SPECTROSCOPY IN NEURORADIOLOGY

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MR spectroscopy (MRS) measures the concentration of certain brain metabolites. This can be achieved by exploiting the minor differences in resonance frequency of these metabolites.

Because of its relative simplicity, proton spectroscopy is most generally used, but MRS of other nuclei, such as phosphorous or fluorine is also possible. The signal of water protons is immense compared with that of the other proton-containing brain metabolites. To appreciate those millimolar concentrations (the metabolic peaks of interest), the water signal has to be suppressed, for example by applying a saturation pulse with the exact frequency of water

COMMON NUCLEI USED IN SPECTROSCOPY

^{1}H e metabolites: 1-11 mmol/l in human body, high sensitivity

Problems: water suppression (110 mol/l !!), water peak is high and obscure other metabolites

^{31}P ~ 10 mmol/l, important in the evaluation of energy metabolism

^{13}C fundamental atom of organic molecules, low senstivity
=> necessary to add the tissue with the isotop ^{13}C

METABOLITES

^{1}H e metabolites

- N-acetil aspartate (NAA)
- Creatine (Cr)
- Choline (Cho)
- Lactate
- Myo-inositol (mI)
- Glutamate (Glu), Glutamine (Gln)
- Gamma-amino butirric acid (GABA)
- Lipids
- Amino acid (valin, taurin etc)

The results obtained by means of MRS can be divided into two categories: specific abnormalities indicating a unique disease condition or changes in the ratios of the normal metabolites.

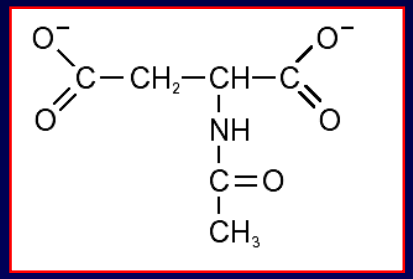
METABOLITES

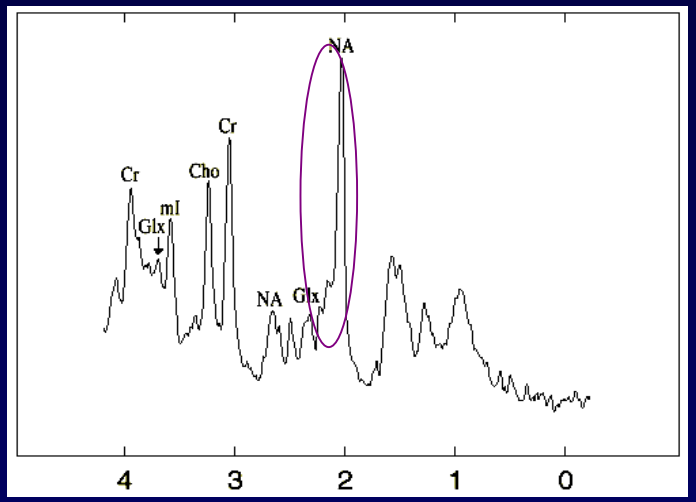
POSITION OF METABOLITES in THE SPECTRUM (ppm)

mI	Cho	Cr	Glx	NAA	Lac
3.56	3.2	3.95 3.0	3.7 - 3.9 2.1 - 2.5	2.0	1.3

METABOLITES

N-acetil aspartate





2-2.5 ppm

METABOLITES

N-acetil aspartate

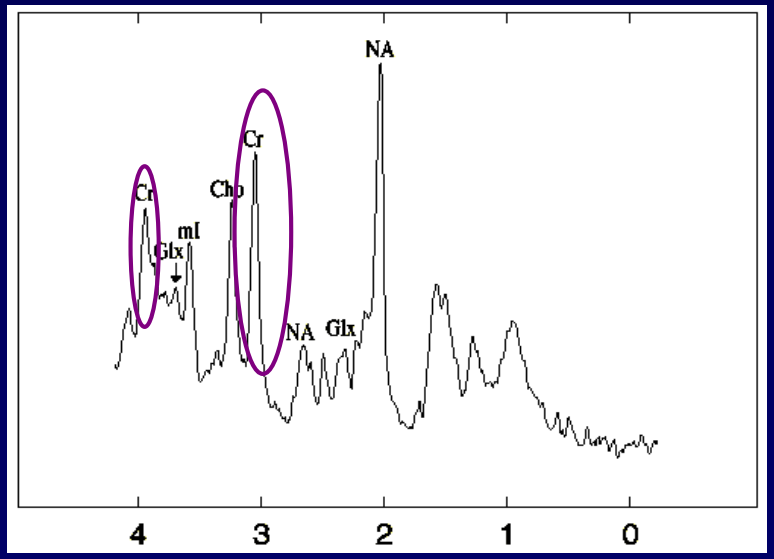
- Neuronal marker, the concentration of NAA varies with age and different brain regions
- Role in the syntesis of fatty acids during myelination
- Carbon transporter from mitochondrial reserve
- Precursor of N-acetilaspartilglutammate (neurotransmiter)
- Possible role in the control of osmotic pressure

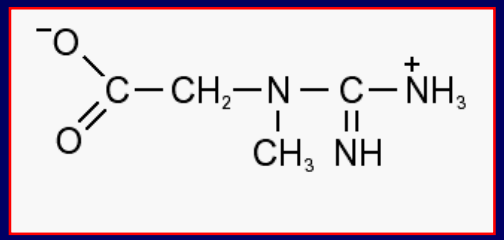
→ Neuronal loss or dysfunction

METABOLITES

Creatine

- Important in storage and transfer of energy
- Tends to be maintained at a relatively constant level, and is predominantly used as a internal standard

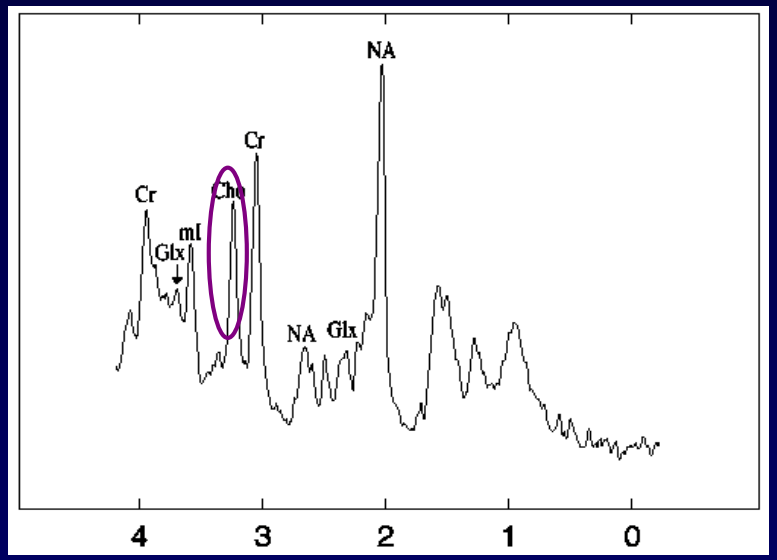


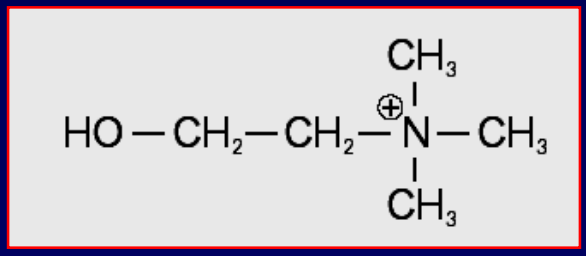


3 (creatine) - 4 (fosfocreatine) ppm

METABOLITES

Choline





3. 2 ppm

METABOLITES

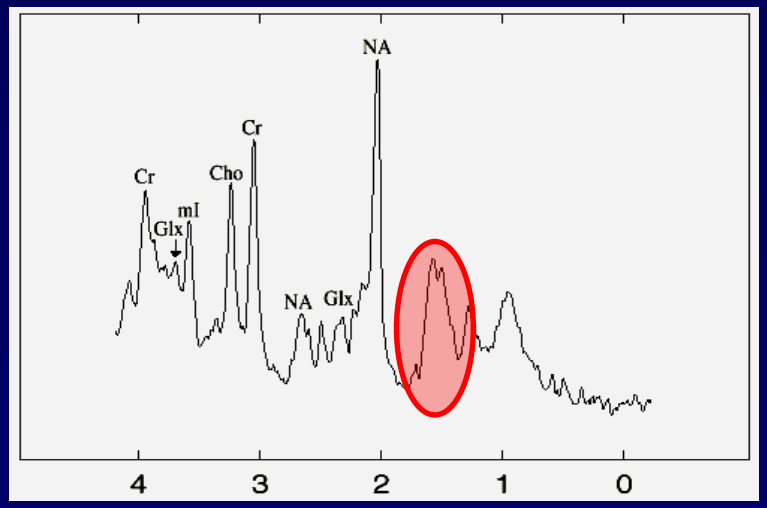
Choline

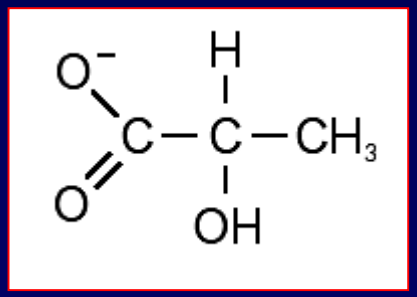
- **Precursor to acetylcholine and cell membrane components.**
- **The peak includes phosphocholine , glycerophosphocoline and free coline (minor contribution)**
- **Marker of cellular membrane turnover, is elevated in neoplasms, demyelination and gliosis.**

METABOLITES

Lactate

- Marker of an anaerobic metabolism
- Concentration < 1 mM
- Correlate to acidosis, increase in necrotic areas, abscesses etc



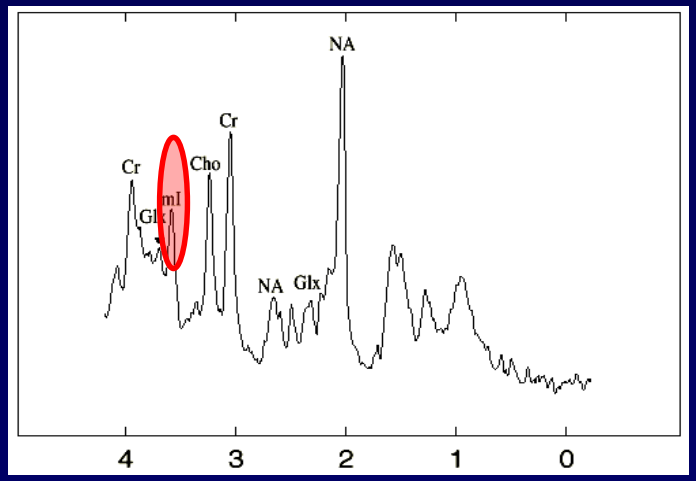


1.3-1.5 ppm

METABOLITES

Myo-innositol

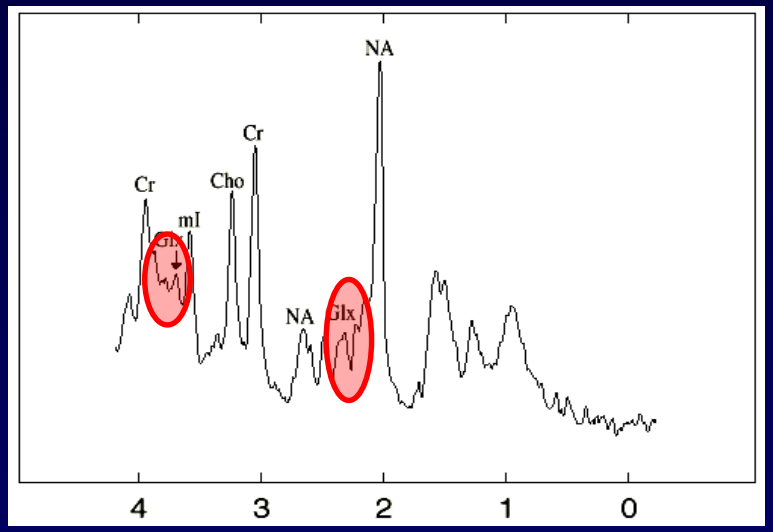
- Myo-innositol (mainly) and myoinnositol phosphate
- Glial marker
- Elevated in gliomas

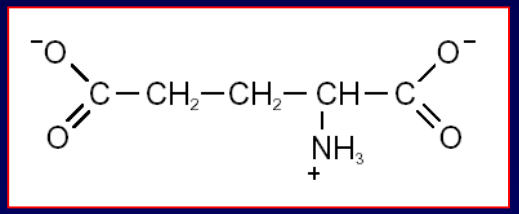


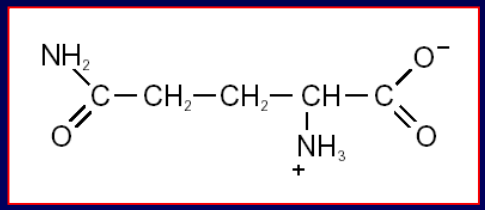
3.54 ppm

METABOLITES

Glutamate-Glutammine







2.1, 2.35, 2.45, 3.75 ppm

METABOLITES

Glutamate - Glutammine

- **Glutamate:**

  neurotransmitters, GABA precursor, involved in Krebs cycle, mithocondrial metabolism, fatty acid syntesis

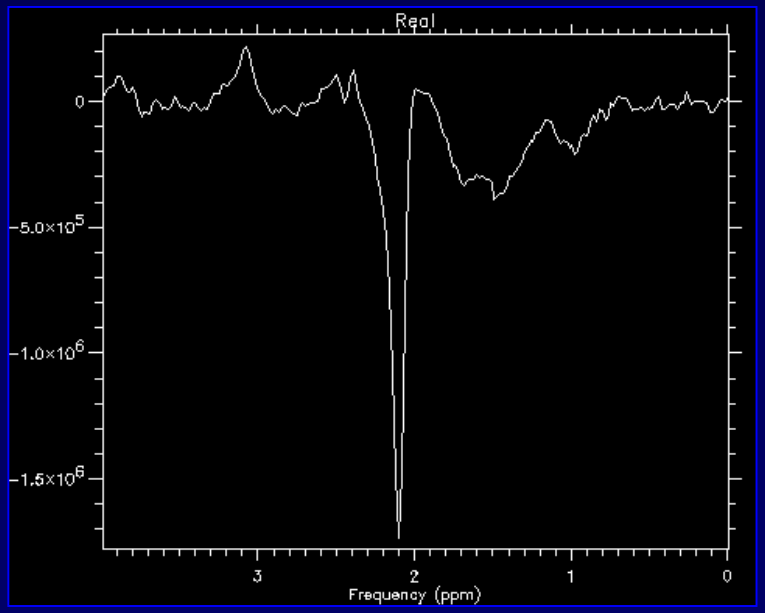
- **Glutammine:**

  modulate neurotransmitter's activity, possible role in the detoxification

METABOLITES

GABA-ammino-butirric acid

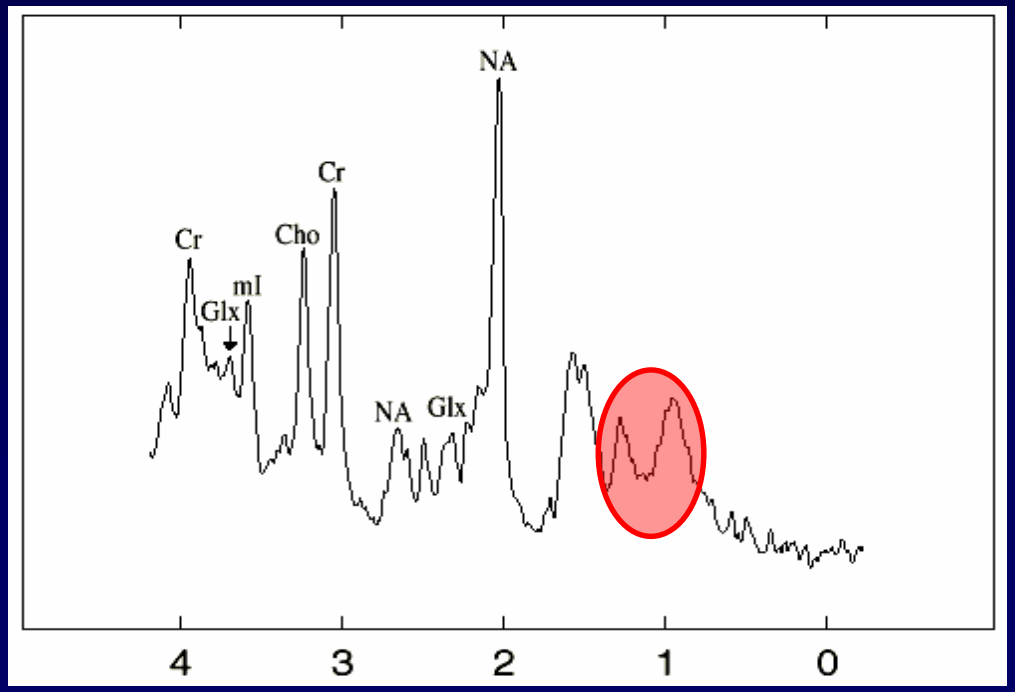
- **Particular sequences are nedeed**
- **Most important inhibitory neurotransmitter in the cortex**



METABOLITES

Lipids

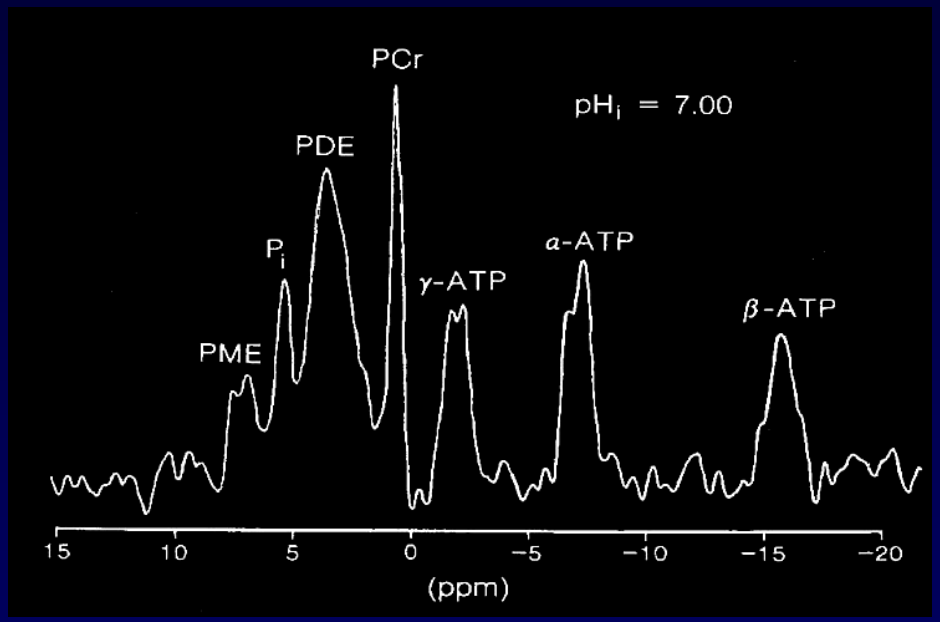
- **Not visible in conventional sequences**
- **Fatty acids and triglycerides, the peak is related to metylene and metyl group**



0.9-1.2 ppm

PHOSPHORUS SPECTROSCOPY (^{31}P)

Metabolites



ADENOSINE 5’ -DIPHOSPHATE (ADP) - stored form of energy

ADENOSINE TRIPHOSPHATE (ATP) - form of energy.

INORGANIC PHOSPHATE (Pi) - breaks down ATP.

PHOSPHOCREATINE (Pcr) - energy buffer.

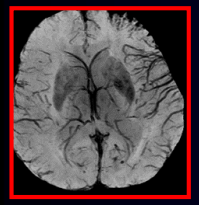
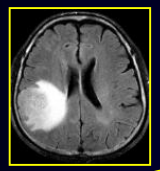
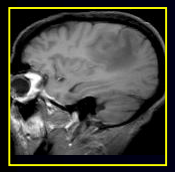
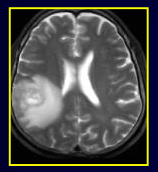
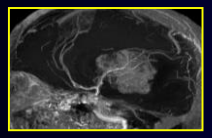
SPECTROSCOPY IN NEURORADIOLOGY

- **complements magnetic resonance imaging (*MRI*) as a non-invasive means for the characterization of tissue.**

- **Tumors**
- **Multiple sclerosis**
- **Inflammation**
- **Epilepsy**
- **Degenerative disease**
- **Leukodystrophy**

- **Aging brain**

Tumors

tumor characterization

MRI st

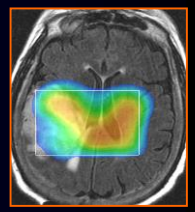
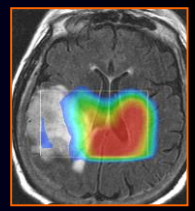
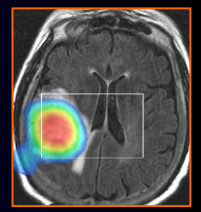
histopatologic markers

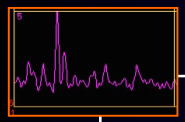
* = significative correlation
NS = non significative

cellularity

proliferative index

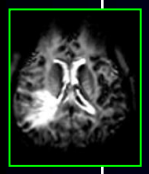
necrosis



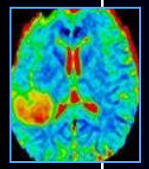
MRS

NAA * **Cho** * **Cr** NS **lipidis**



PWI

rCBV



DWI

ADC

* * ? * NS -* +* NS +* -*

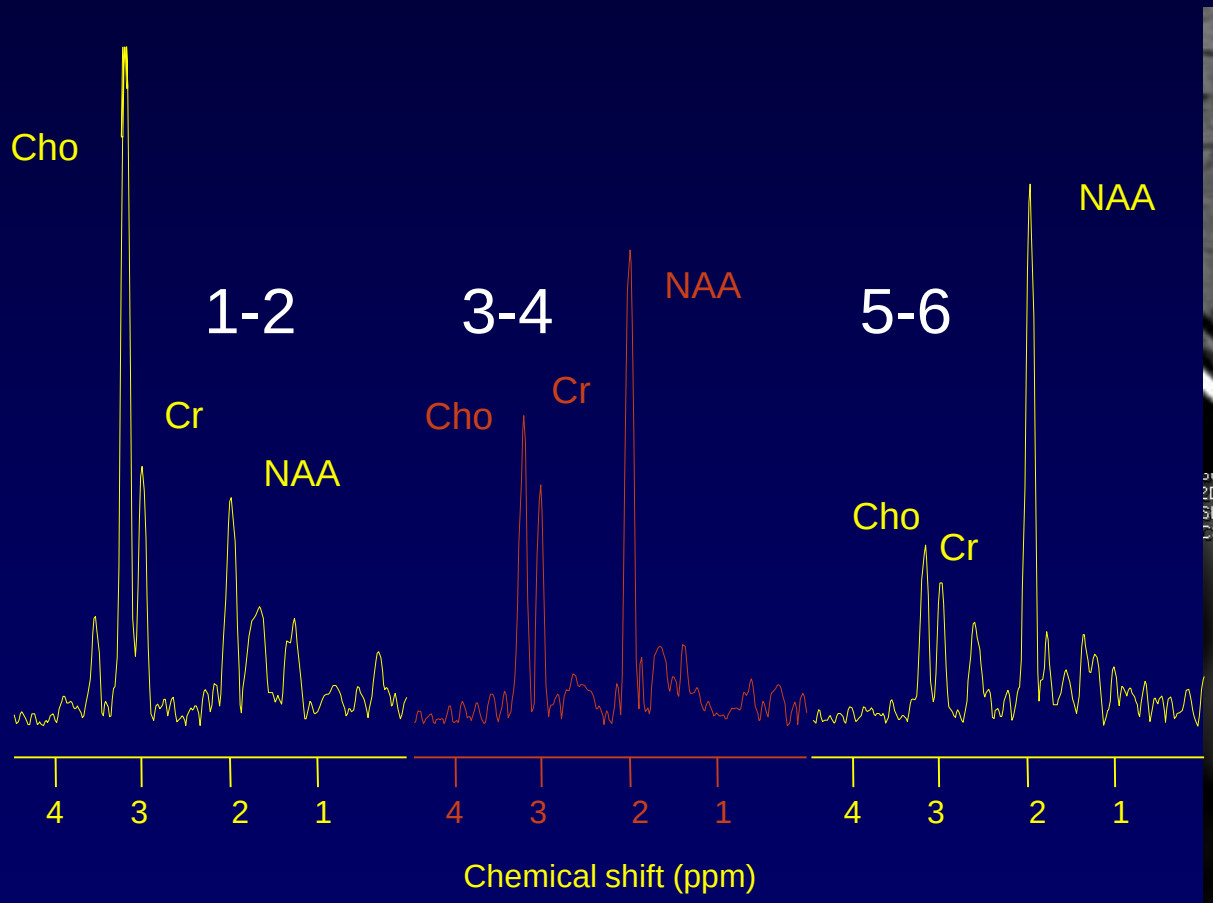
Tzika et al, **Neuroradiology 2003** *(modif.)*
Courtesy of T. Popolizio

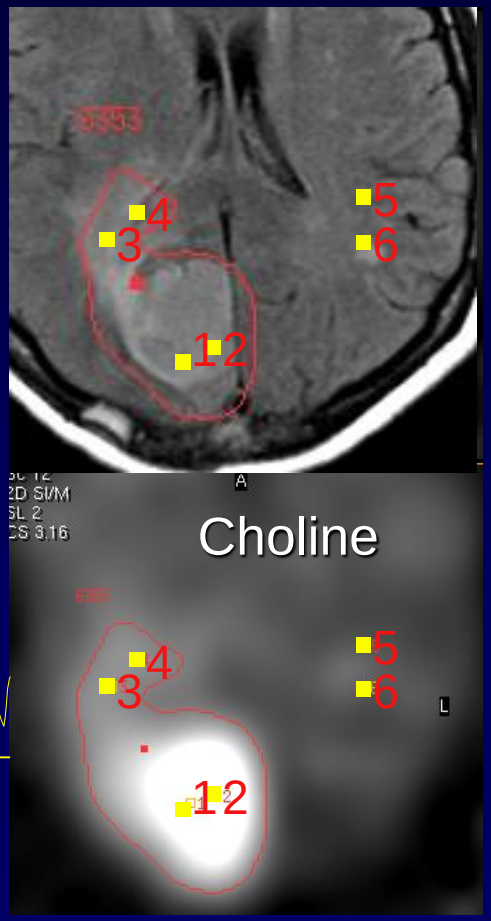
Tumors

- ↑ Cho – tumors with rapid growth, solid portion of the tumor
- ↓ Cho – due to necrosis in the central portion of tumors.
- ↓ NAA – tumor displaced or destroy neurons (non neuronal tumors)
- ↓ Cr/Pcr – due to alteration of energy state in neoplastic tissue
- ↑ Lac – anaerobic glycolysis

→ **Diagnosis and differential diagnosis**

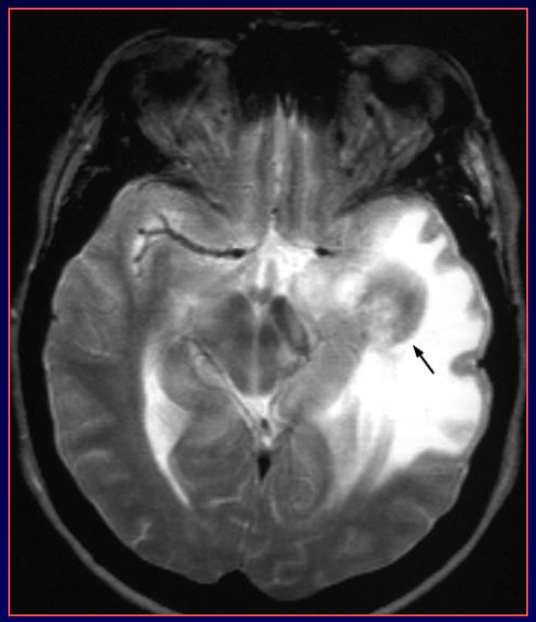
Tumors

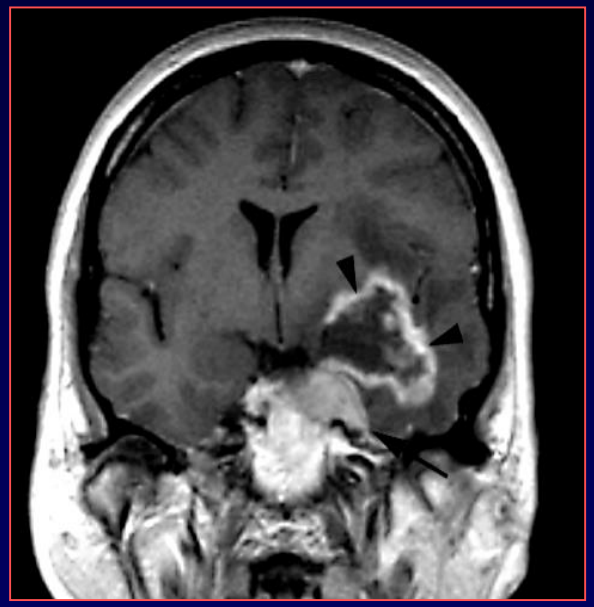

Cho
Cr
NAA
1-2
Cho
Cr
NAA
3-4
Cho
Cr
NAA
5-6
4
3
2
1
Chemical shift (ppm)

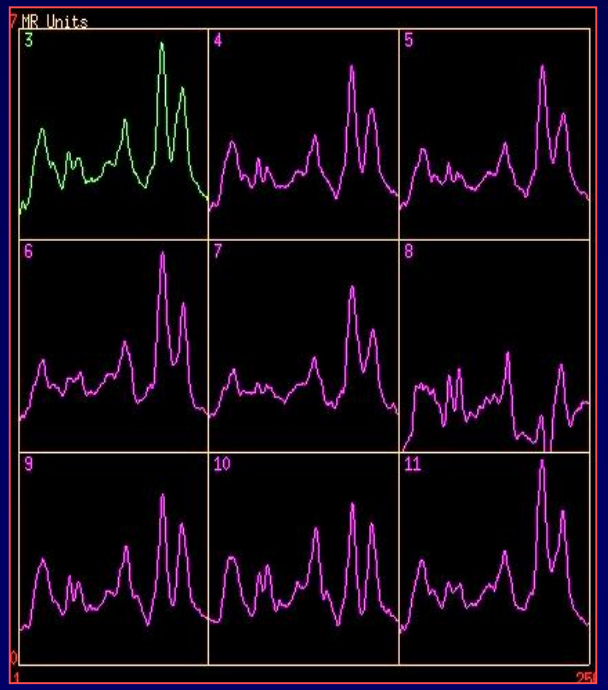

Choline
4
3
5
6
1
2

Tumors: DD

RADIONECROSIS Vs RECURRENCE

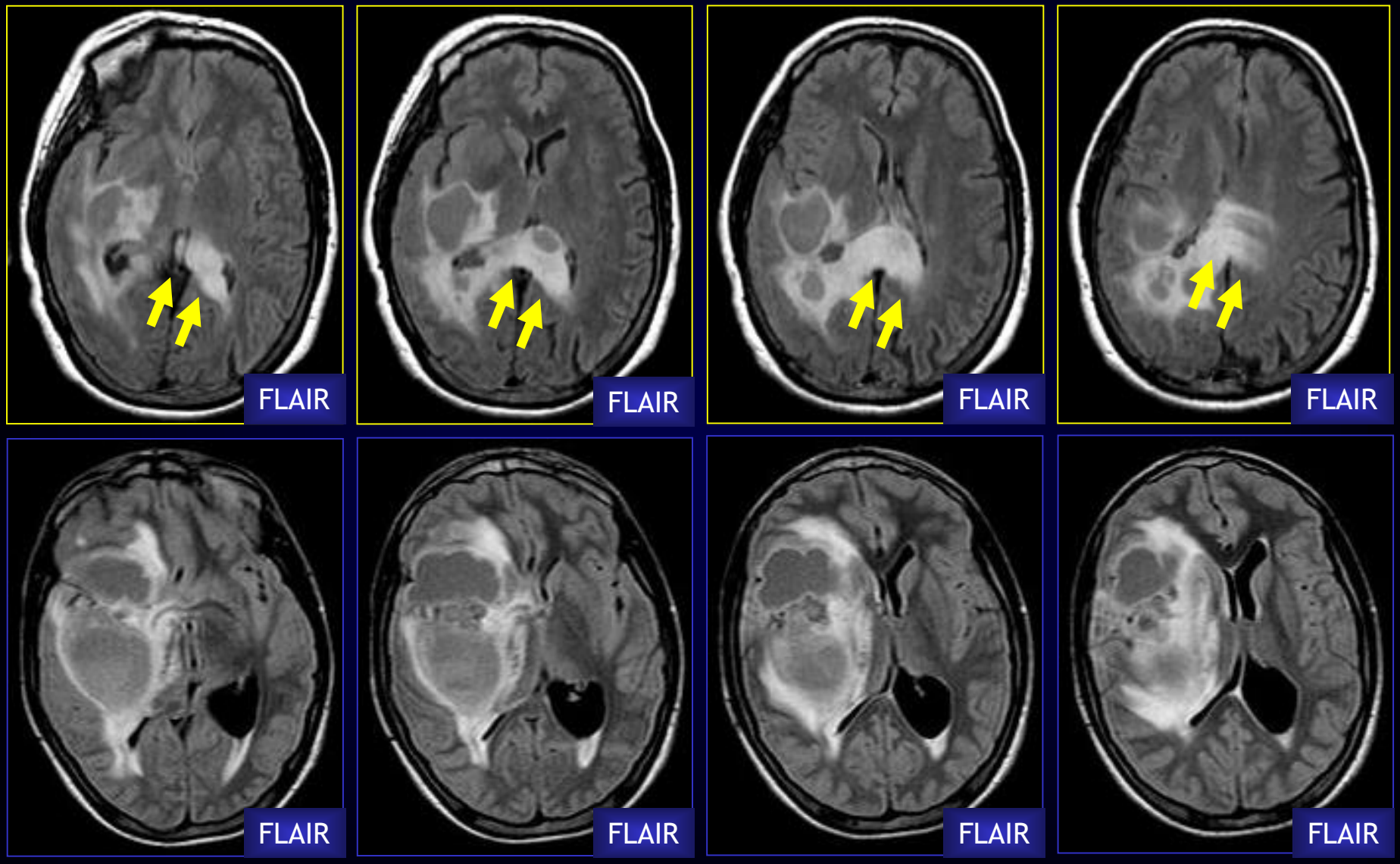




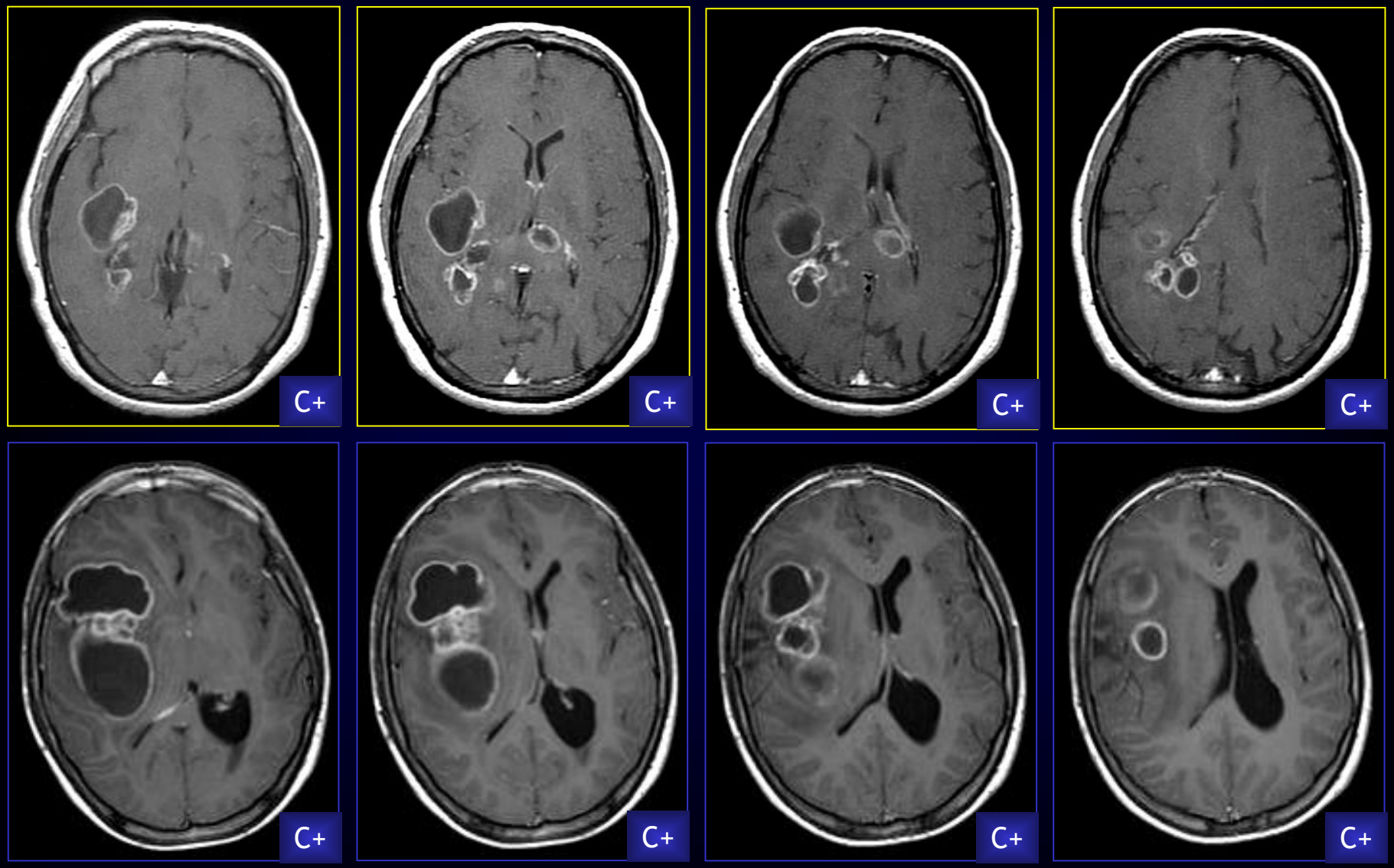


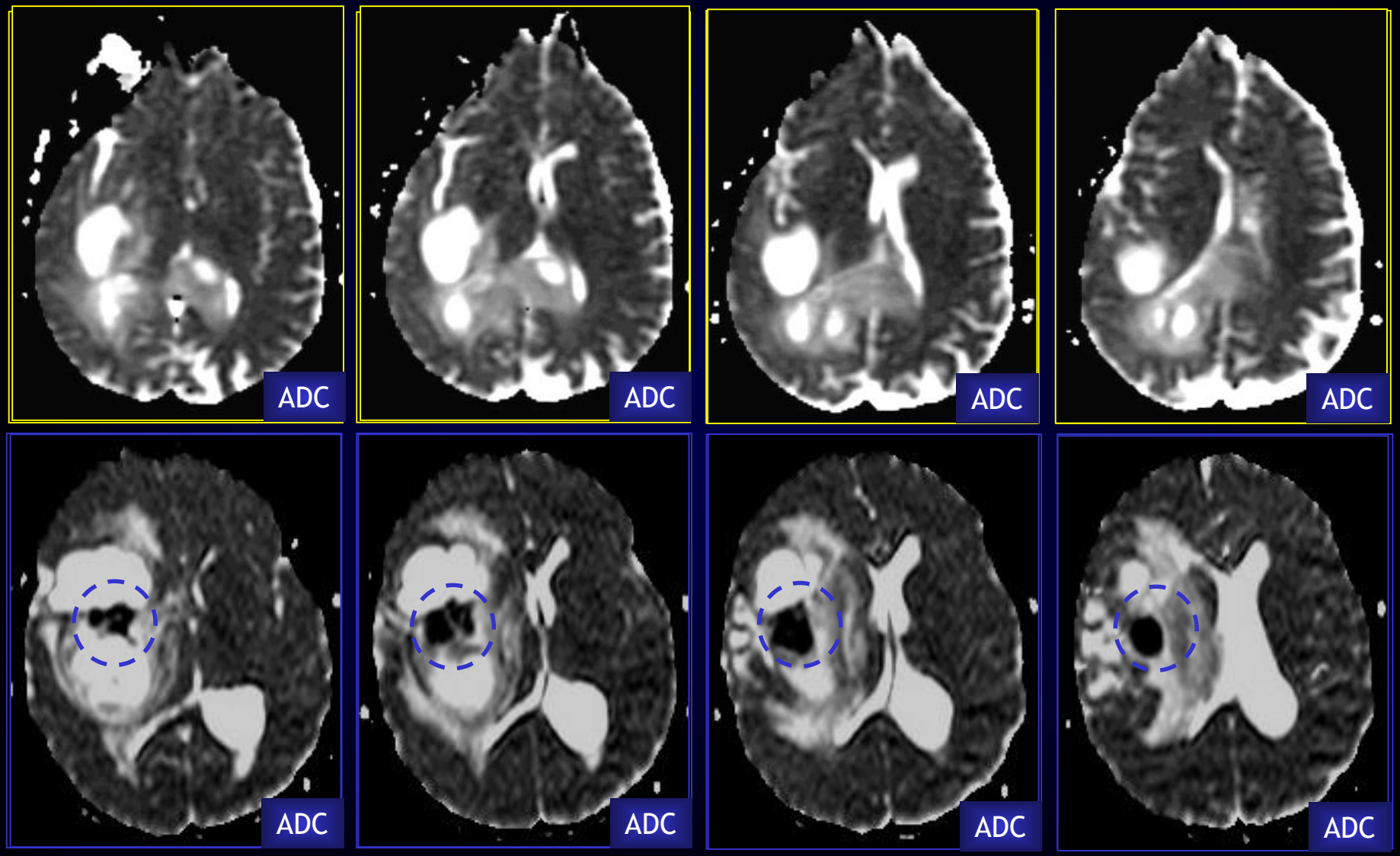
Radionecrosis

TUMOR vs……

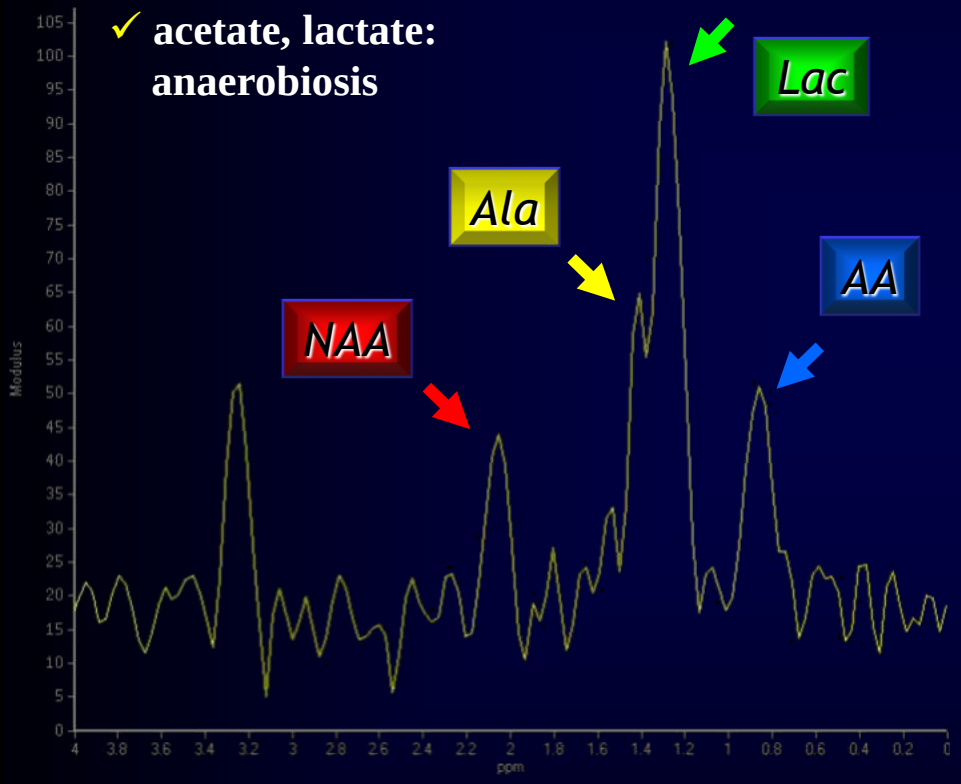


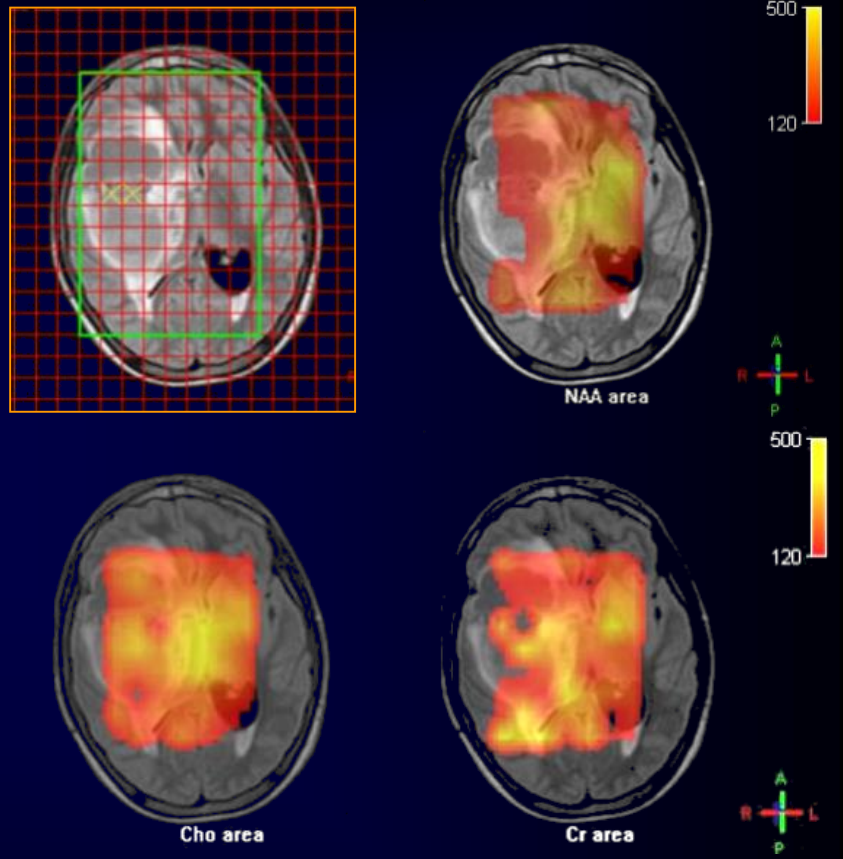
Courtesy of T. Popolizio


C+
C+
C+
C+
C+
C+
C+
C+


ADC
ADC
ADC
ADC
ADC
ADC
ADC
ADC

- ✓ **aminoacids (alanin, valin): due to proteolytic enzyme**
- ✓ **acetate, lactate: anaerobiosis**



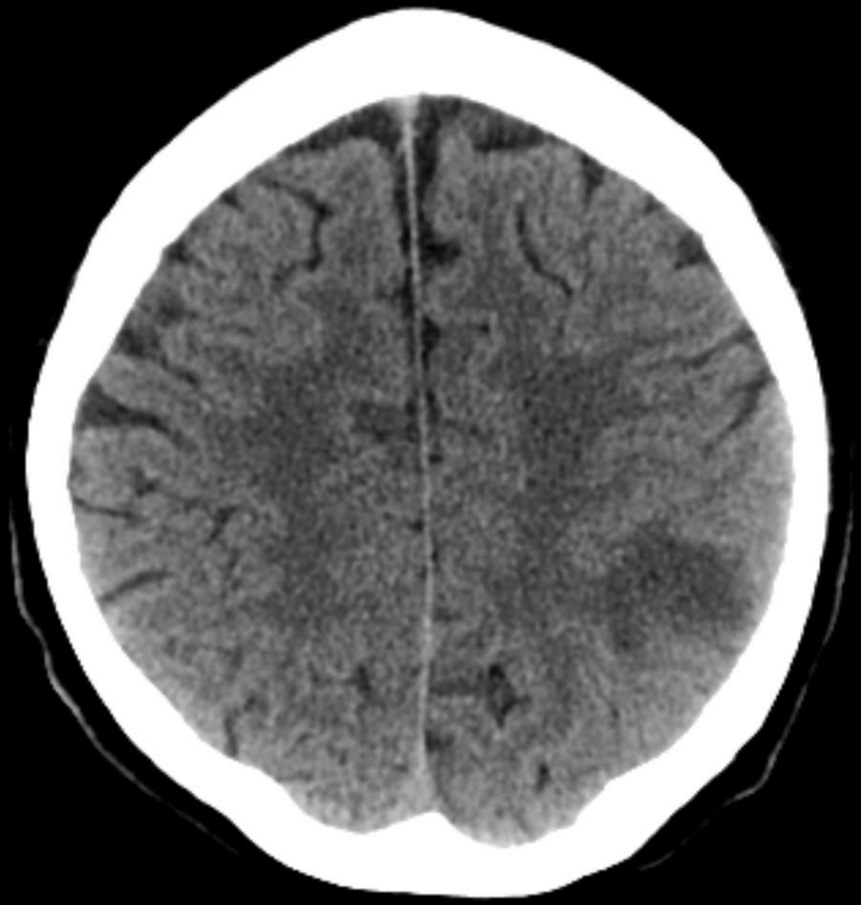


KLEBSIELLA PNEUMONIAE abscess

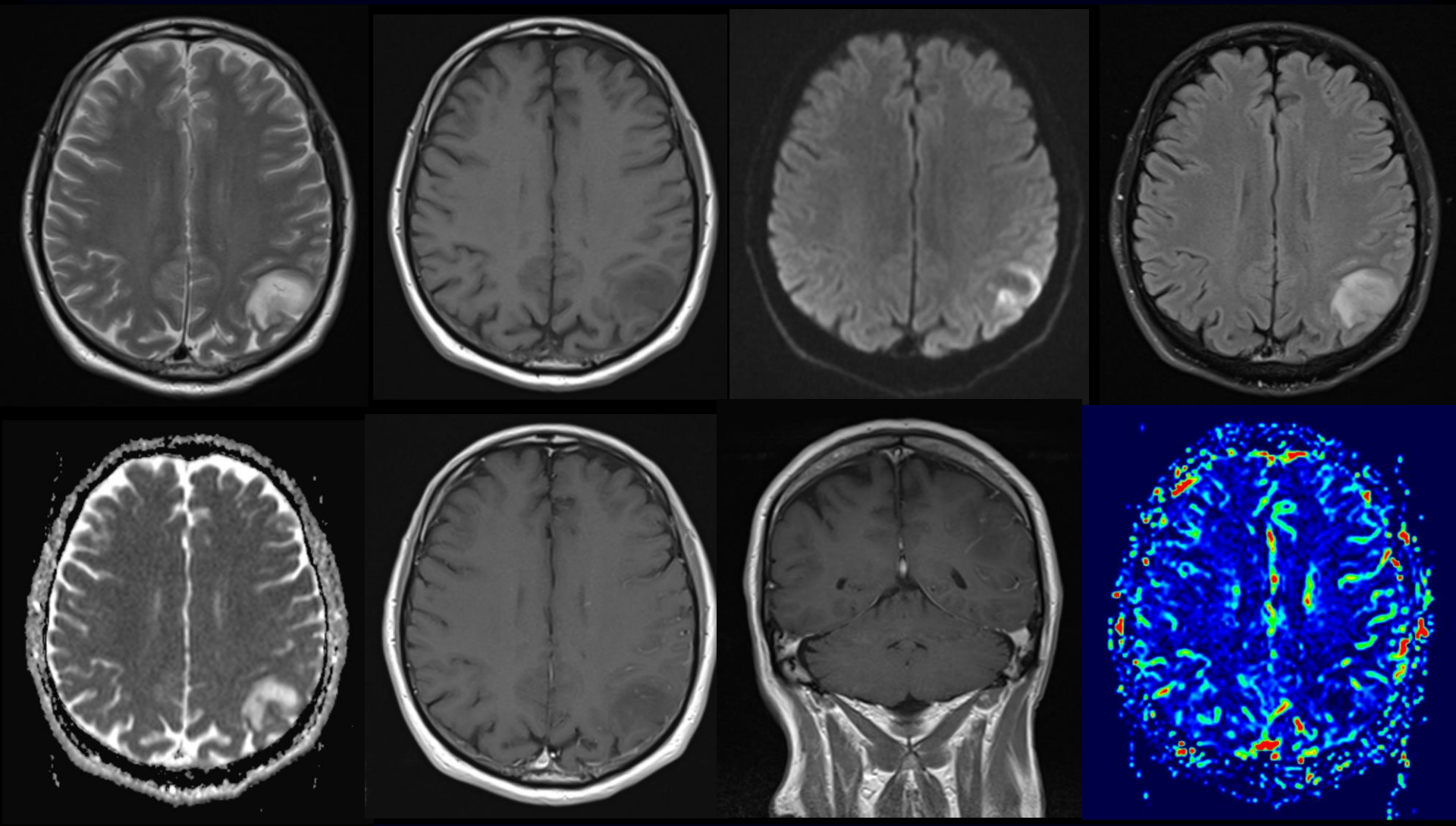
Lutra G et al: *Comparative evaluation of fungal, tubercular, and pyogenic brain abscesses with conventional and diffusion MR imaging and proton MR spectroscopy.* **AJNR 28: 1332-1338, 2007**

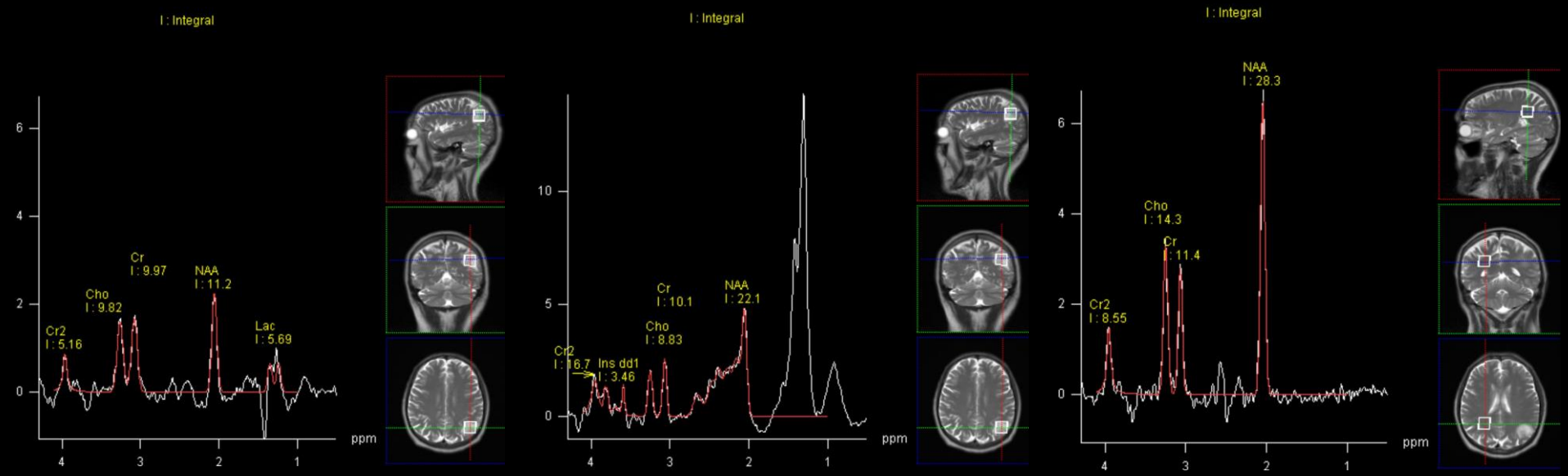
TUMOR vs……

Seizure
HL
Prostate cancer
16/7/18



Courtesy of D. Bagatto



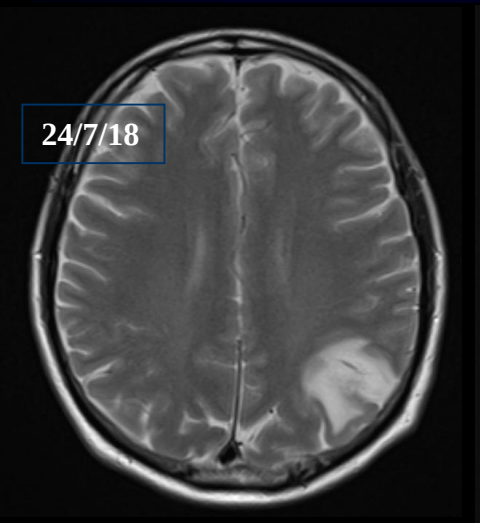

I : Integral
Cr2
I : 5.16
Cho
I : 9.82
Cr
I : 9.97
NAA
I : 11.2
Lac
I : 5.69
ppm
I : Integral
Cr2
I : 6.7
Ins dd1
I : 3.46
Cho
I : 8.83
Cr
I : 10.1
NAA
I : 22.1
ppm
I : Integral
Cr2
I : 8.55
Cho
I : 14.3
Cr
I : 11.4
NAA
I : 28.3
ppm

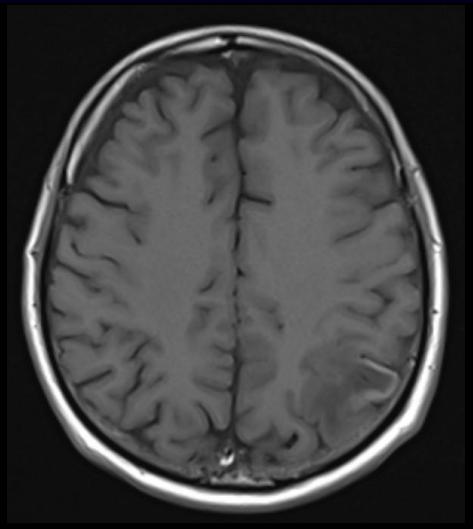
19/7/18

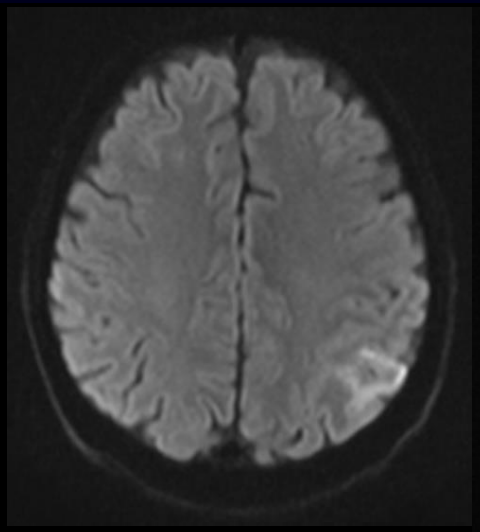
16/7/18

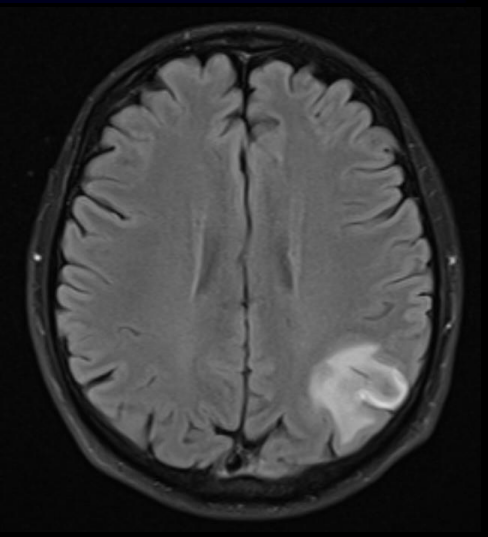
19/7/18

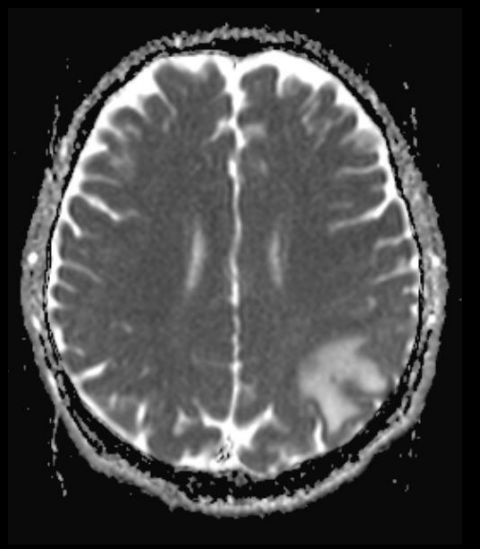
24/7/18

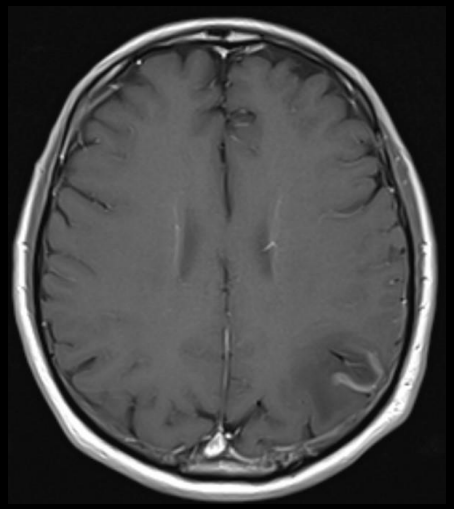


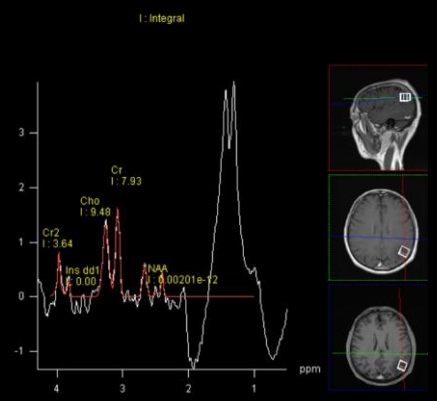


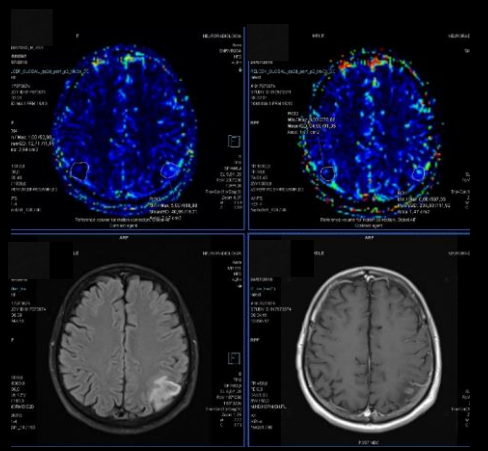




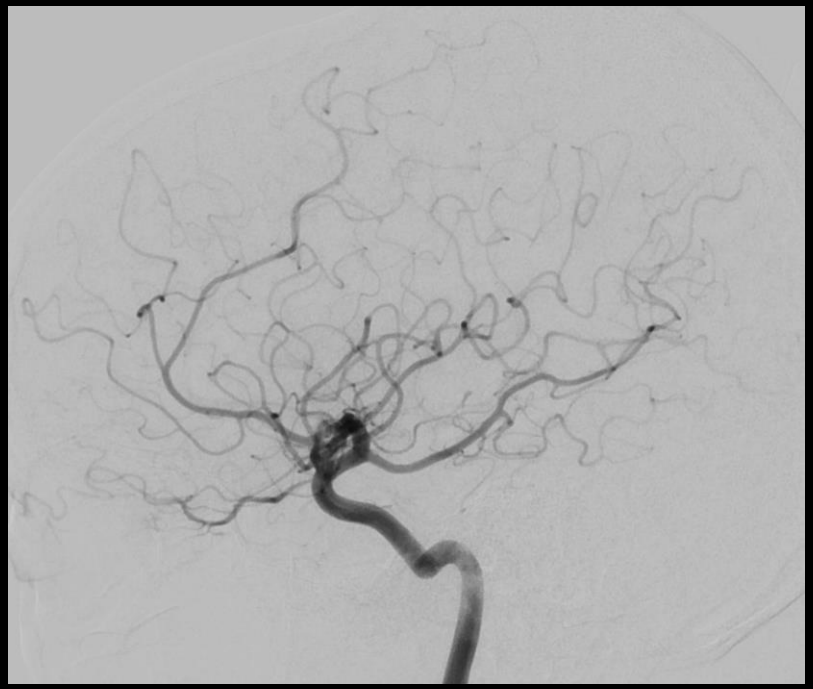


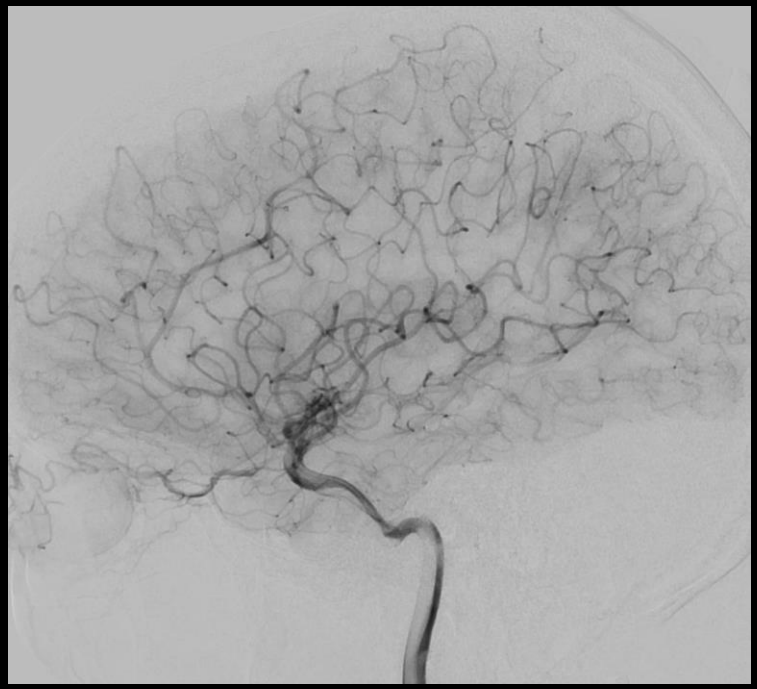


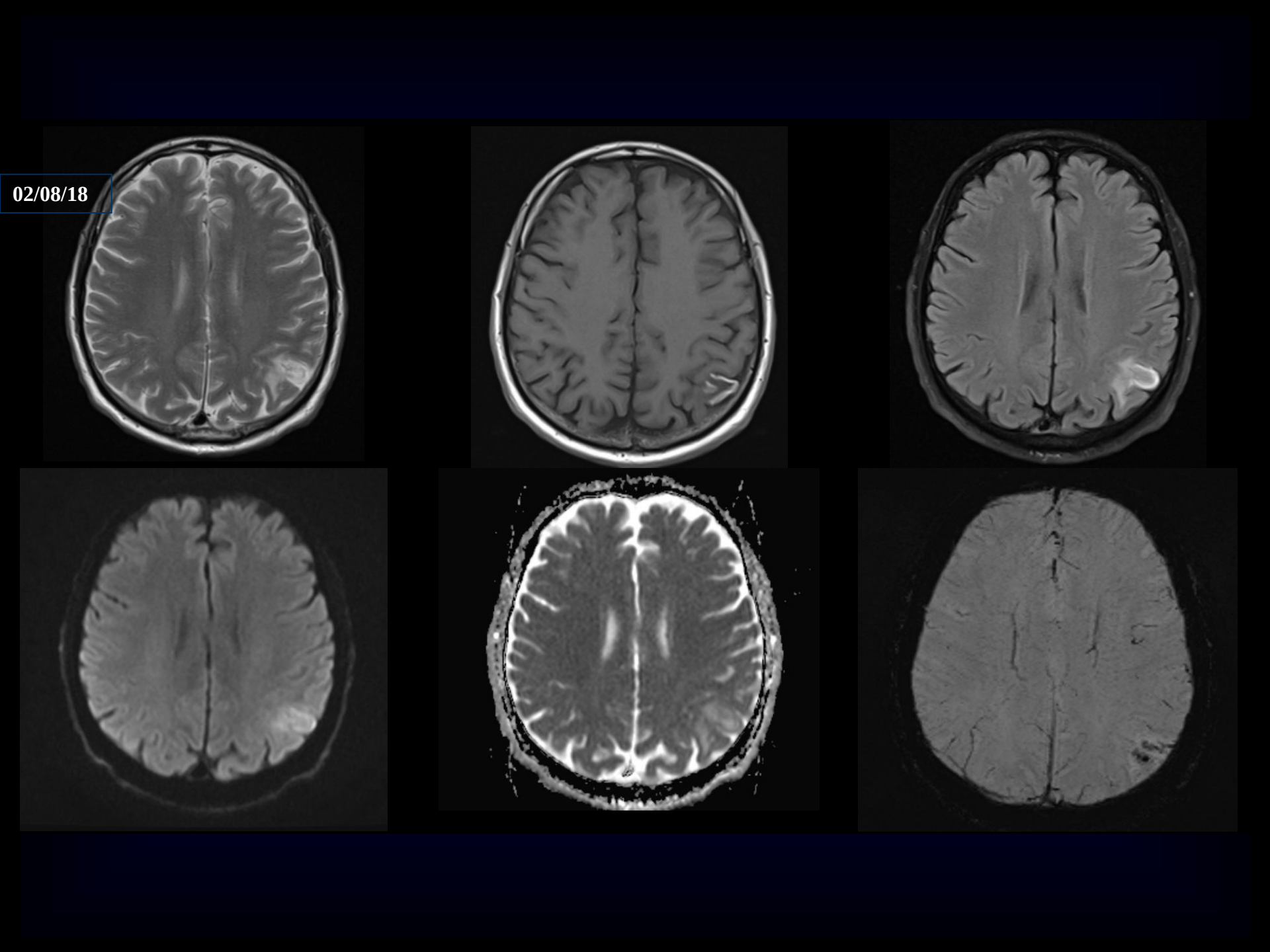

I : Integral
Cr2
I : 3.64
Cho
I : 9.48
Cr
I : 7.93
Ins dd1
I : 0.001
NAA
I : 0.00201e-12
3
2
1
0
-1
4
3
2
1
ppm



26/7/18






02/08/18

SPECTROSCOPY IN NEURORADIOLOGY

ALZHEIMER DISEASE

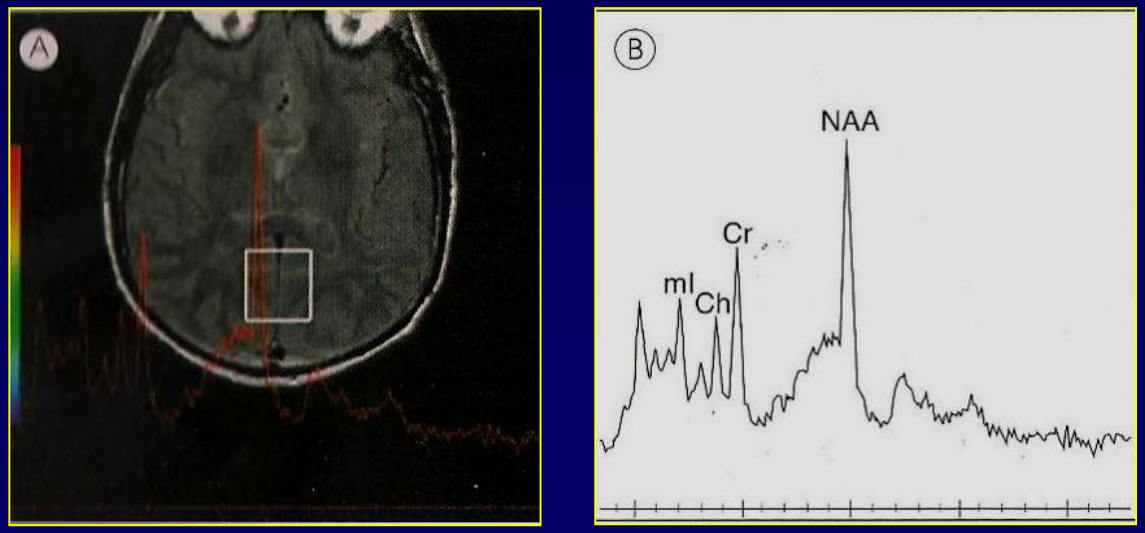
- Most of the MRS studies have been done in the parieto-occipital cortex of patients with AD. Attempts have been made to obtain spectra in the medial temporal lobe, but these are hindered by the close approximation of the hippocampus to the skull base (with associated susceptibility effects).

- In fronto-temporal dementia, one may find MRS abnormalities similar to those described for AD, but in a different anatomical location (as with atrophy).

SPECTROSCOPY IN NEURORADIOLOGY

ALZHEIMER DISEASE

- Evaluation of hyppocampal regions
- Evaluation of posterior cingulate gyrus (progression from MCI to AD)



Caranci, 2009

SPECTROSCOPY IN NEURORADIOLOGY

ALZHEIMER DISEASE

- Reduction of NAA due to neurodegeneration
- Increase of mI due to increase od glial cells
- NAA/ mI, high specifity (95%)
- Not useful in the early setting, not yet validated, trials

SPECTROSCOPY IN NEURORADIOLOGY

ALZHEIMER DISEASE

- ^{31}P spectroscopy
- MD and MCI vulnerable regions

⟶ PCr/ATP, PI/ATP levels

Jett et Al, Front. Aging Neurosci., 2023

NUCLEAR MEDICINE IN NEURORADIOLOGY

Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) both rely on the detection of radioactive signals from alabelled compound (tracer) that selectively binds in the brain. SPECT is technically less demanding and more widely available, whereas PET is more sensitive but technically more demanding. In the past, SPECT was mostly used to evaluate brain perfusion, and PET to evaluate the metabolism of glucose in the brain. However, due to the development of radioligands for in vivo detection of Alzheimer's pathology, SPECT and PET became more important in dementia (especially research).

NUCLEAR MEDICINE IN NEURORADIOLOGY

SPECT

Tracers for SPECT are photon-emitting isotopes. The emitted gamma rays are detected by using a rotating camera containing two to three detectors that convert radioactive rays into electric signals used to compute a cross-sectional image. Due to the low energy of the photons, collimation of the signal and scatter in tissue, resolution is limited to ~1 cm.

One of the advantages of SPECT is that commonly used tracers (e.g. the metastable nuclear isomer 99mTechnetium) can be readily produced from a local 99Molybdenum generator. It can be delivered on a weekly basis to the hospital or can be bought from a central distributor.

NUCLEAR MEDICINE IN NEURORADIOLOGY

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NUCLEAR MEDICINE IN NEURORADIOLOGY

SPECT

1. Blood-Flow and Metabolism

The most commonly used tracer to examine cerebral perfusion is 99mTc-HMPAO (hexamethylpropylene amine oxime). 99mTc has a half-life of 6 h. HMPAO is a general flow tracer that can be used to determine areas of hypoperfusion in dementia, but 123I-IMP and 99mTc ECD are also used for this purpose

NUCLEAR MEDICINE IN NEURORADIOLOGY

SPECT

1. Dopamine Transporter Tracers

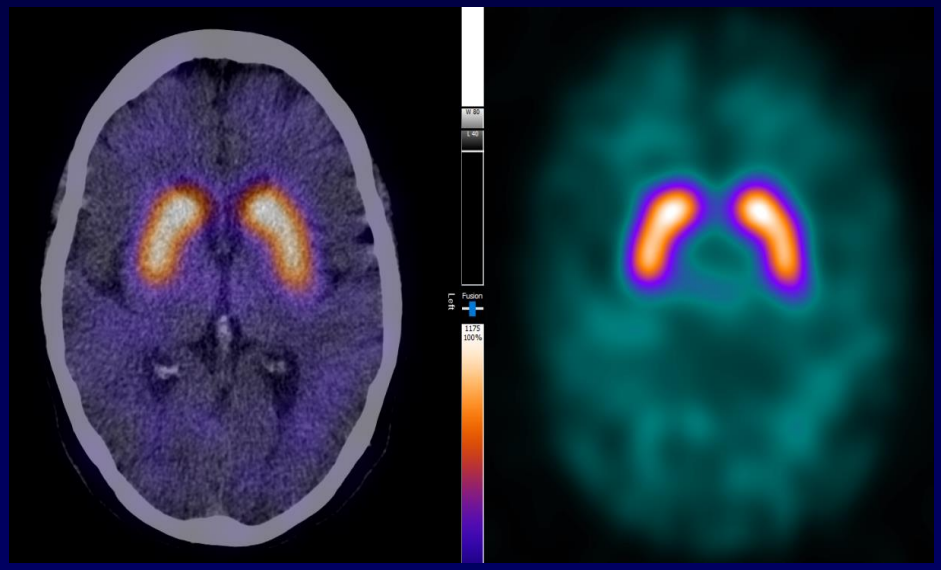
Tracers binding to the pre-synaptic dopamine transporter are well established for the diagnosis of Parkinson's disease and related disorders. 123I FP-CIT (I 123–radiolabelled 2-carbomethoxy-3- (4-iodophenyl)-N-(3-fluoropropyl) nortropane) and 123I-ioflupane, traded under the name DaT-SCAN are the most widely used tracers for this purpose.

NUCLEAR MEDICINE IN NEURORADIOLOGY

SPECT

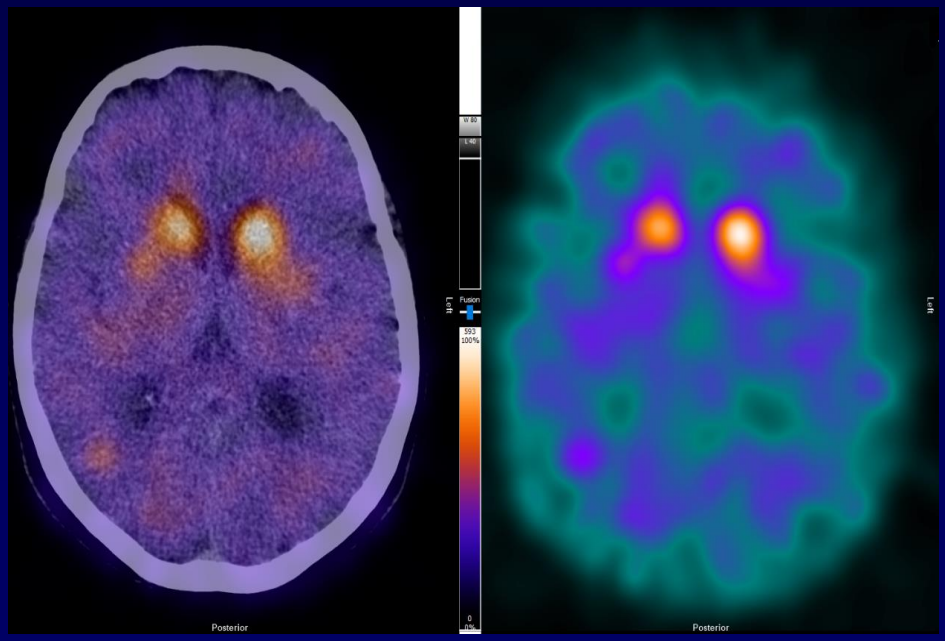
Case 1: negative

DD: essential tremor vs Parkinson's disease.



Case 2: positive

pt with bradichinesia and disautonomia



Courtesy of F. Dore and C. Crisafulli

NUCLEAR MEDICINE IN NEURORADIOLOGY

PET

Contrary to the random directions of photons emitted from a SPECT tracer, positron emission and annihilation lead to the emission of diametrically opposed photons, which can be detected by coincidence detectors. The latter improves sensitivity over SPECT, but comes at the cost of more complex detector systems and tracer production facilities. Recently, PET scanners have been combined with CT scanners. In addition to the advantage of having anatomical reference images, these combined PET-CT scanners also obviate the need to obtain a transmission scan for attenuation correction, and thus increase the speed of the examination.

NUCLEAR MEDICINE IN NEURORADIOLOGY

PET

1.Brain Metabolism (FDG)

[18F]-2-fluoro-2-deoxy-D-glucose (FDG) is a glucose analogue that readily enters the brain and is taken up through the glucose transporter. Once metabolised, it becomes trapped in the cells and thus serves as a marker of cerebral (glucose) metabolism. Being labelled to 18F, FDG has a half-life of 110 min, which obviates the need for local production. Reduced glucose metabolism occurs in many neurodegenerative diseases and reflects diminished metabolism of the tissue. While hypometabolism itself is non-specific, the pattern of abnormalities can be quite helpful and antedate tissue loss on structural imaging, thus allowing an earlier diagnosis.

NUCLEAR MEDICINE IN NEURORADIOLOGY

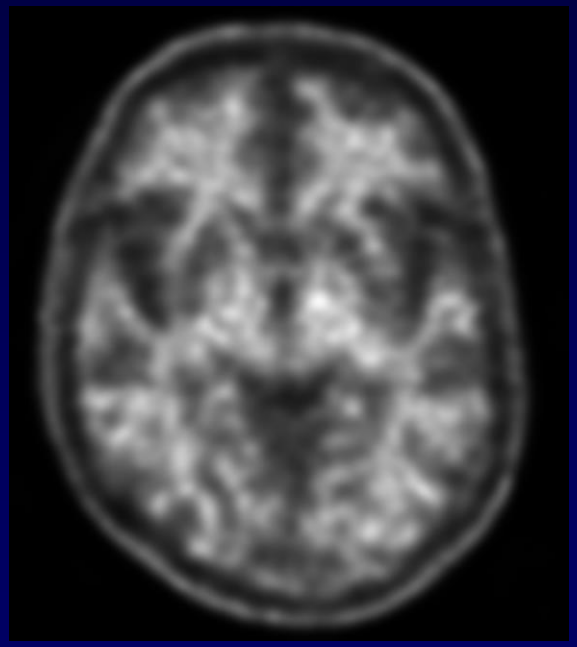
PET

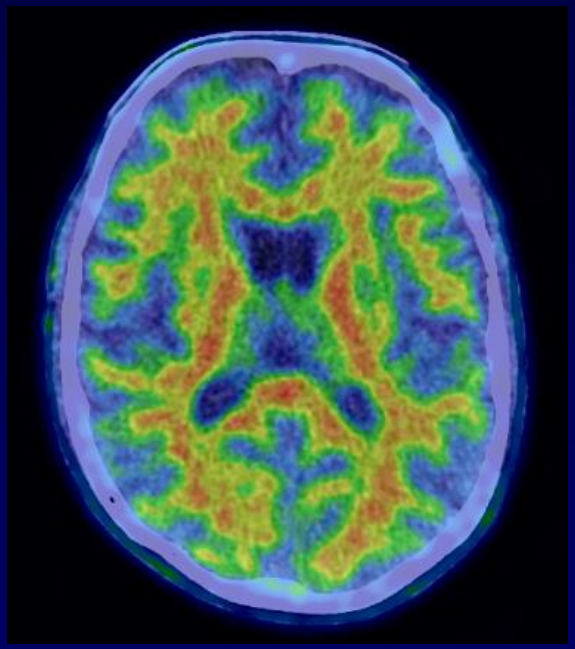
2. Amyloid Tracers

Several amyloid-imaging tracers are being introduced into clinical practice recently, including 18F-FDDNP (2-(1-{6-[(2-18F-fluoroethyl)(methyl)amino]-2-naphtyl}ethylidene)malo nitrile) and 11C -PIB (N-methyl-11C-2-(4'-methylaminophenyl)-6- hydroxy benzothiazole). Both tracers bind with nanomolar affinity to amyloid and are being used to study amyloid deposition in the brain. Currently, 11C-PIB seems superior to 18F-FDDNP for the identification of amyloid in AD on a case-to-case basis, but its widespread implementation is hampered by its short halflife (Fig. 3.23). Both18F-PIB and a number of new 18F-labelled ligands for amyloid imaging are being evaluated, such as 18F-BAY94-9172; these appear to have a good effect size and are likely to be increasingly available

Case 1: negative

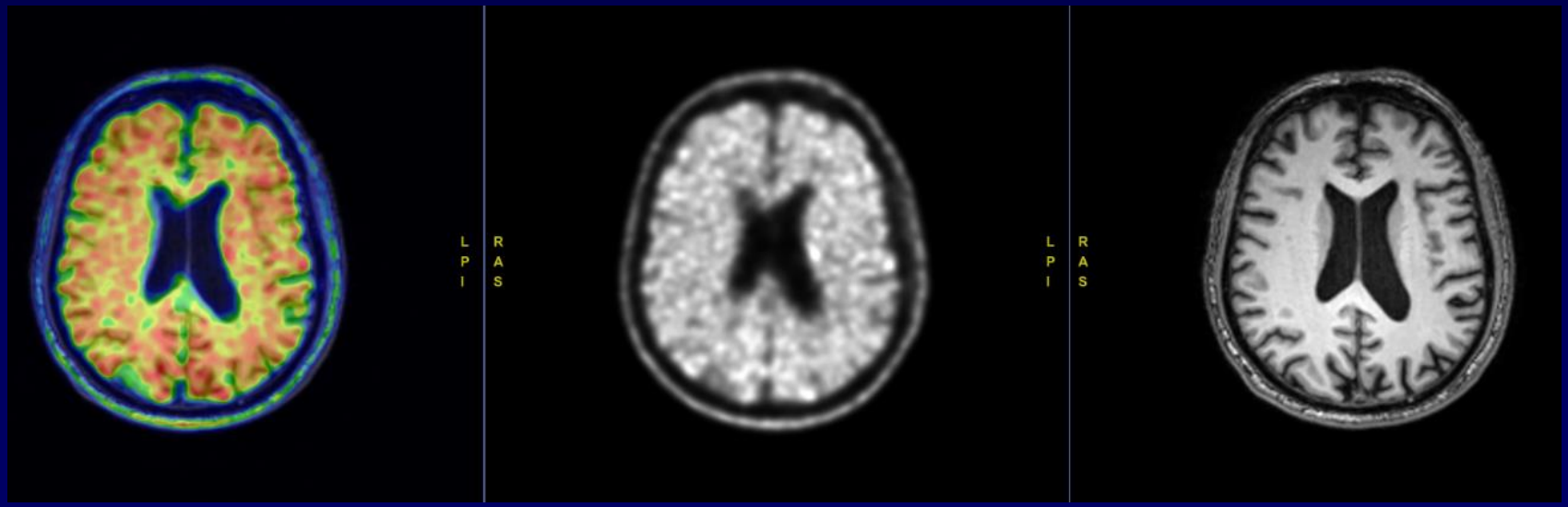
Clinical issue: cognitive decline in patient wih familiarity for AD





Courtesy of F. Dore and C. Crisafulli

Case 2: positive.
Clinical issue: Primary progerssive aphasia (logopenic variant)



Courtesy of F. Dore and C. Crisafulli

NUCLEAR MEDICINE IN NEURORADIOLOGY

3. Amino-acid tracer

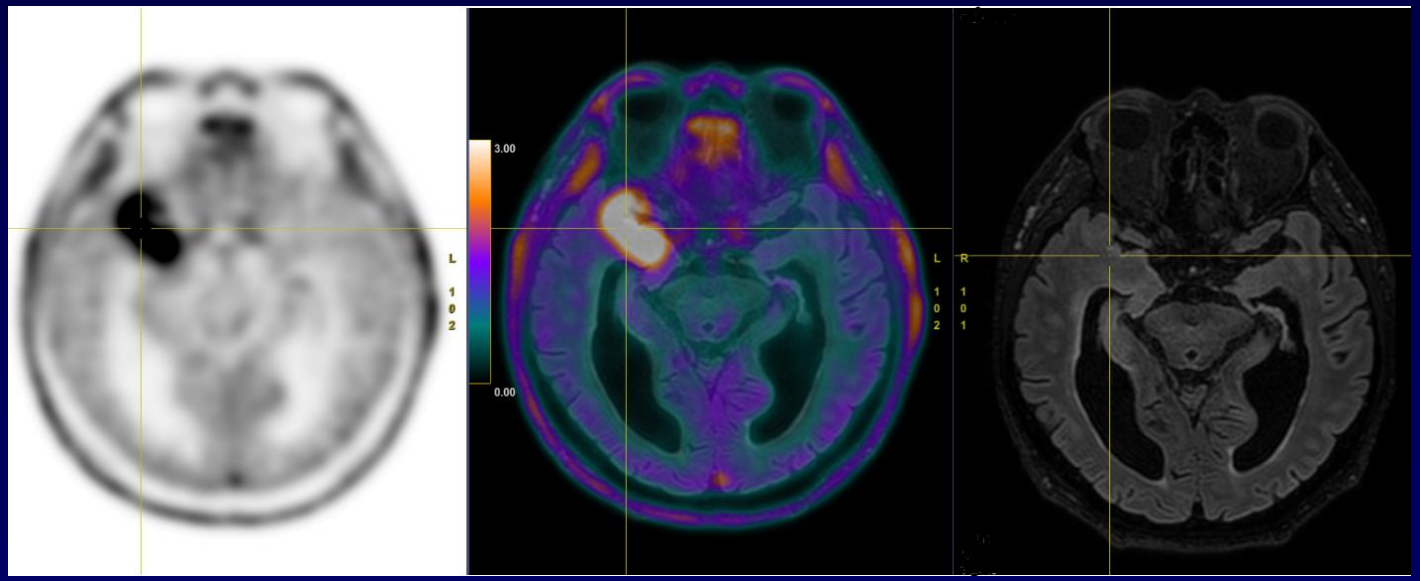
- The tyrosine analog 18F-FET is an 18F-labeled PET tracer highly specific for glioma. 18F-FET uptake mechanism is driven by glioma overexpression of the active transmembrane L-type amino-acid transporter 2 (LAT2) and, to a minor extent, the lesser glioma-specific LAT1. An artificial amino-acid, 18F-FET is not further metabolized within the cell and does not serve as substrate to protein synthesis. 18F-FET uptake in inflammatory cells is low and negligible in the healthy brain. A large neutral amino-acid, 18F-FET cannot cross the intact brain-blood-barrier (BBB), and glioma 18F-FET uptake is not significantly influenced by changes in the BBB permeability

- 18F-DOPA- PET tracer to study brain inflammation

Celli et Al, Front Onc, 2021
Sala et Al, Clin Nucl Med, 2014

1 FET(fluor-etiltirosina)

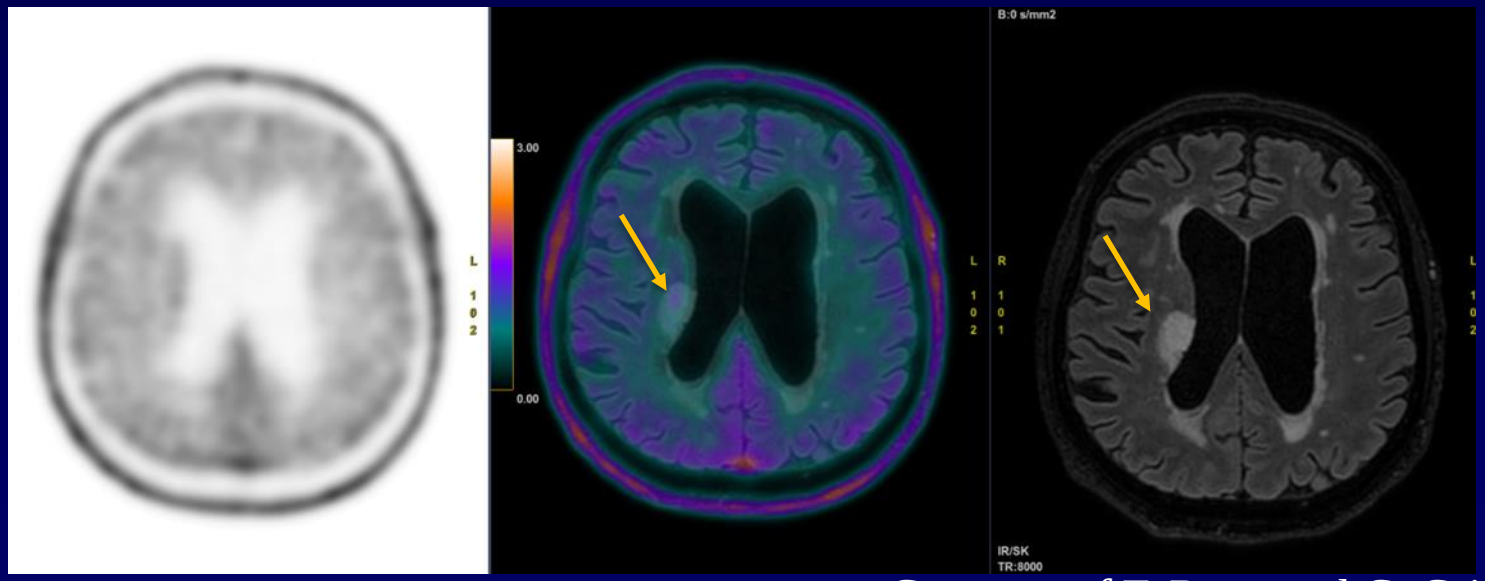
Case 1: MRI: doubtful lesion in right temporal lobe



Courtesy of F. Dore and C. Crisafulli

1 FET(fluor-etiltirosina)

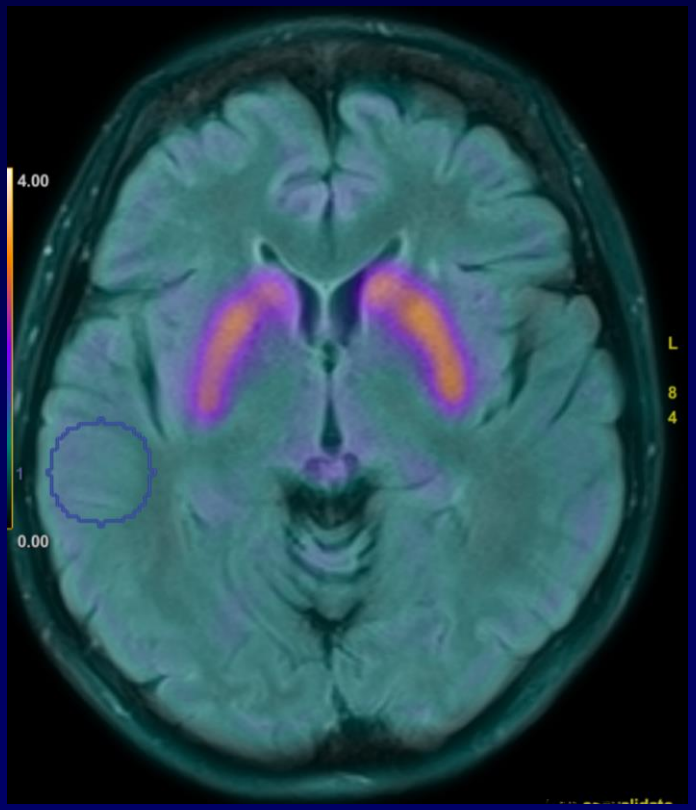
Case 2: MRI – ischemic area, negative PET

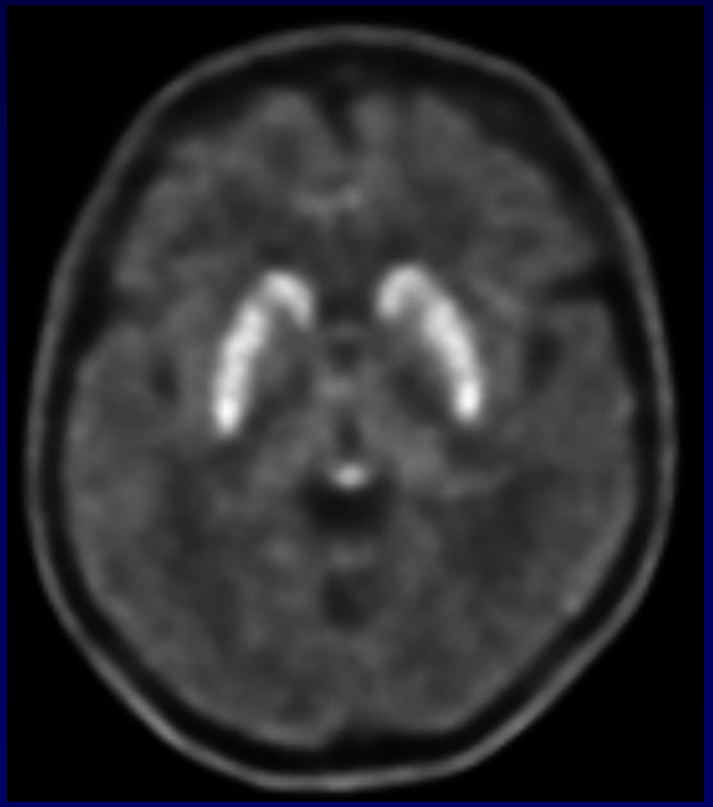


Courtesy of F. Dore and C. Crisafulli

2 DOPA

Case 1: normal distribution of DOPA, normal uptake in basal ganglia

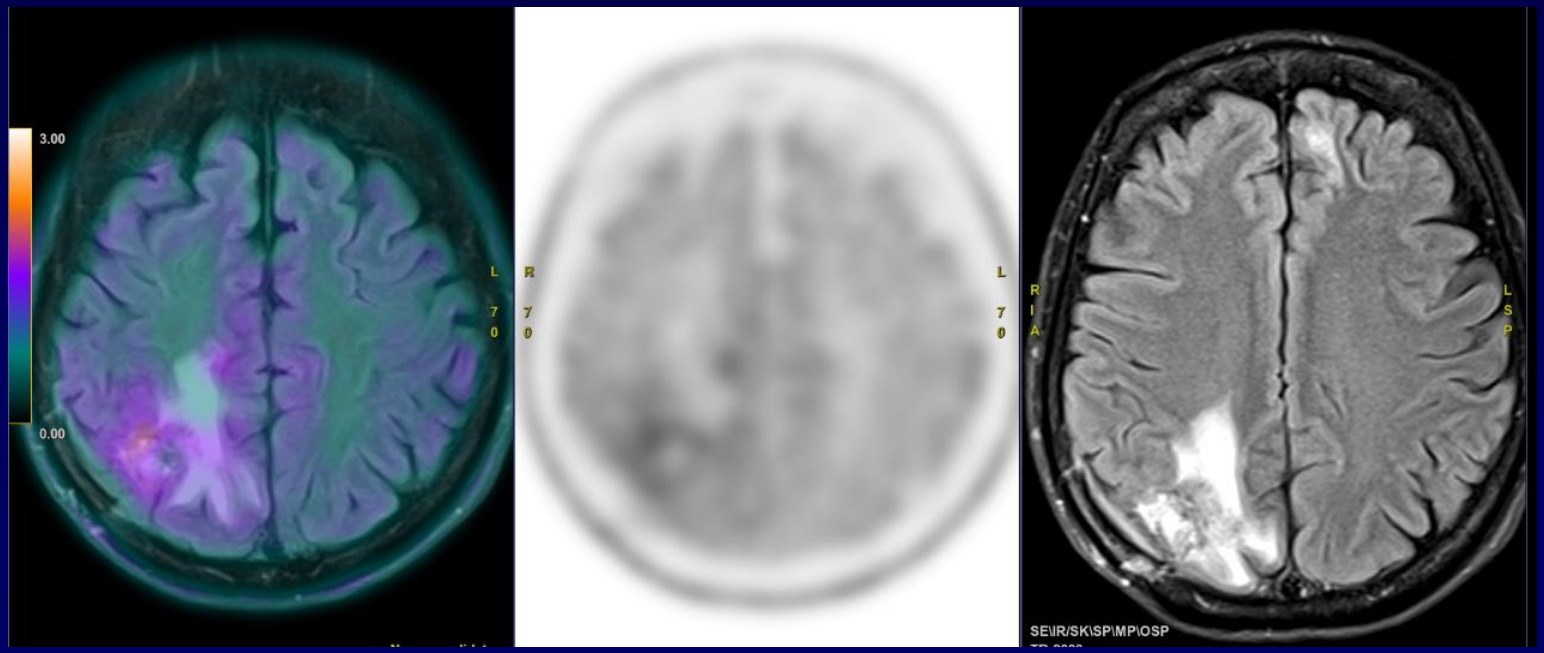




Courtesy of F. Dore and C. Crisafulli

2 DOPA

Case 2: DOPA uptake due to radionecrosis



Courtesy of F. Dore and C. Crisafulli