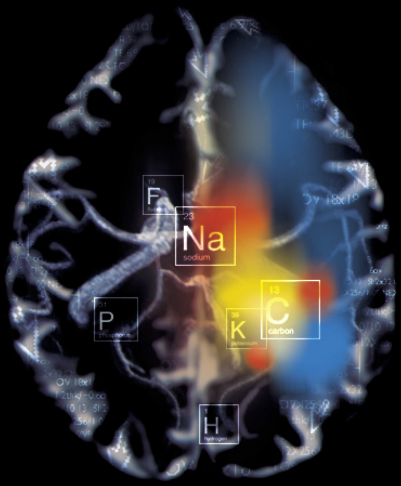
UHF Funding Conference 2015,
NIH, Washington DC



Importance of X-Nuclei for Broadening Uses of Ultrahigh Field MR Imaging in Humans

Keith R. Thulborn, MD, PhD
Professor of Radiology, Physiology & Biophysics
Center for Magnetic Resonance Research
University of Illinois

Sensitivity Requirement: [X] & γ

- Most MRI (based on ^{1}H signals of water & fat)
- Spatially-resolved biochemistry with other elements
- ^{1}H 80M, ^{23}Na 35mM, ^{17}O 16mM, ^{39}K 100mM, ^{31}P 3mM
- gamma {^{1}H = 4x ^{23}Na; 8x ^{17}O; 24x ^{39}K; 2x ^{31}P}

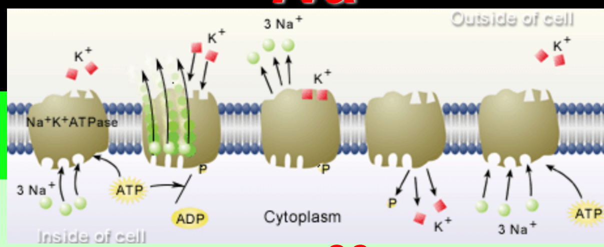
1 H																		2 He
3 Li	4 Be												5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg												13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca		21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
37 Rb	38 Sr		39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
55 Cs	56 Ba	*	71 Lu	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
87 Fr	88 Ra	**	103 Lr	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Uub	113 Uut	114 Uuq	115 Uup	116 Uuh	117 Uus	118 Uuo

*	57 La	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb
**	89 Ac	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No

Goal: Comprehensive Metabolic Model of Human Biochemistry (^{23}Na, ^{39}K, ^{17}O, ^{31}P ^{13}C)

Na^{23}

Workload



K^{39}

Glucose

Cell Membrane

Resting Membrane Potential ~ -70mV

Glucose

$V_m = const.ln(p_i\ [K_i]\ /\ p_o\ [K_o])$

Pyruvate

CO_2

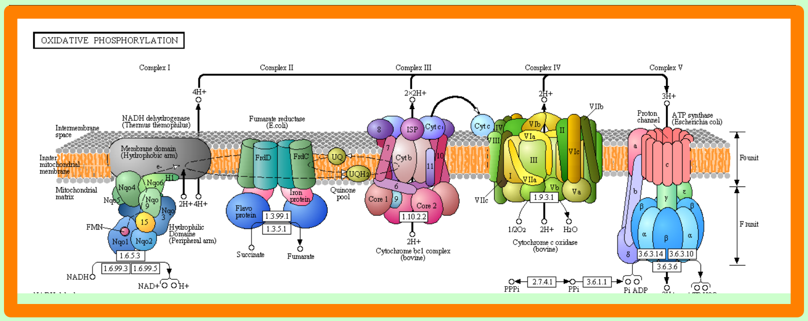
Acetyl CoA

$ATP^{31} \rightarrow P_i + ADP$

$ATP^{31} + Cr \leftarrow ADP + P^{31}Cr$

High energy

~P bioenergetics



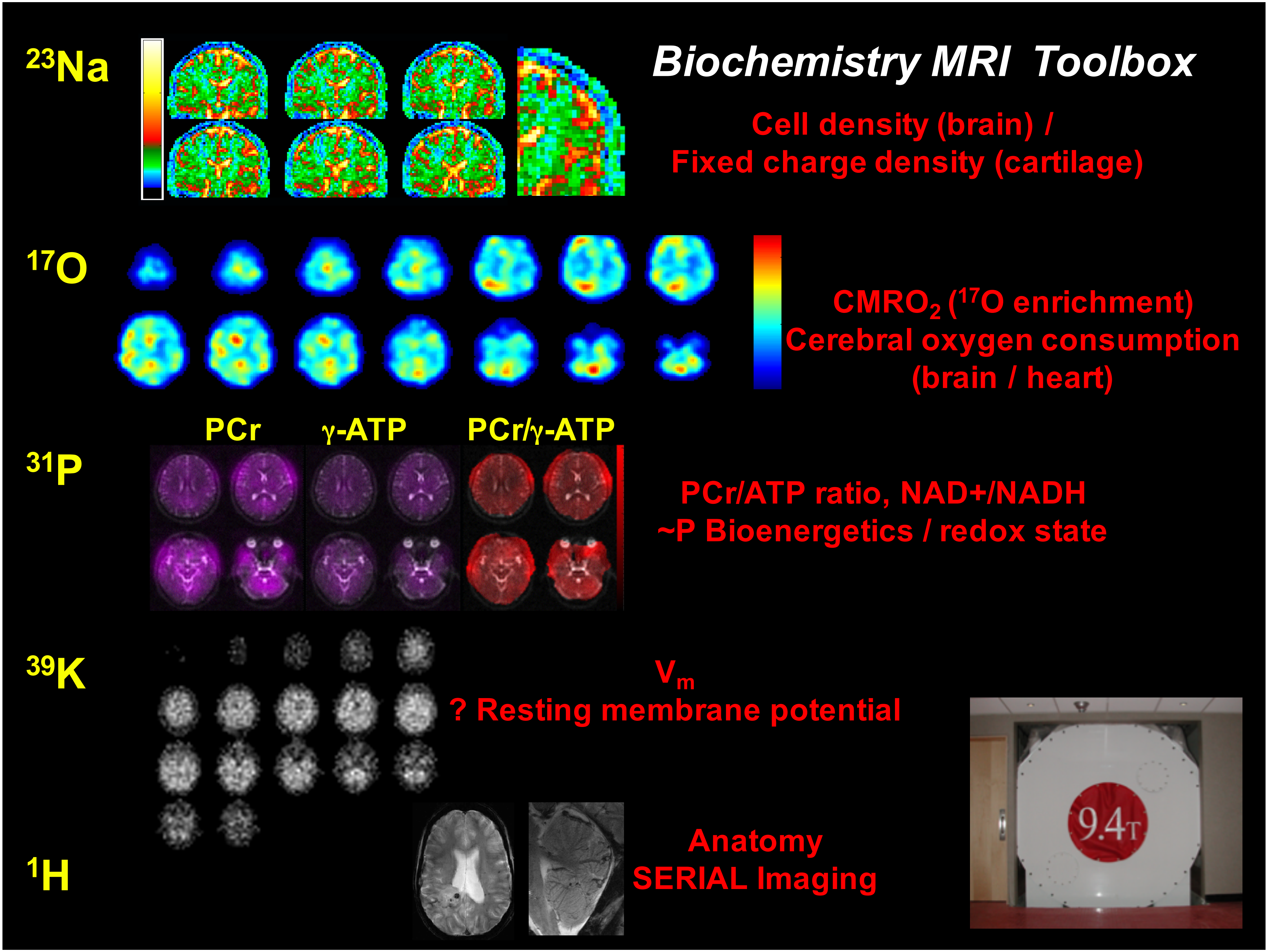
H_2O^{17}

Oxidative Phosphorylation

O_2^{17}

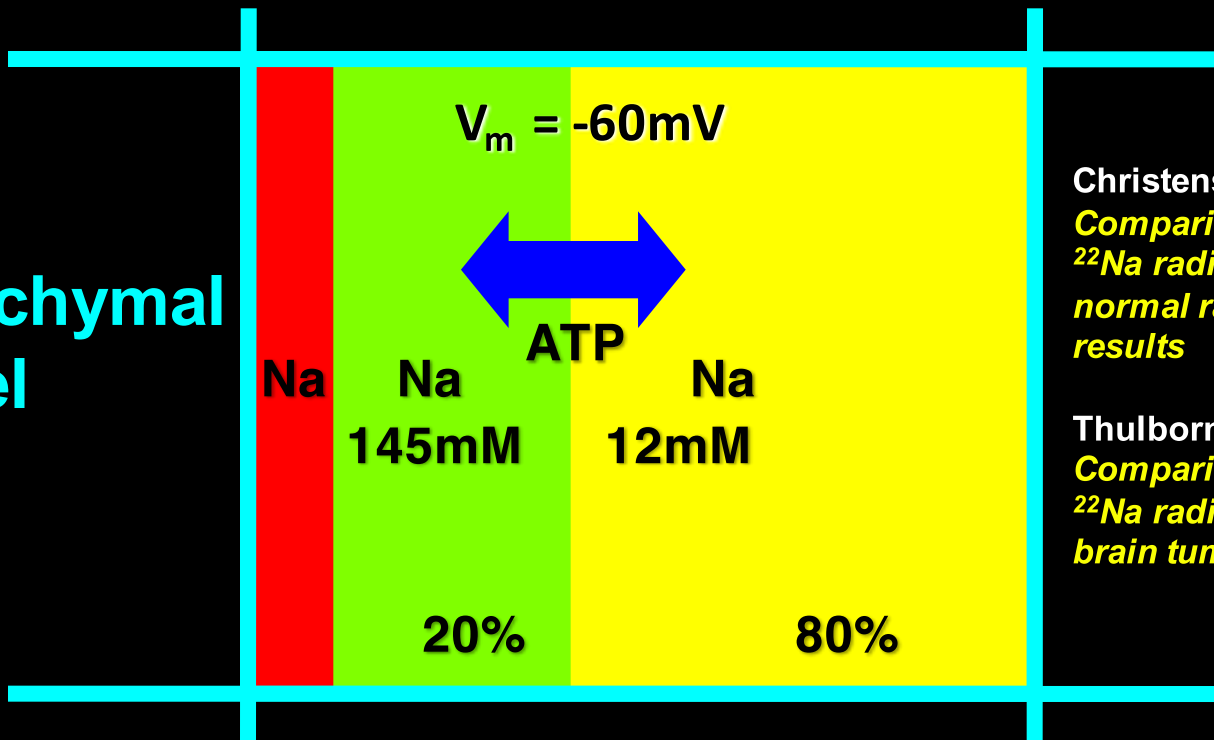
>60% of brain energy used for Na^+/K^+ pump

Brain tissue has high cell density: cell volume fraction 80%


Biochemistry MRI Toolbox
23Na
Cell density (brain) /
Fixed charge density (cartilage)
17O
CMRO2 (17O enrichment)
Cerebral oxygen consumption
(brain / heart)
PCr
γ-ATP
PCr/γ-ATP
31P
PCr/ATP ratio, NAD+/NADH
~P Bioenergetics / redox state
39K
Vm
? Resting membrane potential
1H
Anatomy
SERIAL Imaging
9.4T

^{23}Na Cell Volume Fraction Bioscale (Endogenous)

Intraparenchymal Voxel



Christensen et al., MRM 1996.
Comparison of ^{23}Na MRI & ^{22}Na radioisotope dilution in normal rat brain: equivalent results

Thulborn et al., MRM 1999.
Comparison of ^{23}Na MRI & ^{22}Na radioisotope dilution in rat brain tumors: equivalent results

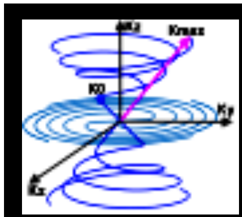
Vascular: Na 140mM, 2% VF_v, Interstitial: Na 145mM, 18% Vf_i but $C_v \sim C_i$

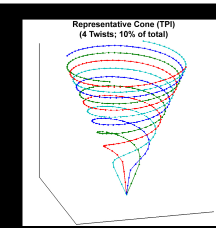
Intracellular: Na 12mM, 80% CVF

$$TSC = CVF.C_c + (1-CVF).C_i \quad < 40 \text{ mM}$$

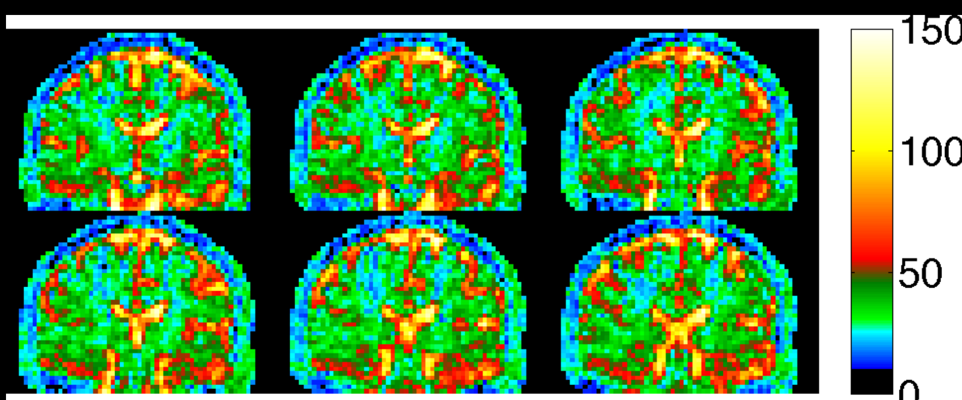
$$CVF = (TSC - C_i)/(C_c - C_i)$$

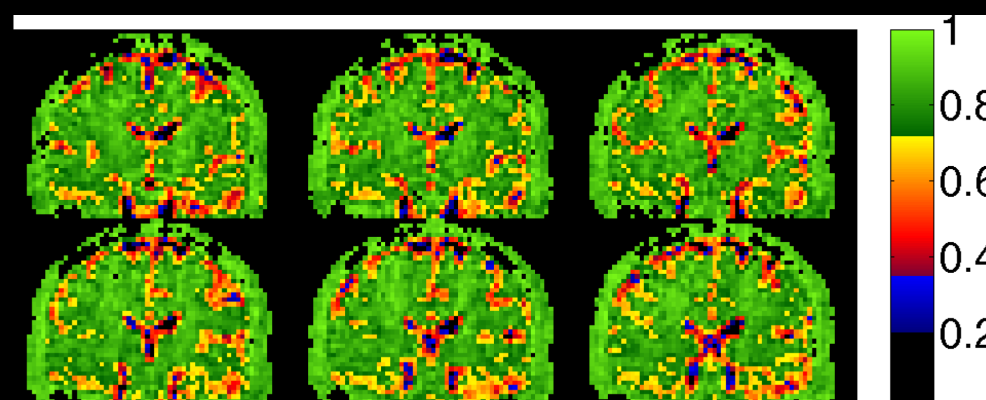
Increasing TSC implies decreasing cell volume fraction CVF





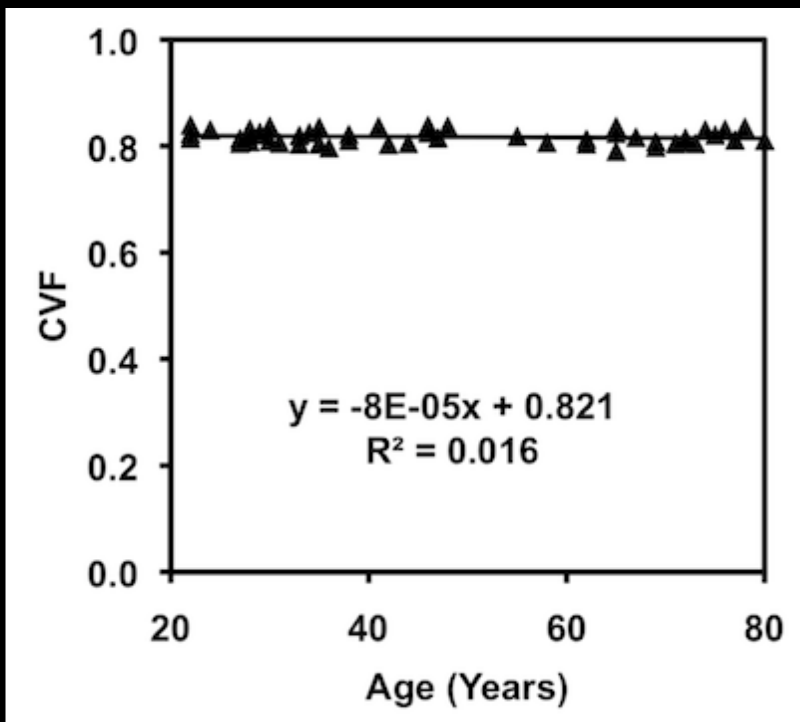
Quantitative Biochemisty

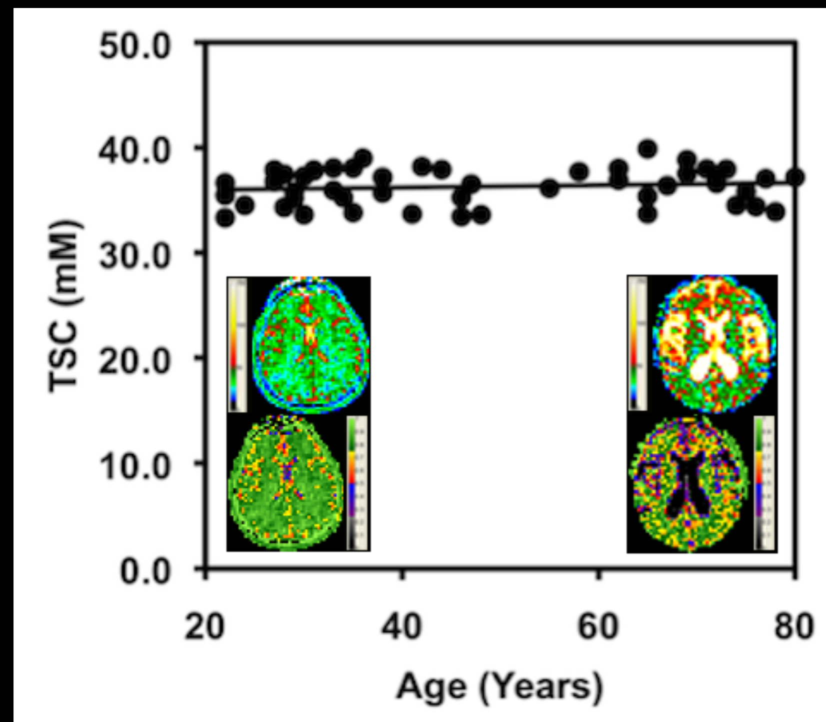




CVF with Normal Ageing

N=49

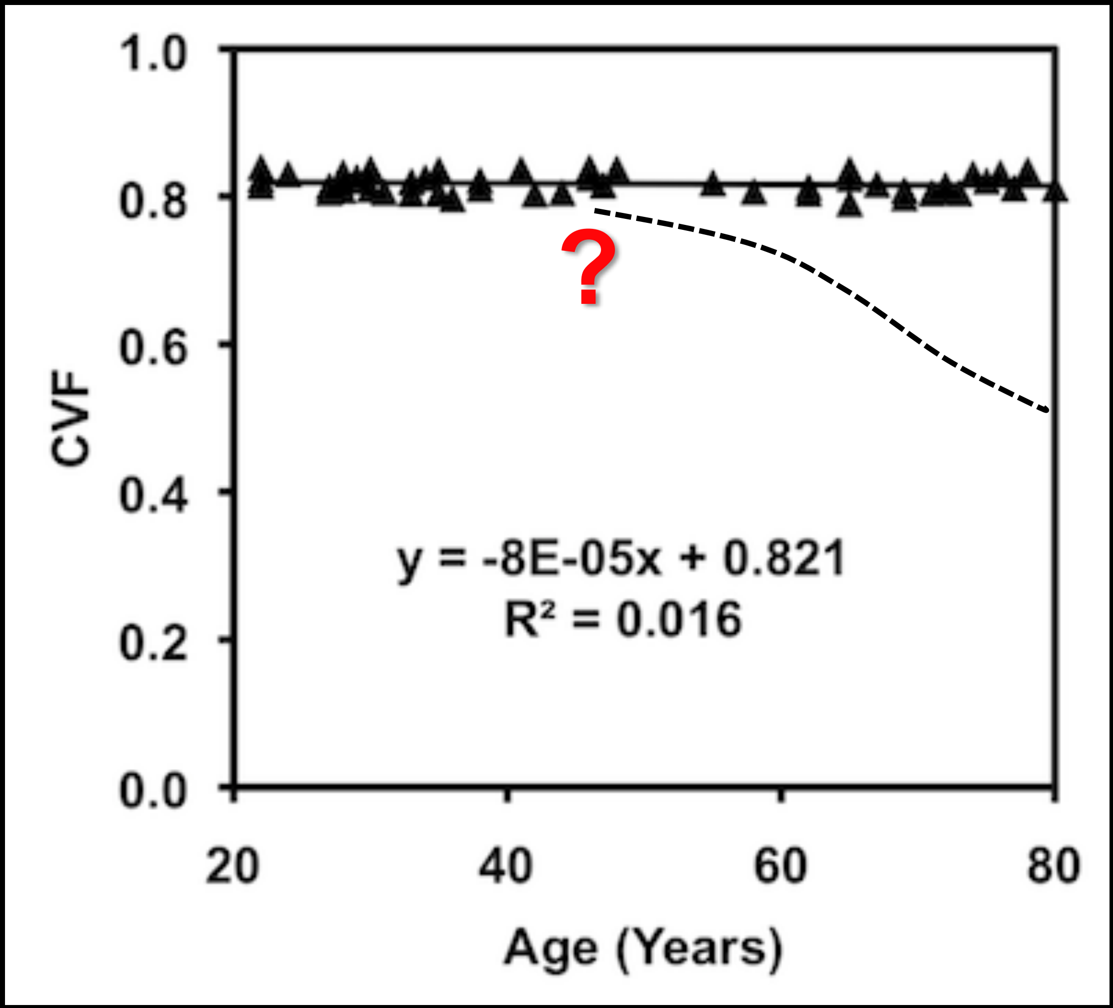




Cell volume fraction is stable with normal ageing!
Neurons become smaller & ECM decreases at same rate *(volume loss is NOT from loss of neurons)*

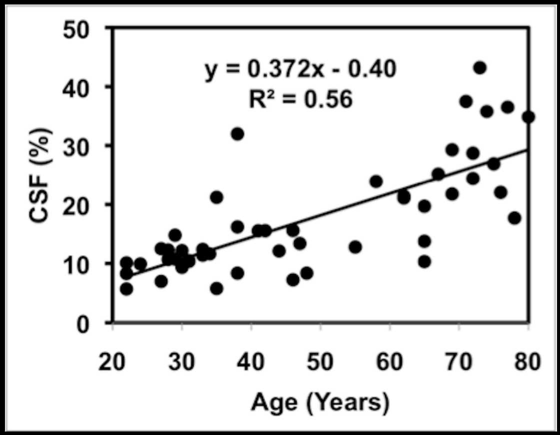
Thulborn et al., NMR Biomed, 2015

A Relevant Medical Question



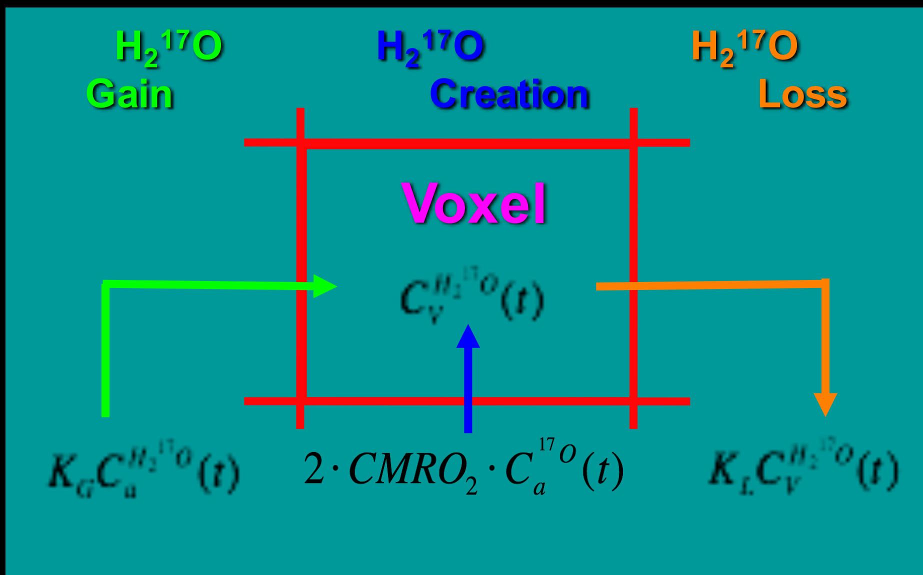
Normal Cognition

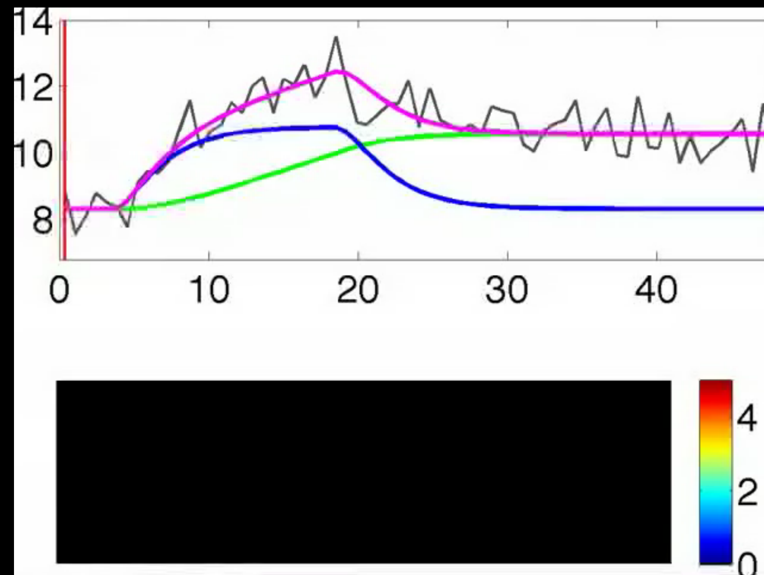
MCI Dementia



Can CVF detect cell loss in early degenerative disease?

^{17}O *MRI* $CMRO_2$ Model (Enrichment)



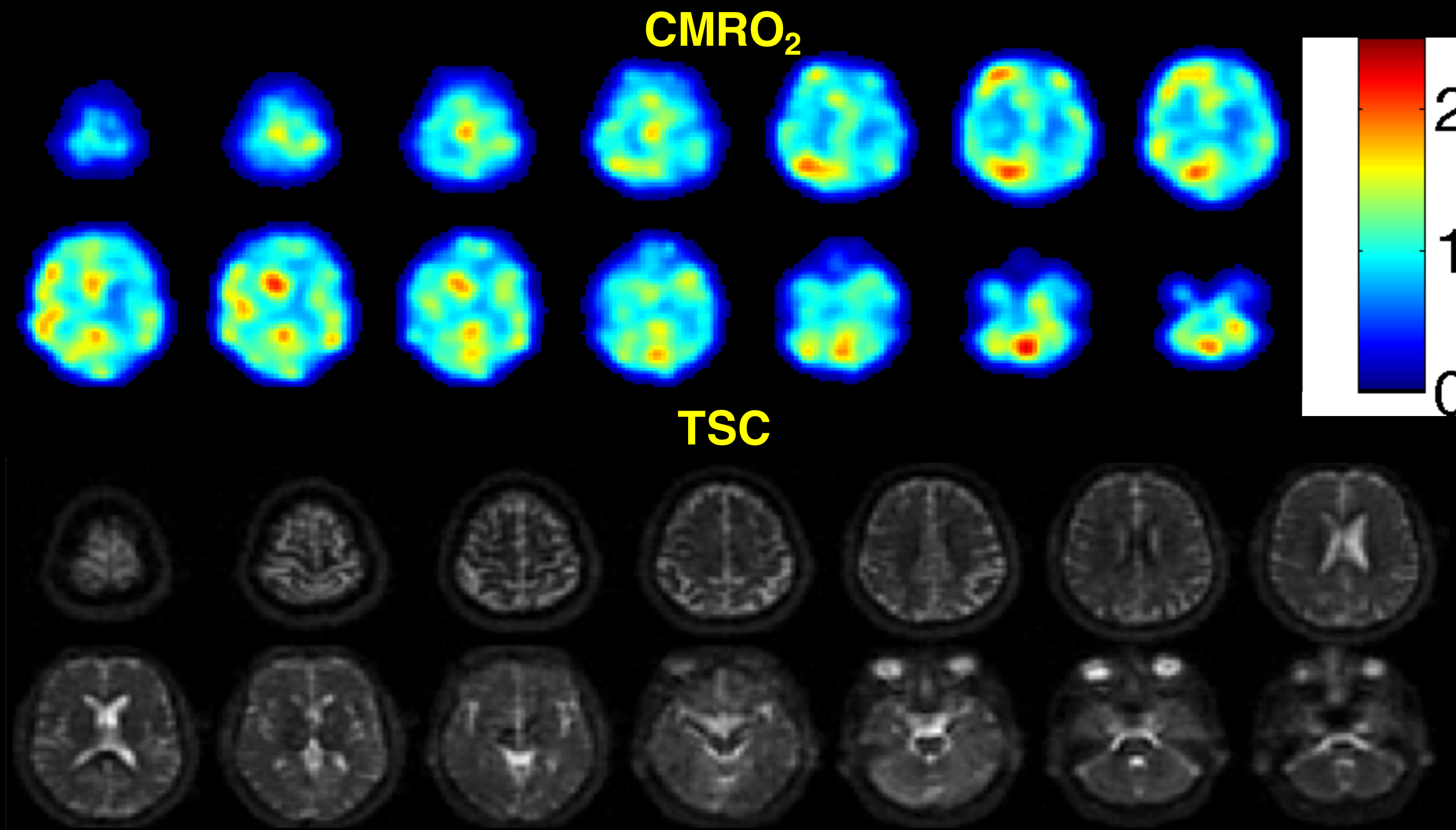


$$\frac{dM_V^{H_2{}^{17}O}(t)}{dt} = 2 \cdot CMRO_2 \cdot A^{^{17}O}(t) - K_L \cdot M_V^{H_2{}^{17}O}(t) + K_G \cdot B^{H_2{}^{17}O}(t)$$

- Rate constants summarize labeled water gain and loss
  - $CMRO_2$: Creation of labeled water
  - K_G: Gain due to wash-in (labeled water in blood)
  - K_L: Loss due to wash-out and conversion

Atkinson & Thulborn, Neuroimage 2010

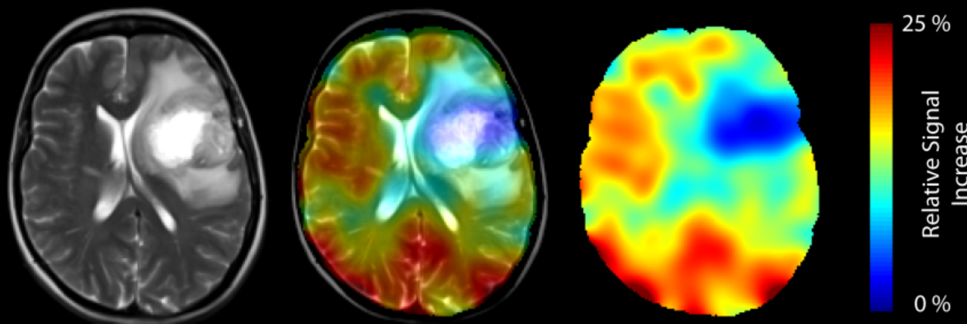
^{17}O CMRO2 corrected for Tissue Mass

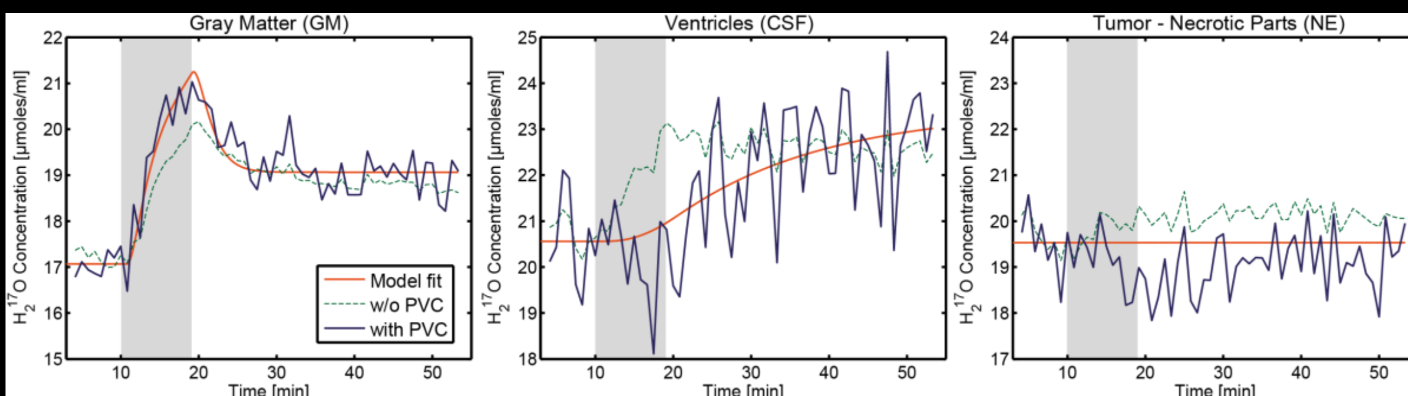


Atkinson & Thulborn, Neuroimage 2010

^{17}O MRI of Glioblastoma: 7T

- Assess oxygen metabolism
- First $^{17}O_2$ inhalation experiment in a tumor patient
- 'Geometric transfer matrix' for correction of partial volume effects
- reduced CMRO2 in tumor compartments



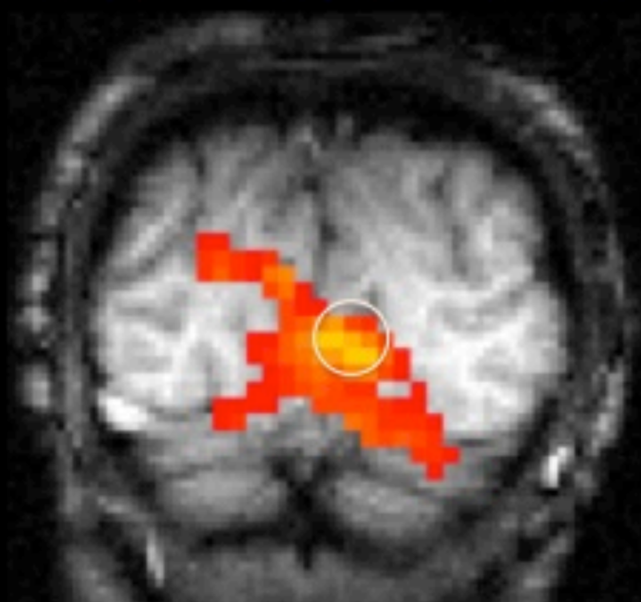


1) Hoffmann, Radbruch, Semmler, Nagel. MAGMA 2014 (2014) 27:579–587 2) Rousset et al. J Nucl Med 39(5):904–911

$CMRO_2$/CBF/OEF changes in activated brain region

(Quantitative cognitive workload)

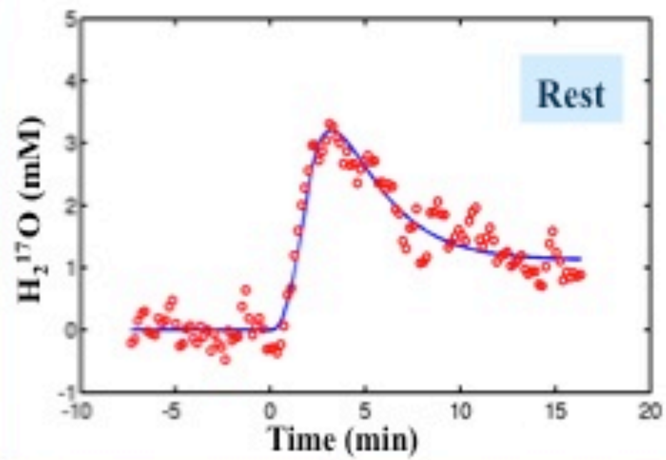
^1H MRI & fMRI Map



$[^{17}O]$ = *89.9%*

Inhalation (rest): *2 min*

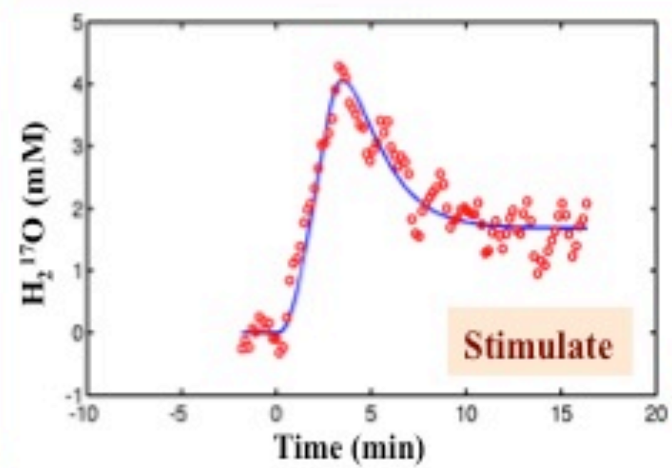
Inhalation (stim): *2.8 min*



$CMRO_2$ = *1.71 μmol/g/min*

CBF = *0.38 ml/g/min*

OEF = *0.53*

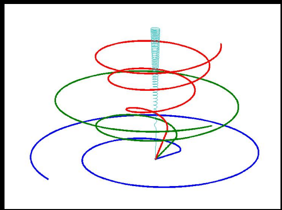


↑ $CMRO_2$ = *1.83 μmol/g/min*

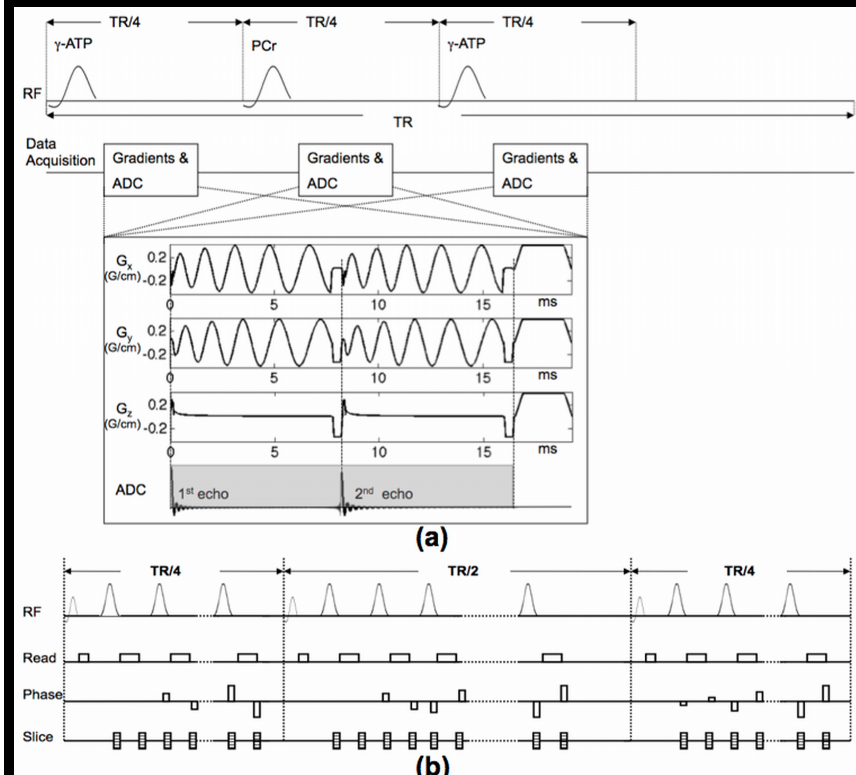
↑ CBF = *0.63 ml/g/min*

↓ OEF = *0.34*

Supplied by Wei Chen, 2015



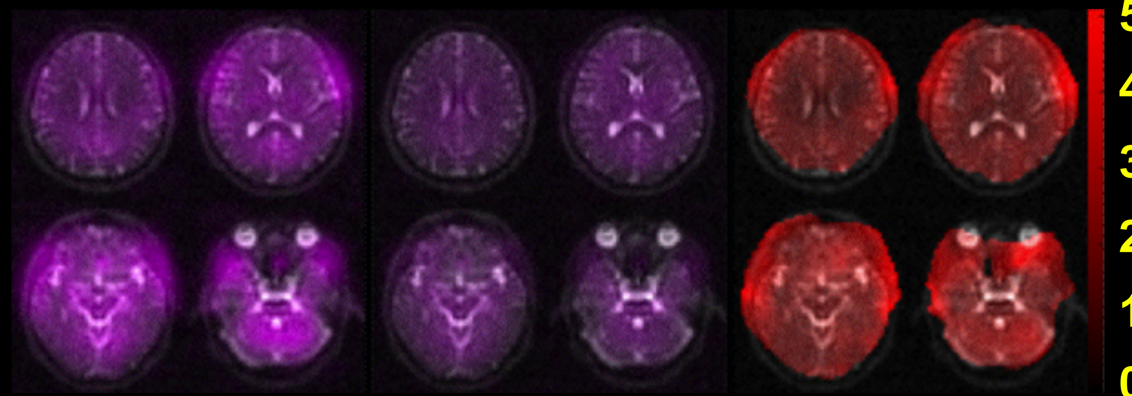
^{31}P MR Imaging



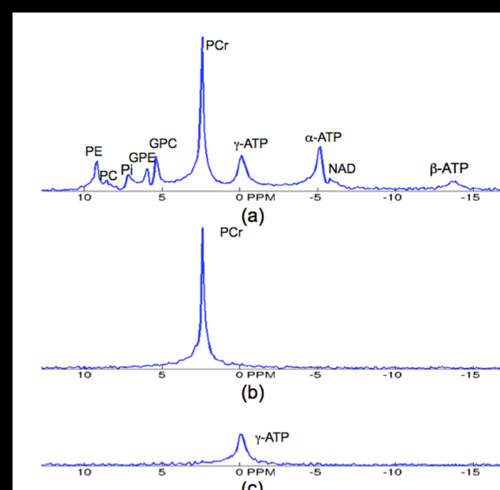
Spectral selective RF pulse with flexTPI readout = SIMPLE-TPI

Lu, Atkinson, Zhou & Thulborn, MRM 2012

PCr γ-ATP PCr/γ-ATP



^{31}P PCr and ATP images over ^{23}Na image



Spectral selective RF pulse whole head spectrum

PCr/γ-ATP ratios for 3 volunteers:

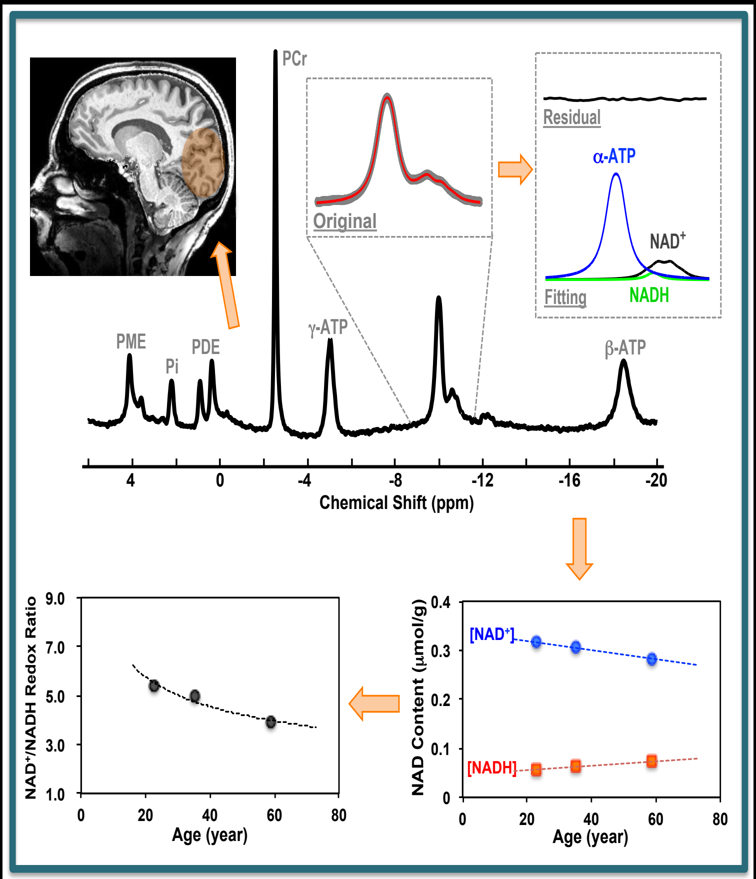
1.46 ± 0.27

1.43 ± 0.26

1.46 ± 0.31

SLE patient 1.54±0.3

NAD+/NADH MRS Redox State in Human Brain



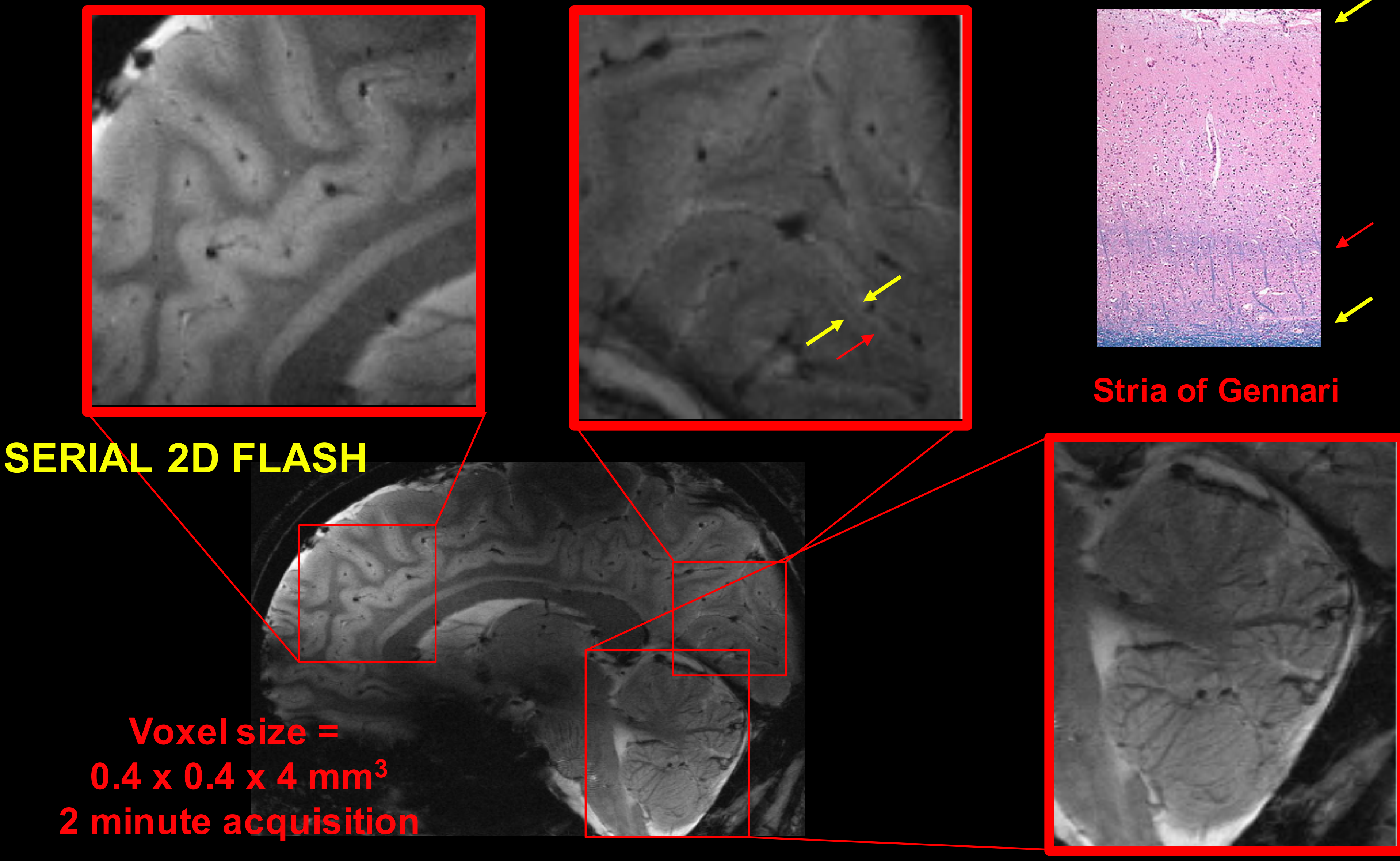
Xiao-Hong Zhu, Ming Lu, Byeong-Yeul Lee, Kamil Ugurbil and Wei Chen

PNAS, 2015;112:2876-2881

Demonstration of the *in vivo* ^{31}P MRS based NAD assay for quantifying cellular NAD^+ and NADH contents in human occipital lobe *(highlighted in the brain anatomic image)* at 7T.

The results revealed a significant decline of $NAD^+/NADH$ redox state in healthy elderly people.

Human SERIAL ^{1}H Images



X-Nuclei Summary: Need for UHF

- Quantification of rates & concentrations is the new dimension, possibly enabling metabolic modeling of human biochemistry, possibly to predict health & illness and to measure longitudinal responses & development without ionizing radiation ("*Man on Moon Mission statement*"):

- Sensitivity enhancement of endogeneous X nuclei (low gamma, low concentration, e.g., ^{23}Na)
- Enrichment approaches (e.g., ^{17}O, ^{7}Li, ^{19}F, …. etc)
- SAR increases at UHF but Quantification reduces duty cycle to avoid T_1 saturation except for very short T_1 species (e.g., ^{39}K)
- Partial Volume Effects due to spatial resolution limit accuracy of quantification