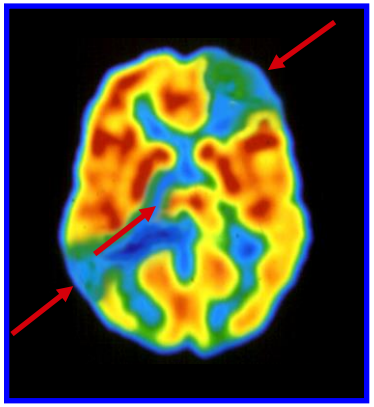
Alzheimer's



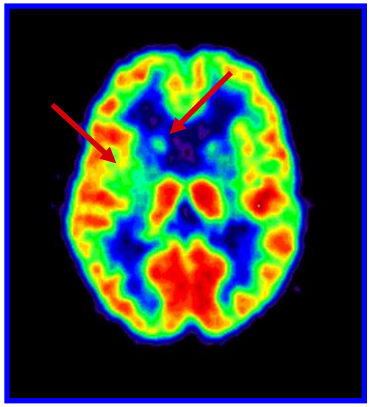
Pick's



Normal



Multiple Infarct Dementia



Huntington's

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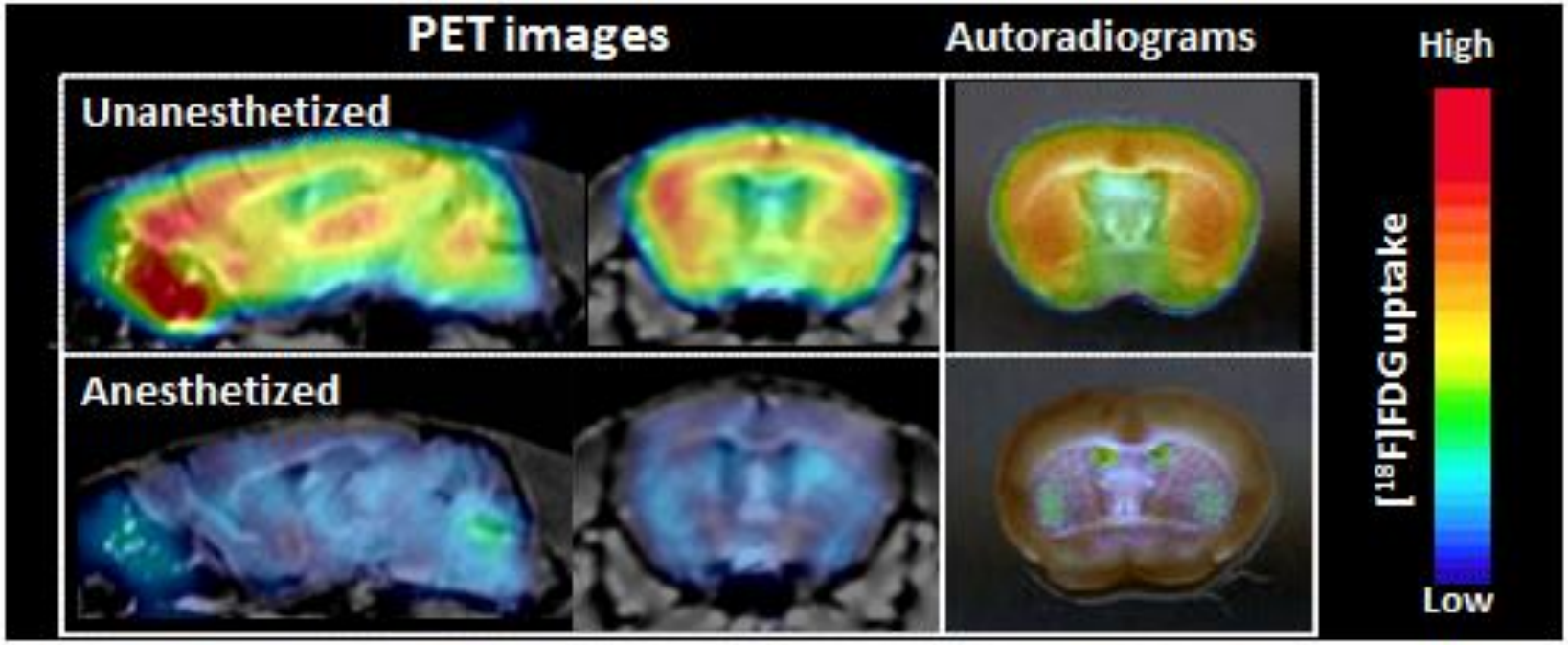
Functional Brain Imaging

Energy Metabolism ^{18}F-FDG



Glucose kinetics in mouse brain under conscious and anesthetized states by [^{18}F]FDG-PET (Mizuma et al. J Nucl Med. 2010)

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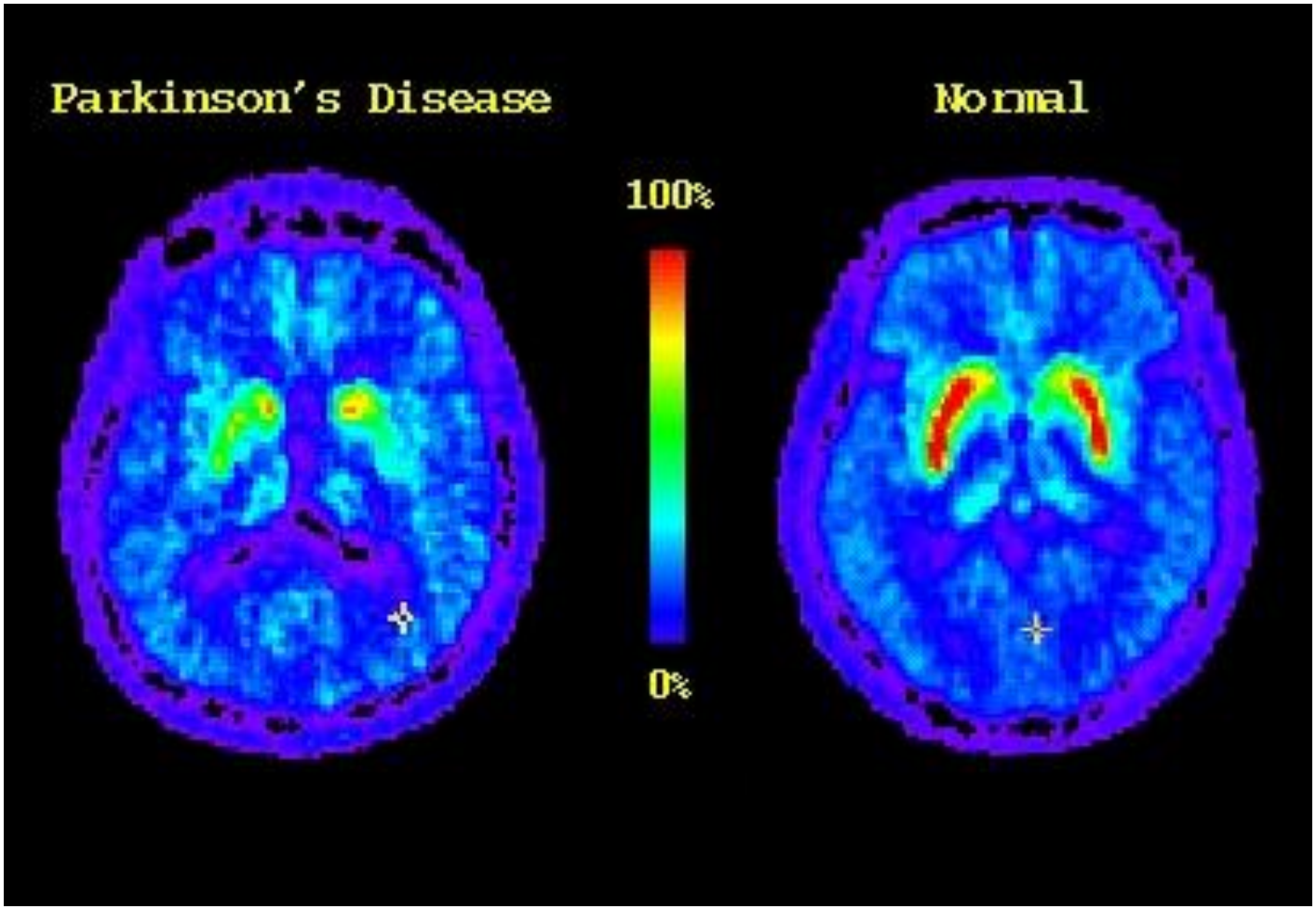
Functional Brain Imaging

Neurotransmitter ^{18}F-FDOPA



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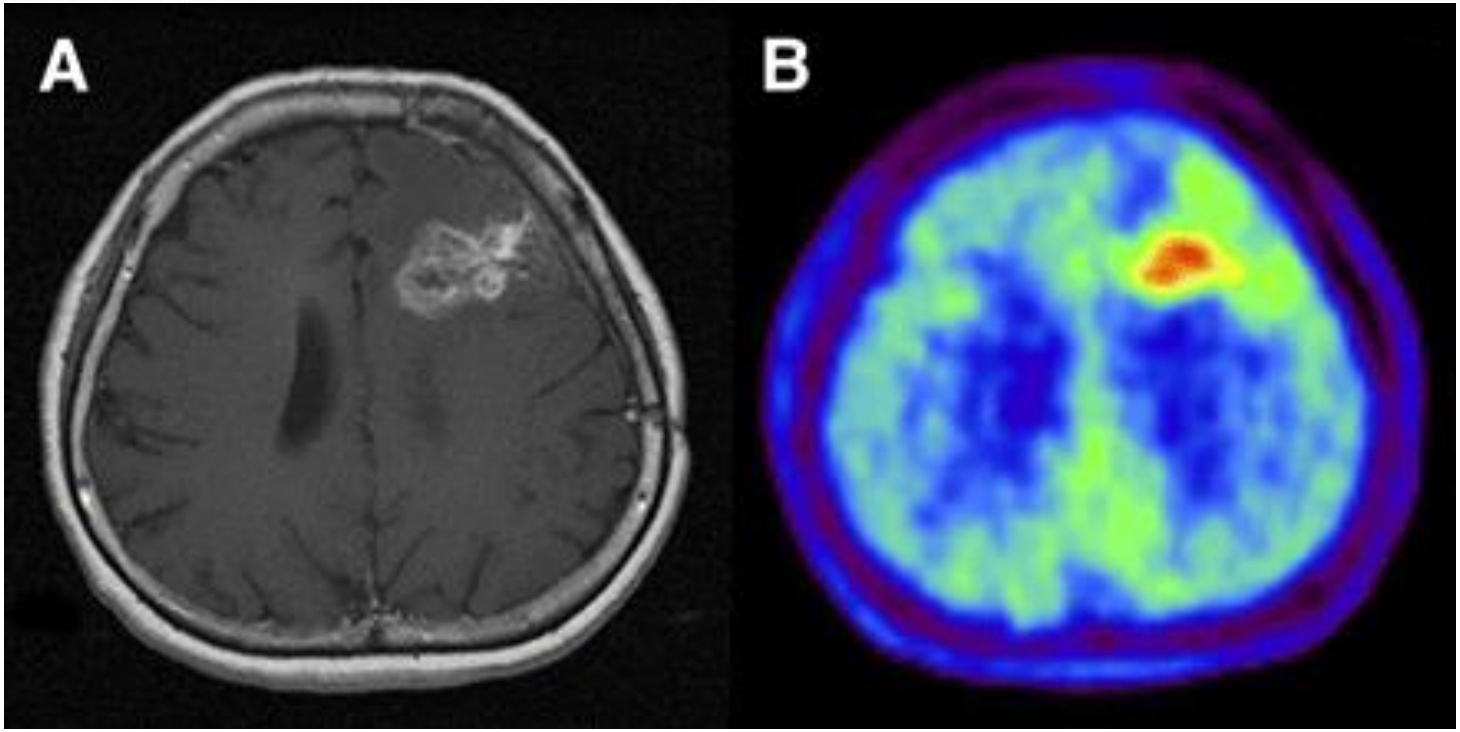
Functional Brain Imaging

Amino Acid Transport



Imaging of 49-y-old woman who had been previously treated for glioblastoma multiforme with tumor resection and conventional radiotherapy at dose of 60 Gy. (A) T1-weighted MR image with contrast medium, obtained 13 mo after initial surgery, showing contrast-enhanced lesion in left frontal lobe. (B) ^{11}C-MET PET image showing obvious accumulation of tracer corresponding to abnormality on MR image. $L/N_{mean}$was 1.70. Recurrent tumor was pathologically confirmed by second surgery.

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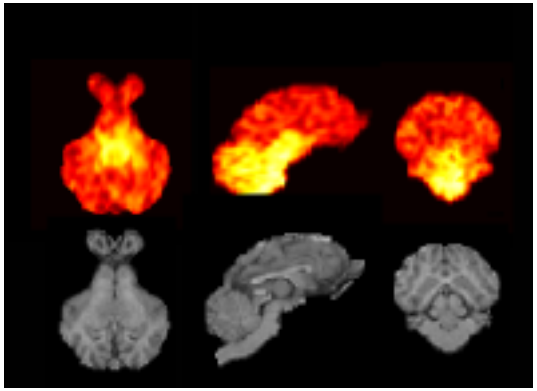
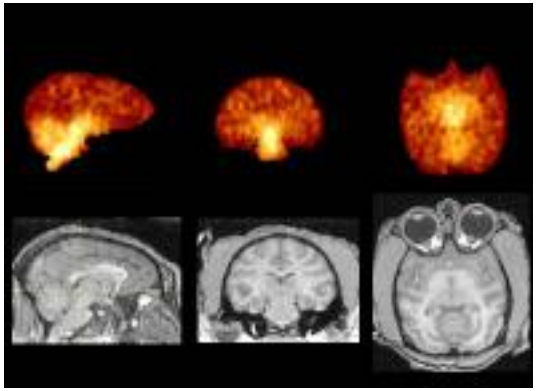
Functional Brain Imaging

Amino Acid Transport – Glycine transporter 1

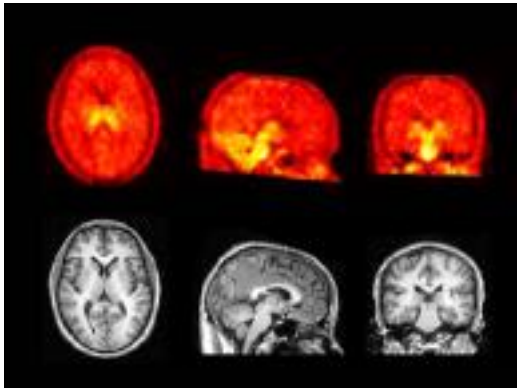
Pig



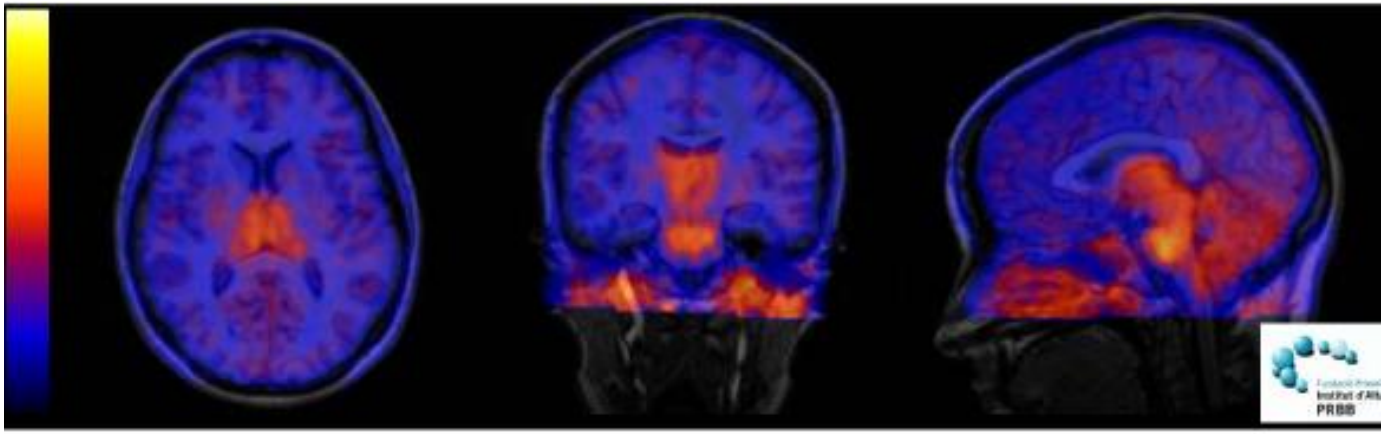
Primate



Human



[^{11}C]GSK931145 distribution in a healthy volunteer



Zubieta et al. - Journal of Cerebral Blood Flow & Metabolism (1998) 18, 619–631

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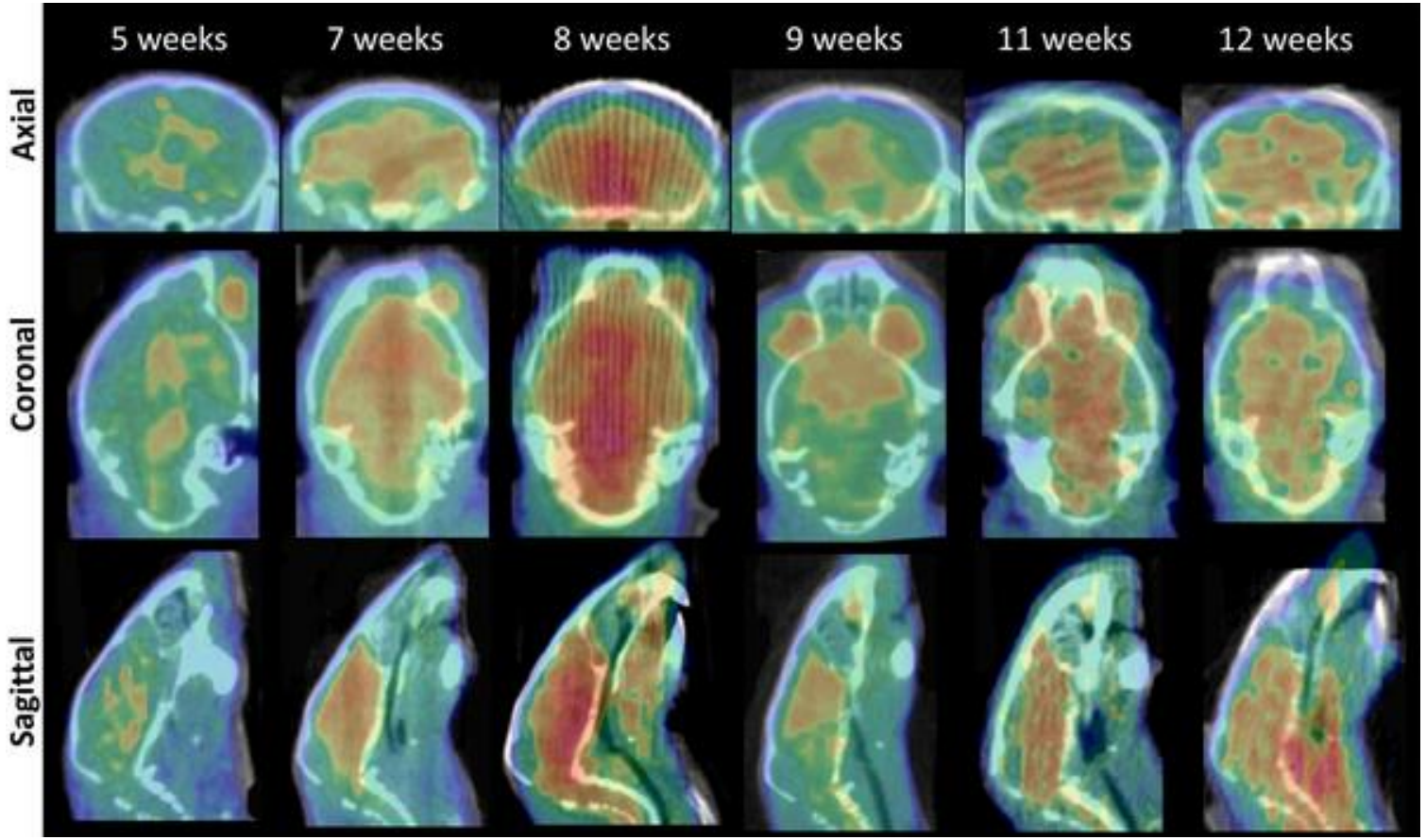
Neuroreceptor Imaging



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Selected Receptor Tracers

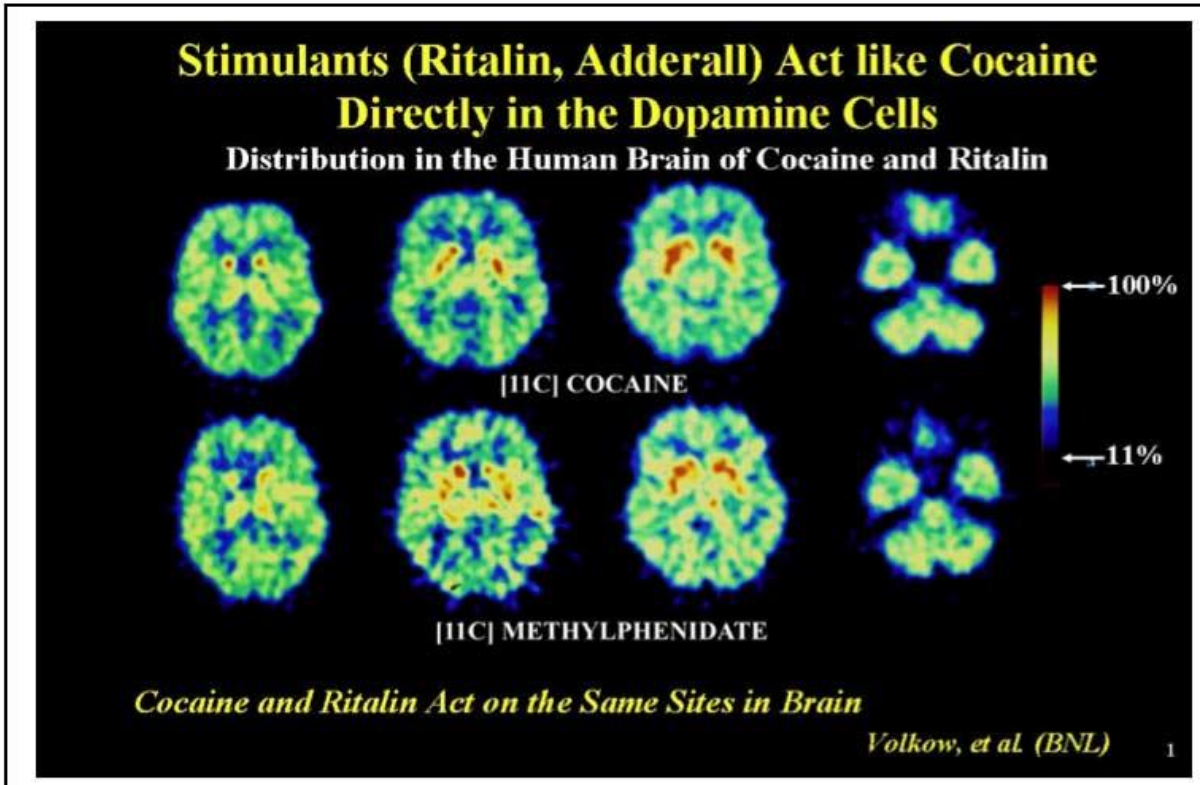
TABLE 1
Selected Receptor Tracers

Tracer	Abbreviation	Target
^{11}C-Cocaine, ^{11}C-methylphenidate		DAT
^{11}C-Nomifensine		DAT
^{11}C-WIN-35428, ^{11}C-PE2I		DAT
^{18}F-2β-Carbomethoxy-3β-(4-fluorophenyl)tropane	CFT	DAT
^{11}C-Dihydrotetrabenazine	DTBZ	$VMAT_2$
^{11}C-SCH-23390		D_1
^{11}C-*N*-Methylspiperone	NMSP	D_2, 5-HT_2
^{18}F-*N*-Methylspiperone		
^{18}F-Fluoroethylspiperone	FESP	D_2, 5-HT_2
^{11}C-Raclopride	RAC	D_2
^{18}F-Fallypride		D_2
N-1-^{11}C-Propylnorapomorphine		D_2 (agonist)
^{11}C-L-Deprenyl		MAO-A
^{11}C-*N*-Methyl-4-piperidylbenzilate	NMPB	Muscarinic receptors
N-^{11}C-Methylpiperdin-4-yl-propionate	MP4P, PMP	AChE
N-^{11}C-Methyl-4-piperidyl-acetate	MP4A, AMP	AChE
^{11}C(+)-McN5652		5-HTT
^{11}C-3-Amino-4-(2-dimethylaminomethyl-phenylsulfanyl)benzonitrile	DASB	5-HTT
^{11}C-WAY-100635	WAY	5-HT_{1A} receptor
^{18}F-Altanserin		5-HT_{2A} receptor
^{11}C-Flumazenil	FMZ	$GABA_A$/benzodiazepine receptors
^{11}C-PK-11195	PK	Peripheral benzodiazepine receptors
^{11}C-Carfentanyl		Opioid μ receptor
^{11}C-Diprenorphine	DPN	Opioid receptors
^{18}F-Cyclofoxy		Opioid receptors
^{18}F-CPFPX, ^{11}C-MPDX		Adenosine A_1 receptor

DAT = dopamine transporter; VMAT2 = vesicular monoamine transporter type 2; D1 = dopamine 1 receptor; D2 = dopamine 2 receptor; 5-HT = 5-hydroxytryptamine (serotonin) receptor; 5-HTT = 5-hydroxytryptamine (serotonin) transporter; MAO-A = monoamino-oxidase A; AChE = acetylcholinesterase; GABA = γ-aminobutyric acid receptor.

Neuro-Receptor Imaging

DAT – dopamine transporter



Ritalin, or methylphenidate, has much in common with cocaine—the two drugs bind to similar sites in the brain and both increase dopamine through the same molecular targets.

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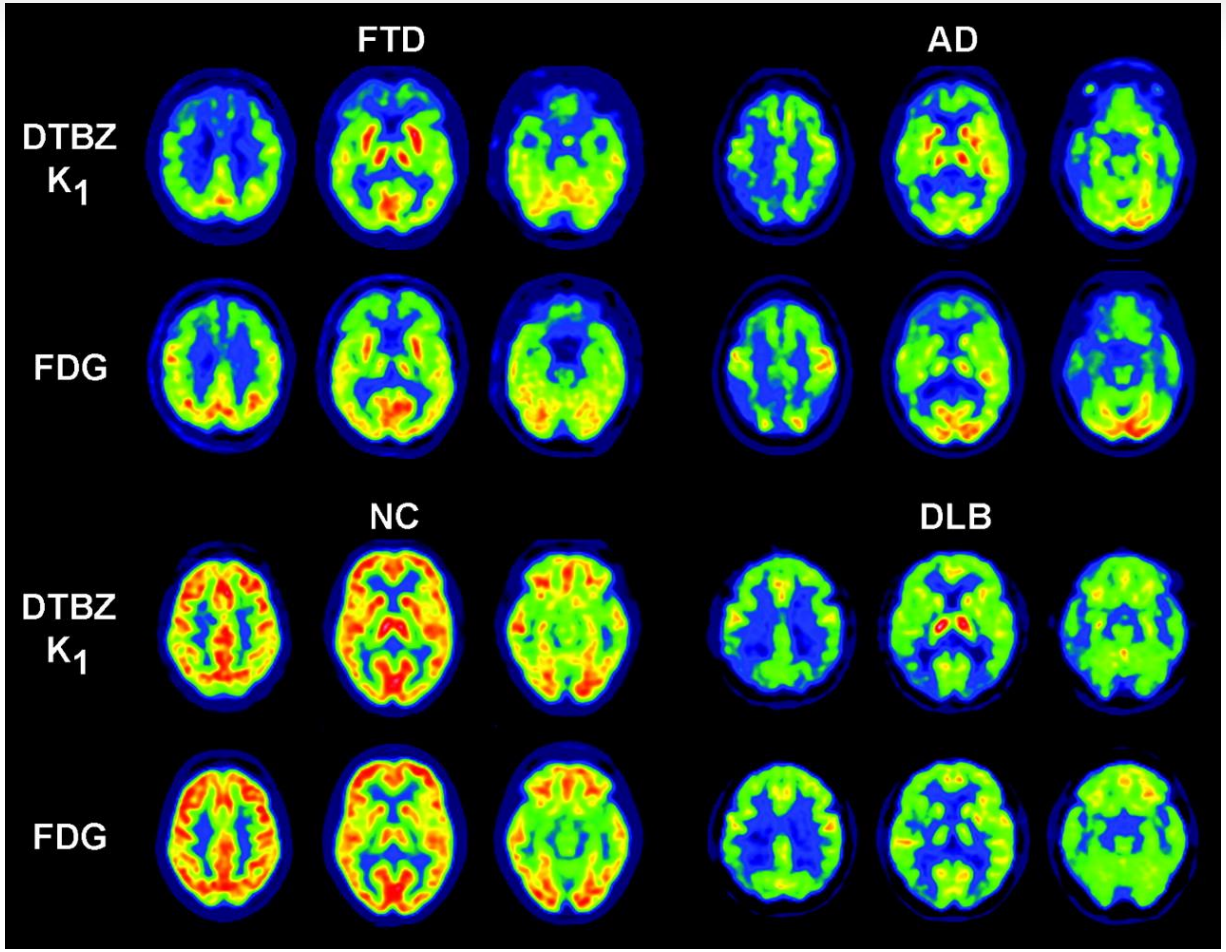
Neuro-Receptor Imaging

VMAT$_2$ – vesicular monoamine transporter type 2



11C-DTBZ K1 and 18F-FDG images at 3 brain levels for one representative subject from each group. Robert A. Koeppe et al. J Nucl Med 2005;46:936-944

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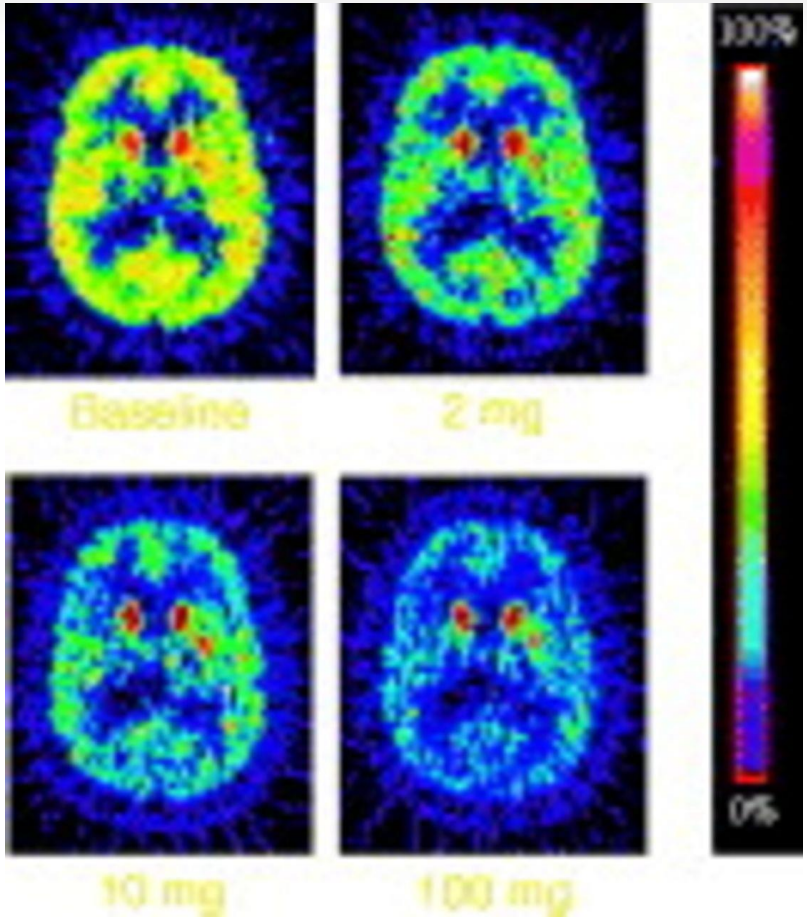
Neuro-Receptor Imaging

5-HT_{2A} receptor



Horizontal PET images showing the uptake of [11C]NMSP in the frontal cortex at the level of the basal ganglia at baseline, and after the administration of 2 mg, 10 mg and 100 mg oral doses of an inverse agonist (ACP-103)

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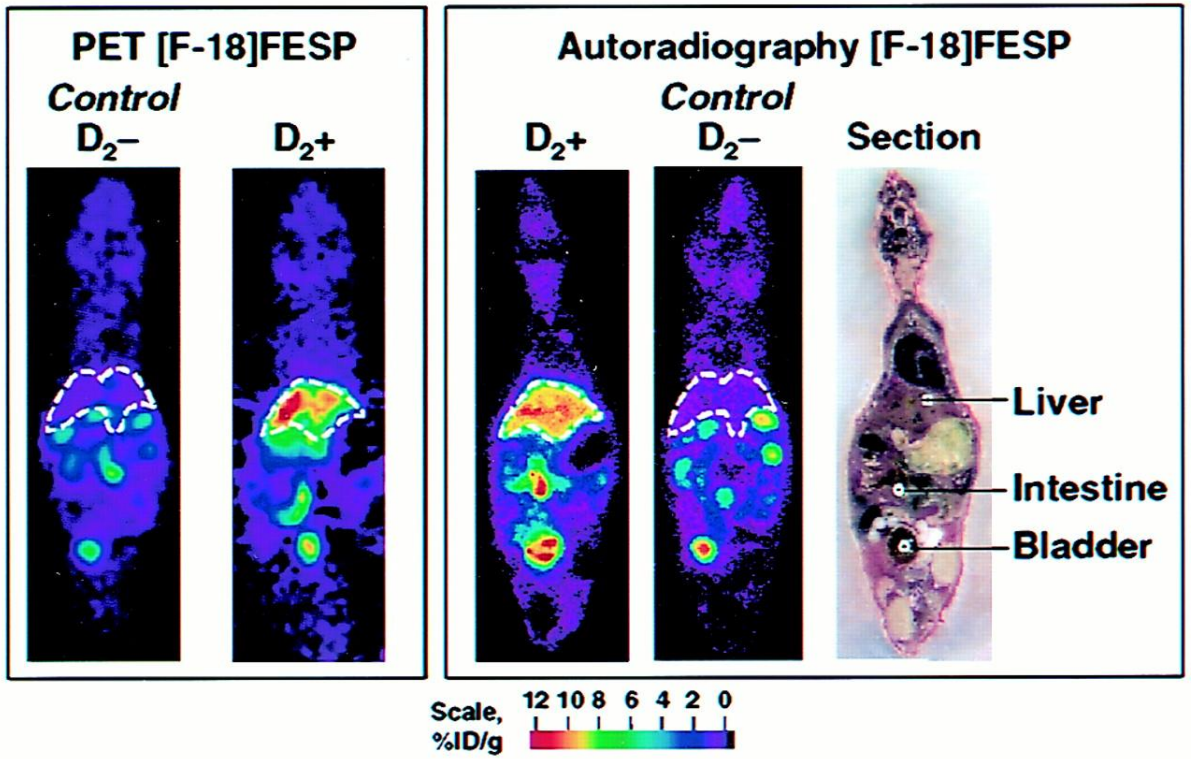
Neuro-Receptor Imaging

D2 receptor – 11c-Fluorethylspiperone (FESP)



microPET and autoradiography studies of PRG/PRP imaging of gene expression in the same mouse. PRG is D_2 receptor, and PRP is FESP. (*Left*) MicroPET image of a single 1.5-mm-thick longitudinal section of living control mouse negative for D_2 receptor (D_2^-) PRG, showing no significant retention of PRP in liver (dashed lines). In animal carrying dopamine receptor reporter gene (D_2^+), there is retention of FESP PET reporter probe in liver reflecting gene expression. Images were taken 50 min after injection of FESP and 2 days after virus administration. (*Right*) After microPET imaging, animals were killed, sectioned, and imaged with autoradiography

Michael E. Phelps PNAS 2000;97:9226-9233

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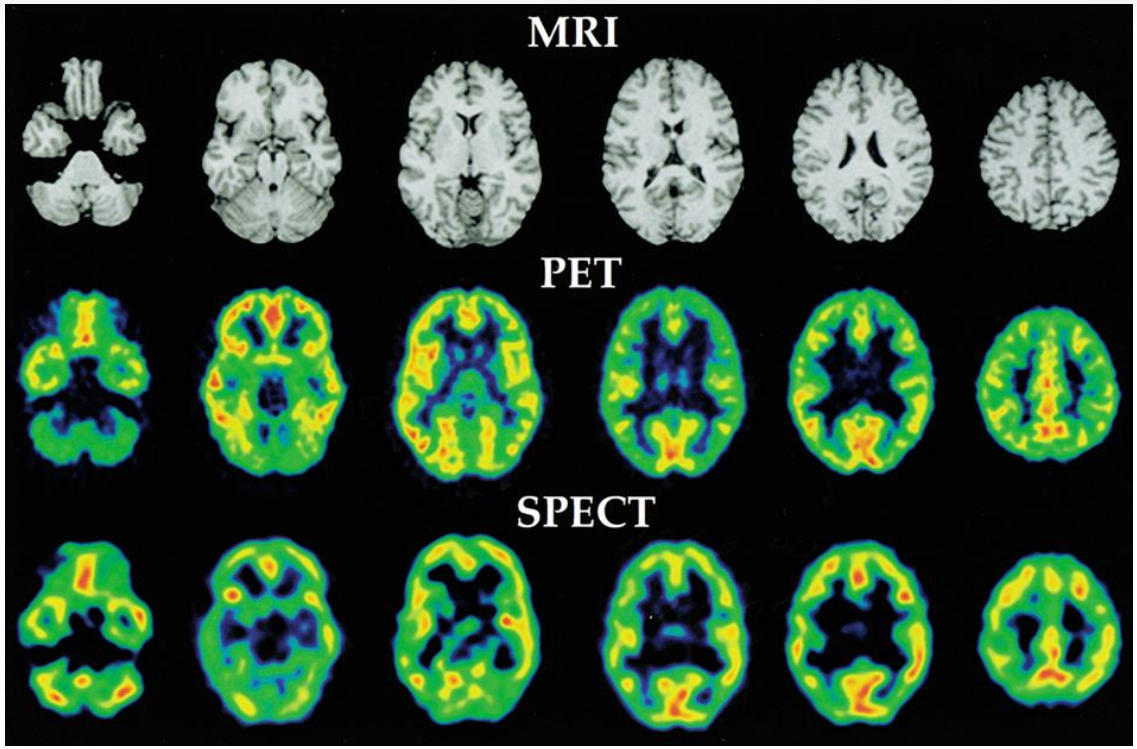
Neuro-Receptor Imaging

$GABA_A$-benzodiazepine receptor



Magnetic resonance imaging (MRI) and delayed-activity positron emission tomography (PET) with [^{11}C]flumazenil and single photon emission computed tomography (SPECT) with [^{123}I]iomazenil images of one subject at different anatomic levels

Millet et al.; Journal of Cerebral Blood Flow & Metabolism (2000) 20, 1587–1603

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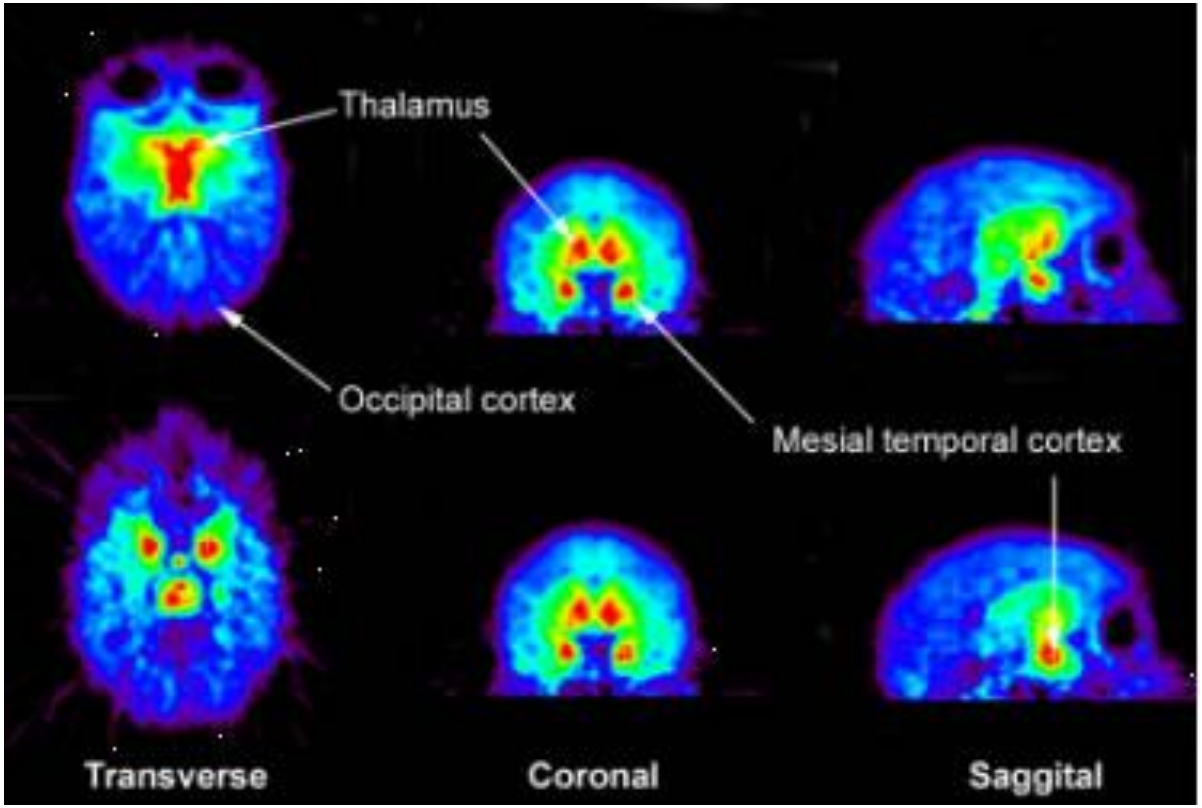
Neuro-Receptor Imaging

Opioid Receptor



PET scan of a six month old rhesus macaque using a [C-11]diprenorphine tracer, specific for opioid receptors.

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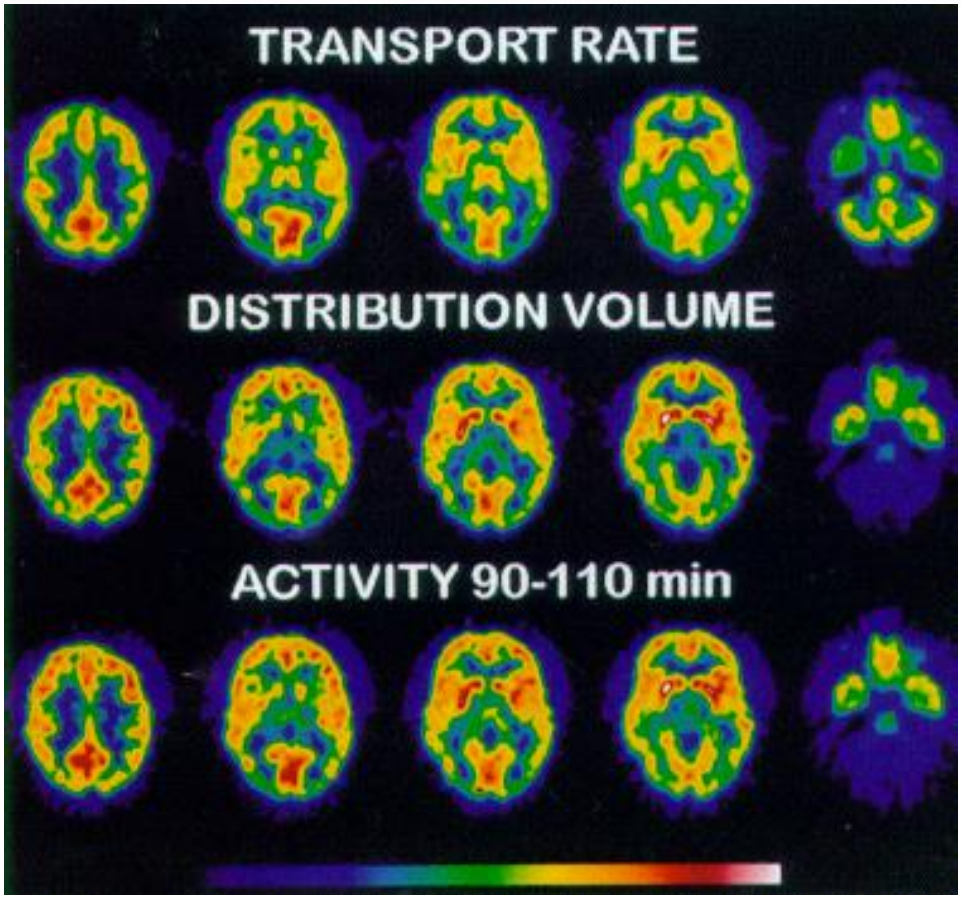
Neuro-Receptor Imaging

Muscarinic Receptor



Quantification of muscarinic cholinergic receptors with [^{11}C]N-methyl-4-piperidyl benzylate ([^{11}C]NMPB) - distribution parameters and activity

Zubieta et al. - Journal of Cerebral Blood Flow & Metabolism (1998) 18, 619–631

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Thank you for your Attention

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