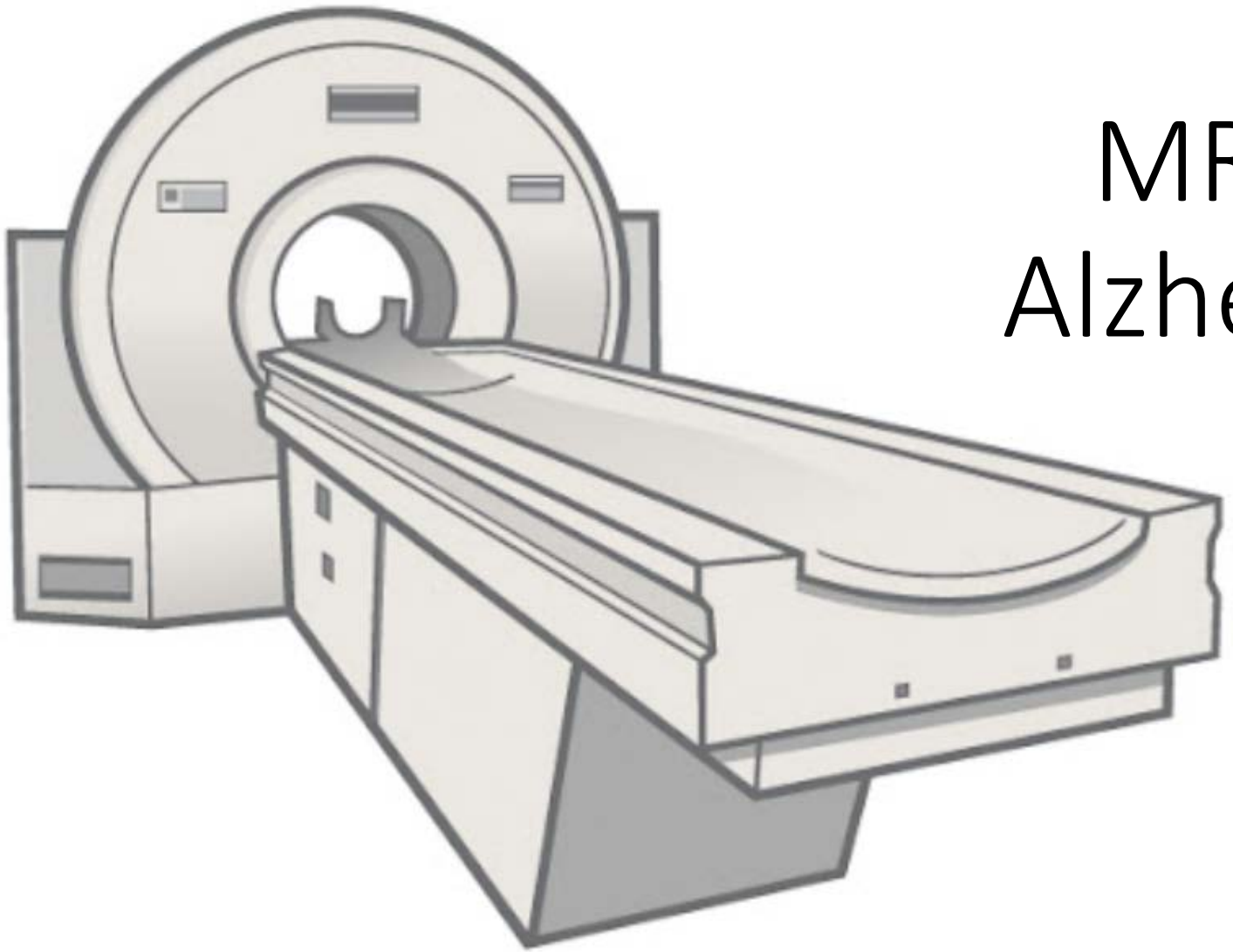
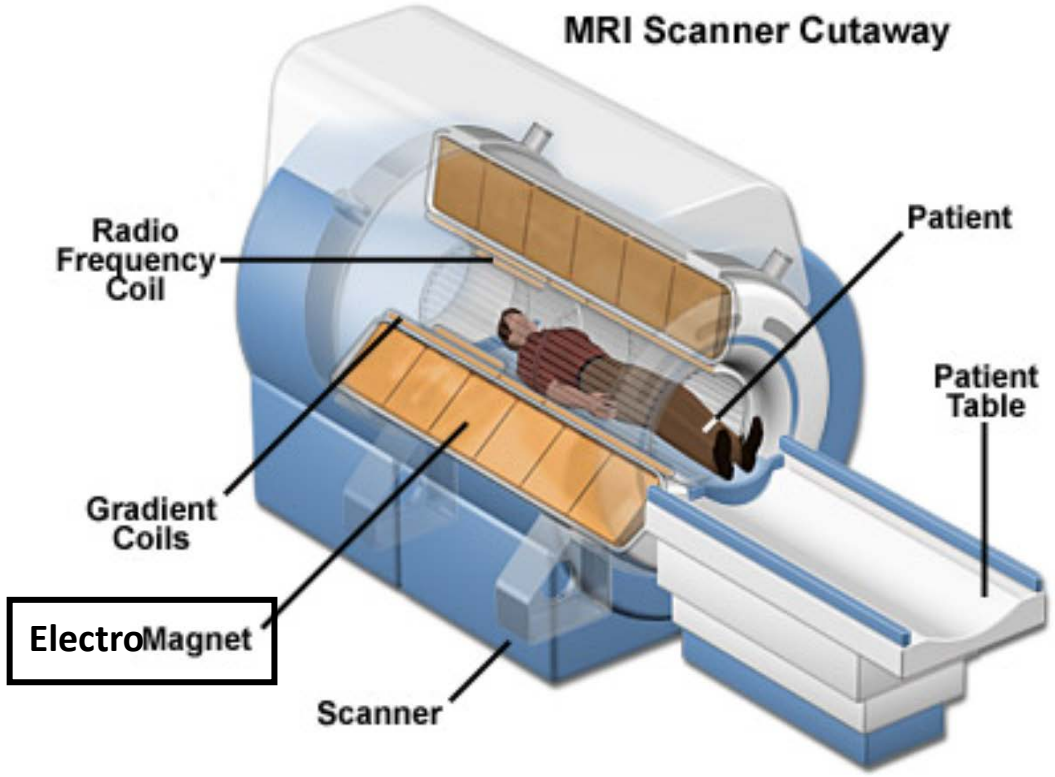


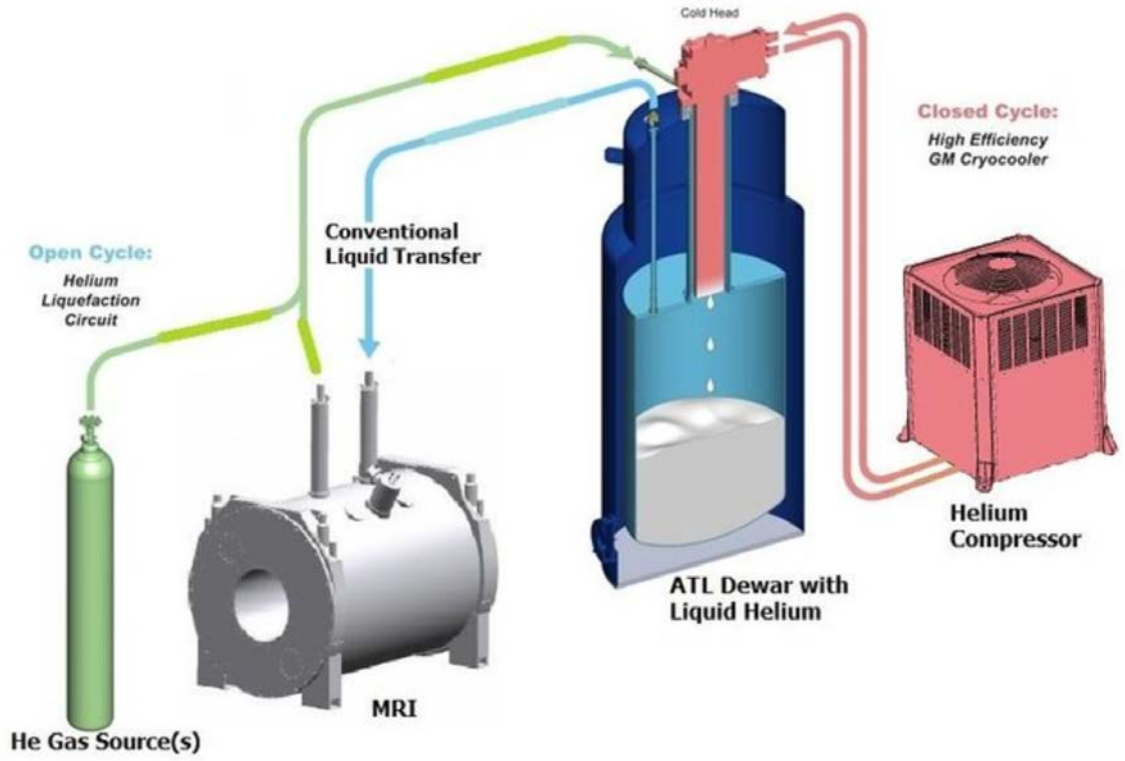
MRI and PET for Alzheimer's disease

Patrick Lao

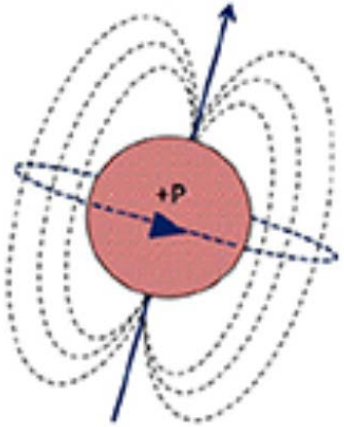
Assistant Professor,
Columbia University

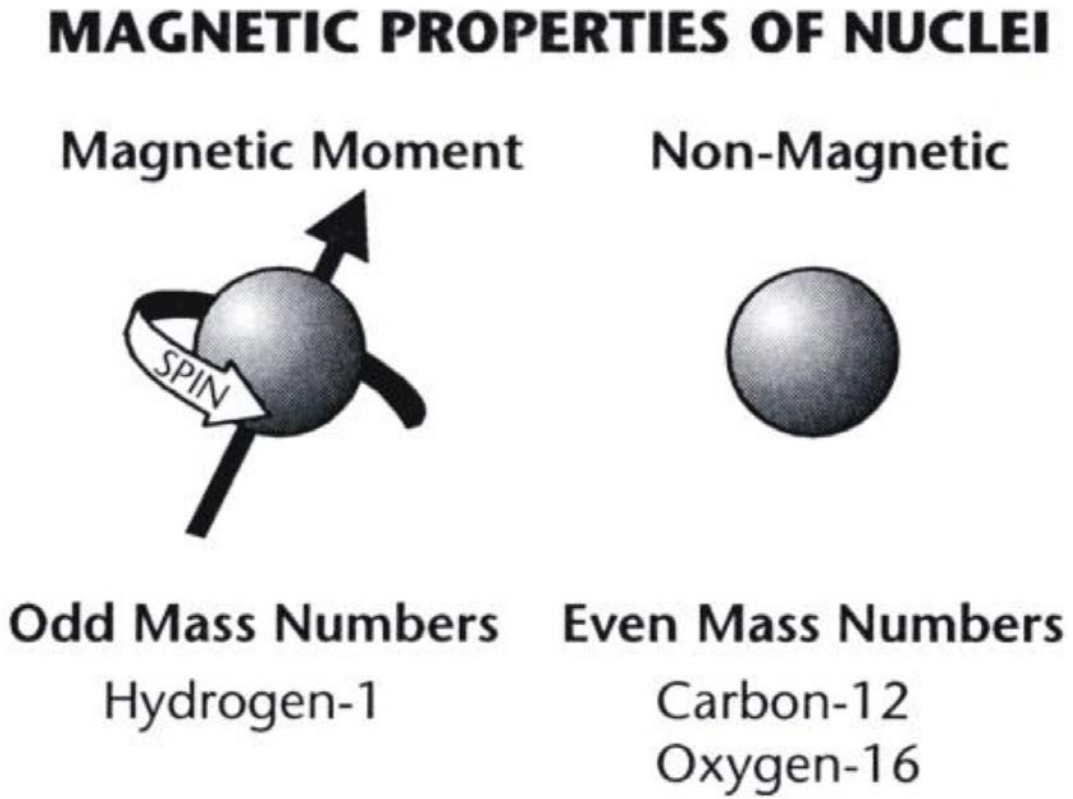
Magnetic Resonance Imaging (MRI)



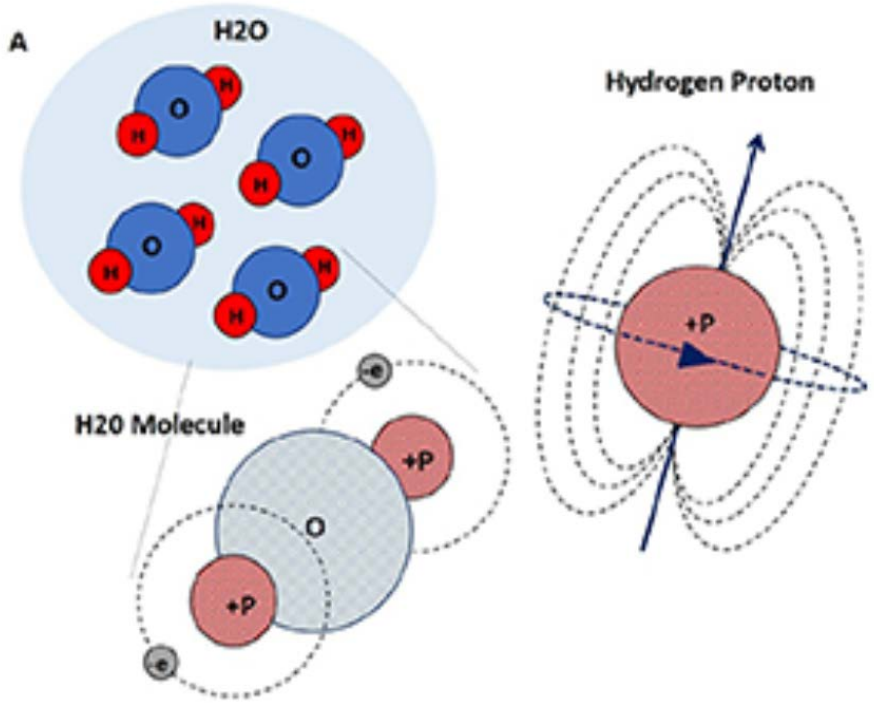


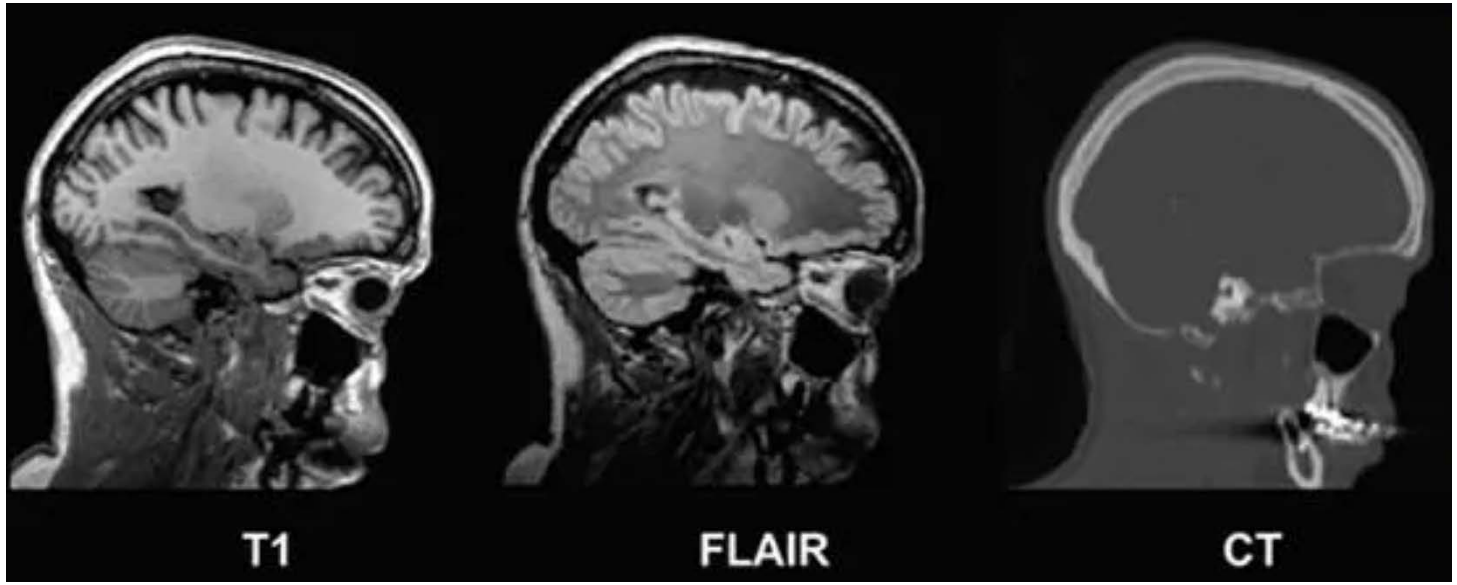
First, what's magnetic in the body?



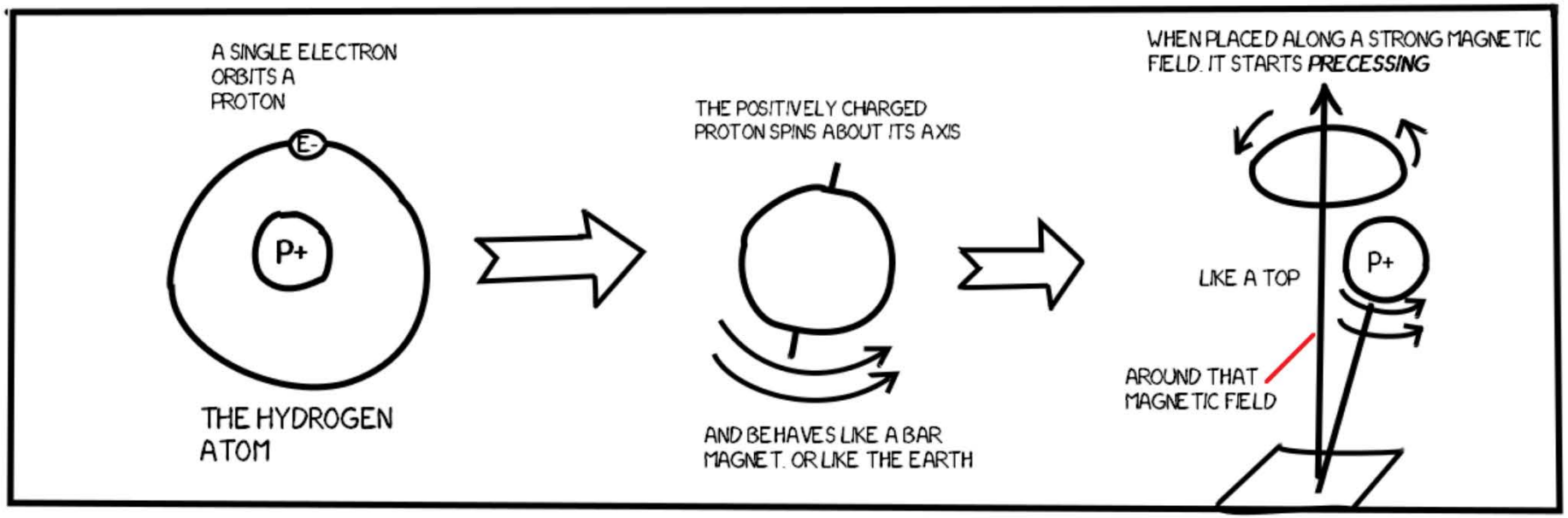


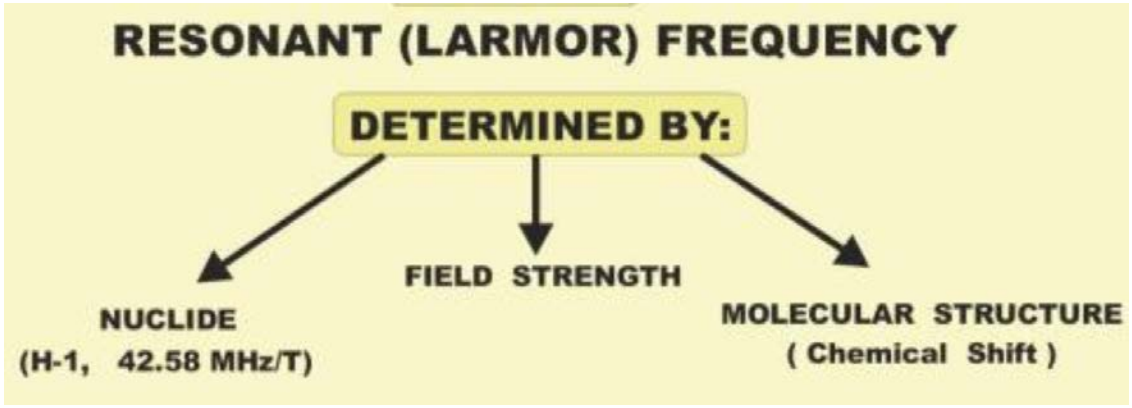
Second, what would give us enough signal?

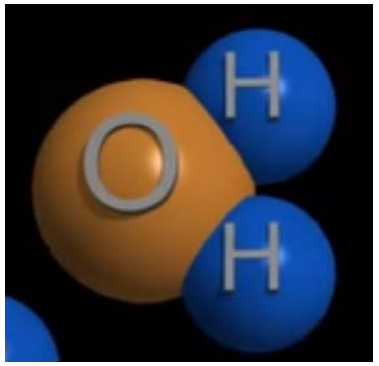




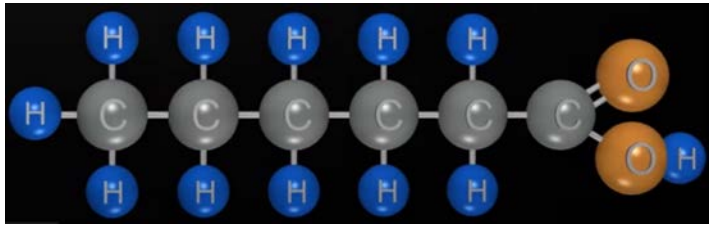
Precession at Larmor frequency



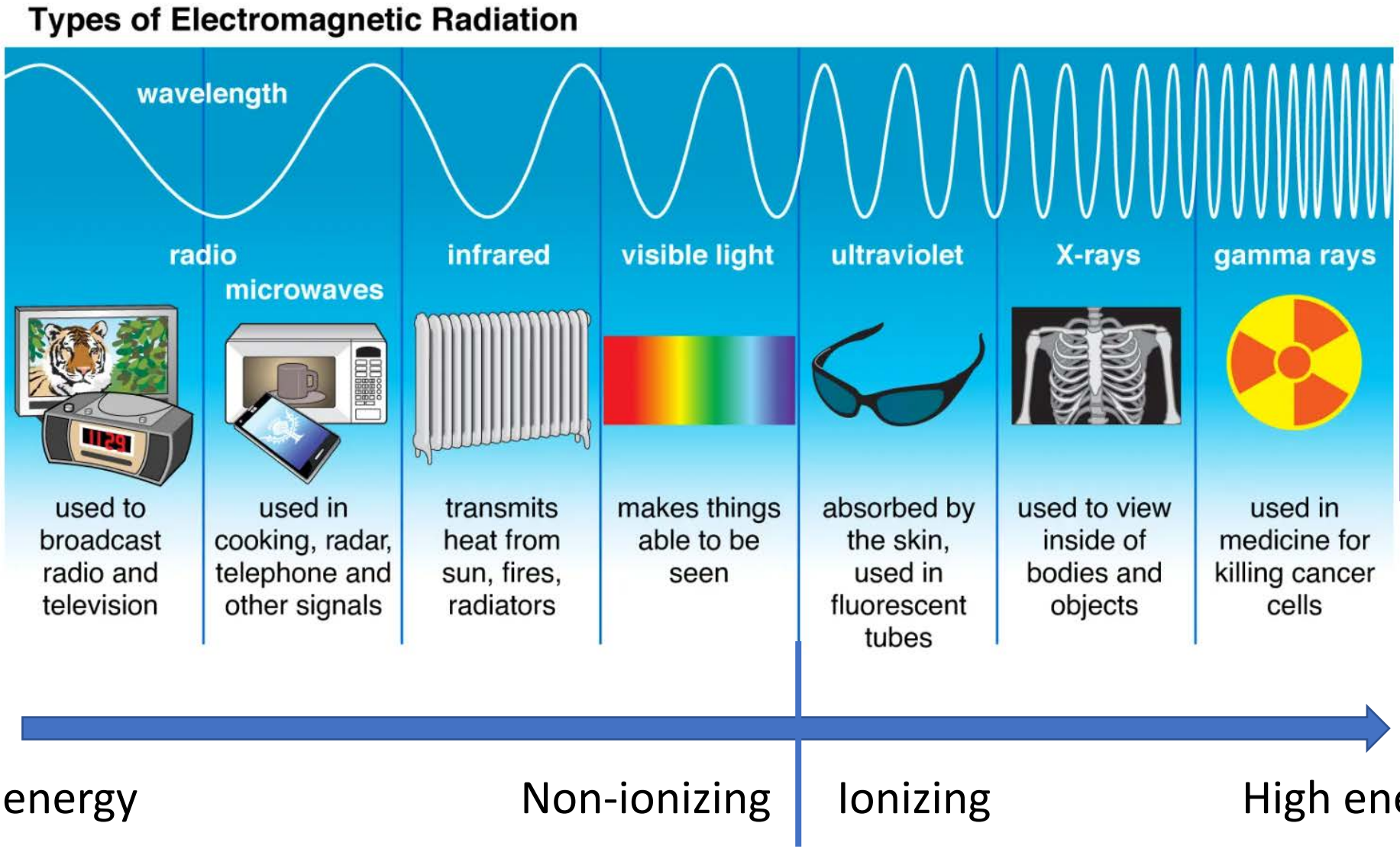




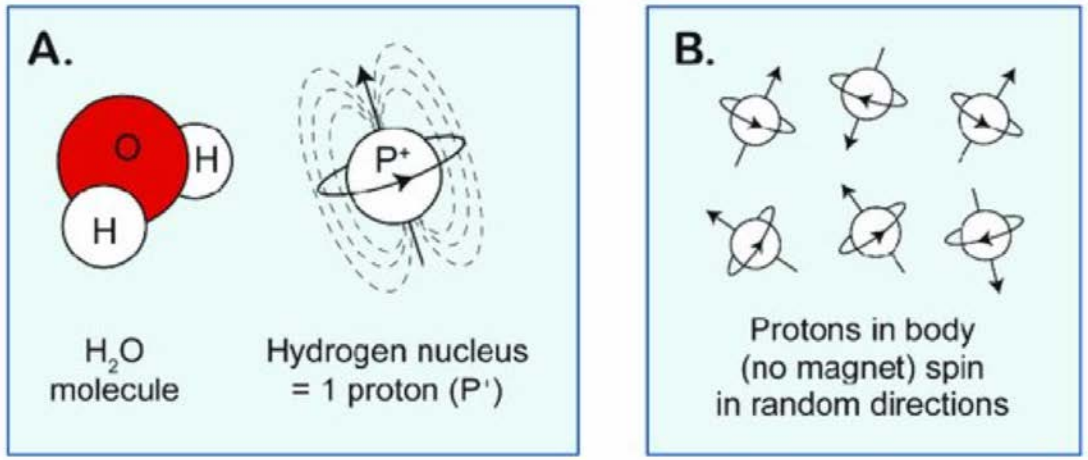
vs

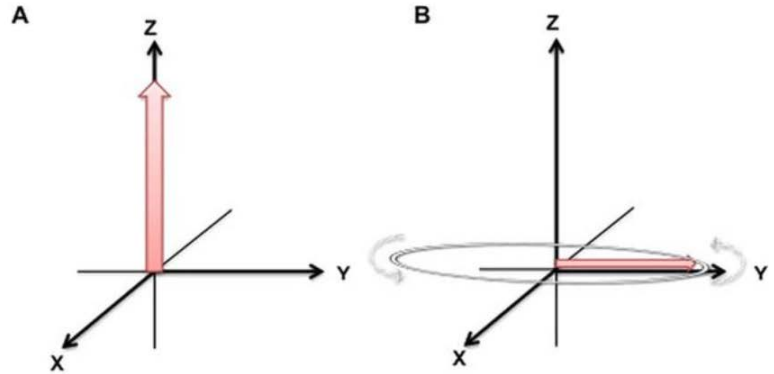


Radiofrequency pulse at Larmor frequency



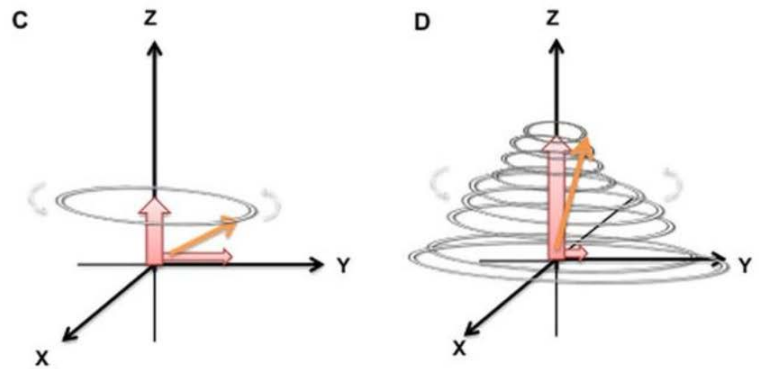
How do we generate signal?





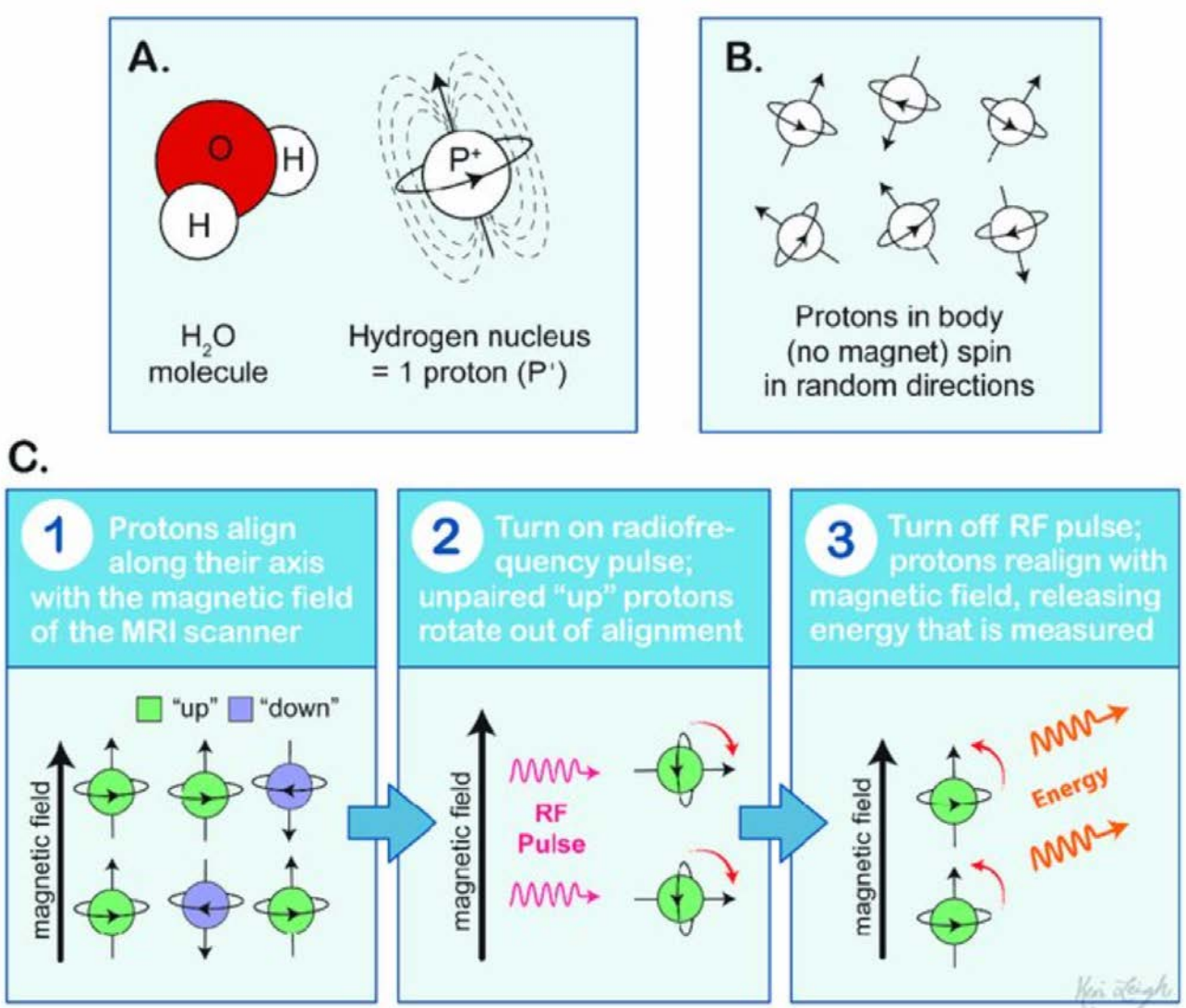
Longitudinal Magnetization (T1)

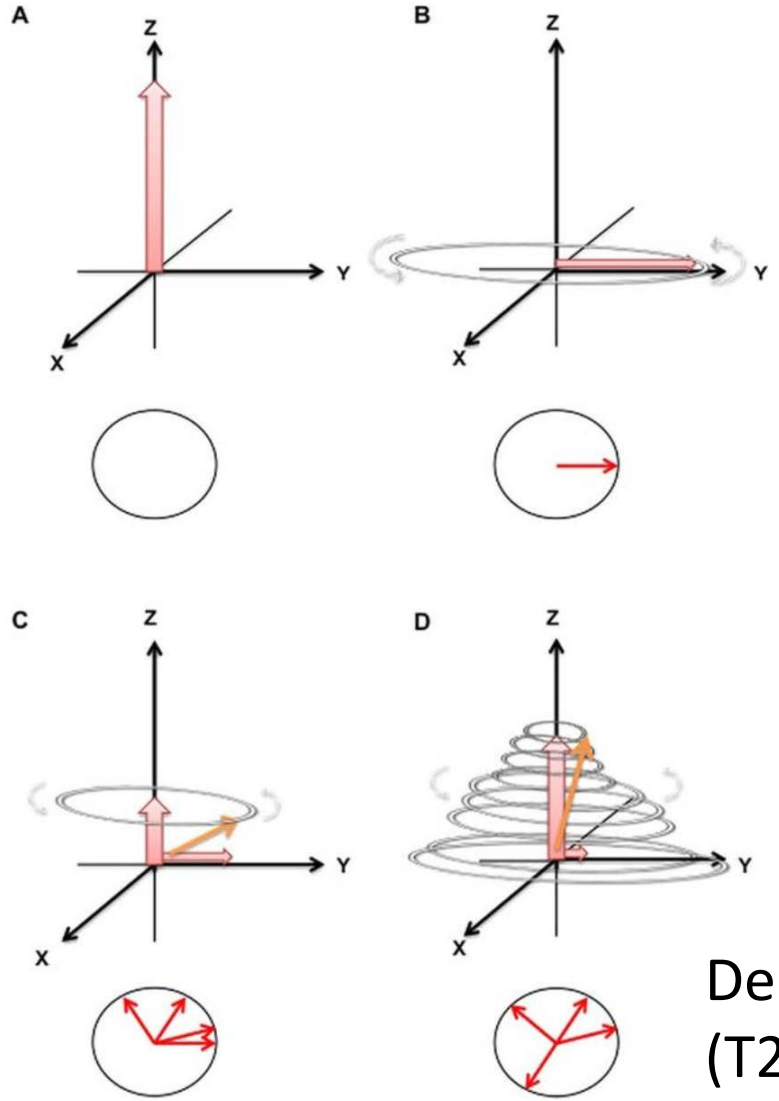
Transverse Magnetization (T2)



Because of precession, the net magnetization can be decomposed into longitudinal and transverse components

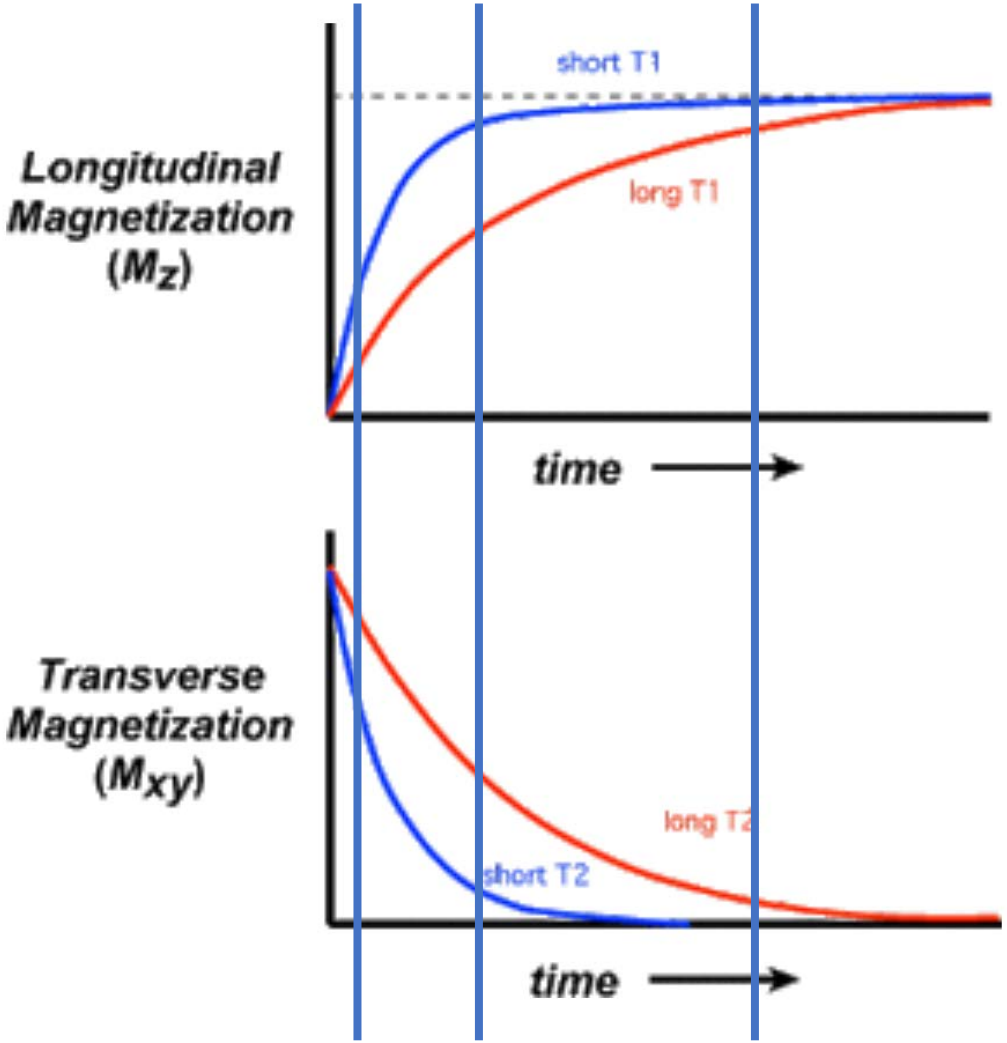
How do we generate signal?

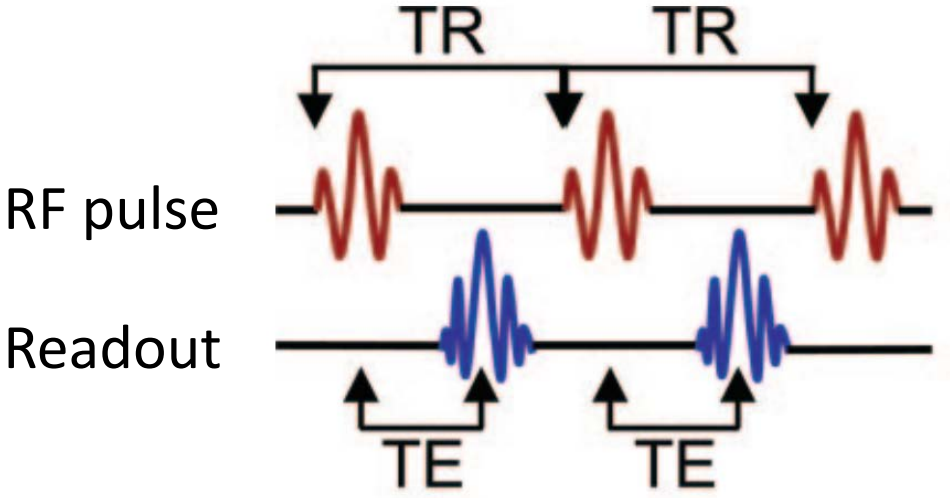


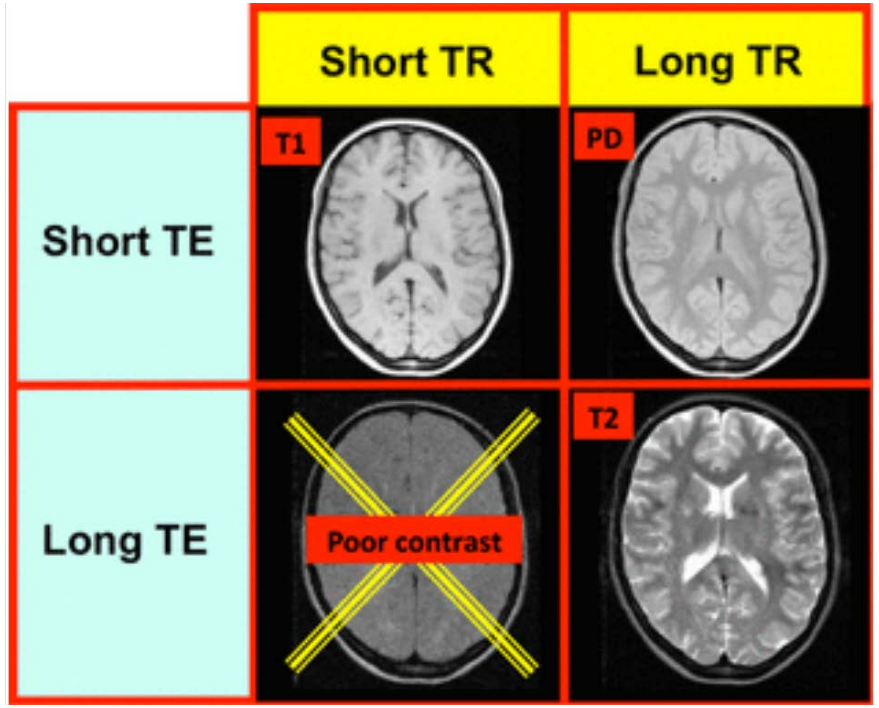


Dephasing (T2* vs T2)

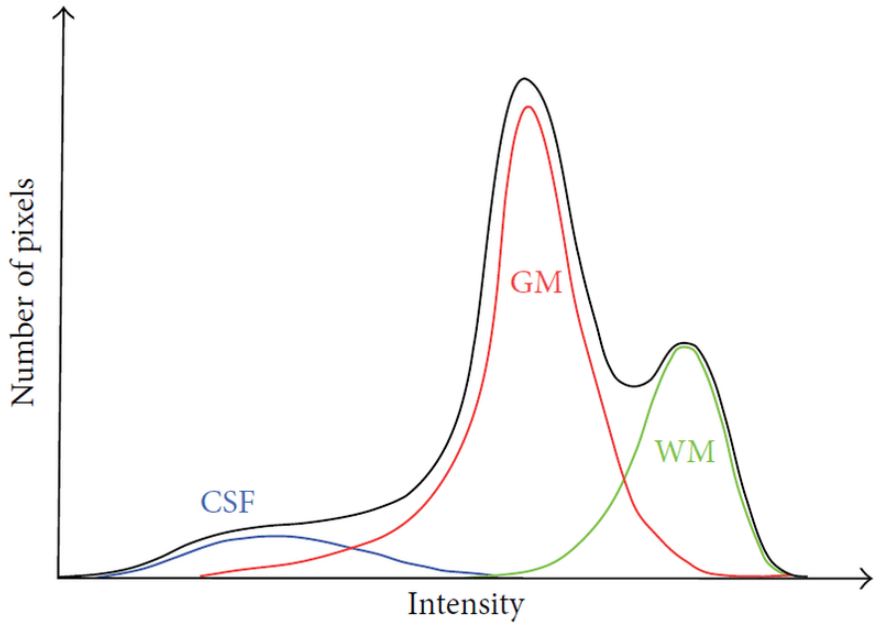
Contrast


short T1
long T1
Longitudinal Magnetization (M_z)
time
long T2
short T2
Transverse Magnetization (M_{xy})
time


TR
TR
RF pulse
Readout
TE
TE


Short TR
Long TR
Short TE
Long TE
T1
PD
T2
Poor contrast

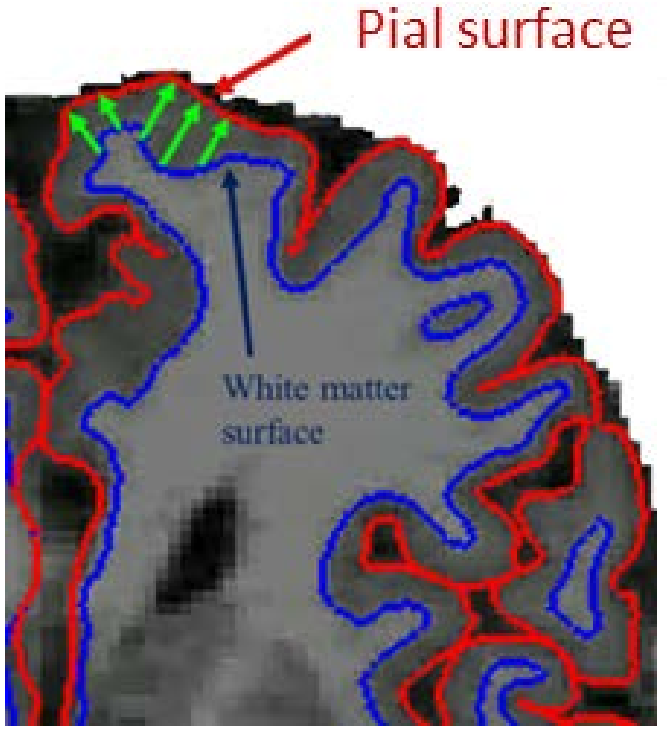
Structural T1-weighted MRI: GM/WM contrast

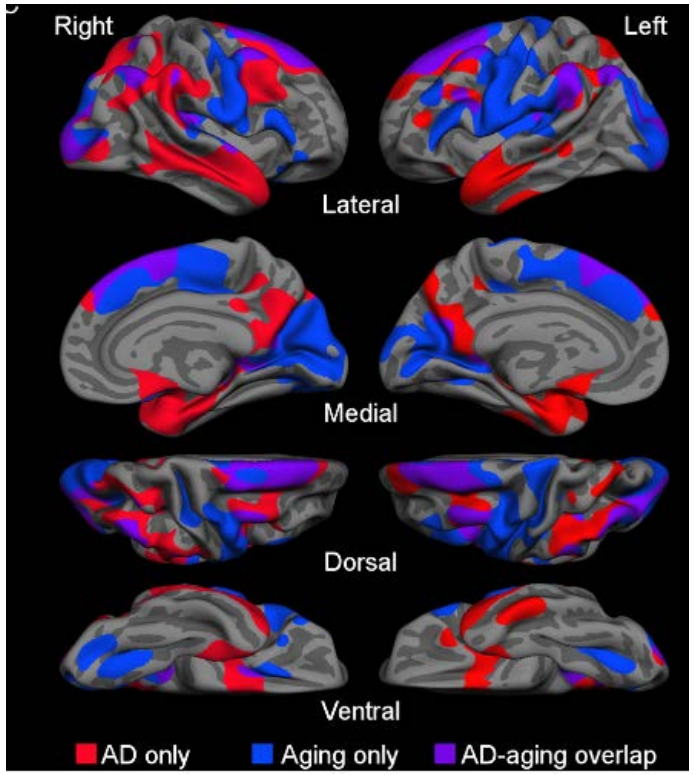


More water

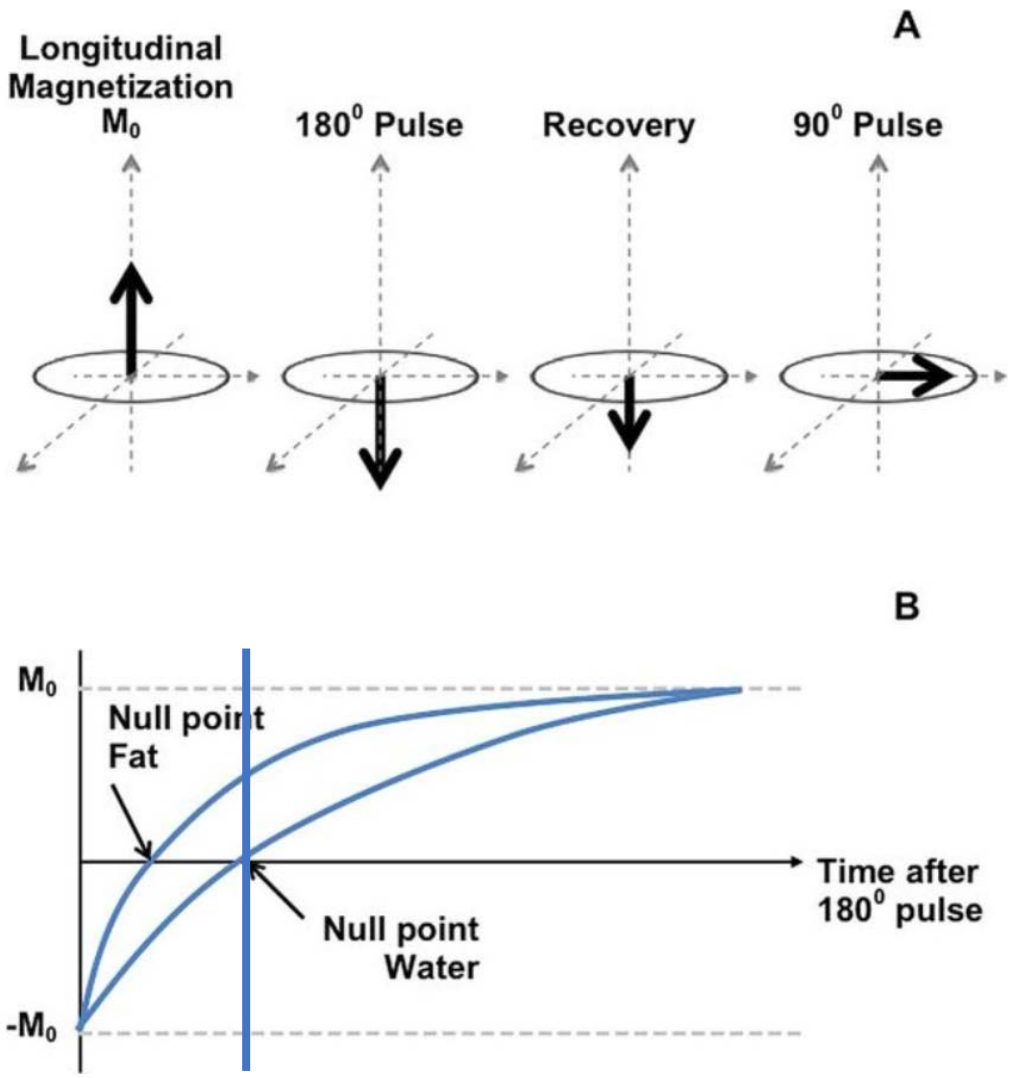
Less water

FreeSurfer segmentation
(Others: SPM12, FSL, ASHS)





FLAIR: FLuid Attenuation Inversion Recovery



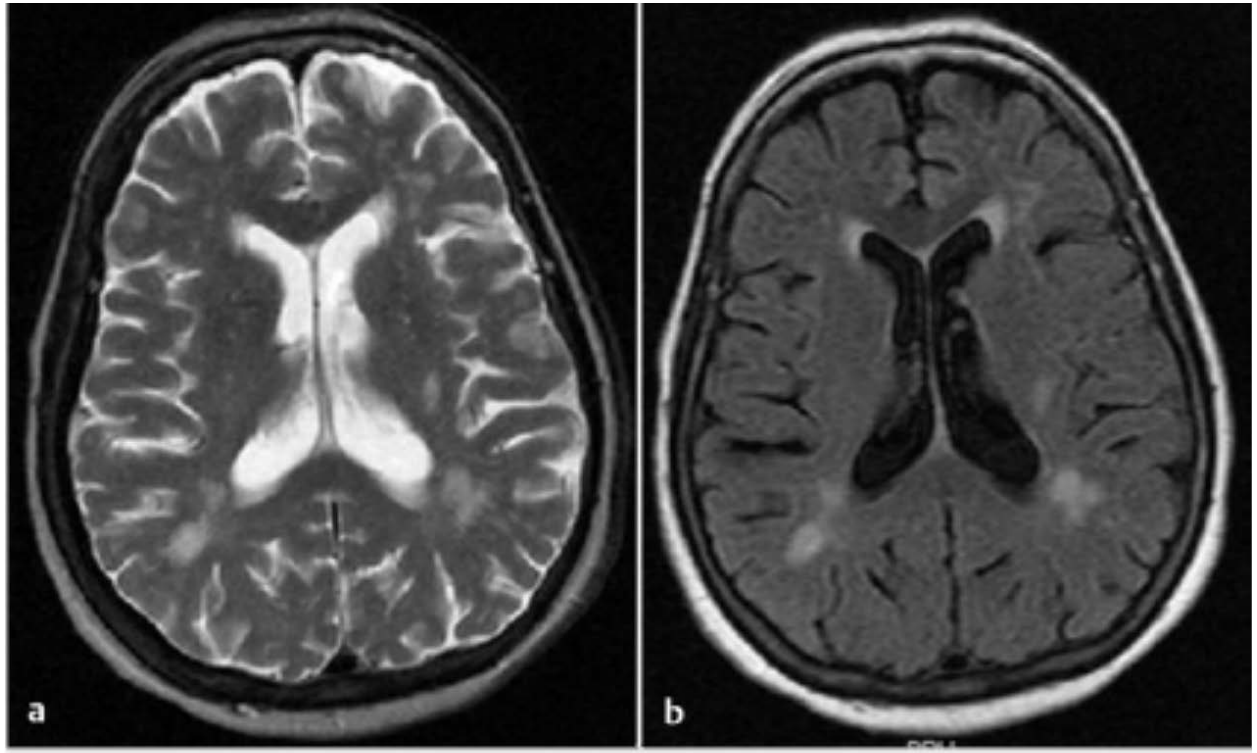
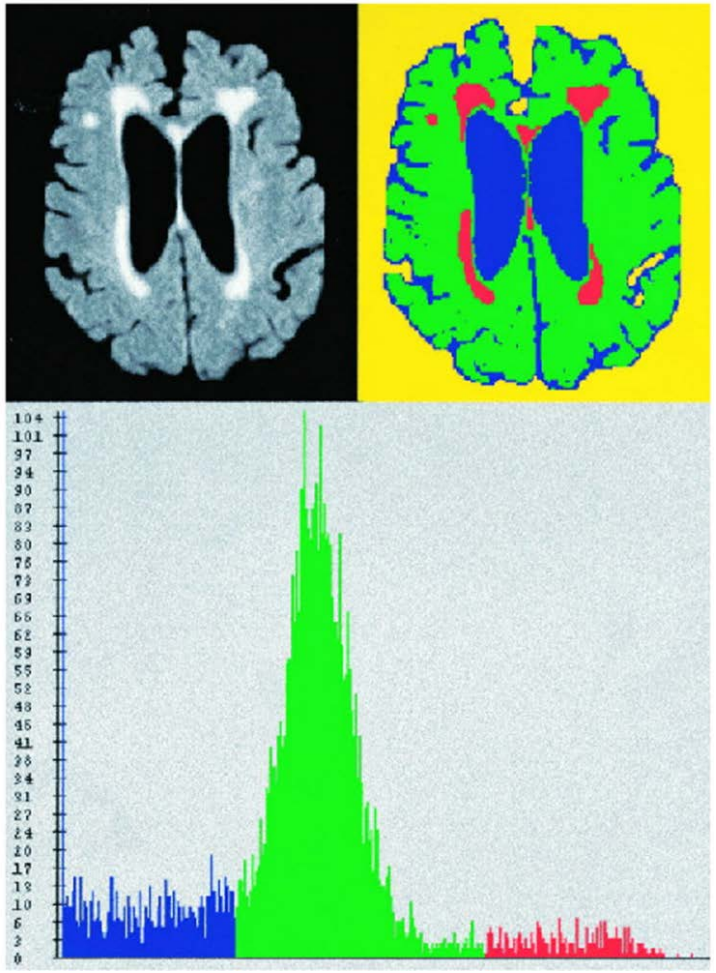
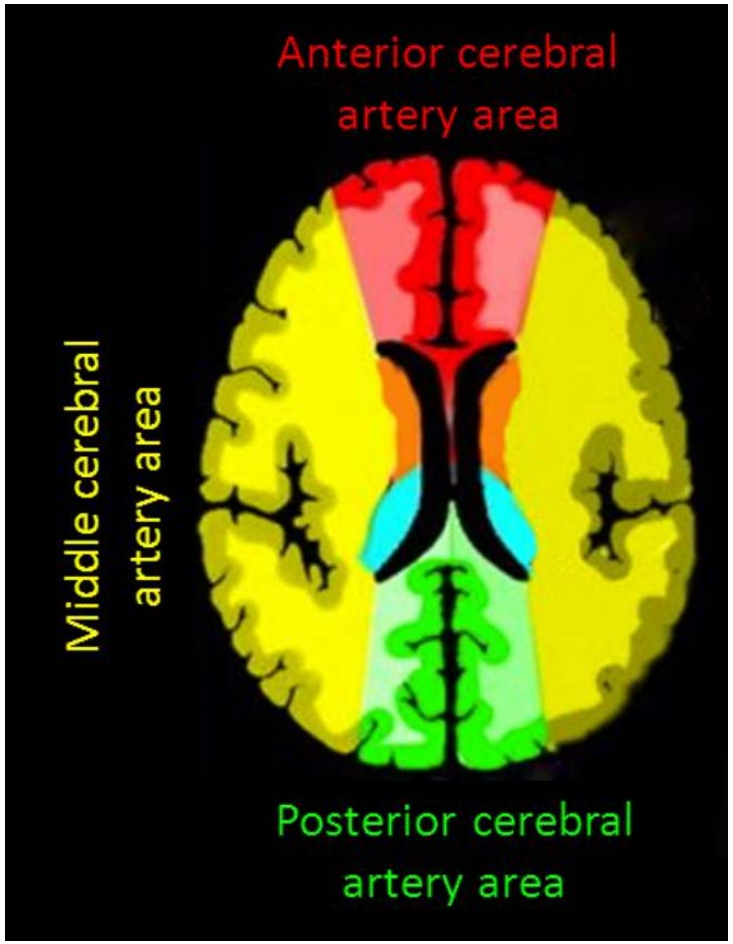


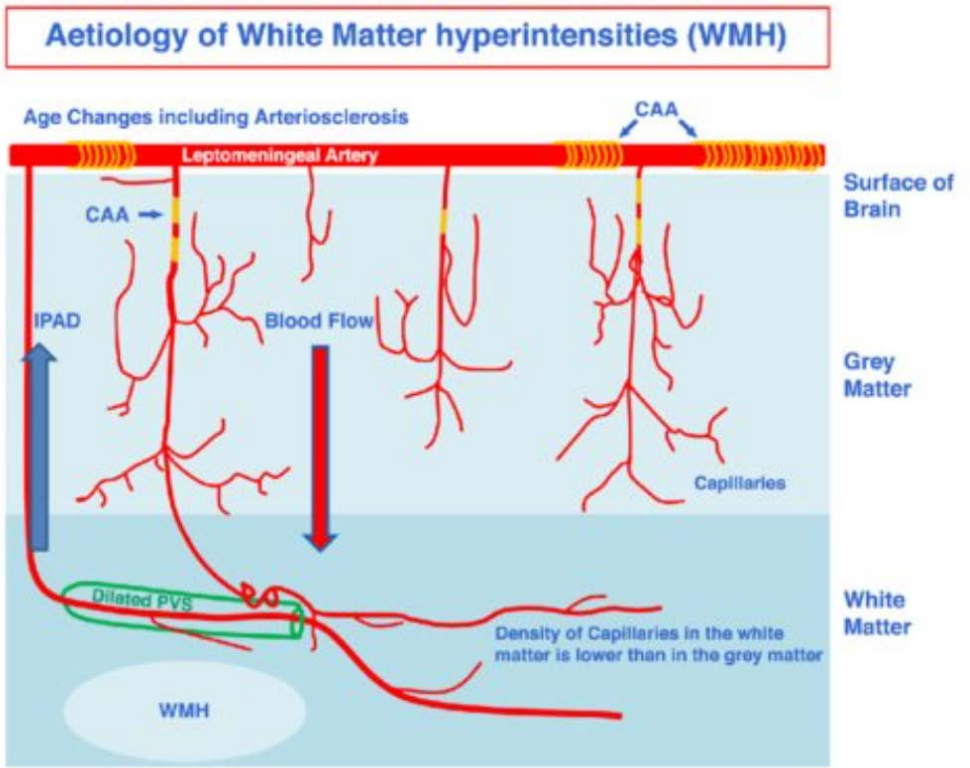
Fig. 4.26 (a) Axial T2-weighted sequence and (b) fluid- attenuated inversion recovery (FLAIR) sequence. Both sequences are T2-weighted, but the cerebrospinal fluid (ventricles and subarachnoid spaces) appears dark on the FLAIR sequence, thereby facilitating observation of periventricular hyperintensities.

T2-weighted FLAIR: Within WM contrast

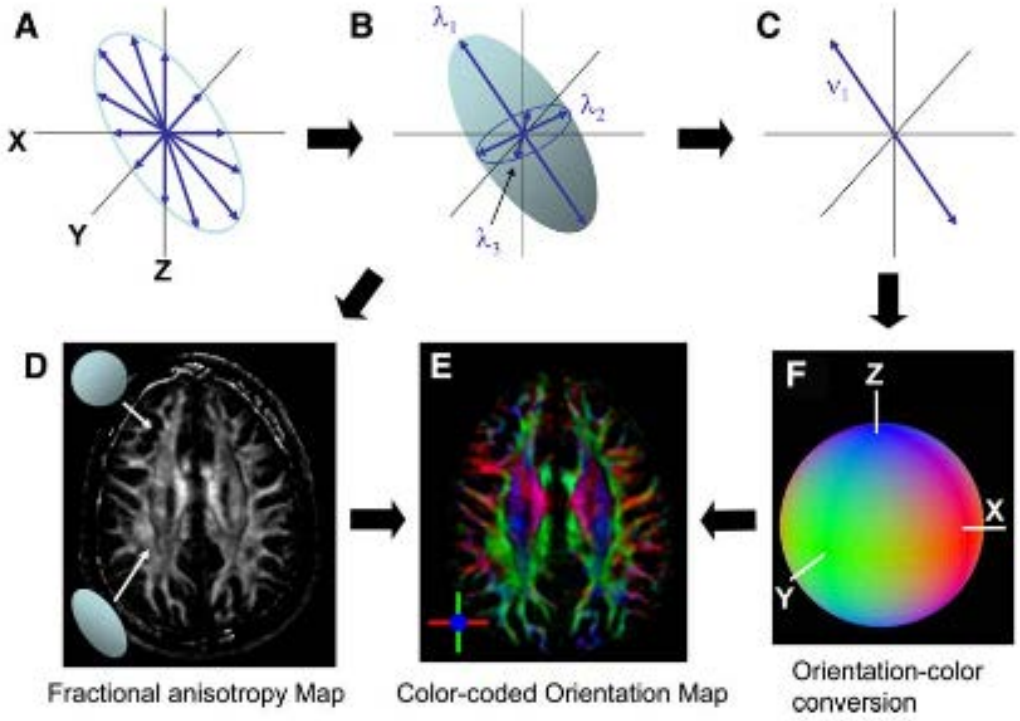


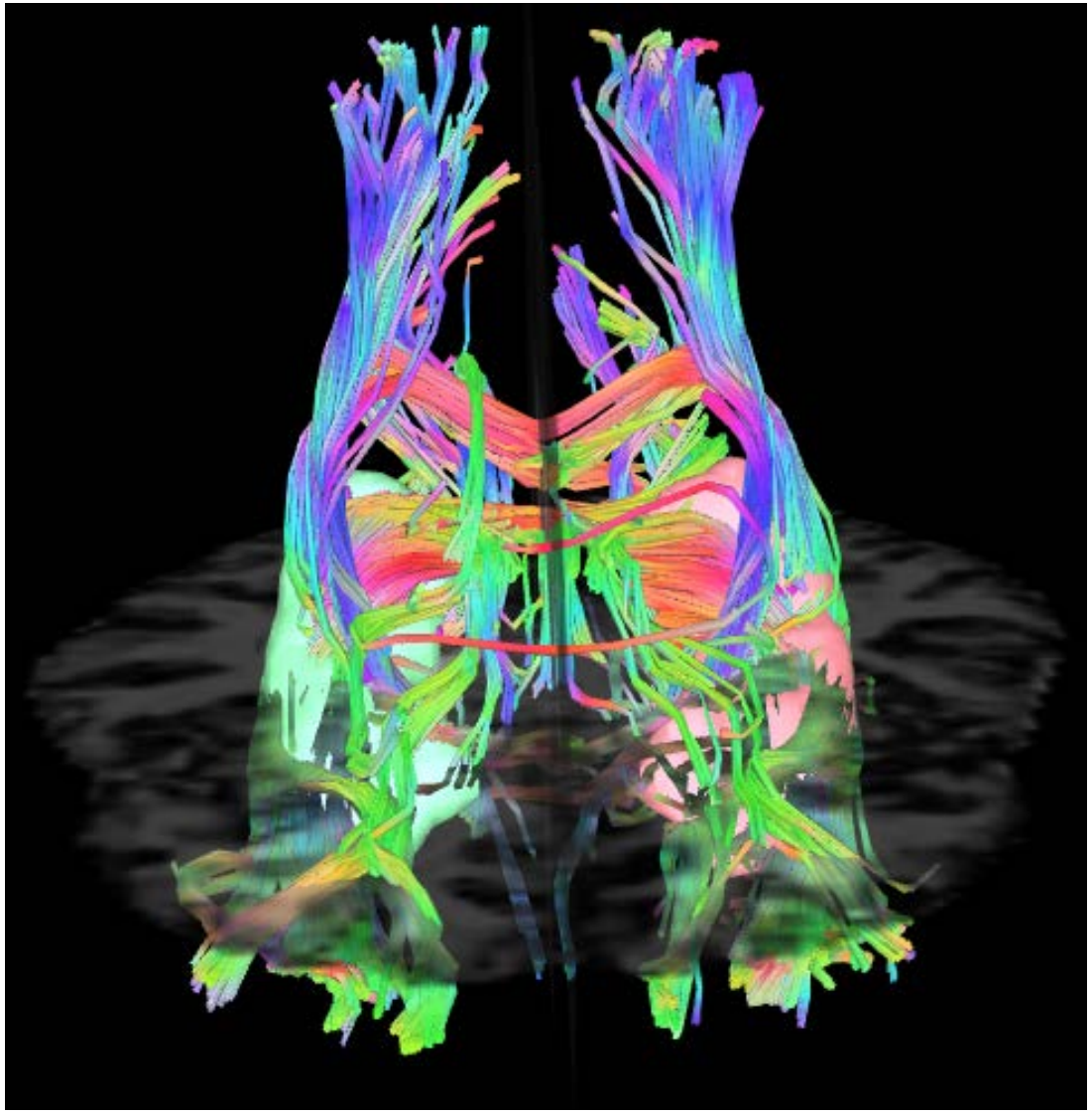
CSF, NAWM, GM, WMH



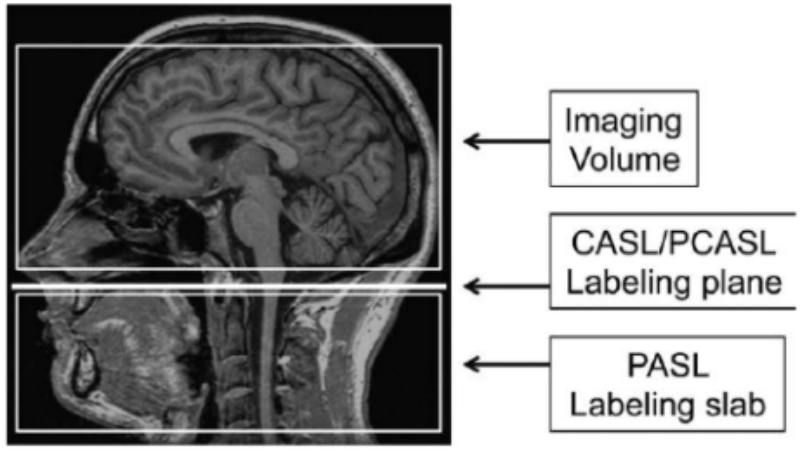


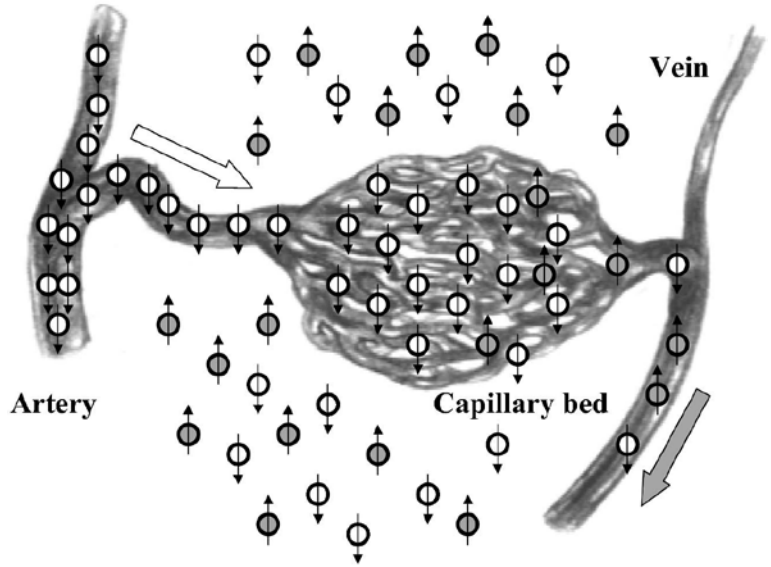
Diffusion weighted imaging: WM microstructure

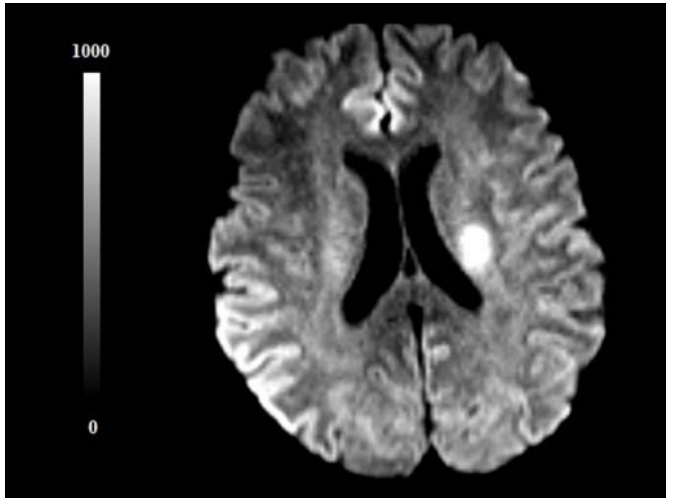




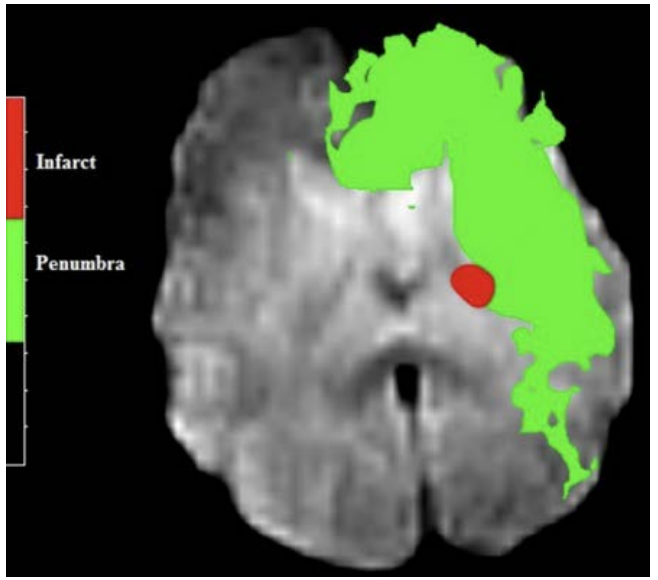
Arterial Spin Labeling: cerebral blood flow





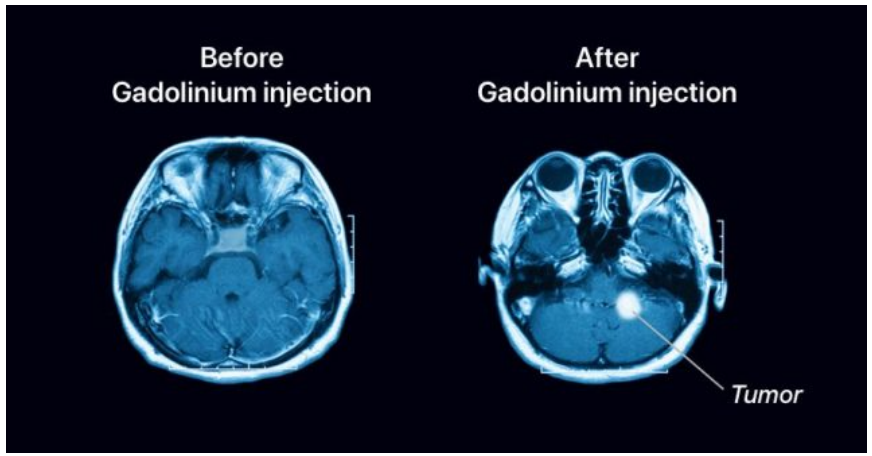


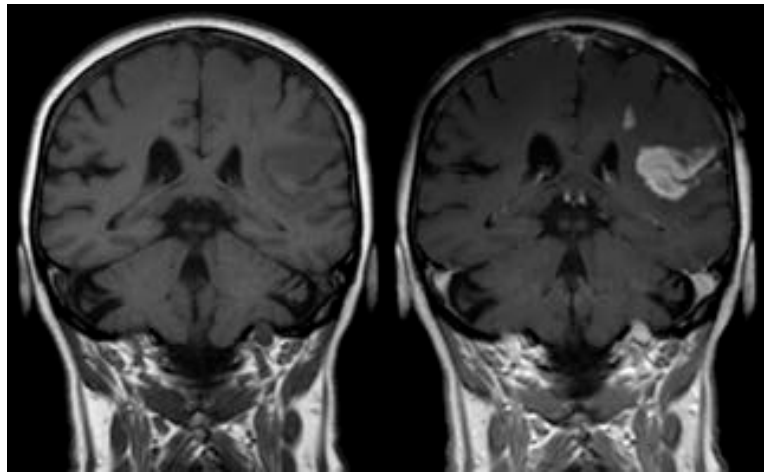
DWI: showing damage in infarct area



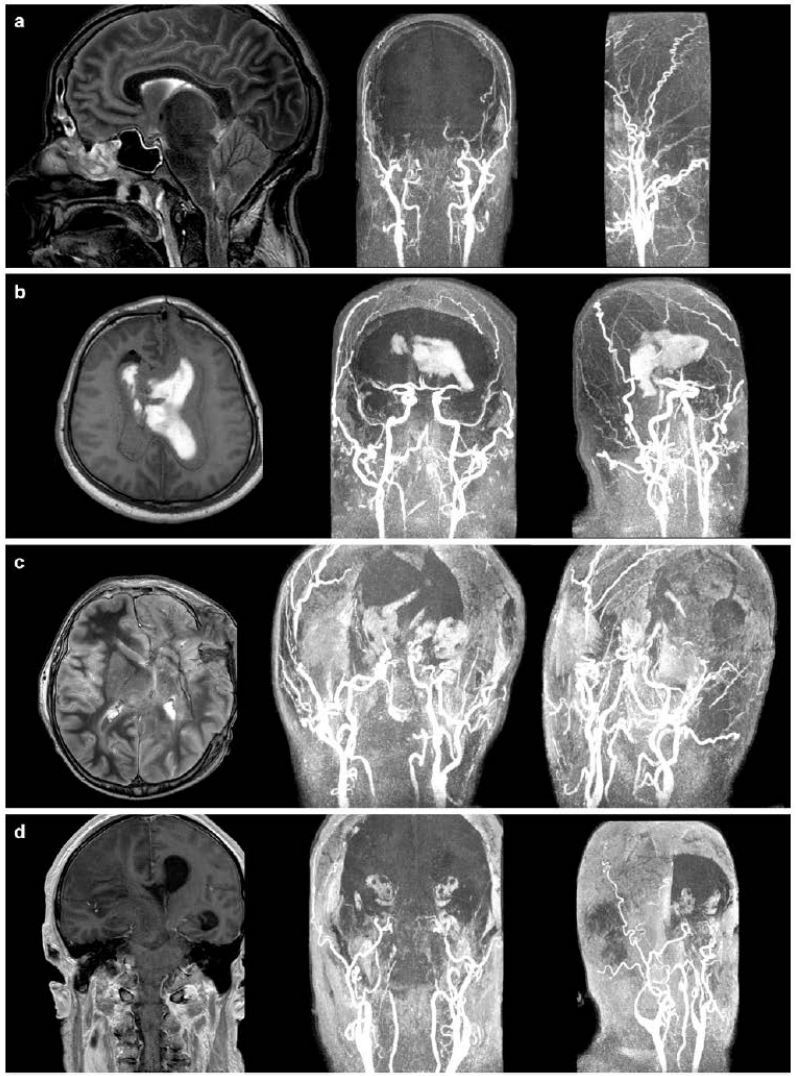
ASL: showing extended region of low cerebral blood flow

Gadolinium-enhanced contrast: increased cerebral blood flow





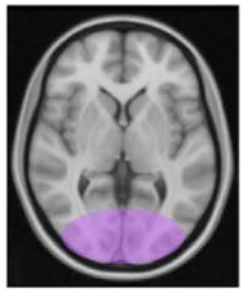
Stroke



Functional MRI: functionally connected regions

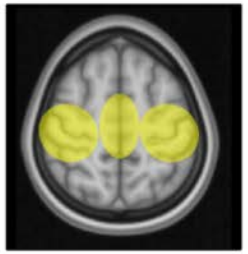
Default mode
- Ventromedial prefrontal cortex
- Precuneus and posterior cingulate
- Bilateral inferior parietal areas

Functions:
- ✓ *Introspective ability and episodic memory*
- ✓ *Deactivated during goal-based and attention-demanding tasks*



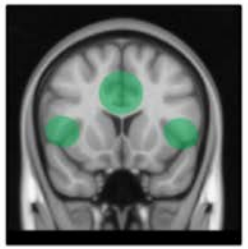
Visual
- Striate cortex
- Occipital pole
- Lateral visual areas

Functions:
- ✓ *Primary and associative visual processes*



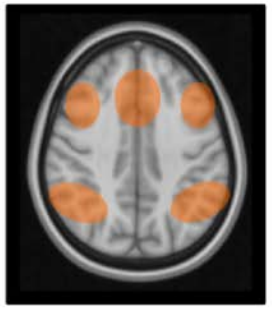
Sensorimotor
- Primary sensorimotor cortex
- Supplementary motor area
- Secondary somatosensory cortex

Functions:
- ✓ *Motor programming and execution*
- ✓ *Sensory integration*



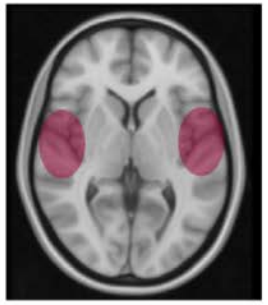
Salience
- Dorsal anterior cingulate
- Bilateral insulae

Functions:
- ✓ *Elaboration of salient inputs*



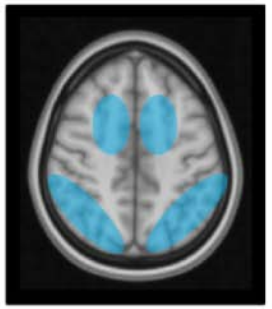
Executive control
- Mesial frontal areas (anterior cingulate)
- Dorso-lateral frontal areas
- Parietal cortex

Functions:
- ✓ *Executive –attentive functions*
- ✓ *Working memory*
- ✓ *Sensorimotor learning*



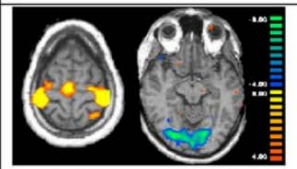
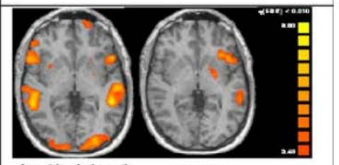
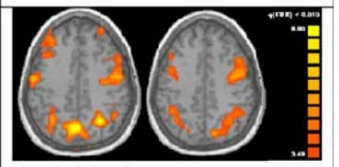
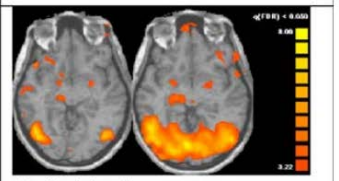
Auditory
- Superior temporal gyrus
- Heschl gyrus
- Primary auditory and associated areas

Functions:
- ✓ *Primary and associative auditory processes*



Dorsal attention
- Superior parietal and inferior parietal sulcus
- Superior frontal areas
- Frontal eye fields

Functions:
- ✓ *Attention and control demanding tasks*

Condition A (probe)	Condition B (control)	Targeted Areas	Representative Slices
Visual - Motor Task (combined)			
Full field radial checkerboard with continuous reversing @ 8 Hz	Bimanual finger press to visually presented cue for finger number	Primary and supplementary motor cortex; primary visual cortex	 motor visual individual maps
Language Task (Verb Generation)			
Think of an appropriate action verb to a presented object noun (i.e. "nail" -> "hit")	Fixate on centrally positioned crosshair	Broca's and Wernike's areas	 individual group
Working Memory Task (Verbal N-Back)			
2-Back: identify target trials where the current letter matches the letter that was presented 2 trials before	0-Back: search sequence of letters for pre-specified target (letter "X")	Dorsolateral prefrontal cortex	 individual group
Emotional Pictures Task			
Set of emotionally charged pictures (aggressive, erotic or stressful) with high arousal scores from IAPS	Set of neutral pictures (common objects or scenes) with low arousal score from IAPS	Limbic structures: amygdala and hippocampus	 individual group

MRI Limitations

- Expensive
- Requires imaging center and expertise (sophisticated sequences, radiological review)
- Loud
- Small bore size
- Need to lay still for long periods
- No implants/wearable devices (some are MRI compatible, but not at very high field strengths)
- Many types of artifacts (SNR increases with higher field strength, but so do artifacts)
- Raw intensity values are meaningless

MRI Strengths

- In vivo
  - as opposed to biopsy/autopsy
  - repeated measurements across the lifespan
- Non-invasive
  - external contrast agents are optional
- No ionizing radiation
  - absorbed energy is heat
- Can optimize pulse sequence (flip angle, FLAIR) and acquisition parameters (TR, TE) to get desired weighting (T1, T2) and derive biologically meaningful measures

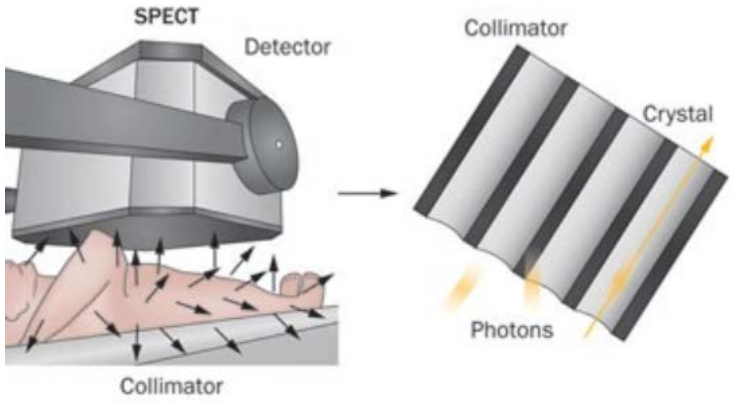
What do we target to generate signal in a conventional MRI?

- A. Helium
- B. Carbon
- C. Hydrogen
- D. Oxygen

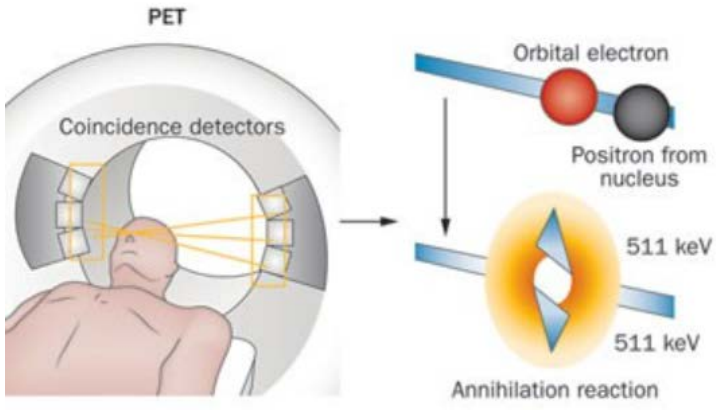
Contrast (i.e., weighting) is determined by

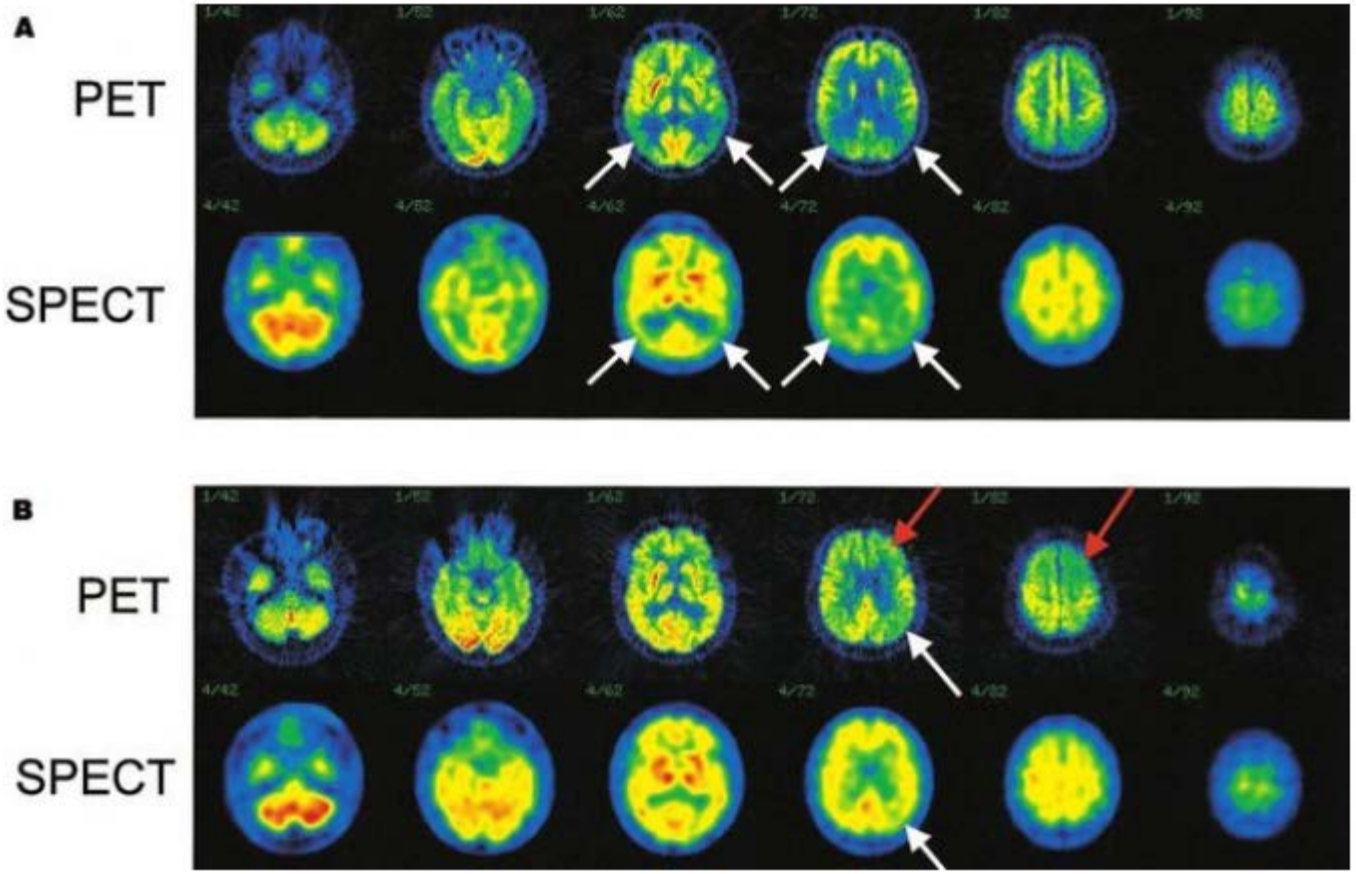
- A. T1 relaxation
- B. T2 relaxation
- C. Pulse sequence
- D. All of the above

SPECT (single photon emission computed tomography) vs PET (positron emission tomography)



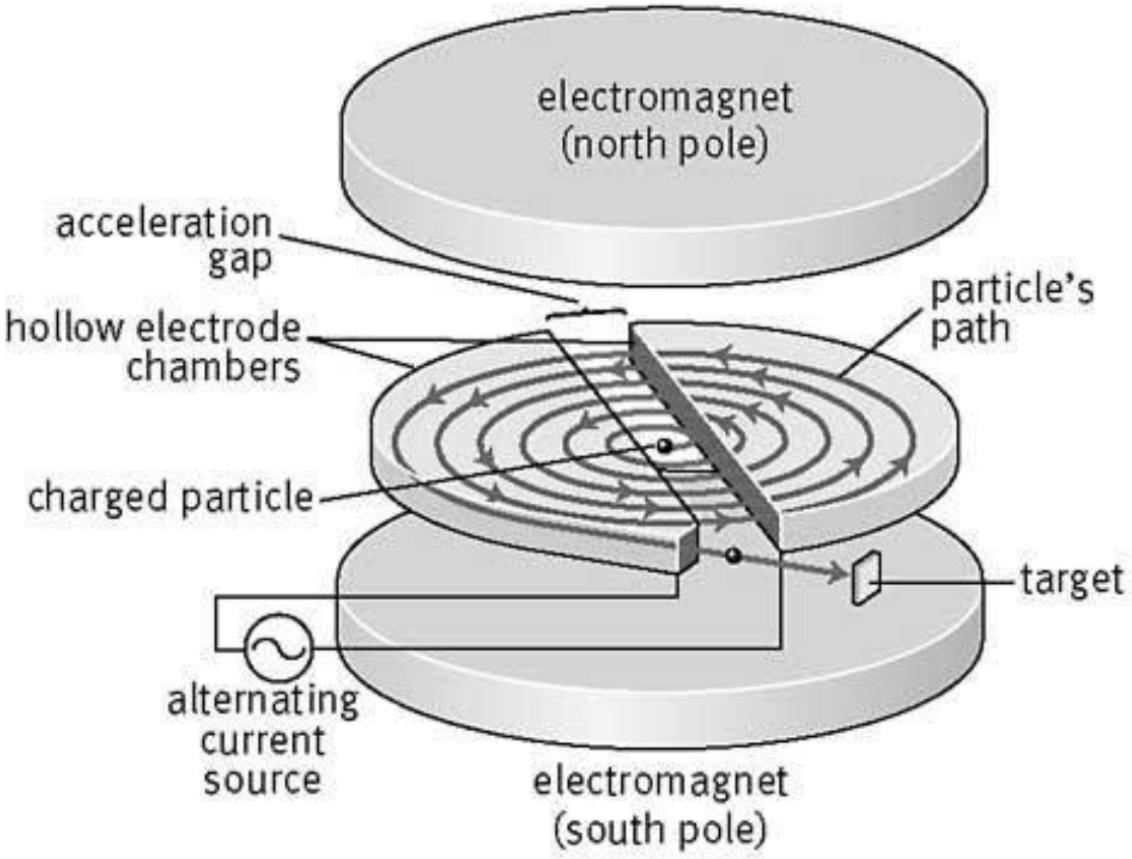
Photon emission -> Photon detection

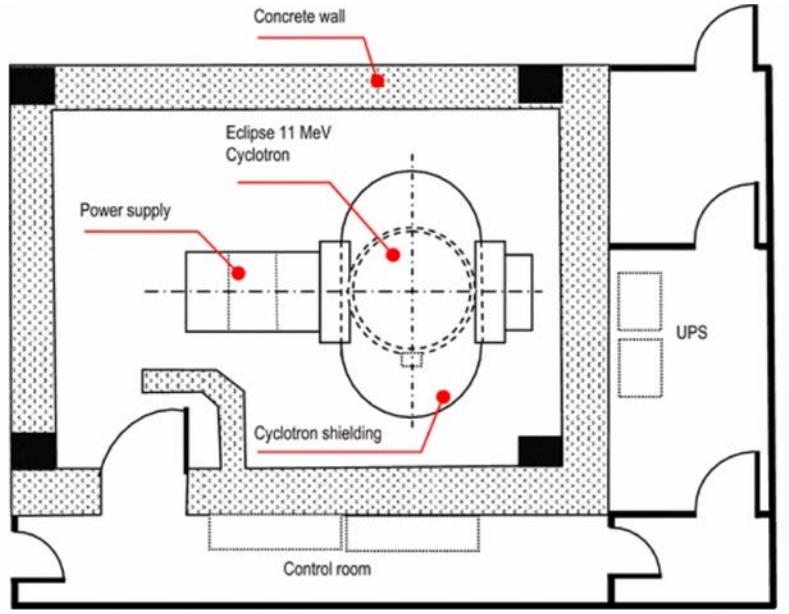




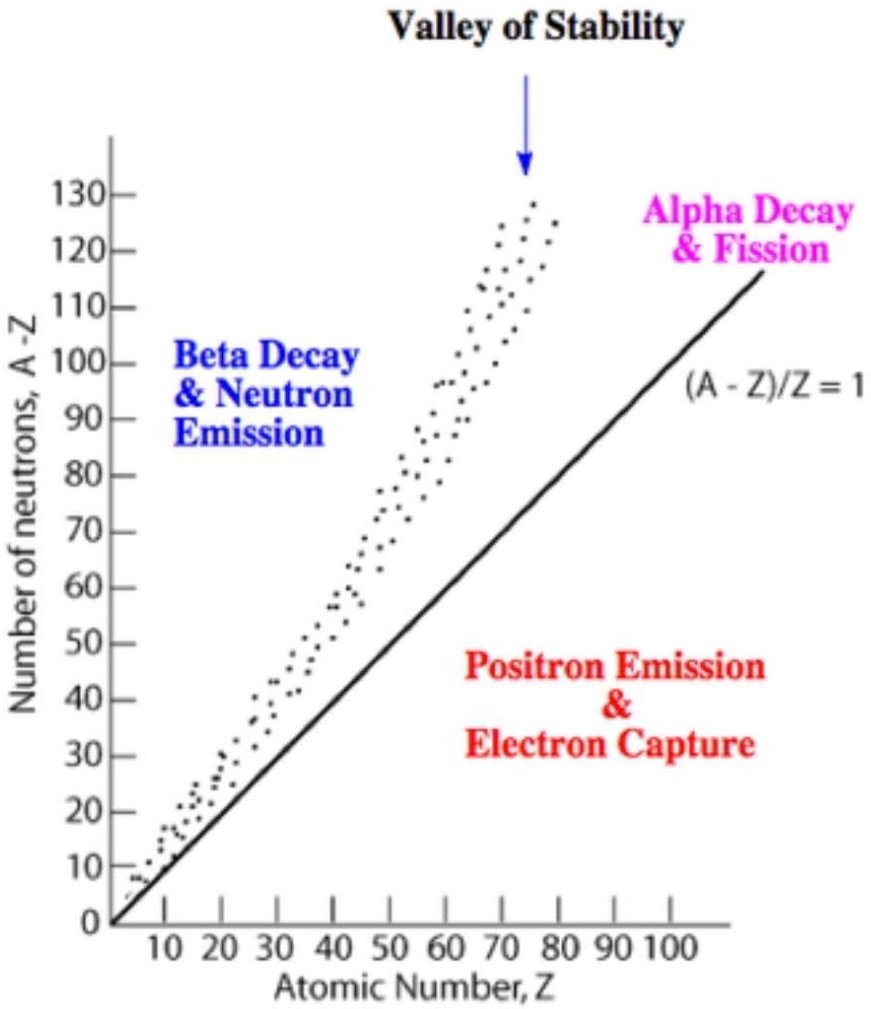
Positron emission -> annihilation with electron -> photon detection

PET signal from radioactivity





Positron emitters

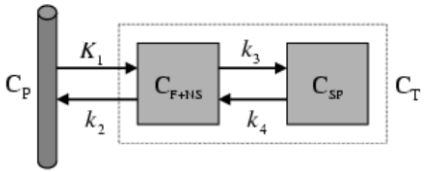


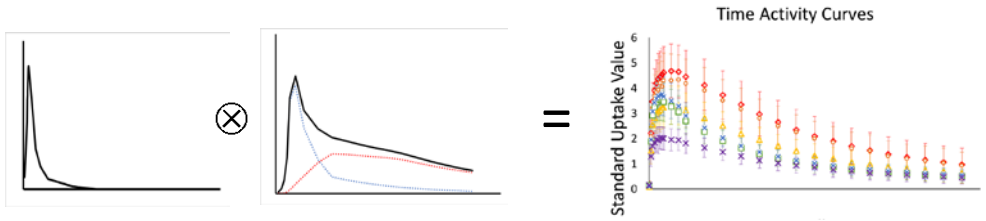
Radionuclide	t½
^{15}O	122 seconds
^{13}N	9.9 minutes
^{11}C	20 minutes
^{68}Ga	68.3 minutes
^{18}F	110 minutes
^{64}Cu	12.7 hours
^{86}Y	14.7 hours
^{76}Br	16.2 hours
^{89}Zr	78.4 hours
^{124}I	100.3 hours

Abbreviations: ^{76}Br, bromodeoxyuridine-76; ^{11}C, carbon-11; ^{64}Cu, copper-64; ^{18}F, fluorine-18; ^{68}Ga, gallium-68; ^{124}I, iodine-124; ^{13}N, nitrogen-13; ^{15}O, oxygen-15; PET, positron emission tomography; ^{86}Y, yttrium-86; ^{89}Zr, zirconium-89.

Quantification methods

	Volume of distribution
Arterial sampling	Yes
Dynamic data	Yes
Reference region	No
Fitting	Non-linear
Interpretation	Total tissue to plasma ratio, proportional to Target density

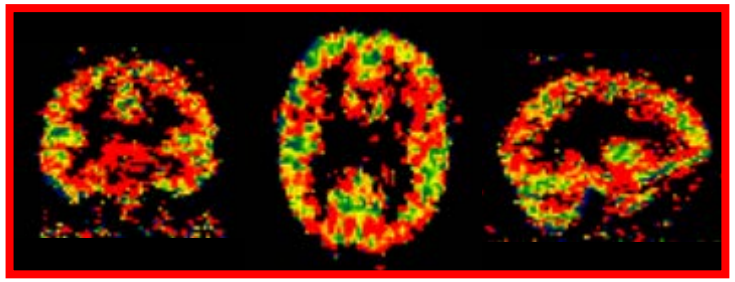


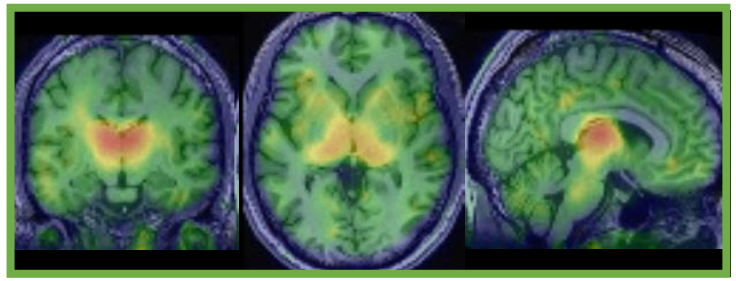


Input Function (measured with arterial sampling)

Impulse Response Function (non-linear curve fitting)

Time Activity Curves (measured with PET)

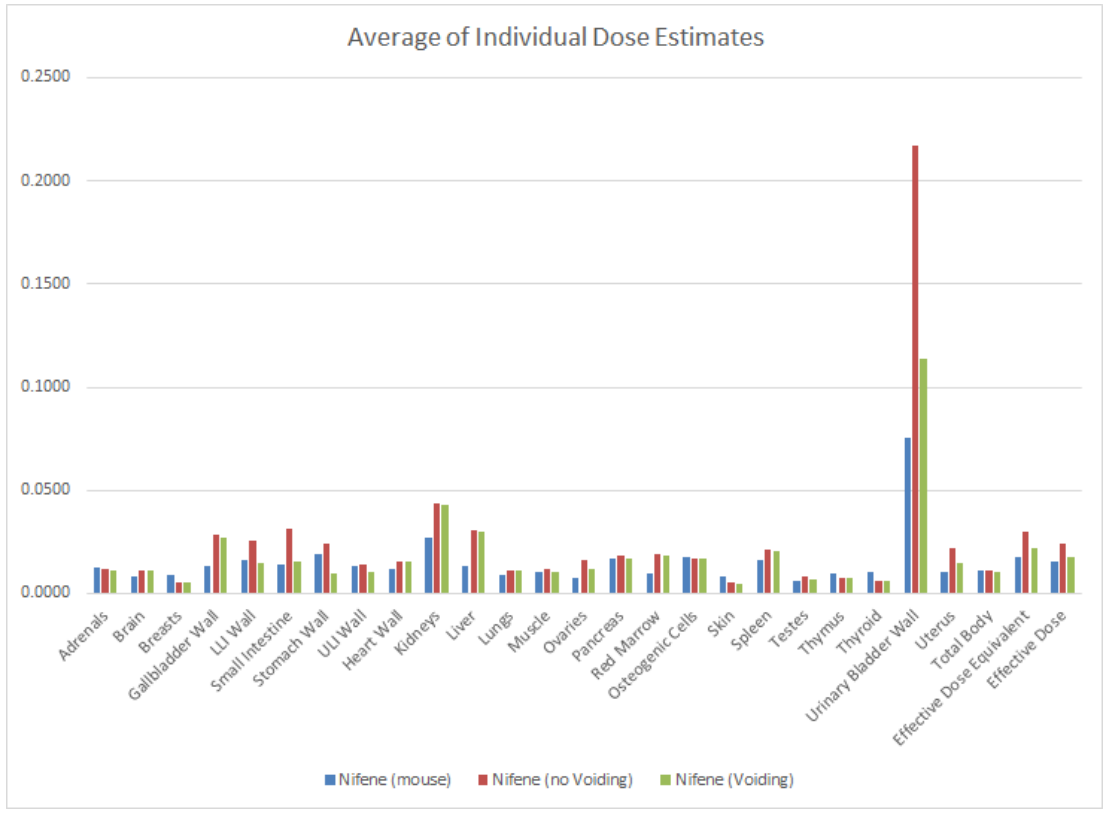


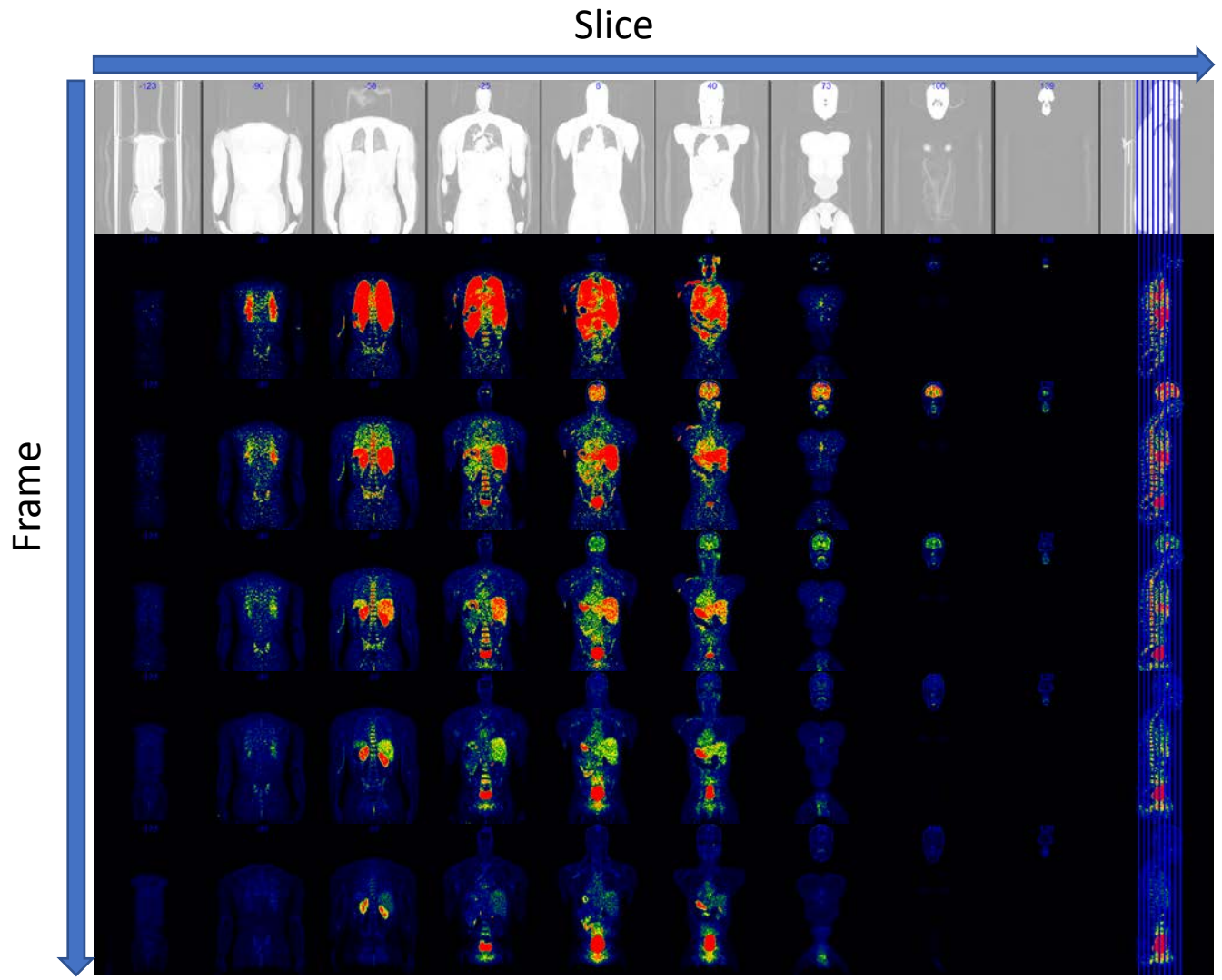


$$\frac{\int_0^T C(t)dt}{C(T)} = DVR\left[\frac{\int_0^T C'(t)dt + C'(T)/k_2}{C(T)}\right] + int$$

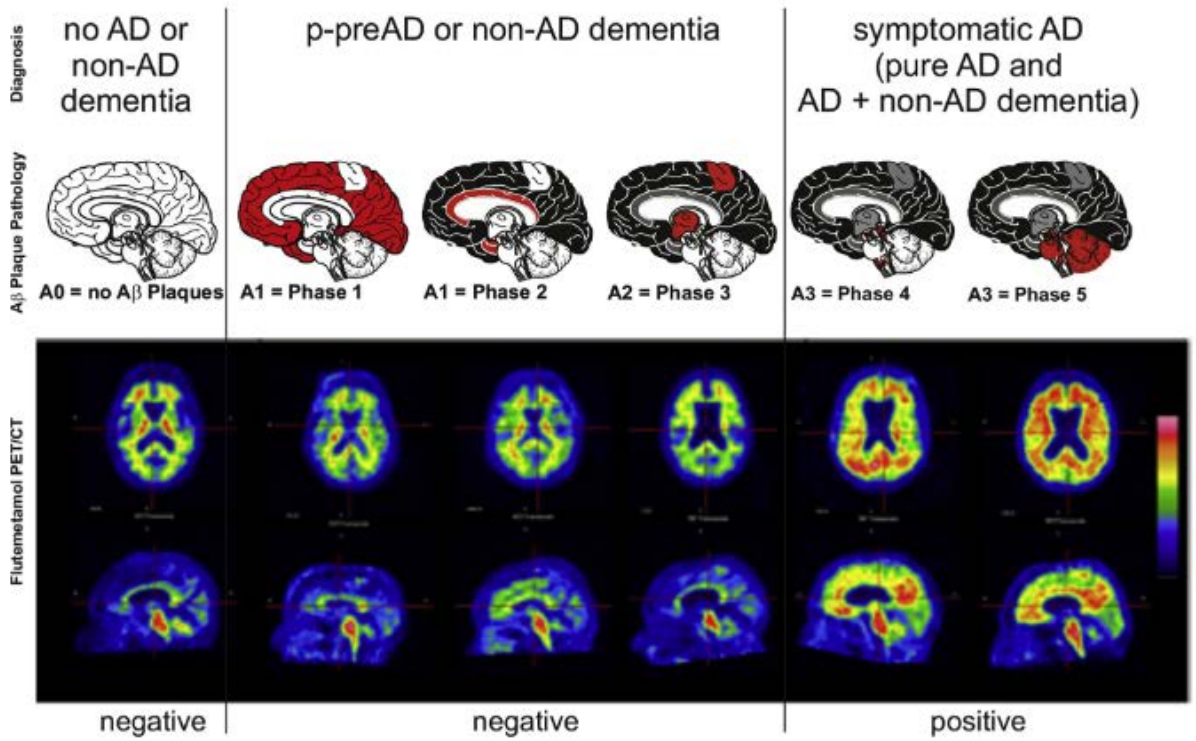
$C(t)$ = Activity Concentration in tissue
$C'(t)$ = Activity Concentration in reference region
DVR = distribution volume ratio (measure of specific binding)

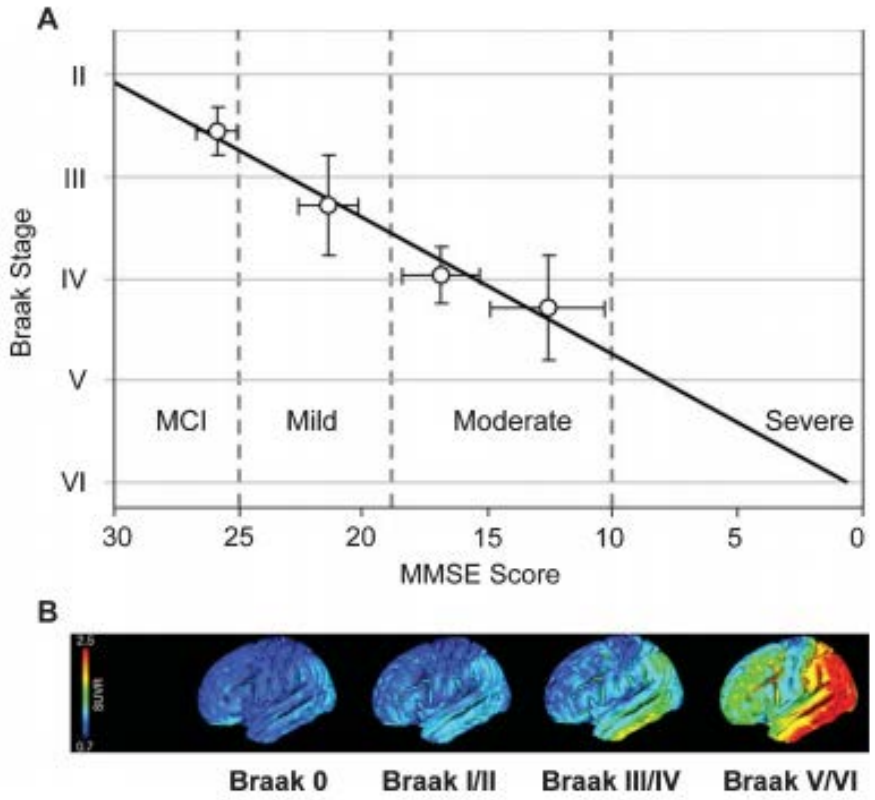
Dosimetry


Average of Individual Dose Estimates
0.2500
0.2000
0.1500
0.1000
0.0500
0.0000
Adrenals
Brain
Breasts
Gallbladder Wall
LLI Wall
Small Intestine
Stomach Wall
ULI Wall
Heart Wall
Kidneys
Liver
Lungs
Muscle
Ovaries
Pancreas
Red Marrow
Osteogenic Cells
Skin
Spleen
Testes
Thymus
Thyroid
Urinary Bladder Wall
Uterus
Total Body
Effective Dose Equivalent
Effective Dose
Nifene (mouse)
Nifene (no Voiding)
Nifene (Voiding)


Slice
Frame

Amyloid-β plaques, neurofibrillary tau tangles -> Alzheimer's Disease





Water -> Cerebral blood flow

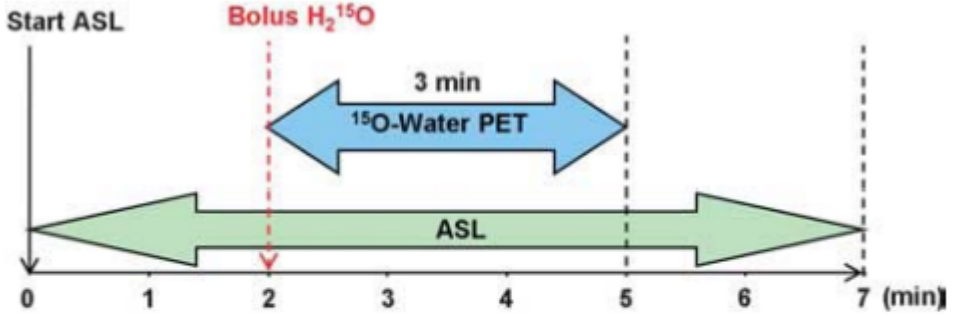


Figure 1. Timeline of the simultaneous measurement of [^{15}O]water PET and ASL in a 3T hybrid MR-PET scanner. ASL takes 7 minutes and PET takes 3 minutes. After a bolus injection of 555 MBq [^{15}O]water PET listmode data were recorded for 3 minutes. ASL, arterial spin labeling; MR, magnetic resonance; PET, positron emission tomography.

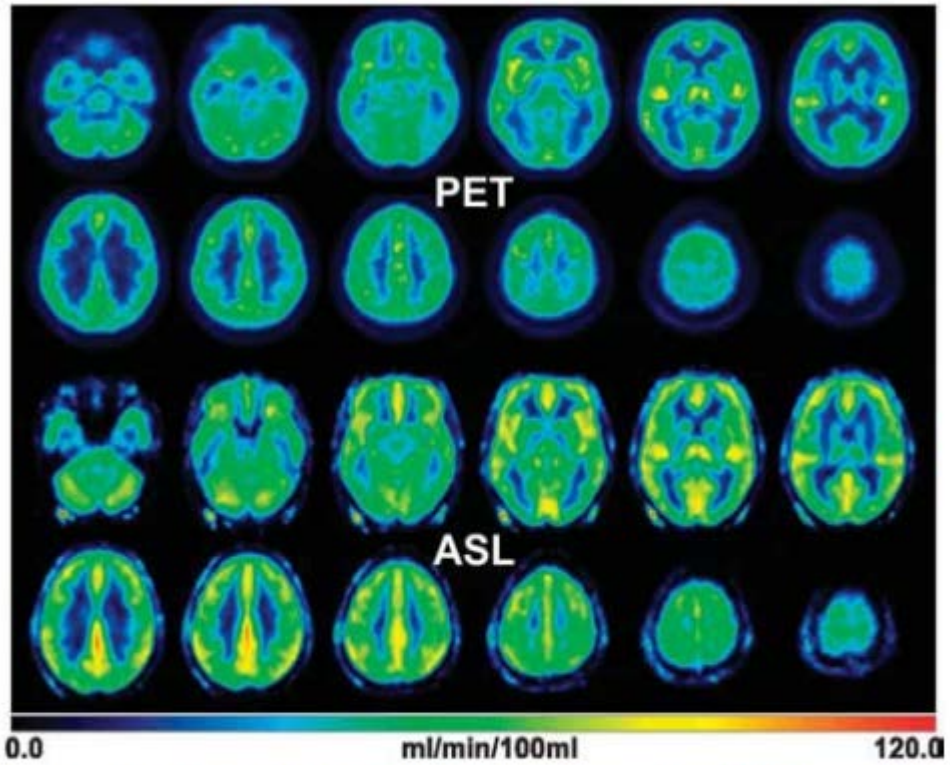
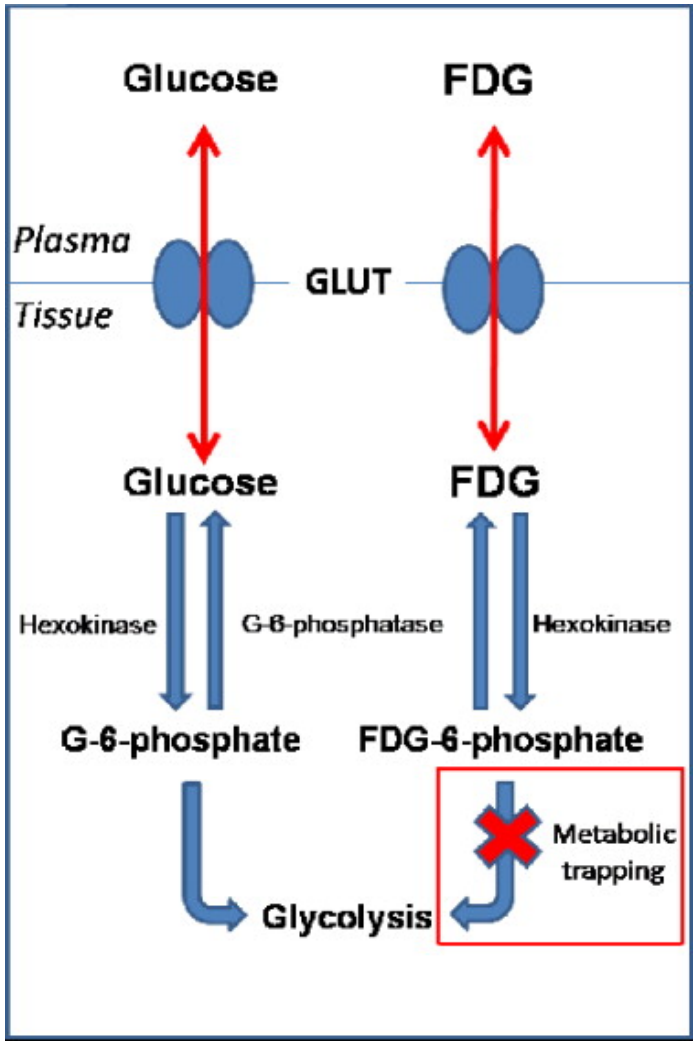


Figure 2. Averaged PET and ASL-CBF images ($n = 10$) after normalization into the MNI space. The CBF values from both methods show an agreement in the value range of 0 to 120 mL per 100 g per minute. The averaged whole-brain CBF from PET is 43.3 ± 6.1 mL and 51.9 ± 7.1 mL per 100 g per minute from ASL. ASL, arterial spin labeling; CBF, cerebral blood flow; MNI, Montreal Neurological Institute; PET, positron emission tomography.

Fluoro-deoxyglucose -> metabolism



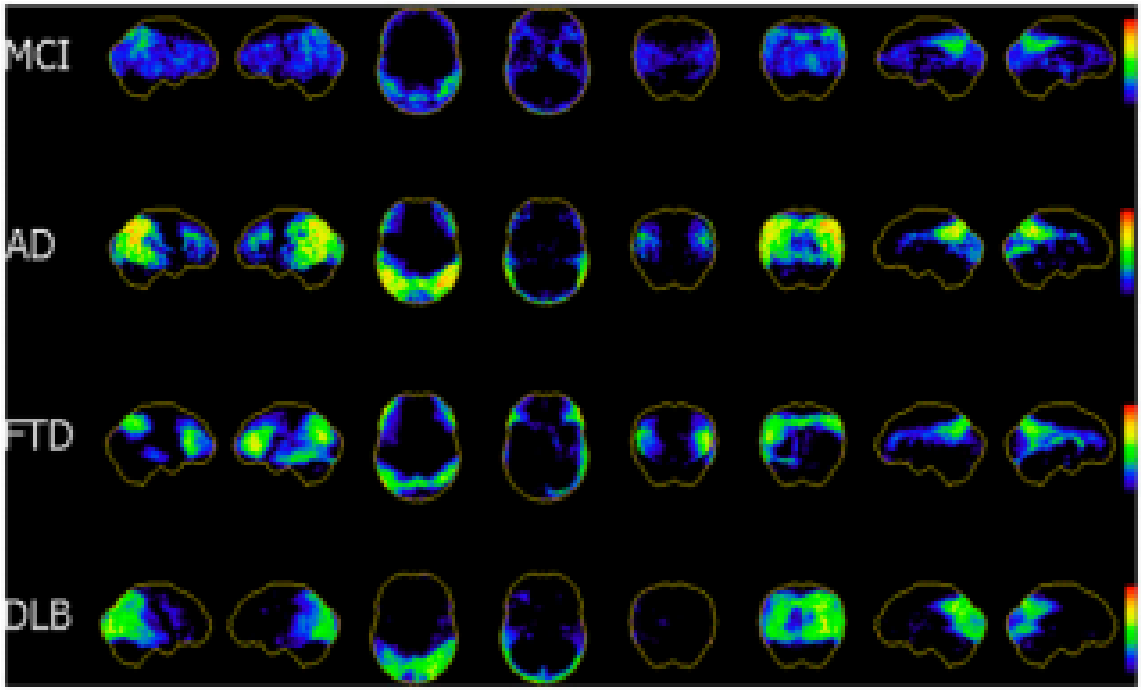
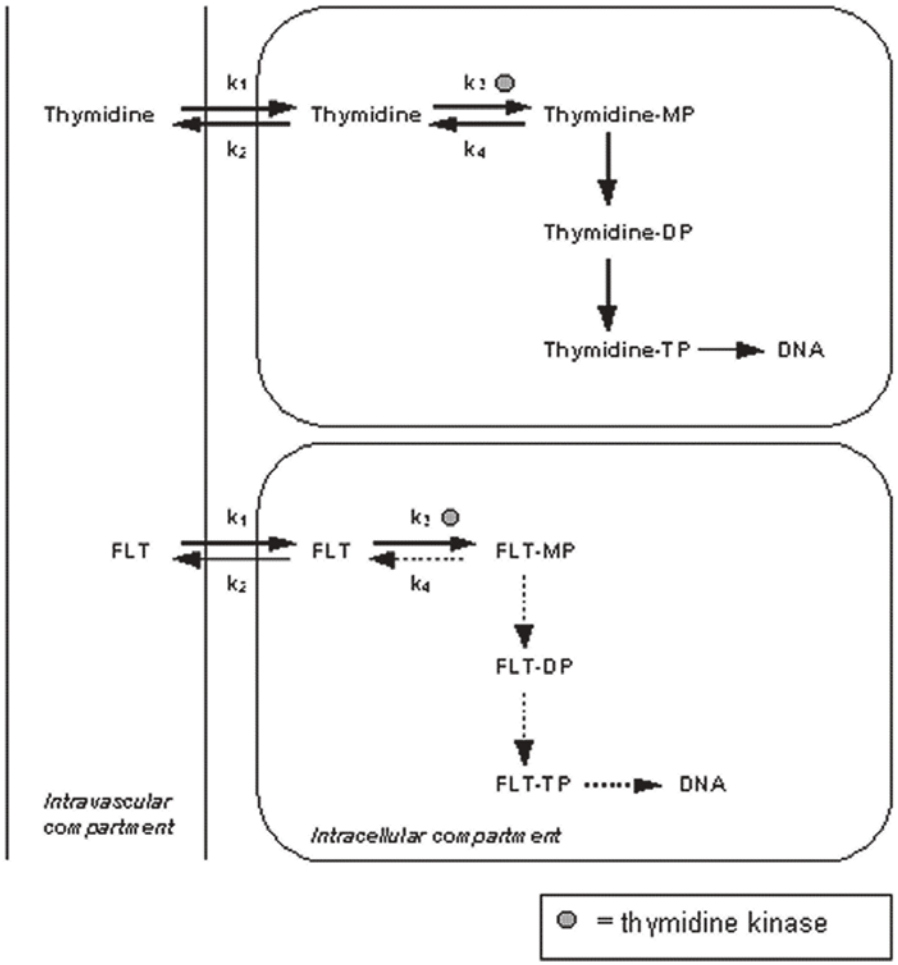


FIGURE 1. Representative cortical ^{18}F-FDG PET patterns in NL, AD, DLB, and FTD. 3D-SSP maps and corresponding *Z* scores showing CMRglc reductions in clinical groups as compared with the NL database are displayed on a color-coded scale ranging from 0 (black) to 10 (red). From left to right: 3D-SSP maps are shown on the right and left lateral, superior and inferior, anterior and posterior, and right and left middle views of a standardized brain image.

Fluoro-thymidine -> cellular proliferation

Fig. 1. Uptake mechanism of thymidine and [^{18}F]FLT. After uptake, [^{18}F]FLT is phosphorylated by TK_1 and trapped intracellularly. Incorporation in DNA is limited.



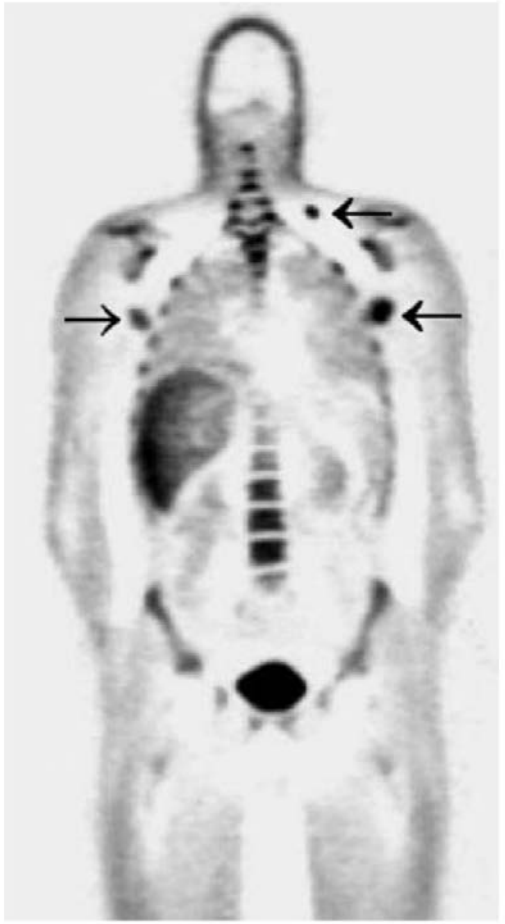
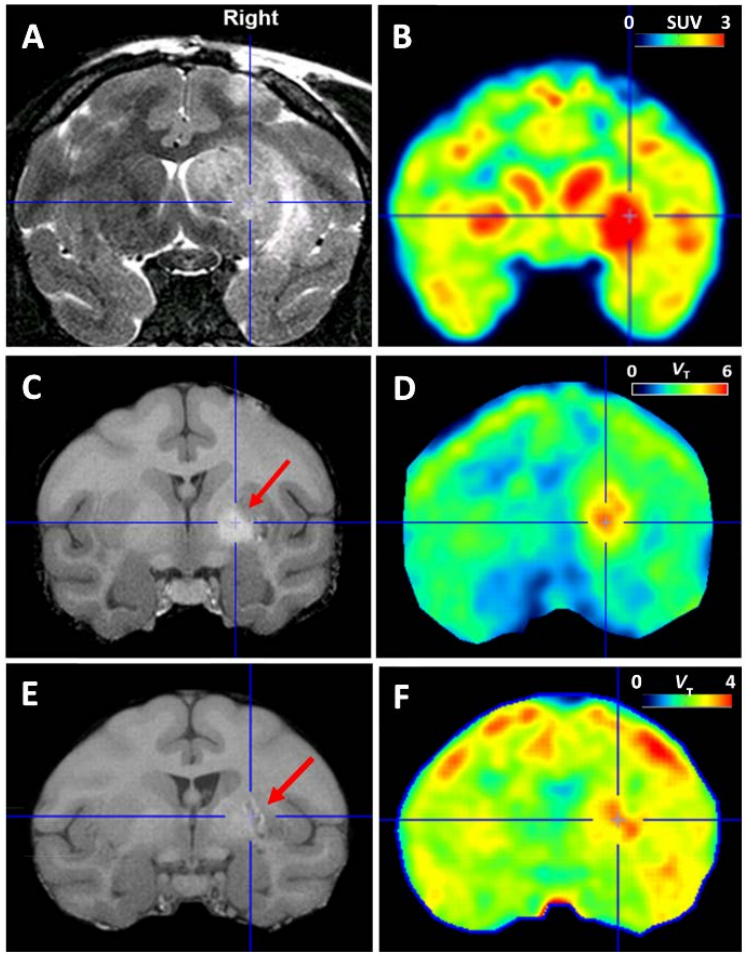


Fig. 5. Whole-body [^{18}F]FLT-PET of a patient with metastatic melanoma. This 34-year-old male patient presented with axillary node metastases 2 months after resection of a primary melanoma of the back. [^{18}F]FLT-PET showed uptake in both axillary regions and in a supraclavicular lymph node (*arrows*).

COX2/TSPO/etc -> Neuroinflammation



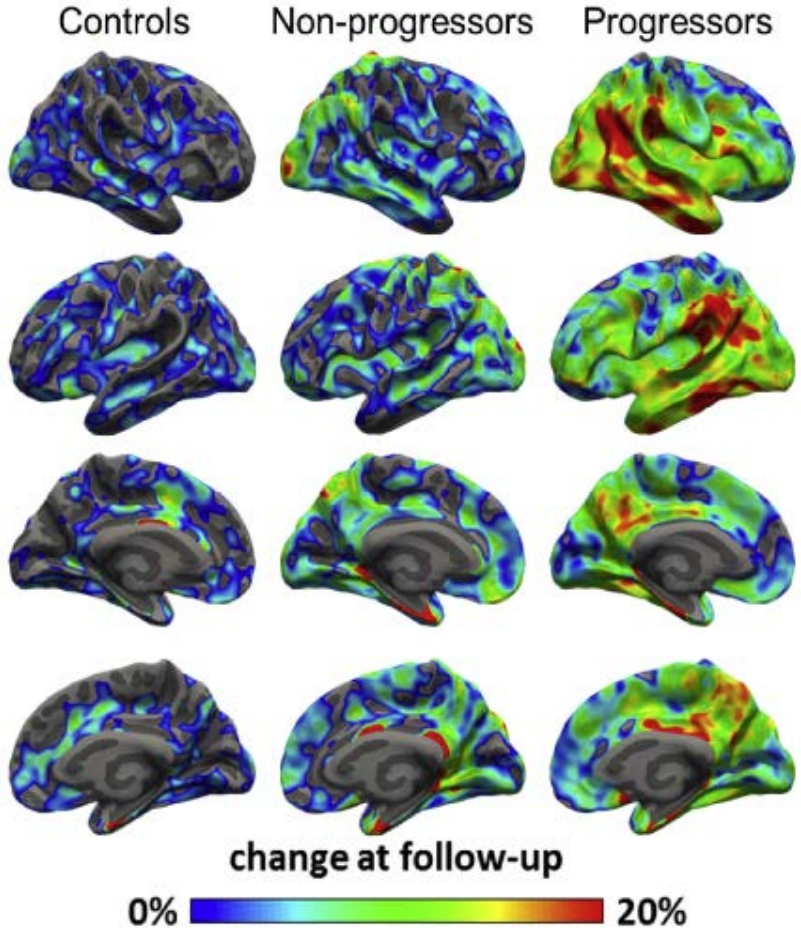


Fig. 4. Average percent change in ^{11}C-PBR28 binding from baseline, overlaid on semi inflated cortical surface. Patients who showed clinical progression during the study interval (n = 9) had greater increases in ^{11}C-PBR28 binding than nonprogressors (n = 5) or controls (n = 8), with the greatest change observed in inferior temporal and parietal cortices.

PET Limitations

- Ionizing radiation, but in trace (small) amounts, with dosimetry studies and Joint Radiation Safety Council approval (~3 per year) -> limited scanning in same individual
- Expensive, On-site radiochemical production for [11C] and limited delivery for [18F], Often requires FDA approval, Requires imaging center (with safety measures in place) and expertise -> limited accessibility
- Low spatial resolution -> needs to be paired with MRI
- Photon attenuation -> needs to be paired with CT

PET Strengths

- In vivo, (limited) repeat measurements across the lifespan
- Can be used when MRI cannot (metal implants, claustrophobia)
- Measure related to target density/causal pathology
  - Sensitivity and specific
  - Quantitative
  - Flexible targets given suitable tracer properties
- Spatial information critical for diagnosis
- Informs pharmacological intervention strategies
  - Theranostics

PET tracers emit _____ and PET scanners detect _____

- A. electrons, photons
- B. positrons, photons
- C. photons, electrons
- D. electrons, positrons

PET is typically used alone.

- A. True
- B. False

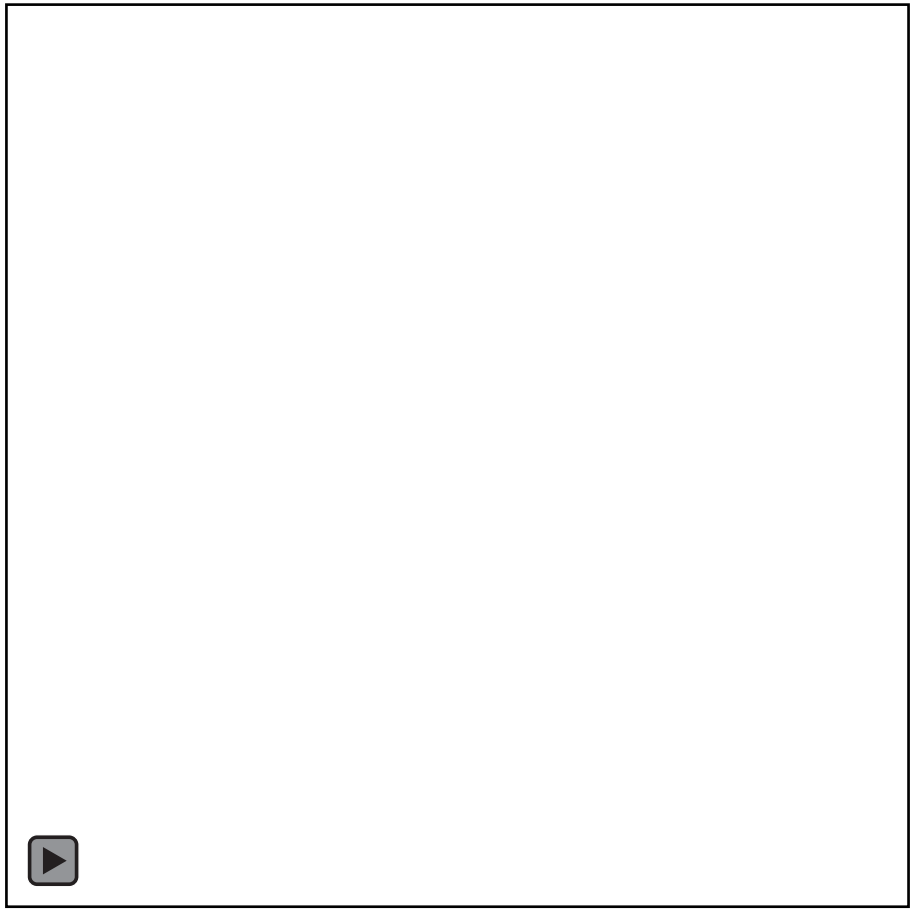
PET Processing Walkthrough

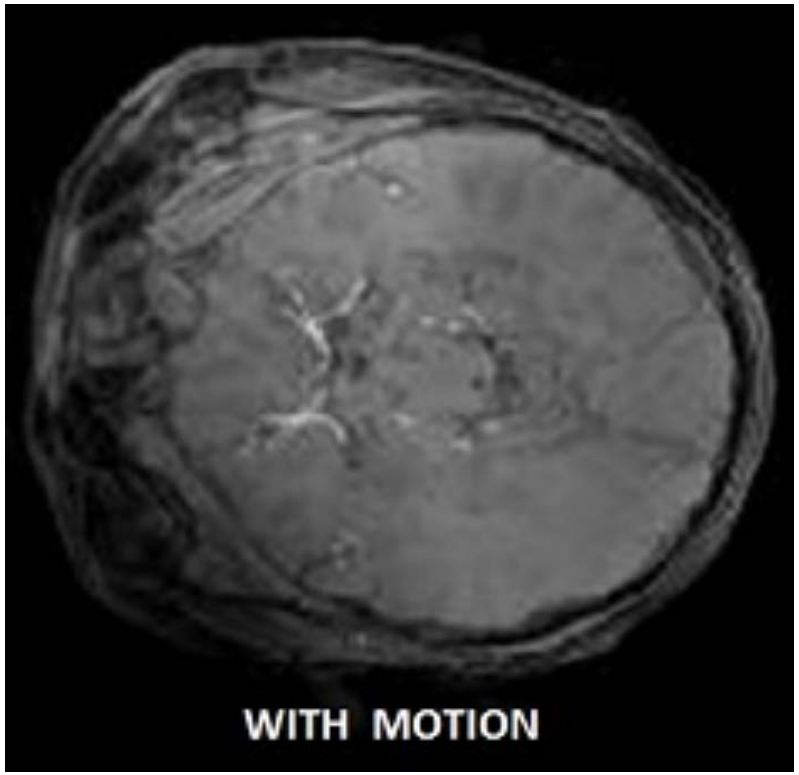
- DICOM vs Nifti: header/file size difference; de-identification/face scattering
- Motion correction: possible for PET (collected in frames), but not MRI (averaged over entire acquisition; new ultrafast sequences with enough SNR in each frame)
- Registration: origin/bounding box, match high contrast edges, interpolation
- Normalization: MRI (more information compared to PET) to atlas (group average)
- Group average images + voxelwise analysis

File type

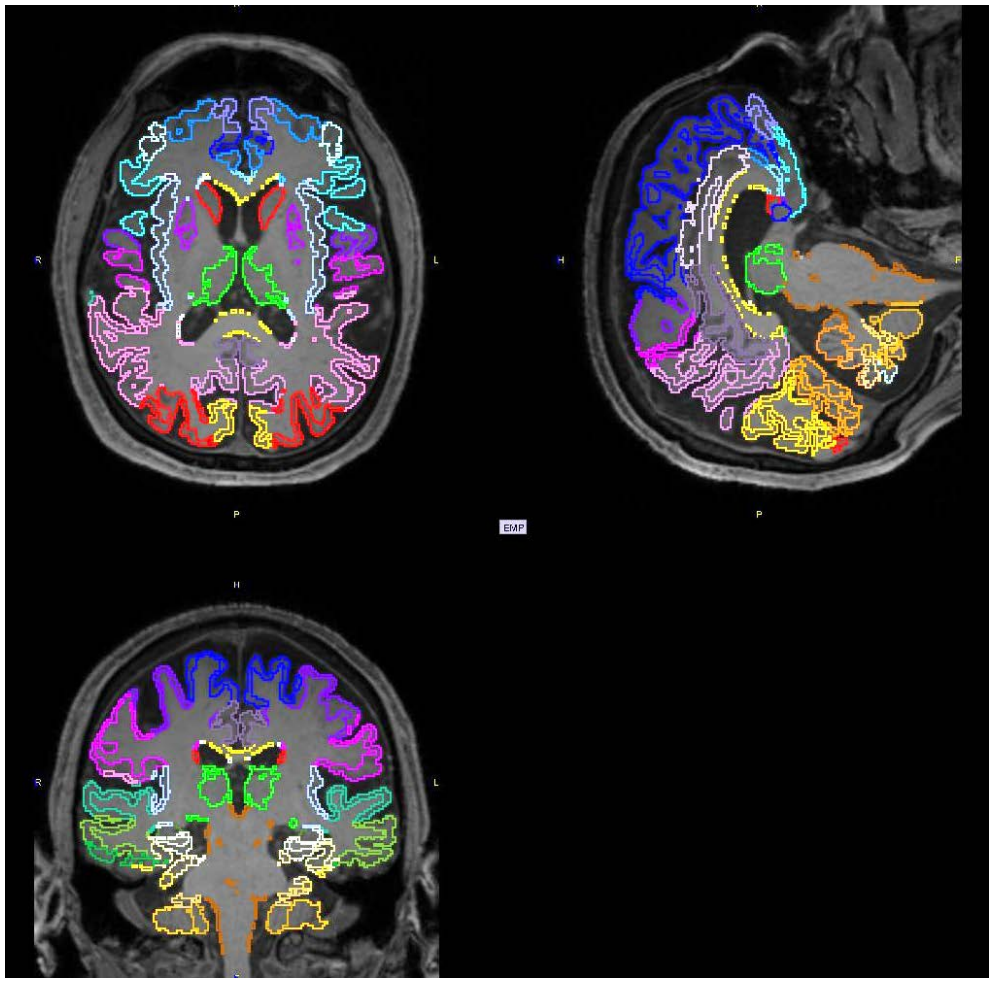
	DICOM	NIfTI
File extension		.nii .nii.gz
File representation	One slice	3D image
Header contains	many fields, protected health information, hospital-related data	Image meta-data, no patient information
Storage	Different directories per subject, more complex data structure	Different files can be in same directory

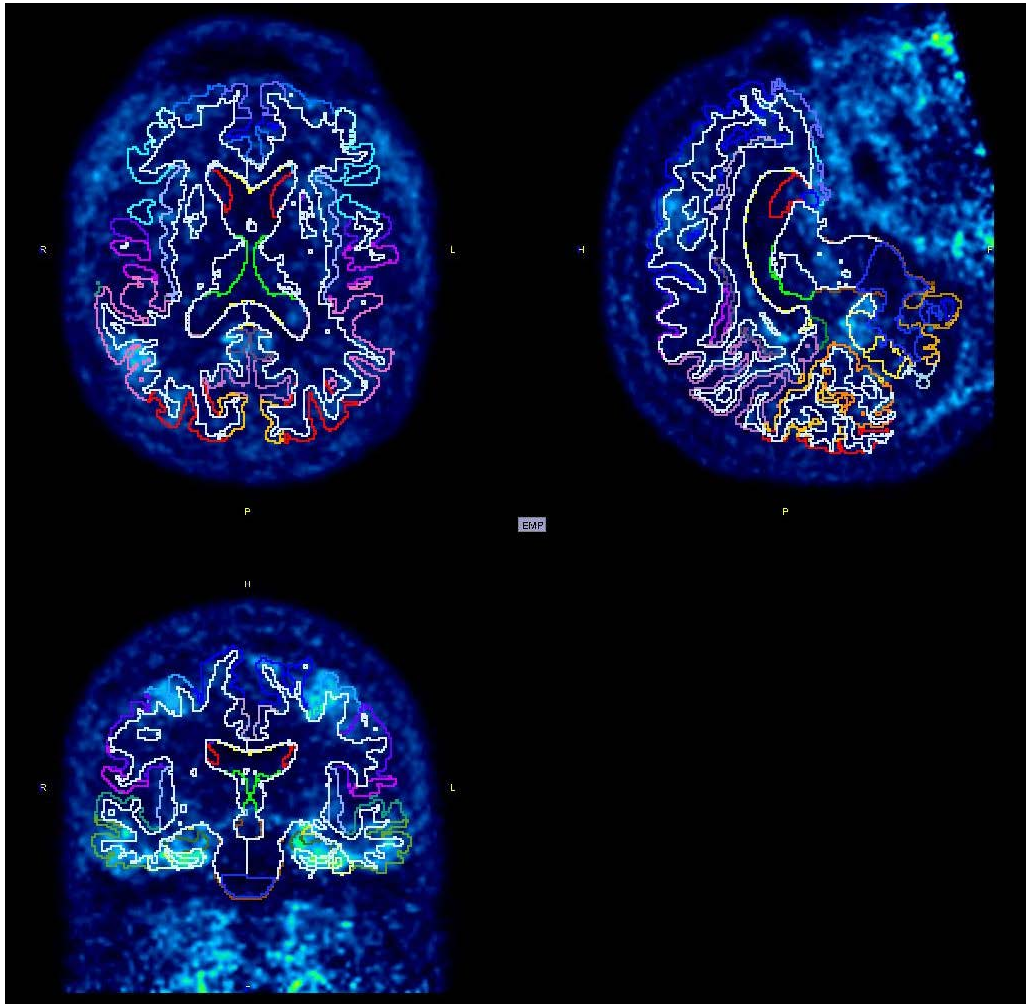
Motion correction



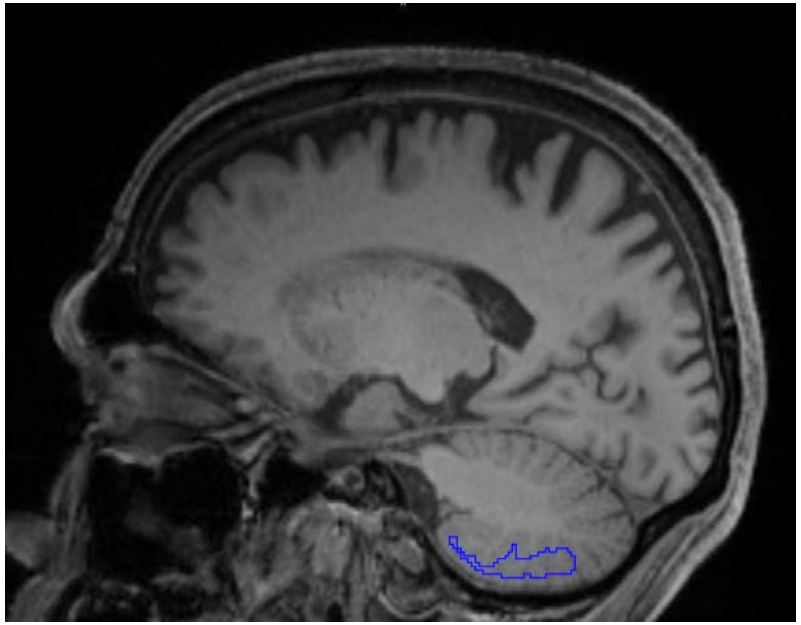


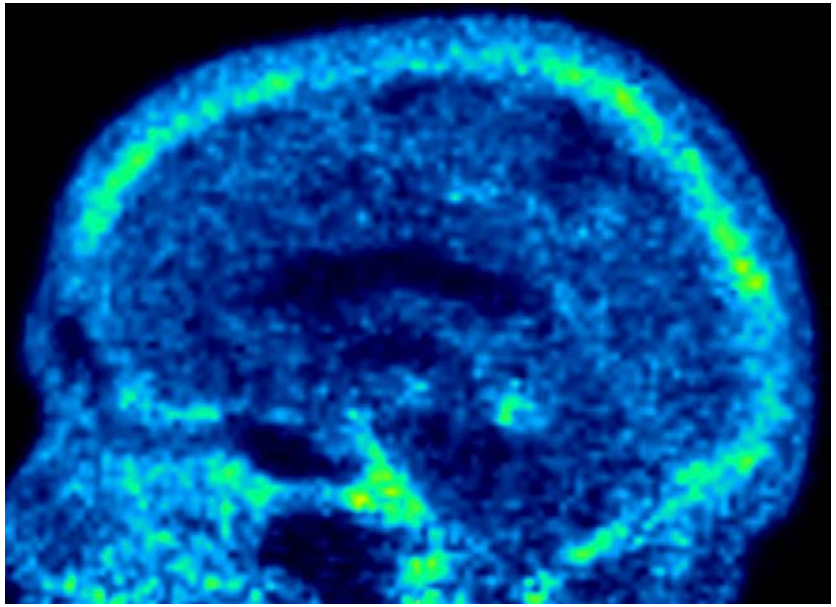
Anatomical Segmentation and Registration



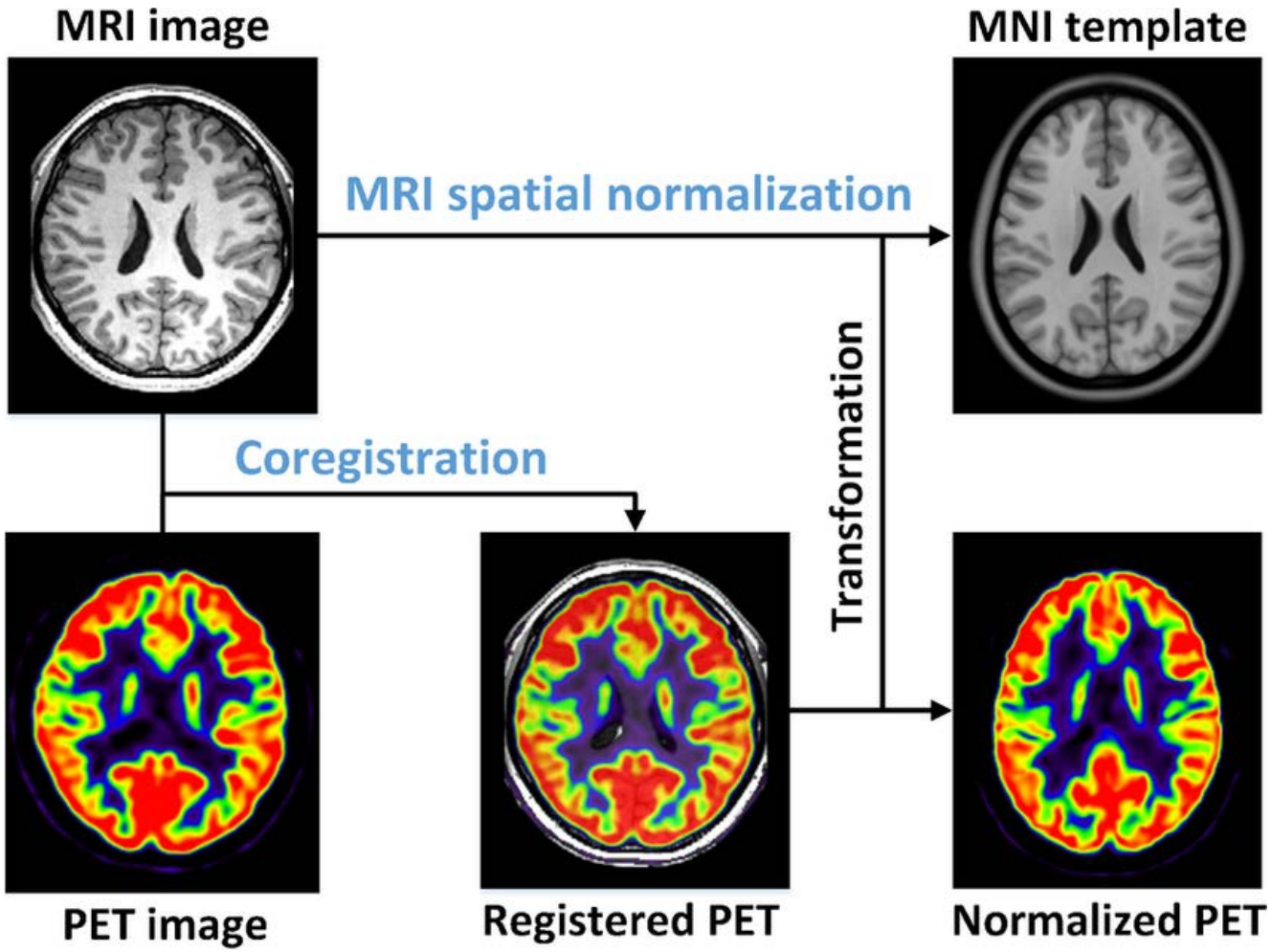


Reference Region



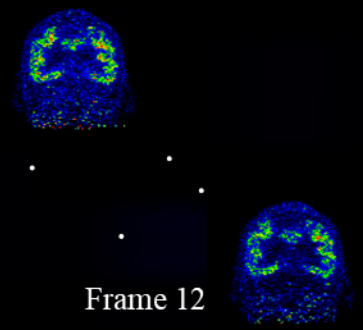


Spatial normalization



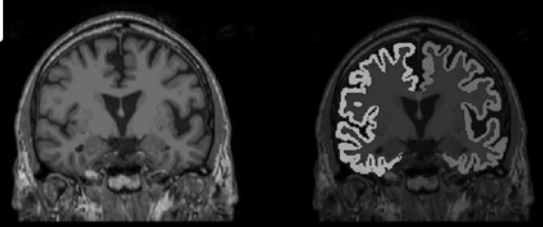
Processing Pipeline

1a



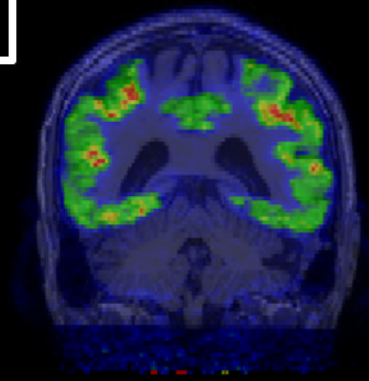
Realign PET frames and create mean PET image

1b



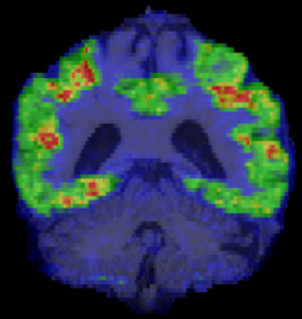
Automated anatomical segmentation of structural T1 MRI

2

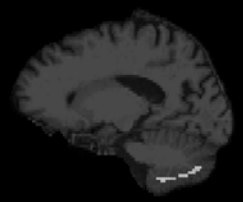


Co-register structural T1 MRI to mean PET image

3

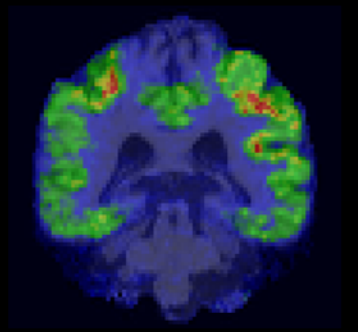


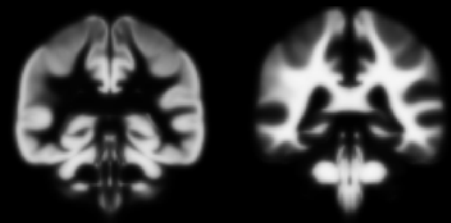
Calculate parametric SUVR image and skull strip



Inferior cerebellar gray matter as reference region

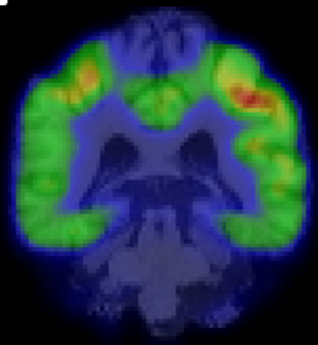
4





Normalize T1 MRI to T1 tissue-probability map in MNI space

5



Smooth for voxel-wise analysis

Resources

- SPM (Matlab toolbox): https://www.fil.ion.ucl.ac.uk/spm/doc/
- PMOD: https://www.pmod.com/web/?page_id=648
- MRIcron: https://www.nitrc.org/projects/mricron
- ITK snap: http://www.itksnap.org/docs/viewtutorial.php
- ImageJ: https://imagej.net/ij/docs/index.html
- FIJI: https://imagej.net/software/fiji/