



AN INTRODUCTION TO MR NEUROIMAGING & SPECTROSCOPY

Lijing Xin

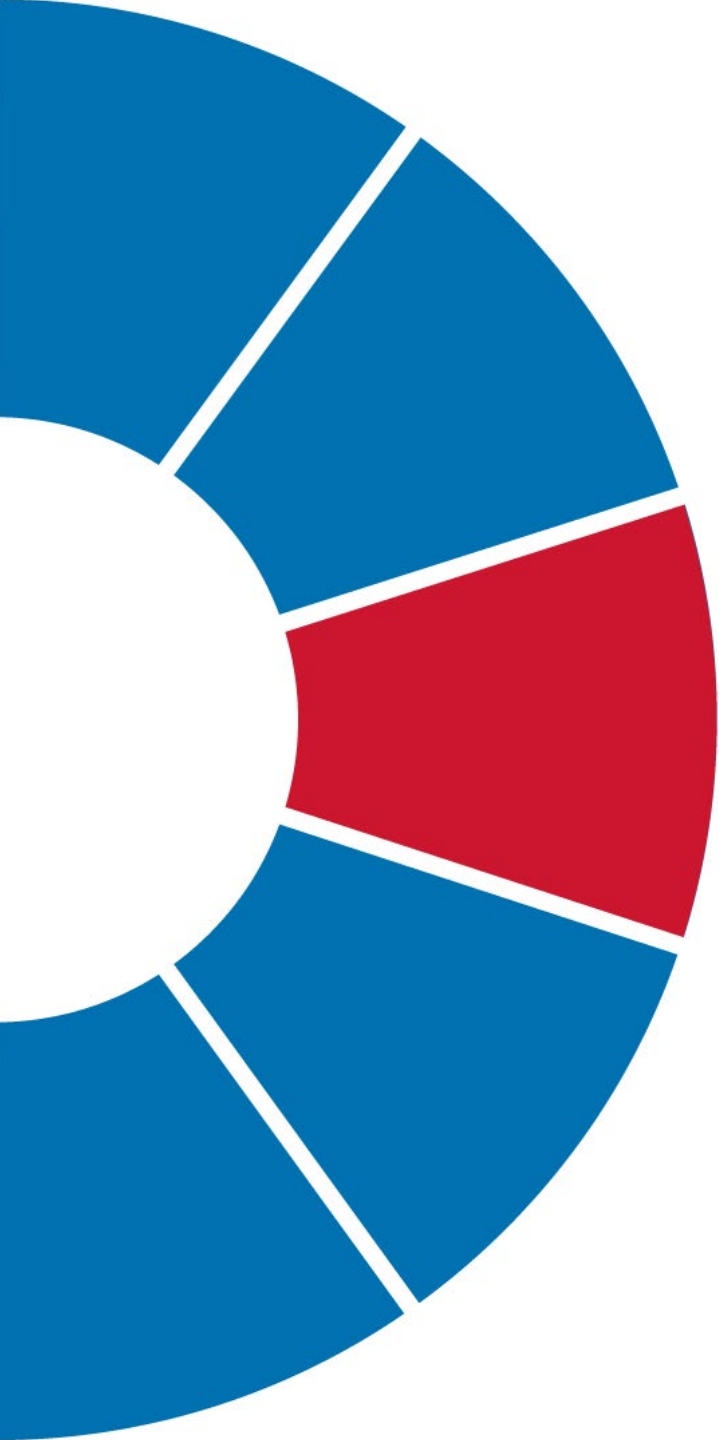
CIBM EPFL MRI

27.02.2025



C I B M . C H

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INTRODUCTION TO THE COURSE

TEACHERS

Bernard Lanz



Cristina Cudalbu



Lijing Xin



Daniel Wenz



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Ileana Jelescu



Ruud van Heeswijk



Antoine Klauser



Antoine Kaiser



PROGRAM OF THE COURSE

Thursday 13:15-17:00



Session 1: Feb 27, 2025	Session 3: Mar 6, 2025	Session 5: Mar 20, 2025	Session 7: Apr 3, 2025 (Campus Biotech, Geneva)
08:15 – 09:00: Introduction to MRI and MRS (Xin) 09:15 – 10:00: Introduction to MRI and MRS (Xin) 10:15 – 11:00: Ethics for Human Study (Fornari) 11:15 – 12:00: Ethics for Animal Study (Cudalbu)	13:15 – 14:30: Fast MR Imaging Methods (Zerbi) 14:45 – 15:45: Functional Magnetic Resonance Imaging and Applications (Zerbi) 16:15 – 17:00: MRI Sequences and Applications of Diffusion-Weighted Imaging (Jelescu)	13:15 – 14:00: RF Theory: Introduction and Demonstration (Wenz) 14:15 – 17:00: Hands-On: RF Coil Construction and Characterization at the Bench (Wenz)	13:15 – 17:00: human MRI & MRS practical teaching (Xin, Kaiser)
Session 2: Feb 27, 2025	Session 4: Mar 13, 2025	Session 6: Mar 27, 2025	Session 8: Apr 10, 2025
13:15 – 14:00: Basics of Nuclear Magnetic Resonance I (Wenz) 14:15 – 15:00: Basics of Nuclear Magnetic Resonance II (Lanz) 15:15 – 16:00: Basics of MRI (Cudalbu) 16:15 – 17:00: Basic MR Sequences (van Heeswijk)	13:15 – 14:00: RF Theory: Introduction and Demonstration (Wenz) 14:15 – 17:00: Hands-On: RF Coil Construction and Characterization at the Bench (Wenz)	13:15 – 14:00: Introduction of MRS I (Xin) 14:15 – 15:00: Introduction of MRS II (Xin) 15:15 – 16:00: Basics of MRSI (Cudalbu) 16:15 – 17:00: Basics of MRSI (Cudalbu)	13:15 – 14:00: X nuclei MRS (¹³ C, ³¹ P, ¹⁵ N, ² H). (Xin) 14:15 – 15:00: MRS Quantification (Cudalbu) 15:15 – 17:00: Interpretation of dynamic X-nuclei experiments with metabolic modelling (Lanz)

PROGRAM OF THE COURSE

Thursday 13:15-17:00

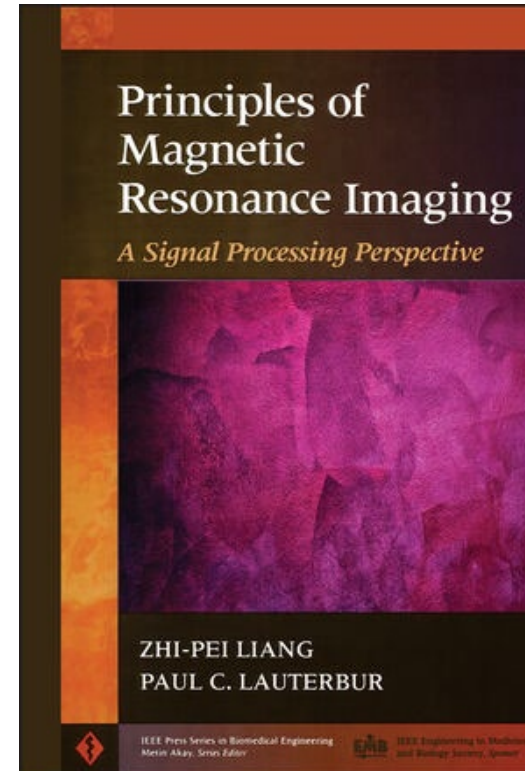
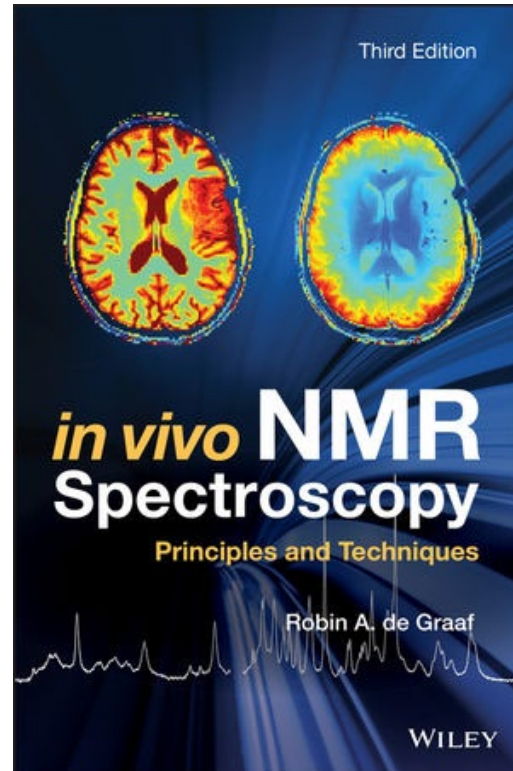


Session 9: Apr 17, 2025	Session 11: May 8, 2025	Session 13: May 22, 2025	
13:15 – 16:00: - 1H MRS quantification(Cudalbu) 16:15-17:00 - Fast Magnetic Resonance Spectroscopic Imaging and reconstruction techniques (Klauser)	13:15 – 17:00: Lab for structure MRI processing (VBM and SBM) and fMRI (Bach Cuadra & Fornari)	13:15 – 17:00: Animal MRI & MRS practical teaching (Lanz, Cudalbu)	
Session 10: May 1, 2025	Session 12: May 15, 2025		
13:15 – 17:00: Theory of clinical MRI segmentation and registration. Introduction to surface and voxel based morphometry (VBM and SBM) and fMRI processing. (Bach Cuadra & Fornari)	13:15 – 17:00: Data processing using in-house developed tools for MRS and MRI (Cudalbu)		

LEARNING OUTCOMES

- Know the essential elements in designing a translational neuroimaging study
- Understand the physical principles of MRI and MRS
- Know how to establish MRI and MRS acquisition protocols
- Know how to perform experiments independently on clinical and preclinical scanners, and analyze results for the research topic of interest.
- Know how to interpret results of neuroimaging and MRS data

STUDY RESOURCE



- <https://www.youtube.com/playlist?list=PL471uBfQUs9qcODBkQGJTZkcbIIKrjKry>

EXAM: MINI PROPOSAL Submission deadline: June 15th



Topics: free-choice, including novel elements (methods or topics) beyond your current project

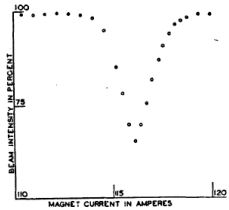
1. Project summary (max. 1 page)
2. Project plan (max. 5 pages)
 - background
 - hypothesis and aims
 - research approaches (study design, MR protocols, justification for methods of choice, data processing methods, statistical plan)
 - description of the potential impact of the research project
3. Bibliography

OUTLINE

- History: from NMR to MRI
- Introduction to MRI & MRS: structure, function, and metabolism
- Translational applications in psychiatric diseases
- MRI procedure & safety

HISTORY: FROM NMR TO MRI

- (1924) By Pauli, nuclear particles have angular momentum (spin)
- (1937) By Rabi, measurement of magnetic moment of nucleus, "magnetic resonance"
- (1946) Edward Purcell, matter absorbs energy at a resonant frequency
- (1946) Felix Bloch, nuclear precession can be measured in detector coils
- (1959) Singer, measurement of blood flow using NMR (in mice)
- (1972) Damadian, patent idea for large NMR scanner to detect malignant tissue
- (1973) Paul Lauterbur, publish generating images using NMR gradients
- (1975) Ernst, develop 2D-Fourier transform for MR
- (1990) Ogawa and colleagues, obtain functional images using BOLD contrast
- (2005) UHF 7.0 T MRI developed by Harvard, NIH, Gachon, and Magdeburg



Magnetic

Resonance

Imaging

1920 1930 1940 1950 1960 1970 1980 1990 2000 2010 2020

- (1944) Rabi, award Nobel Prize in Physics



- (1952) Purcell and Bloch, share Nobel Prize in Physics



- (1973) Peter Mansfield, published gradient approach to MR

- (1980s) 1.5 T and 2.0 T superconducting MRI developed by Goldstar, GE, and Siemens

- (2003) Lauterbur and Mansfield, share Nobel Prize in Physiology and Medicine

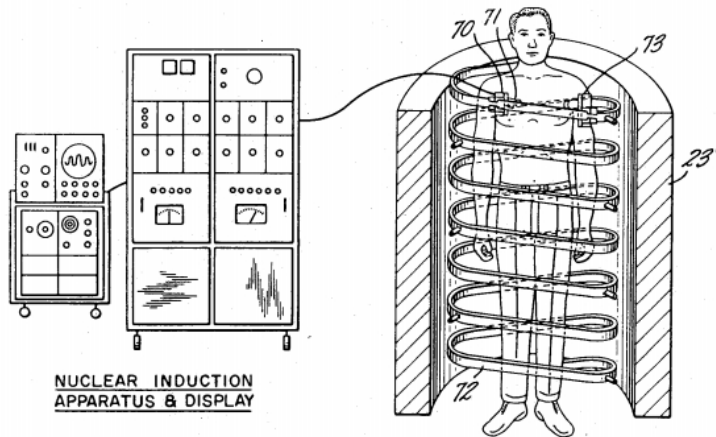


- 1991: Richard Ernst Chemistry (High-resolution pulsed FT-NMR)

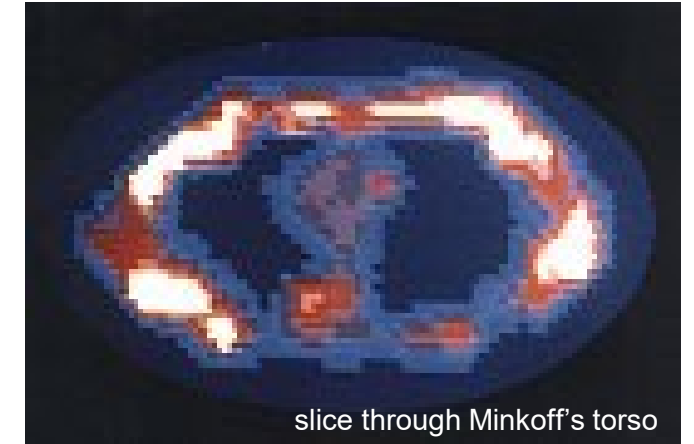


FIRST HUMAN MRI (1977)

Damadian's grad student, Larry Minkoff, in "Indomitable", the first MRI scanner



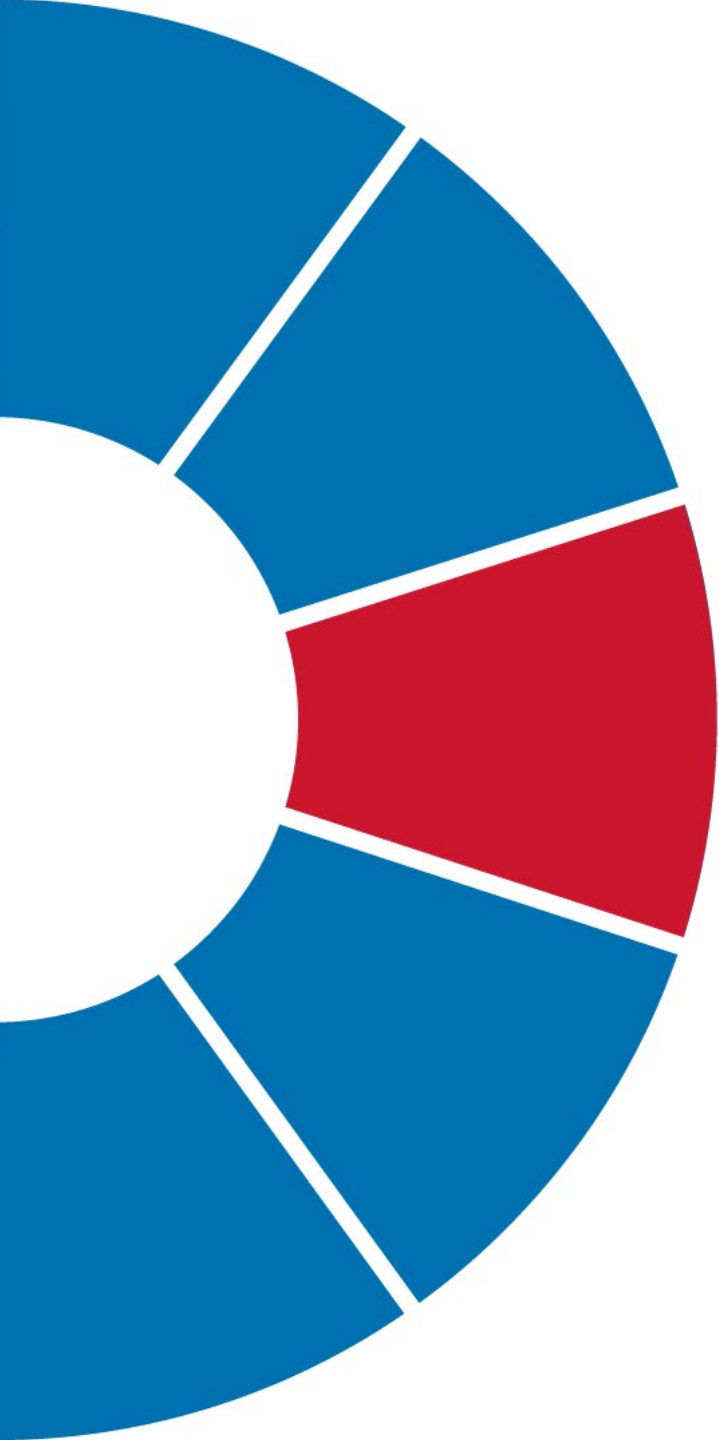
Damadian's 1972 patent application



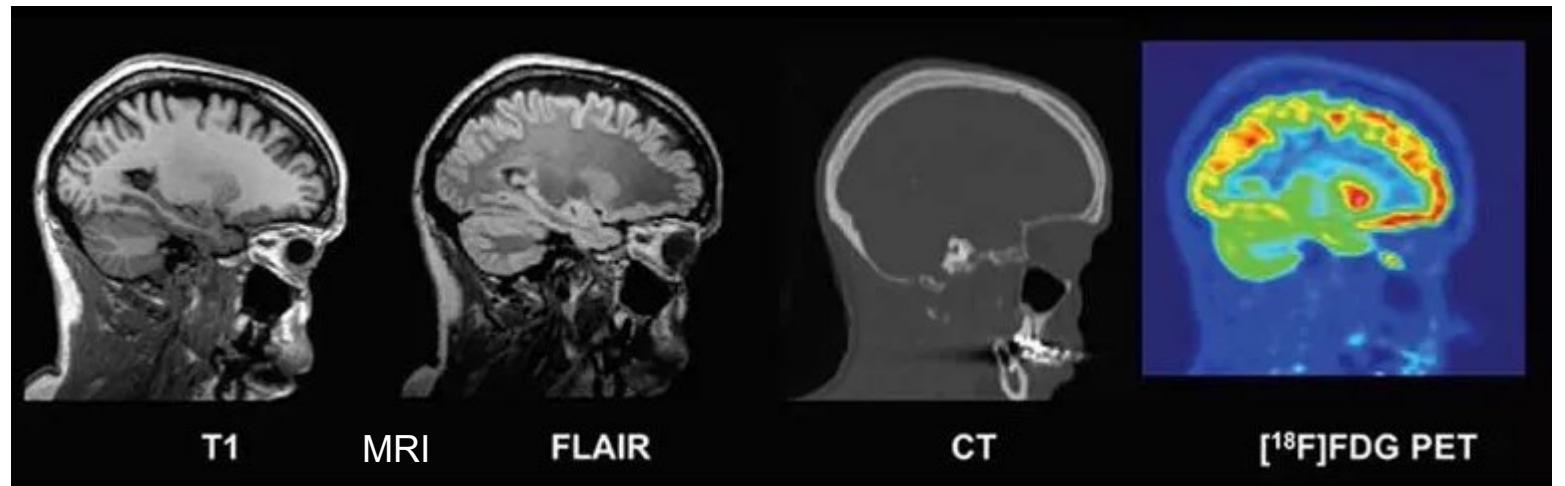
slice through Minkoff's torso

4 hours to get one slice

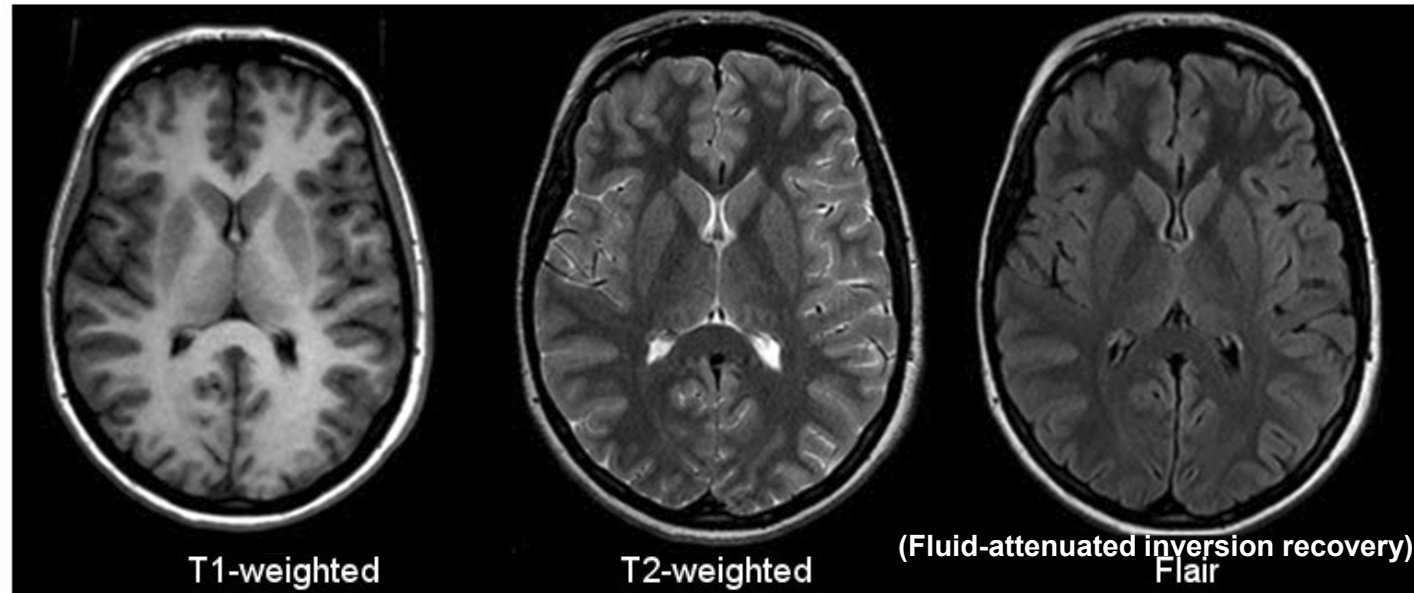
<https://www.smithsonianmag.com/science-nature/the-indomitable-mri-29126670/>



MRI: STRUCTURE, FUNCTION, METABOLISM



STRUCTURAL MRI: TISSUE CONTRAST

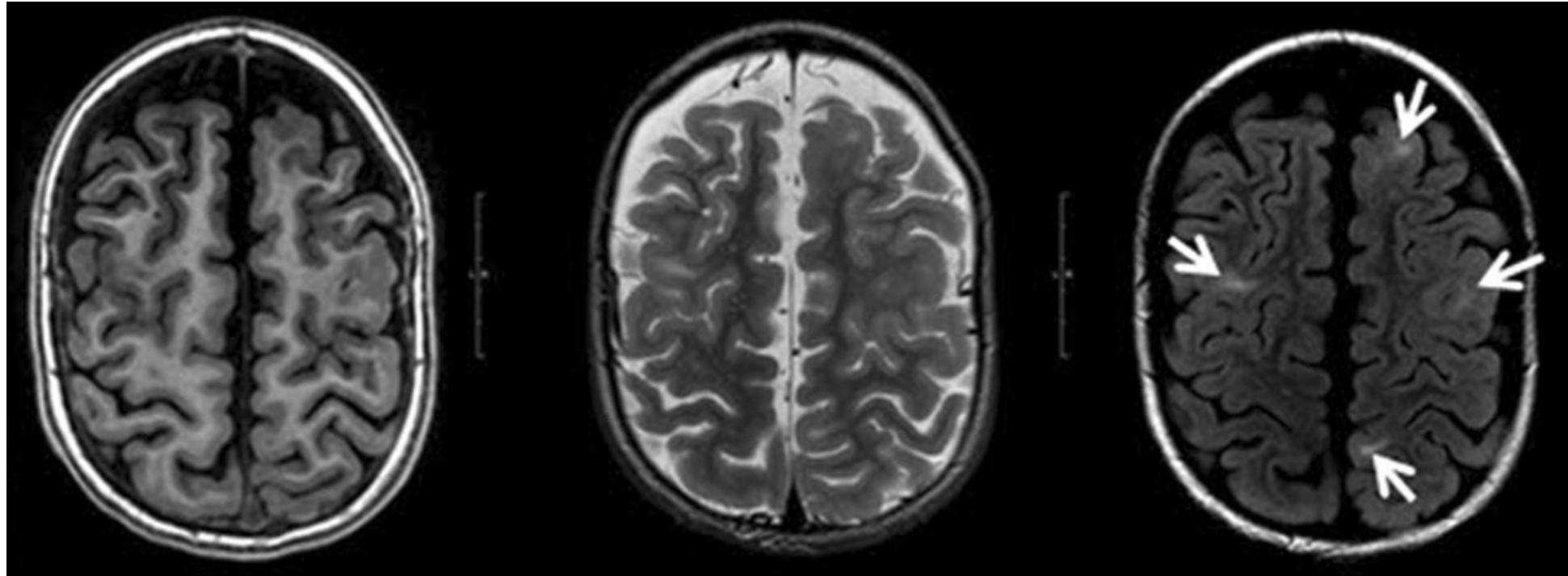


Various tissue contrasts :
for different purposes

Tissue	T1-Weighted	T2-Weighted	Flair
CSF	Dark	Bright	Dark
White Matter	Light	Dark Gray	Dark Gray
Cortex	Gray	Light Gray	Light Gray
Fat (within bone marrow)	Bright	Light	Light
Inflammation (infection, demyelination)	Dark	Bright	Bright

<https://case.edu/med/neurology/NR/MRI%20Basics.htm>

MRI IN TUBEROUS SCLEROSIS



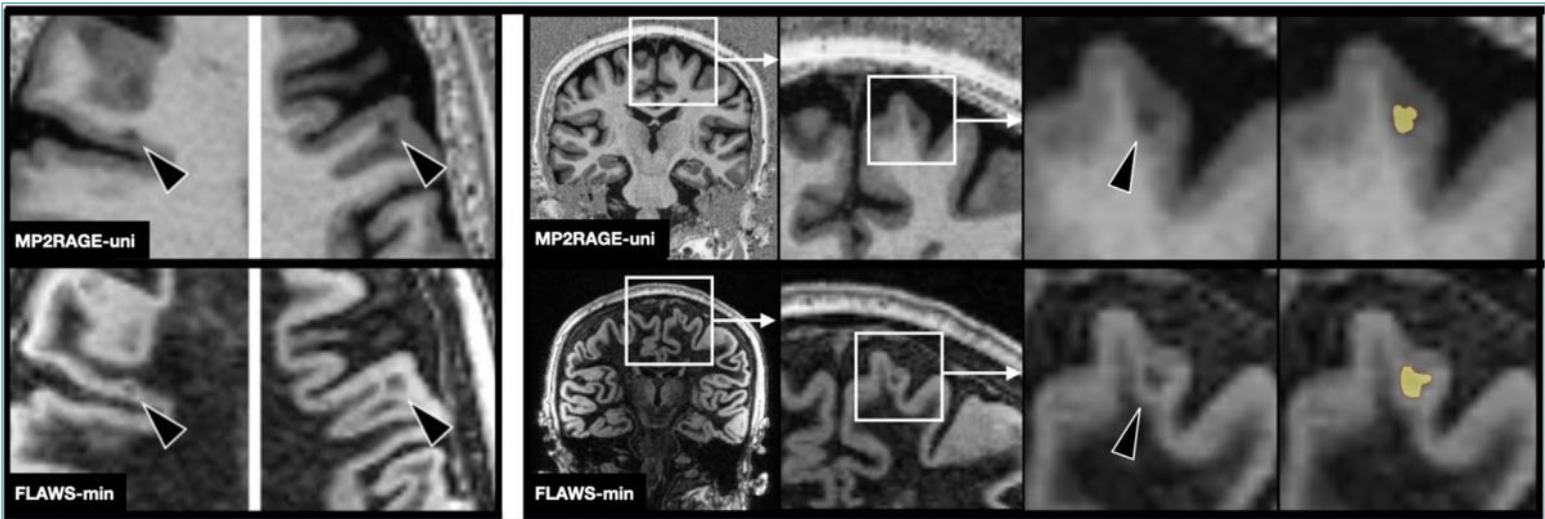
T1-weighted

T1-weighted

T2-FLAIR

CORTICAL LESION DETECTION IN MULTIPLE SCLEROSIS

MP2RAGE: T1 weighted



FLAWS: T1 weighted + fluid and white matter suppression

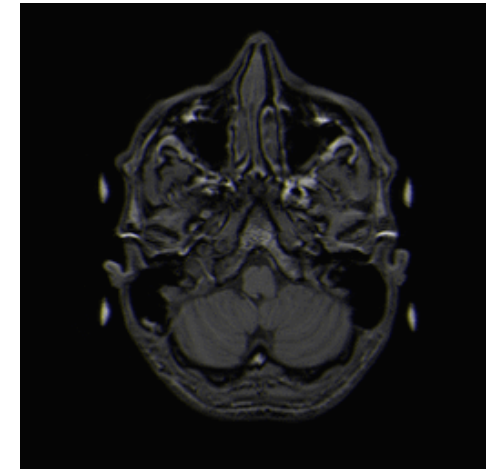
TABLE 1 - Magnetic Resonance Imaging Sequence Parameters

	MP2RAGE	FLAWS
Resolution, voxel size, mm ³	1.0 × 1.0 × 1.0	1.0 × 1.0 × 1.0
Orientation	Sagittal	Sagittal
Phase encoding	Anteroposterior	Anteroposterior
FoV, mm ³	256 × 240 × 176	256 × 240 × 192
TR/TE, ms	5000/2.98	5000/2.19
Ti 1, ms	700	449
Ti 2, ms	2500	1270
Flip angle 1, degrees	4	5
Flip angle 2, degrees	5	6

FLAWS, fluid and white matter suppression; FoV, field of view; MP2RAGE, magnetization prepared 2 rapid acquisition gradient echo; TE, echo time; Ti, 1 inversion time 1; Ti, 2 inversion time 2; TR, repetition time.

STRUCTURAL MRI MEASURES

- Total brain volume: atrophy, ventricular enlargement (e.g. in Alzheimer's disease)

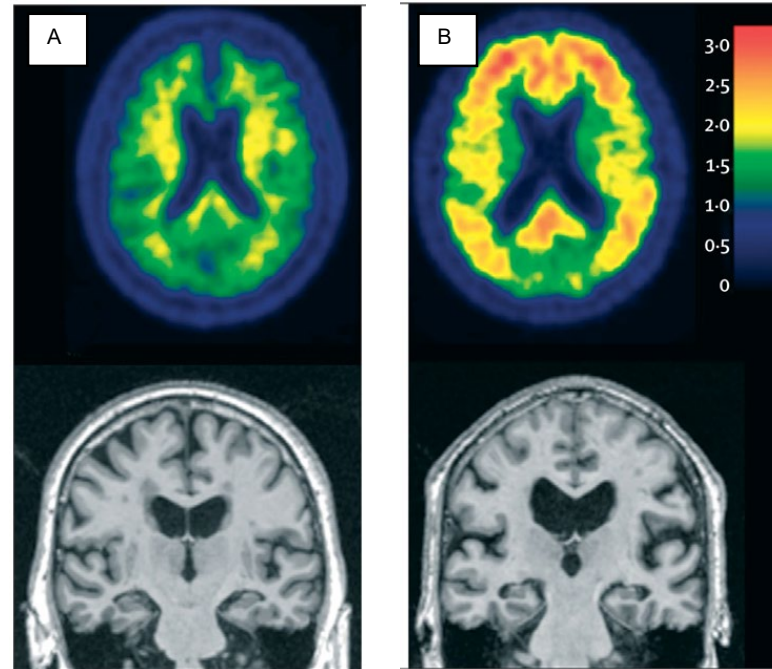


MRI IN ALZHEIMER'S DISEASE

PET Amyloid-Beta($A\beta$) Imaging
Brain $A\beta$ -plaque deposition



MRI
Neurodegeneration



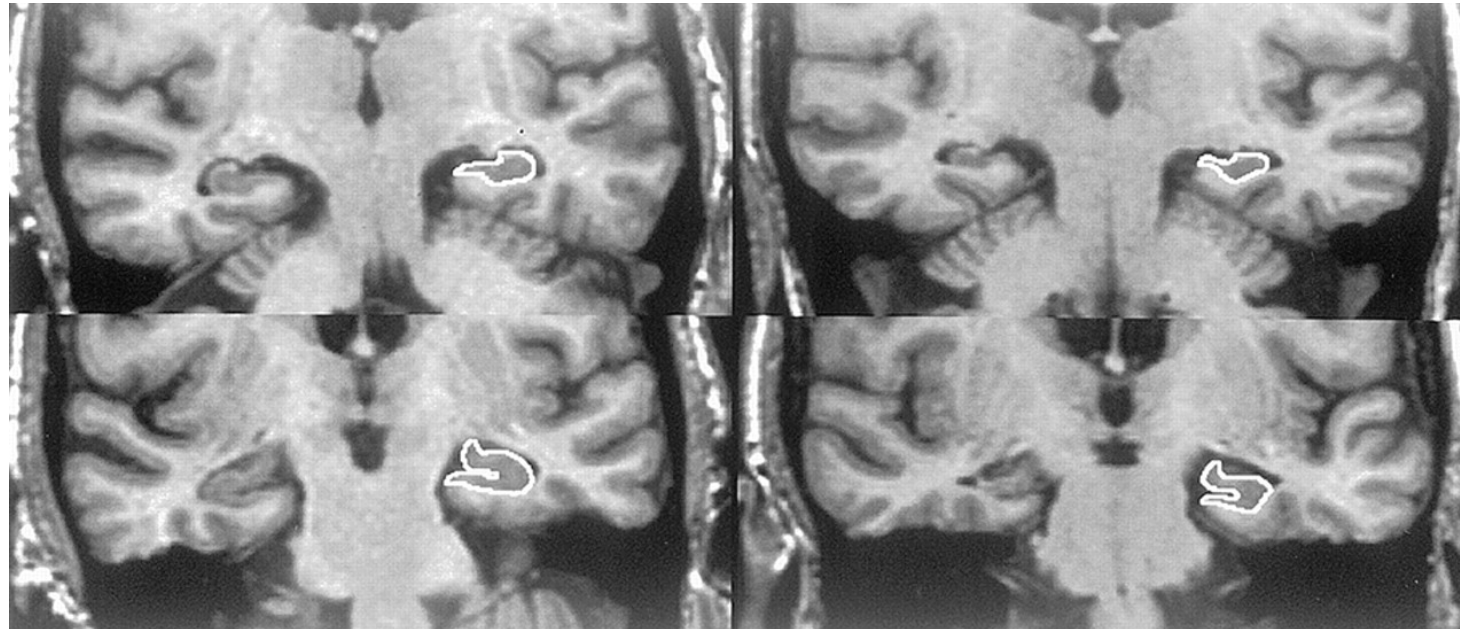
- A. A cognitively normal individual with no evidence of $A\beta$ on PET amyloid imaging and no evidence of atrophy on MRI.
- B. An individual who has dementia and a clinical diagnosis of Alzheimer's disease, a positive PET amyloid imaging study, and neurodegenerative atrophy on MRI.

STRUCTURAL MRI MEASURES

- Total brain volume: atrophy, ventricular enlargement (e.g. in Alzheimer's disease)
- Volume of specific brain structure (e.g Hippocampus: reduction in dementia)

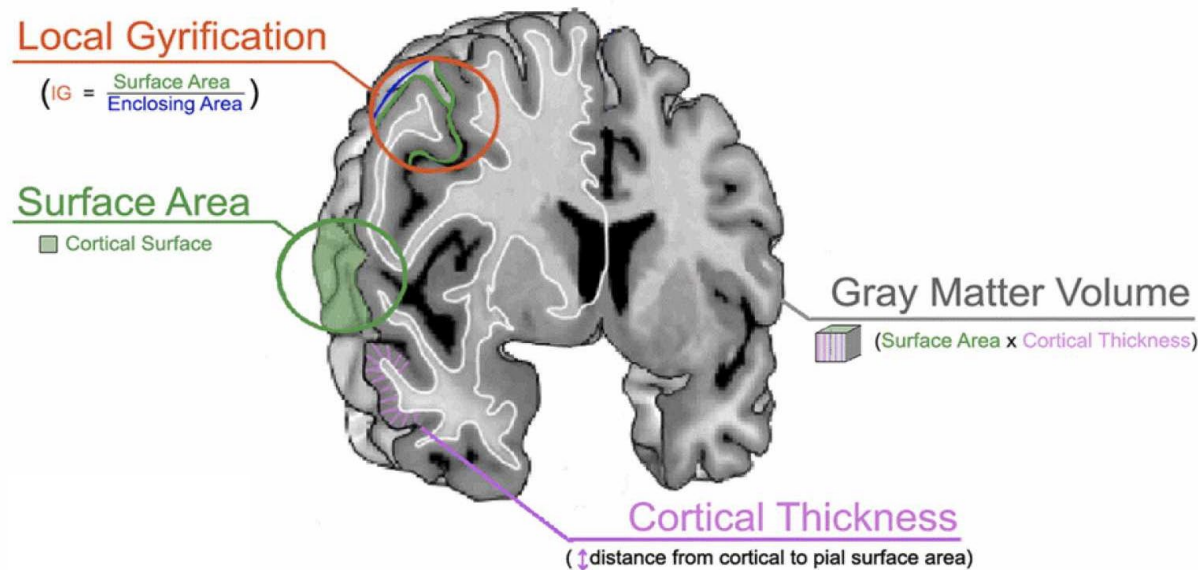
Patient (mild cognitive impairment)

Patient (AD)

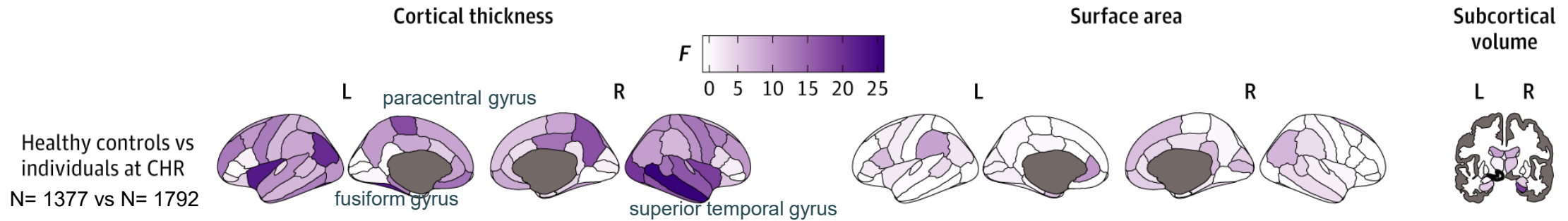


STRUCTURAL MRI MEASURES

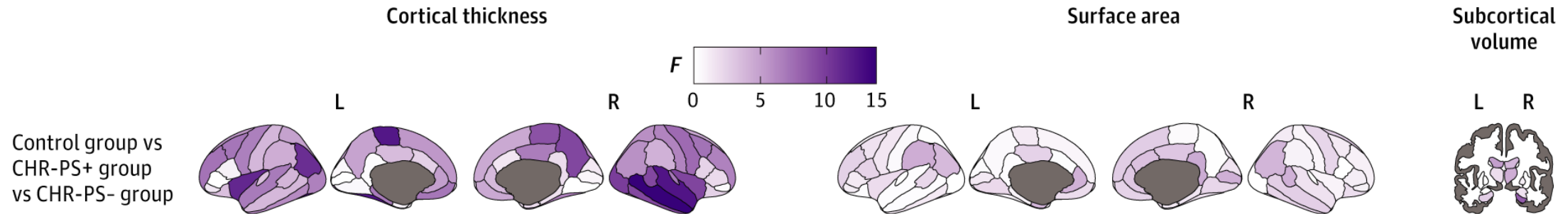
- Total brain volume: atrophy, ventricular enlargement (e.g. in Alzheimer's disease)
- Volume of specific brain structure (e.g Hippocampus: reduction in dementia)
- Cortical volume, surface area, thickness, gyrification



STRUCTURAL MRI MEASURES IN INDIVIDUALS AT CLINICAL HIGH RISK FOR DEVELOPING PSYCHOSIS



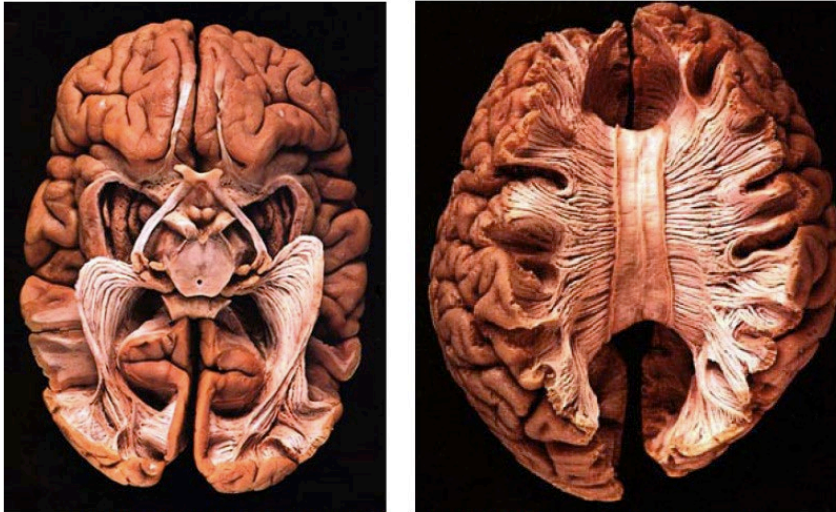
Low cortical thickness in individuals at clinical high risk (CHR)



Transition to psychosis was robustly associated with lower cortical thickness

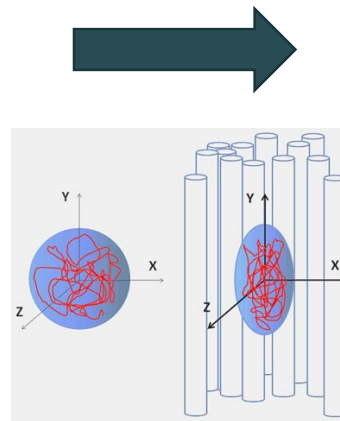
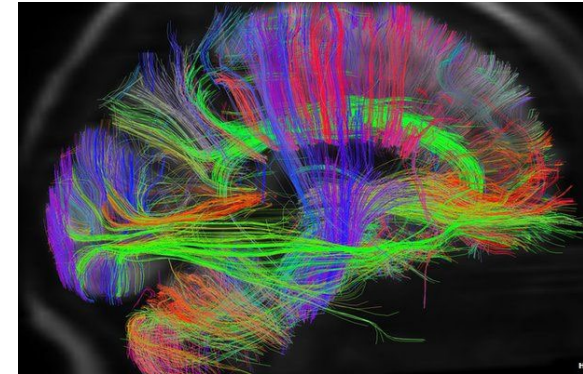
DIFFUSION MRI

white matter tracts in dissected brain



From: The Virtual Hospital (www.vh.org); TH Williams, N Gluhbegovic, JY Jew

white matter tracts in the living brain



Brownian motion of water

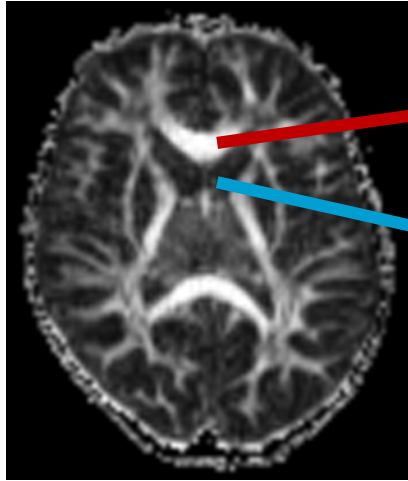
Diffusion MRI

- red = left-right
- green = anterior-posterior
- blue = superior-inferior

C I B M . C H

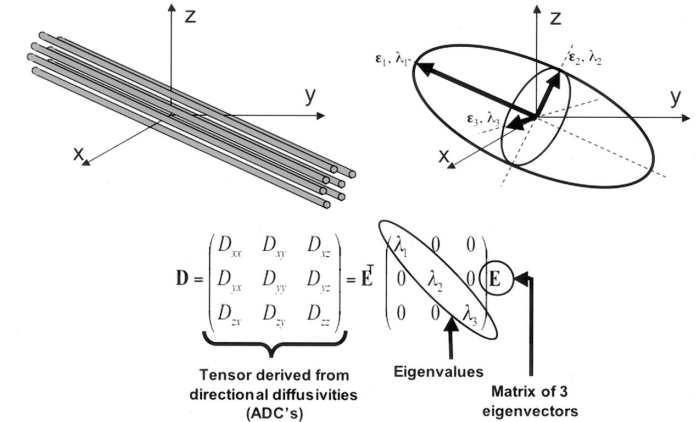
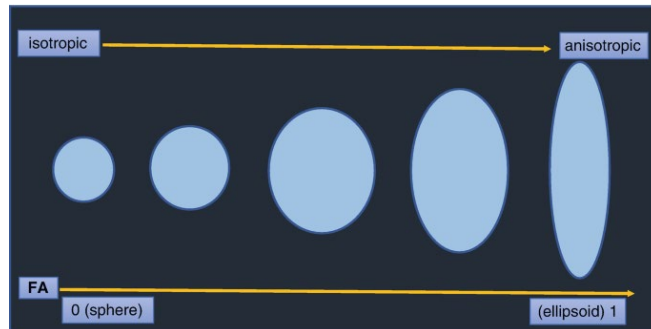
DIFFUSION TENSOR IMAGING (DTI) MEASURES

Fractional Anisotropy (FA) mapping



High FA, anisotropic, high WM integrity

Low FA, isotropic, low WM integrity



■ Fractional Anisotropy (FA)

- the directionality of water diffusion in brain tissue
- integrity and organization of white matter tracts

$$\sqrt{\frac{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$$

low high

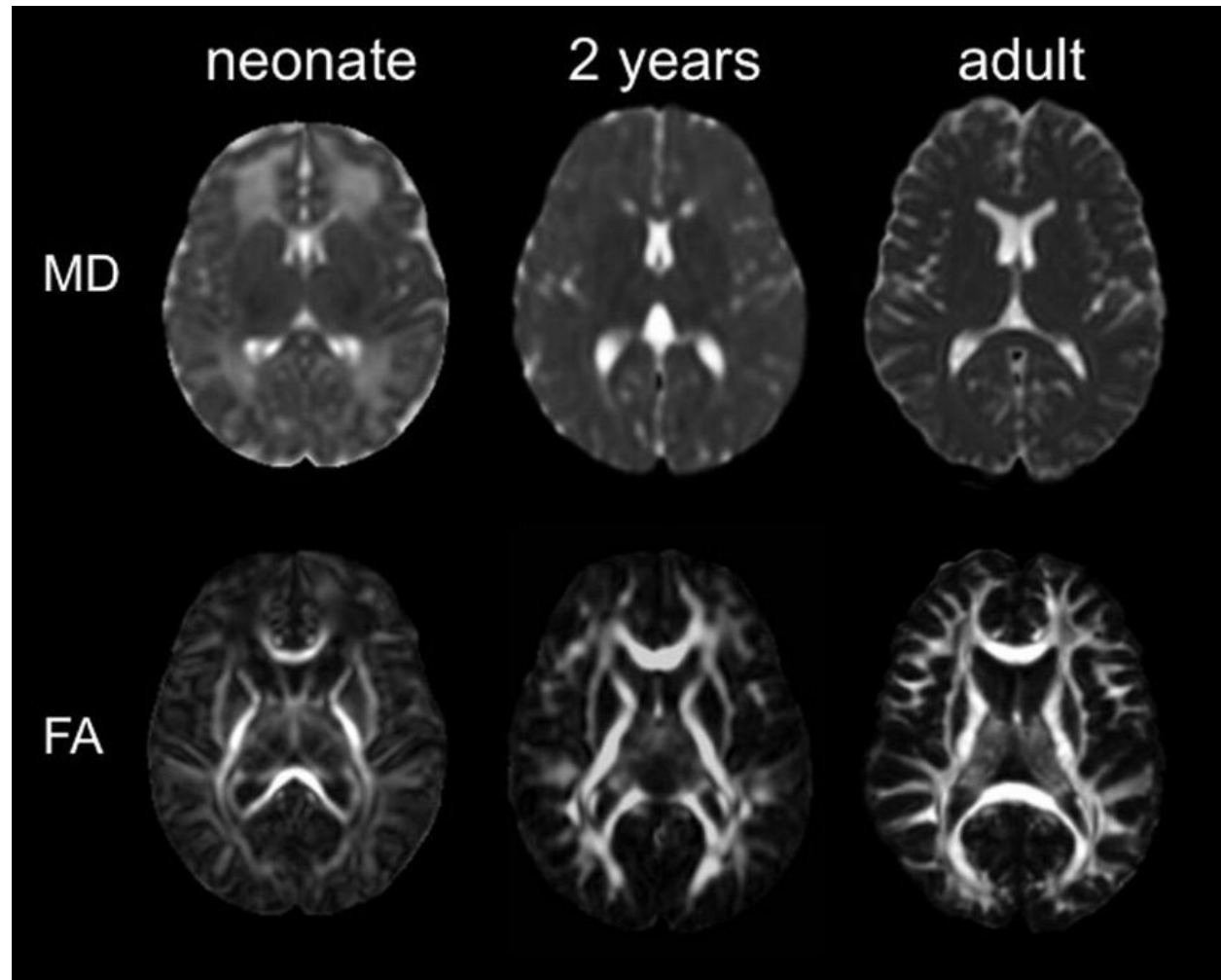
■ Mean Diffusivity (MD)

- average water diffusion in one voxel
- cellularity of white matter tracts

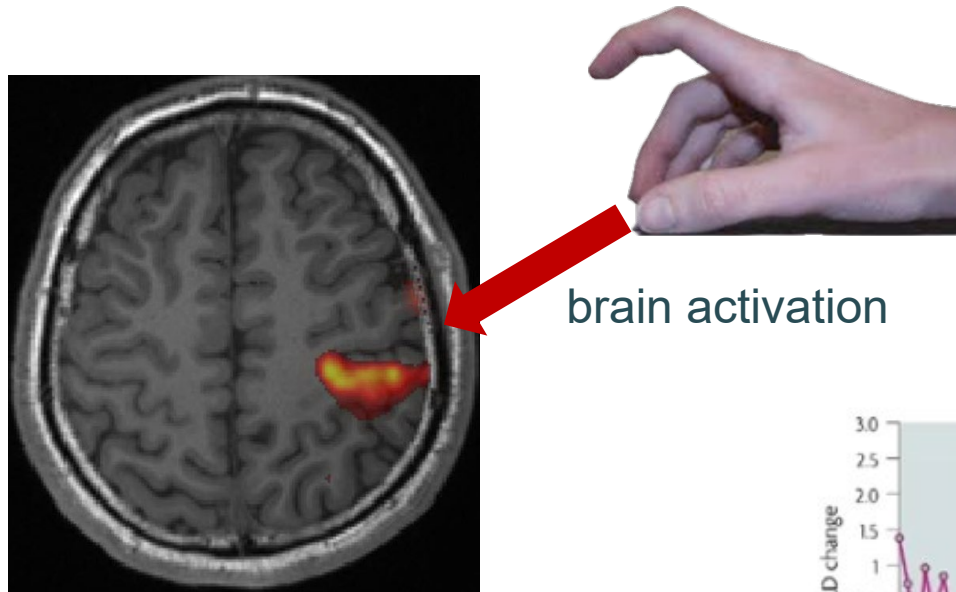
$$\frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

low high

DIFFUSION TENSOR IMAGING (DTI) MEASURES

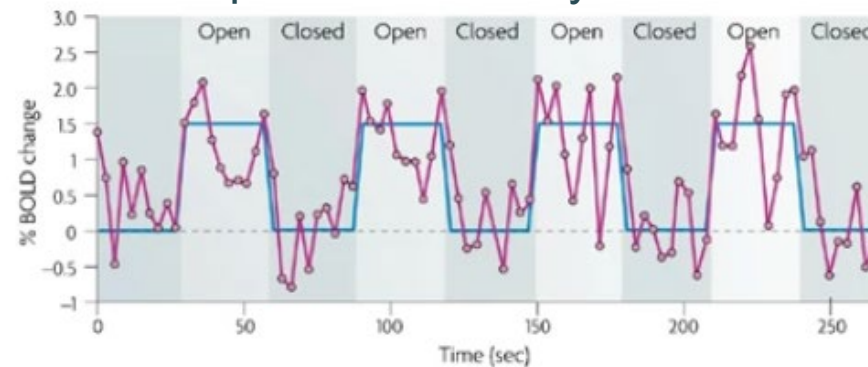


FUNCTIONAL MRI (fMRI)

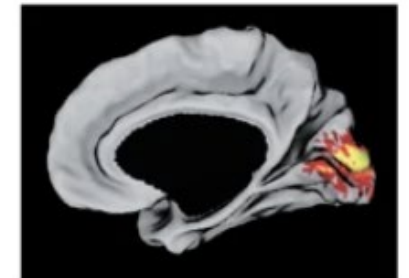


brain activation

open and close eyes



Open - Closed =

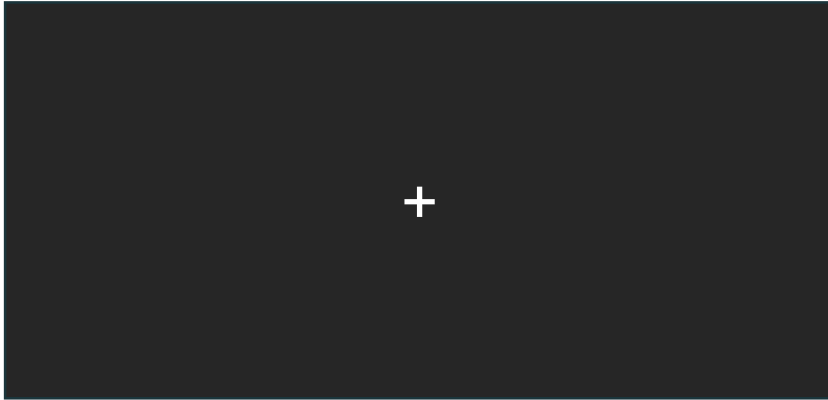


Blood Oxygen Level Dependent signal (BOLD)

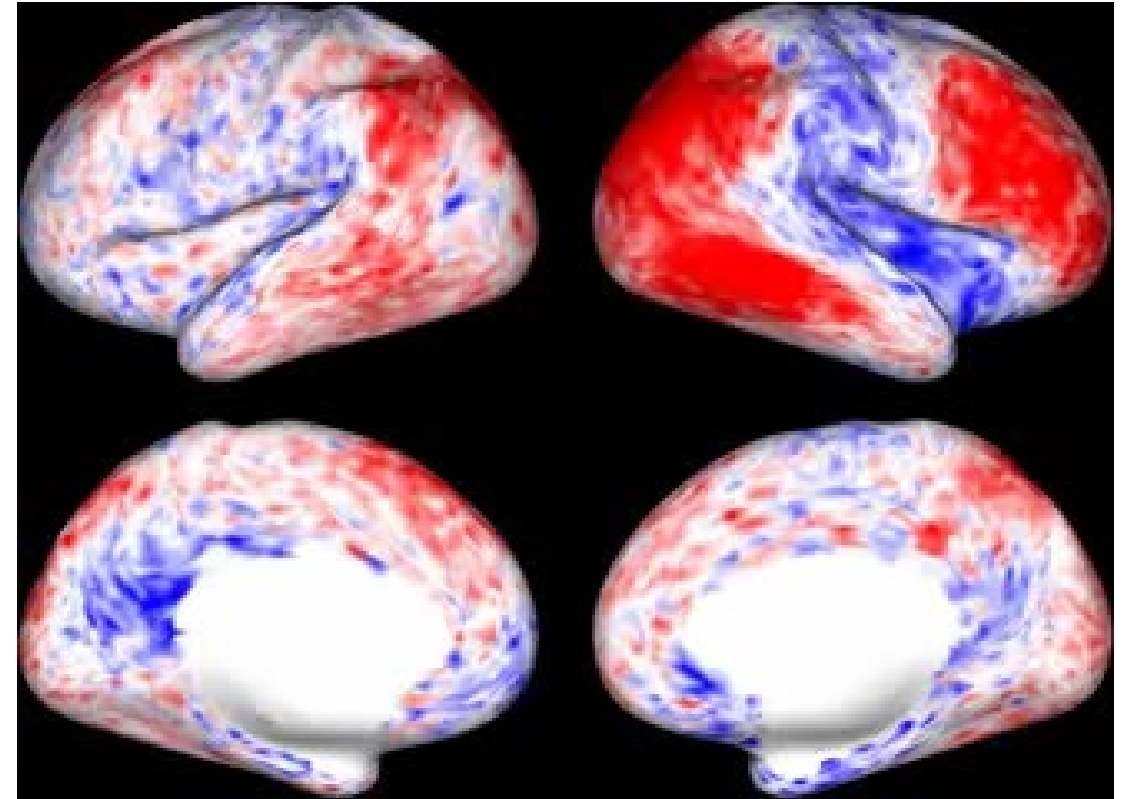
↑neural activity → ↑ blood flow → ↑ oxyhemoglobin → ↑ T2* → ↑ MR signal

RESTING STATE FMRI

Activity Fluctuations During Rest



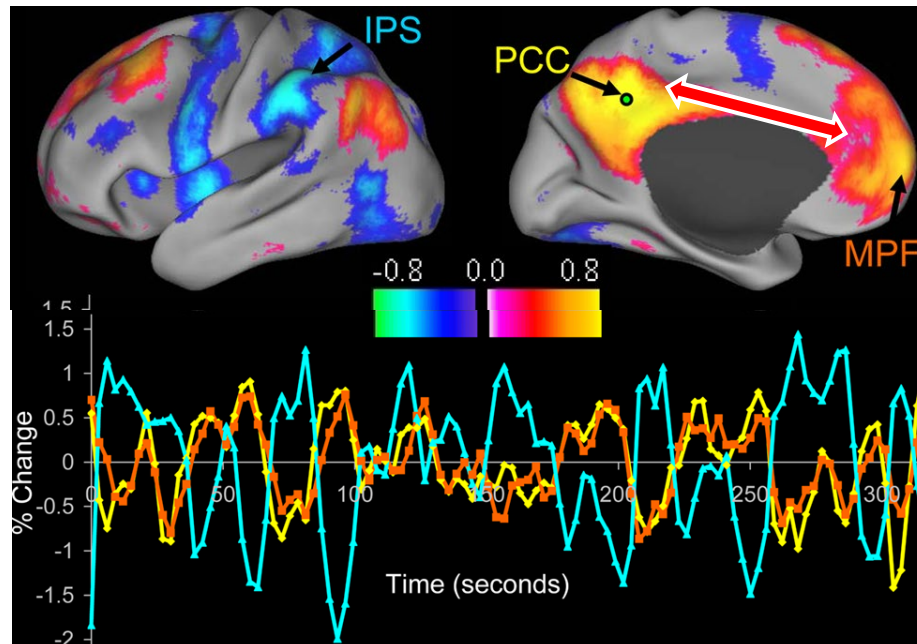
“Please look at the white cross in the middle of the screen, try not to fall asleep, and let your mind wonder.”



<https://en.wikipedia.org/wiki/File:Temporal-Non-Local-Means-Filtering-Reveals-Real-Time-Whole-Brain-Cortical-Interactions-in-Resting-pone.0158504.s002.ogv>

FUNCTIONAL CONNECTIVITY

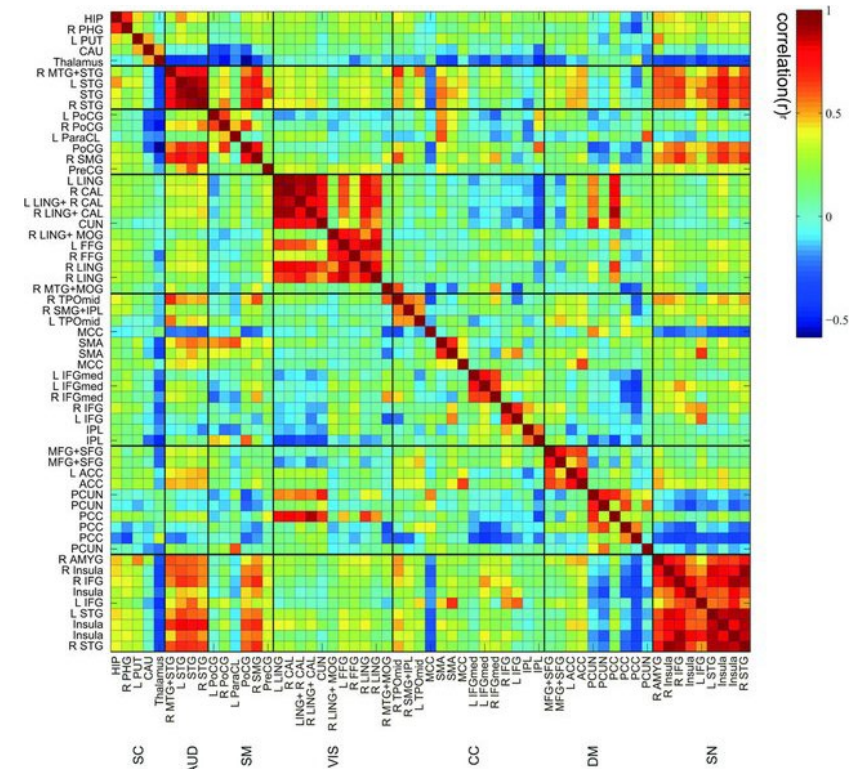
■ Temporal correlation between spontaneous BOLD signal



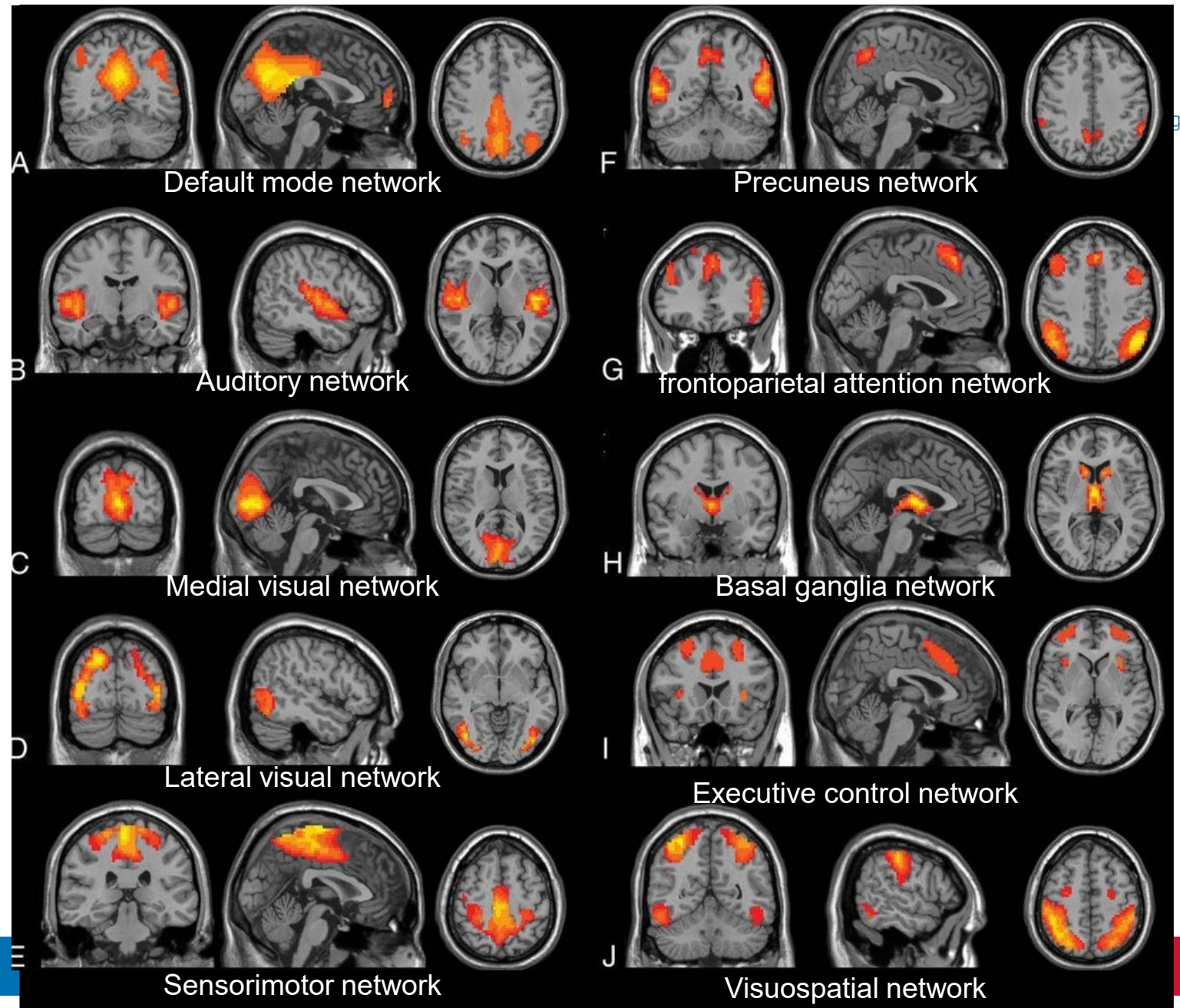
Inferior parietal cortex (IPS)

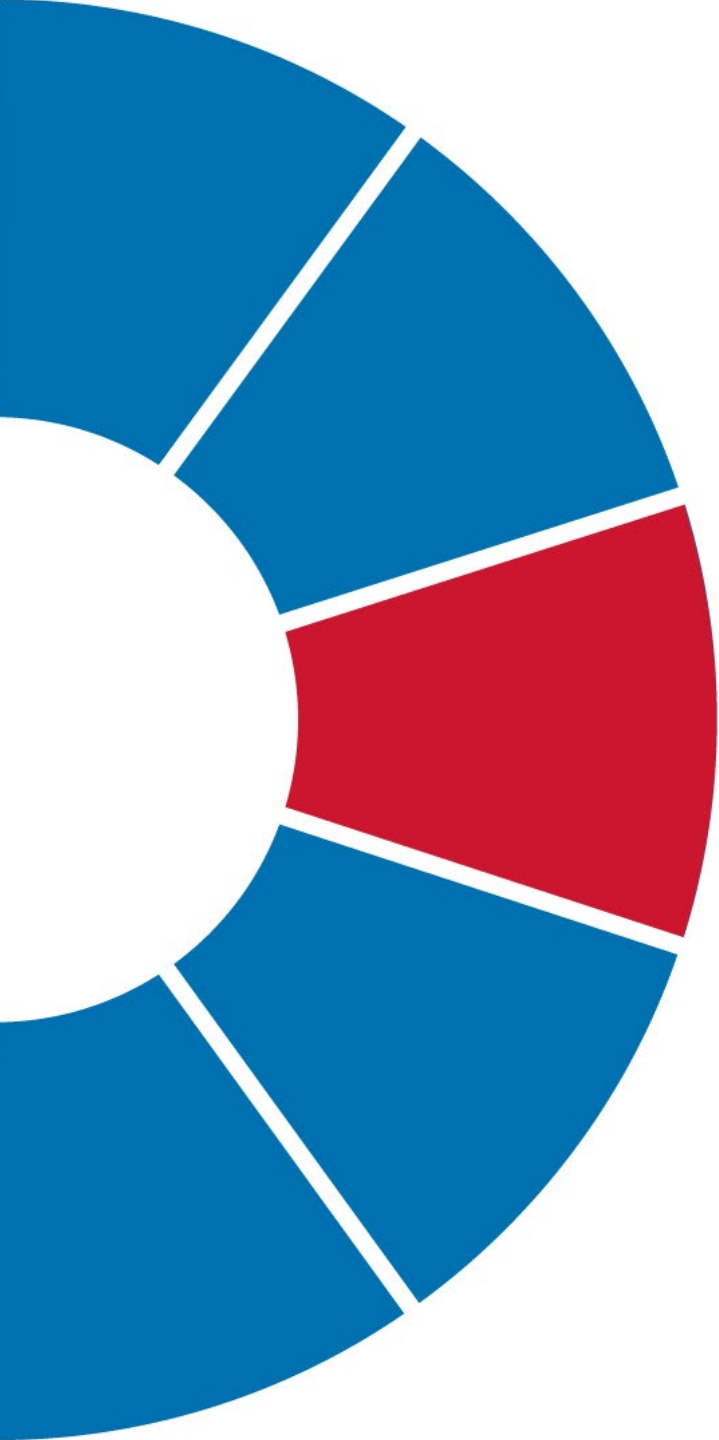
Posterior cingulate cortex (PCC)

Medial prefrontal cortex (MPFC)



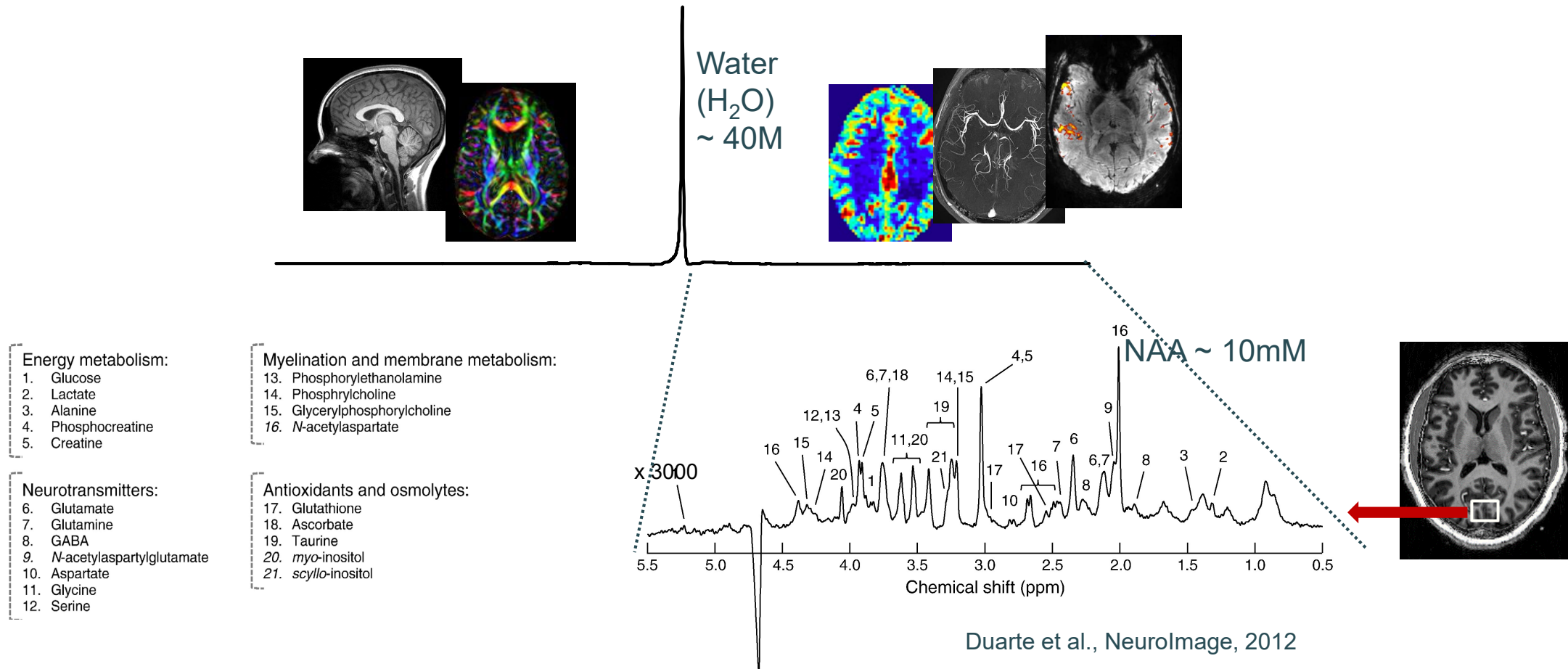
TYPICAL NETWORKS





BREAK

METABOLISM: MR SPECTROSCOPY (MRS)



ROLE OF MAJOR BRAIN METABOLITES

¹H MRS

Single metabolites

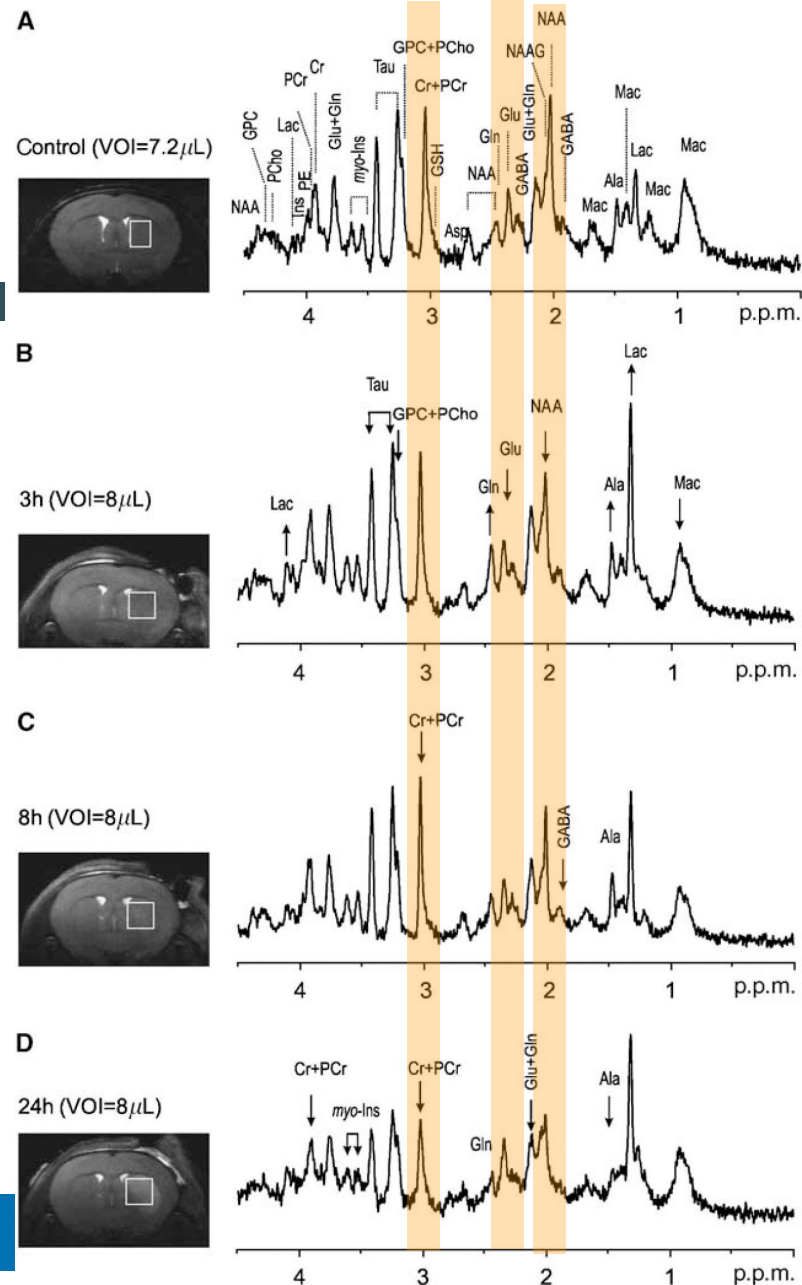
Lactate (Lac)	End product of anaerobic glycolysis Marker of inflammation in the subacute phase
Creatine (Cr), phosphocreatine (PCr)	Energy metabolism, PCr is a reserve of high-energy phosphates
N-acetylaspartate (NAA)	No complete understanding of its function, but reduced levels with brain injury Possibly a marker of neuronal viability, density, and mitochondrial function Also present in oligodendroglia progenitors Precursor of N-acetylaspartylglutamate
Myoinositol	Osmolyte, marker of glial cell proliferation
Choline (Cho)	Marker of cell membrane synthesis and breakdown, precursor for acetylcholine
Lipids	Marker of membrane degradation
Glutamate	Excitatory neurotransmitter, high concentrations in neurons
Glutamine	Derivative of glutamate, de novo synthesis exclusively in astrocytes
GABA	Neurotransmitter with excitatory properties in the immature brain (inhibitory in the adult brain)
Aspartate	Excitatory neurotransmitter
Taurine	Osmolyte, antioxidative properties, inhibitory neurotransmitter
Glutathione	Antioxidant

Berger et al., Dev neurosci,(2017)

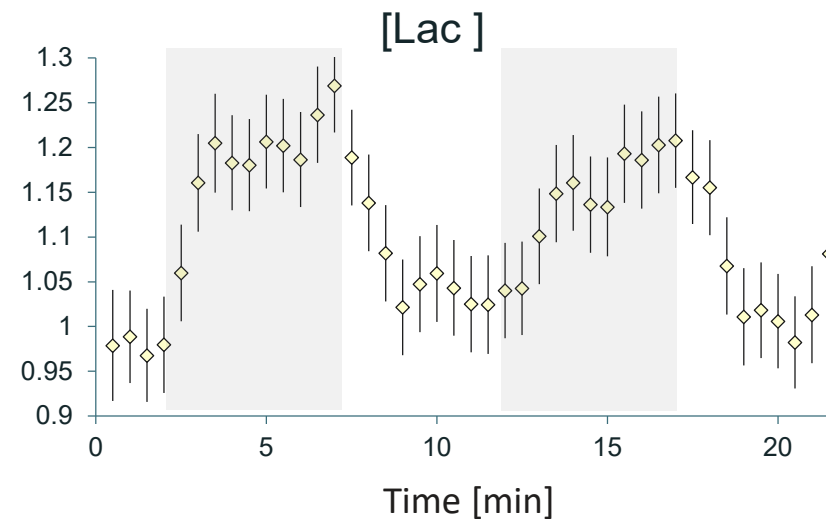
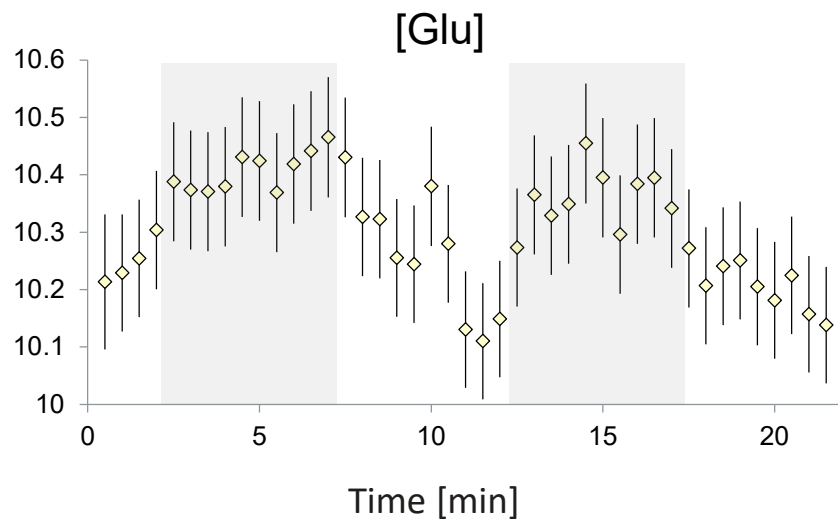
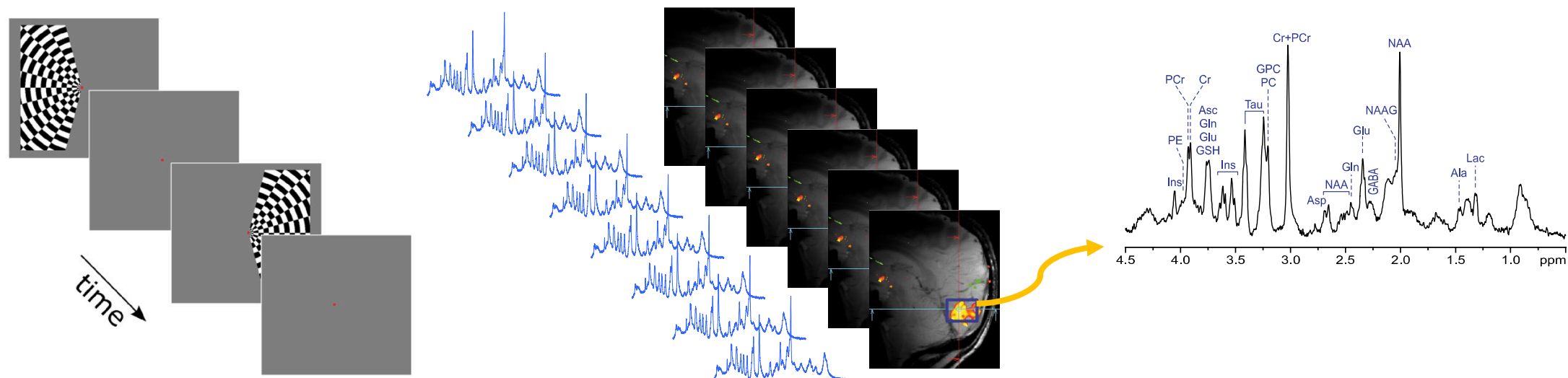
APPLICATION OF ^1H MRS

Evolution of the neurochemical profile after ischemia (30 mins of middle cerebral artery occlusion)

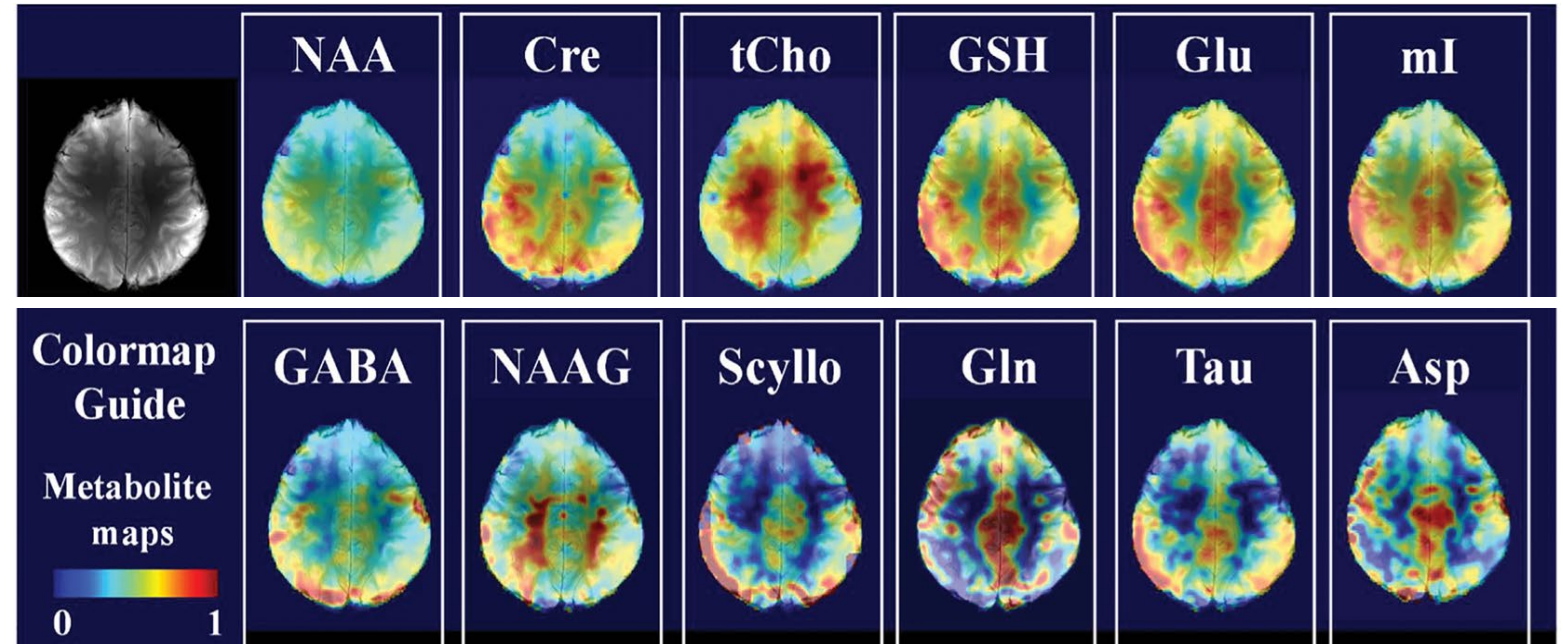
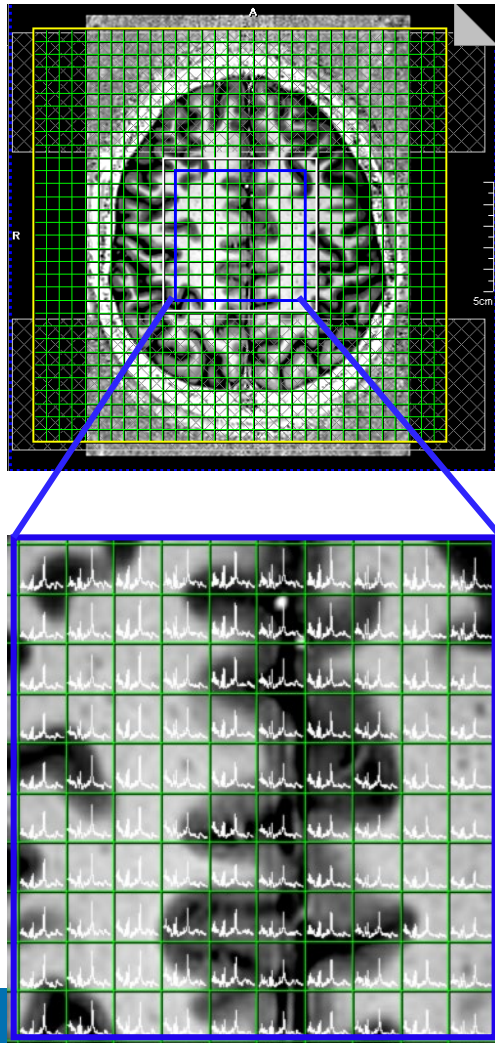
- energy metabolism
- glutamate excitotoxicity
- neuronal viability



FUNCTIONAL MRS

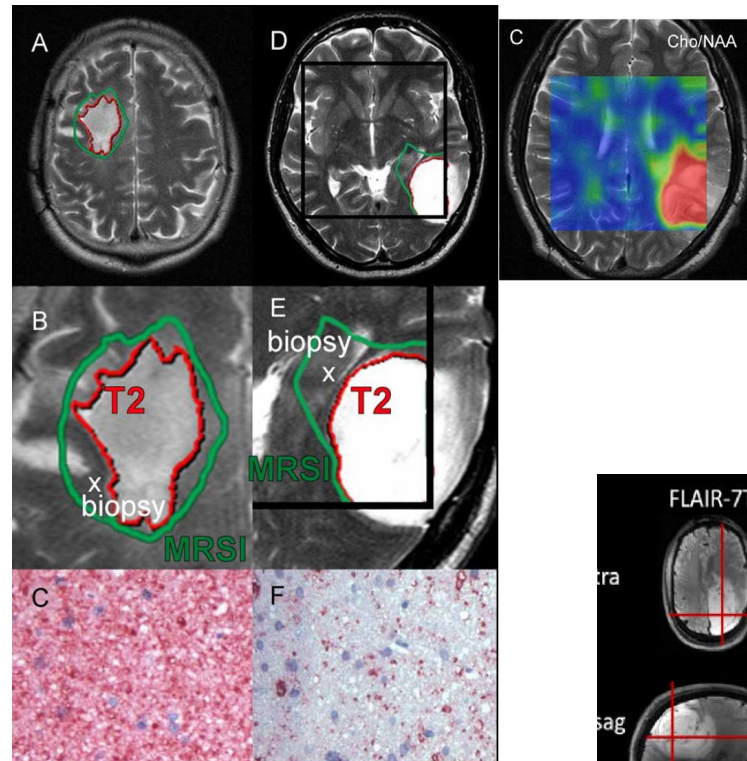


^1H MR SPECTROSCOPIC IMAGING (MRSI)

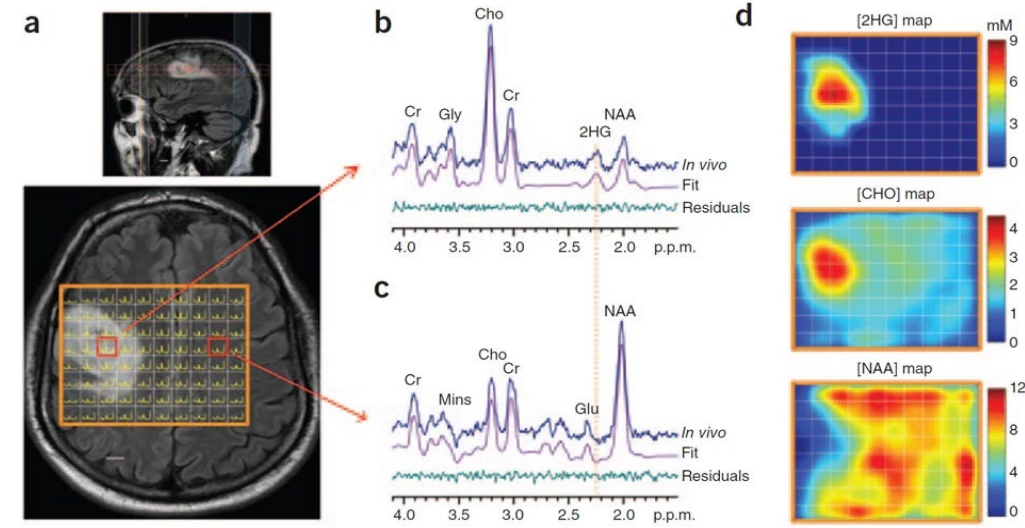


Nassirpour et al., NeuroImage (2018).

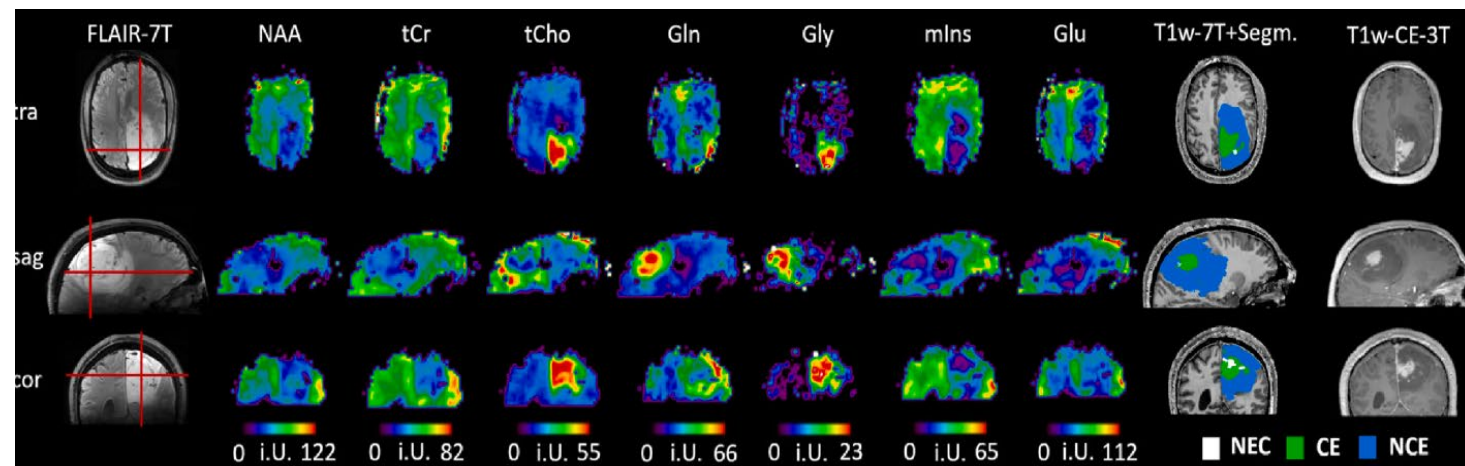
^1H MRSI IN BRAIN TUMORS



Stadlbauer et al., NeuroImage (2004)



Choi et al., Nature Medicine (2012)



Hangel et al., NeuroImage: Clinical (2020)

X-NUCLEI (BEYOND ^1H)

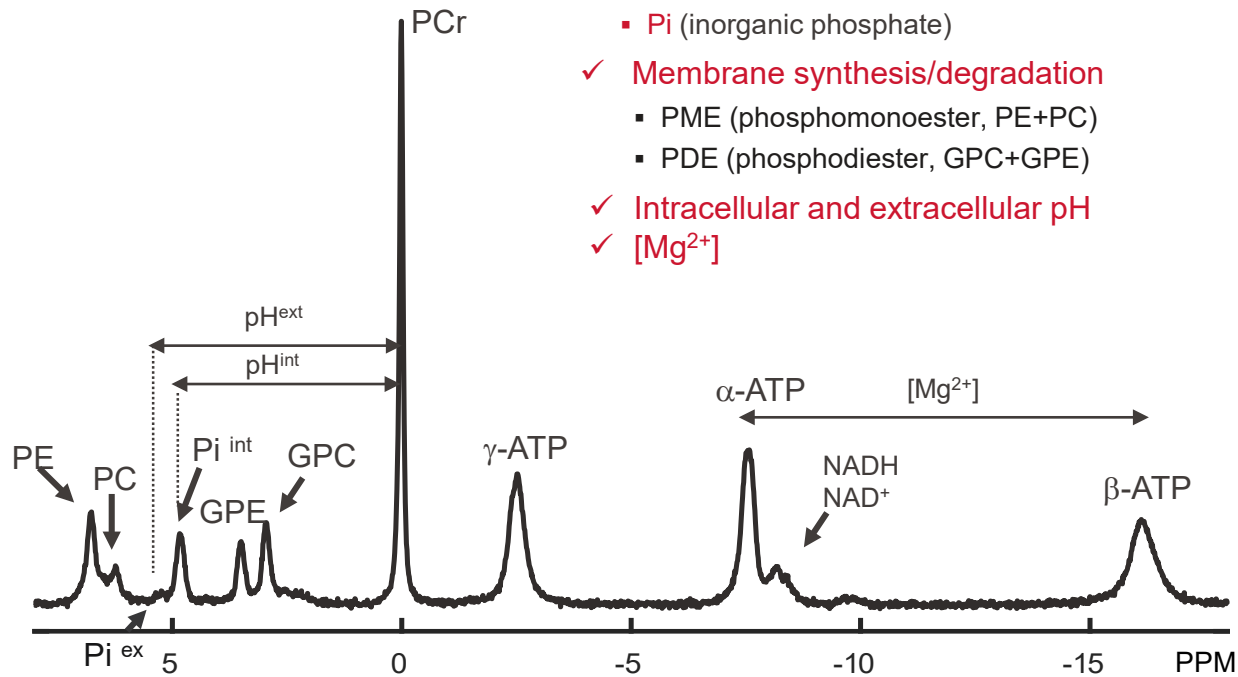
Isotope	Natural abundance	γ ($10^6 \text{ rad} \cdot \text{s}^{-1} \text{ T}^{-1}$)	Highest sensitivity, Mostly used in MRI and MRS
^1H	0.99985	267.522	
^2H	0.00015	41.066	
^{12}C	0.989	—	
^{13}C	0.01108	67.283	
^{14}N	0.9963	19.338	
^{15}N	0.0037	-27.126	
^{16}O	0.99963	—	
^{17}O	0.00037	-36.279	
^{23}Na	1	70.801	
^{31}P	1	108.394	

Low
natural abundance

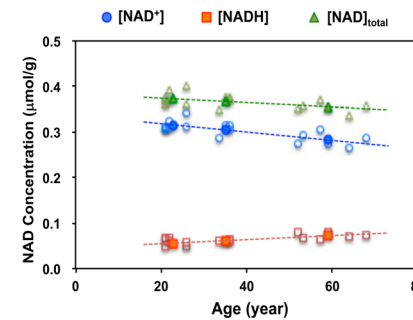
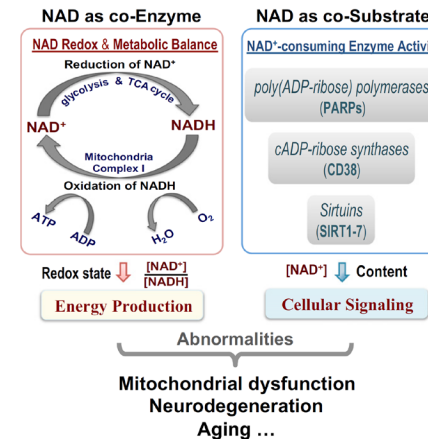
low sensitivity

^{31}P MRS

- ✓ Energy metabolites
 - ATP (adenosine triphosphate)
 - PCr (phosphocreatine)
 - Pi (inorganic phosphate)
- ✓ Membrane synthesis/degradation
 - PME (phosphomonoester, PE+PC)
 - PDE (phosphodiester, GPC+GPE)
- ✓ Intracellular and extracellular pH
- ✓ $[\text{Mg}^{2+}]$

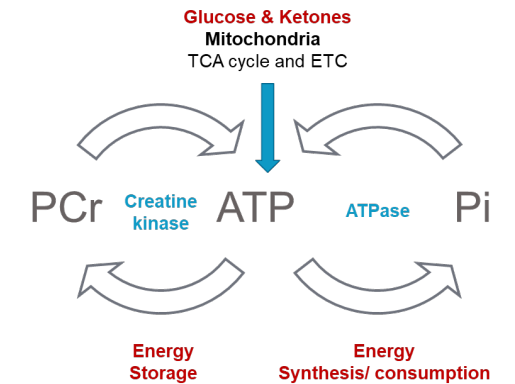


- ✓ Nicotinamide adenine dinucleotide (NAD^+/NADH)

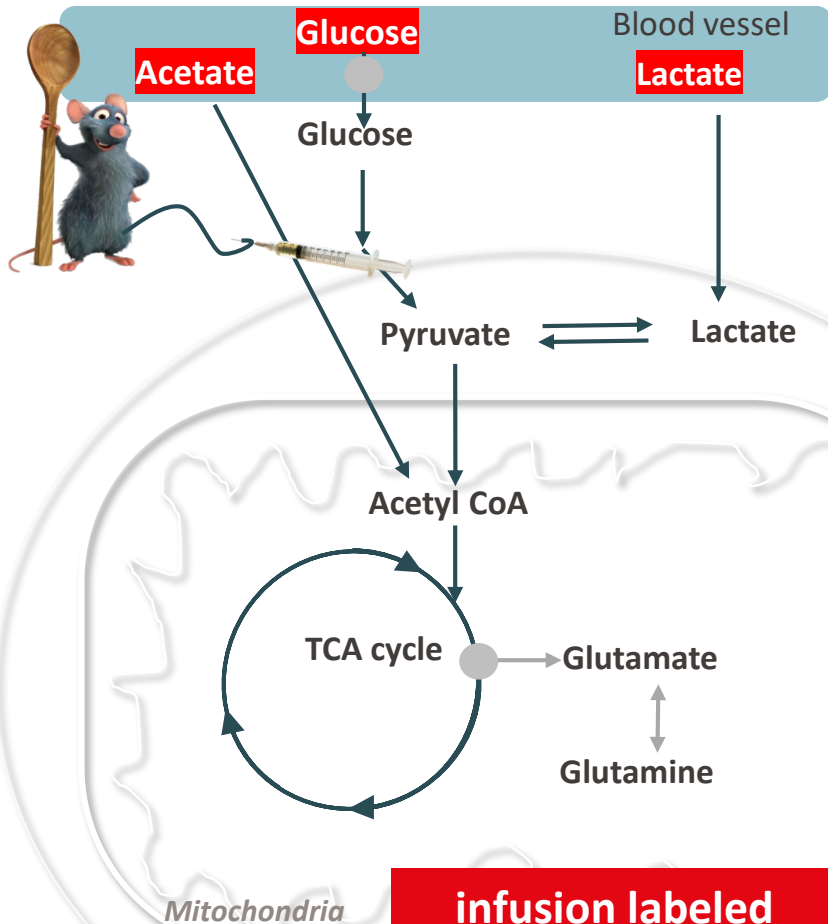


Zhu et al., PNAS, (2015)

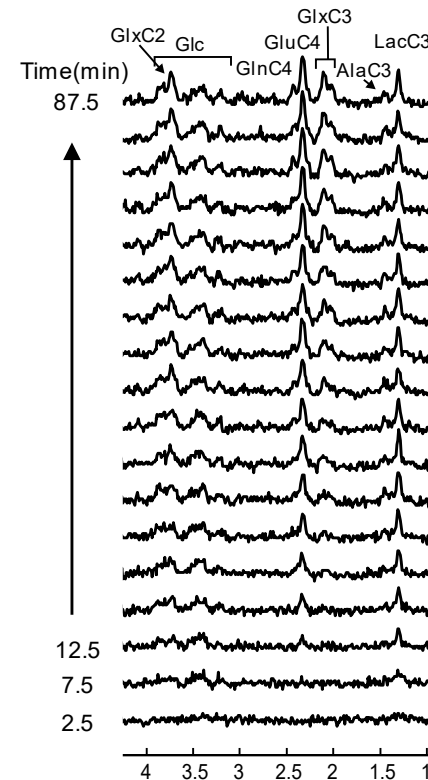
- ✓ ATP metabolism



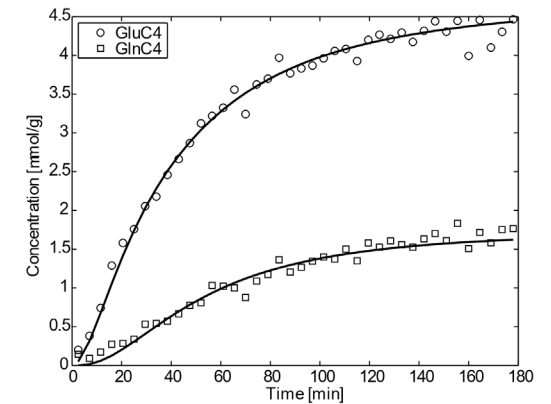
DYNAMIC X-NUCLEI MRS: METABOLIC FLUX



**infusion labeled
substrate
(¹³C, ¹⁷O, ¹⁵N, ²H)**



**probe labeling time
course**



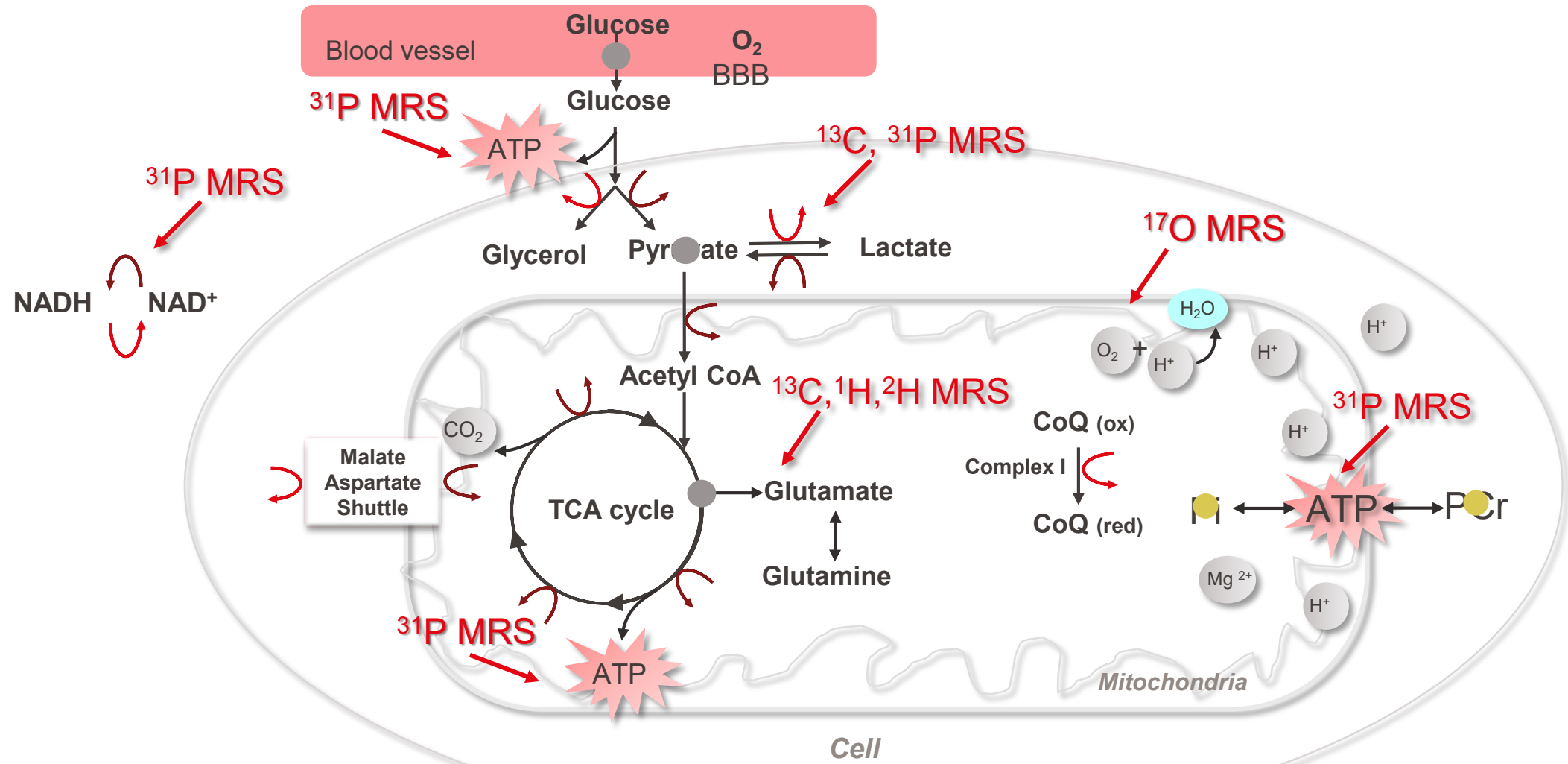
$$\frac{d[P^*]}{dt} = \frac{[S^*]}{[S]} V_1 - \frac{[P^*]}{[P]} V_2$$

neuron TCA flux (V_{TCA_n})
glial TCA flux (V_{TCA_g})
Glu-Gln cycling flux (V_{NT})

**mathematic modeling
(metabolic fluxes)**

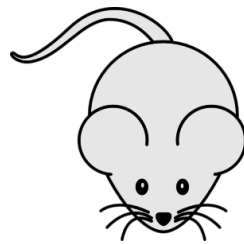
C I B M . C H

X-NUCLEI MRS FOR BRAIN METABOLISM

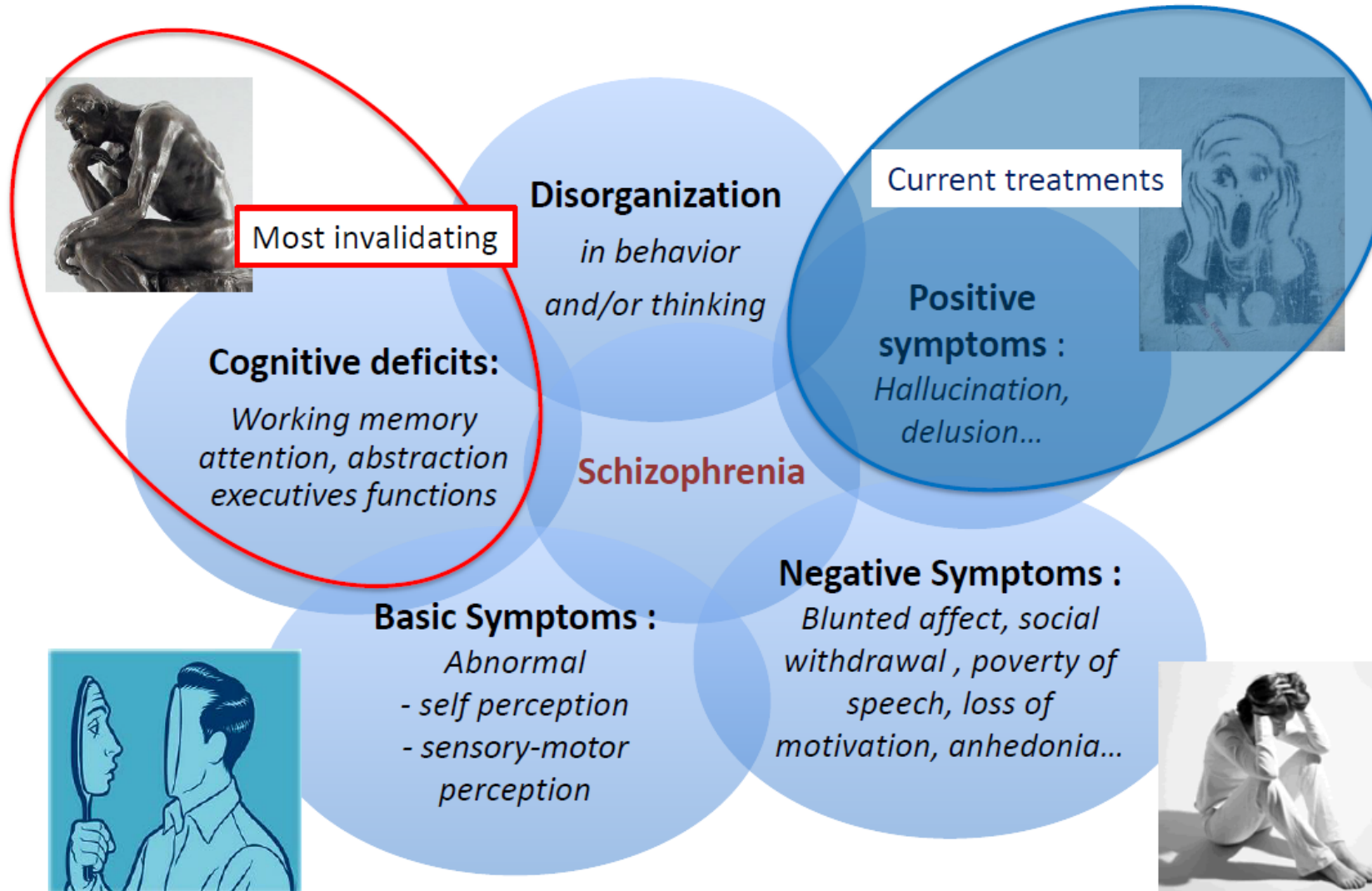




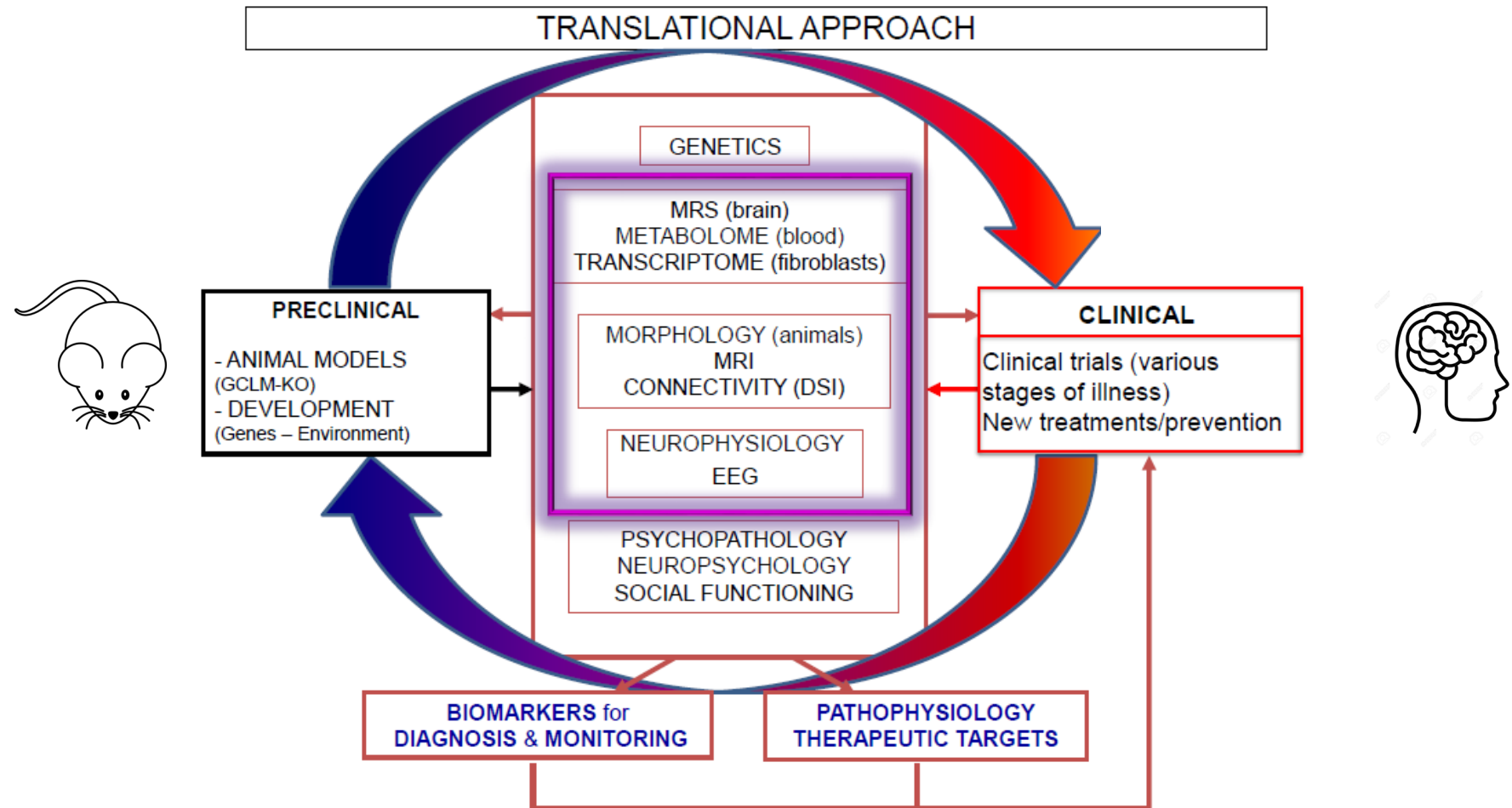
TRANSLATIONAL APPLICATION IN PSYCHIATRIC DISORDERS



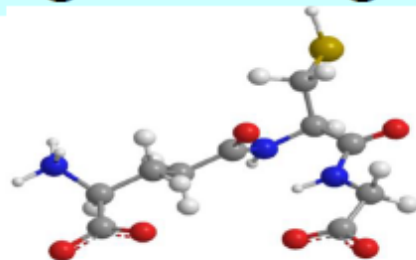
Clinical characteristics of schizophrenia



2008 – 2022: NCCR-SYNAPSY (CHUV, UNIL, EPFL, CIBM)



Schizophrenia vulnerability factor: Redox dysregulation / glutathione synthesis deficit



Tripeptide: γ Glutamyl-Cysteinyl-Glycine

Glutathione (GSH): endogenous **redox regulator** and **antioxidant**

- protect cells from damage by **reactive oxygen species (ROS)**

GSH ↓ prefrontal cortex & cerebrospinal fluid

Do&al. Eur J Neurosci 2000

GSH ↓ in post-mortem brain

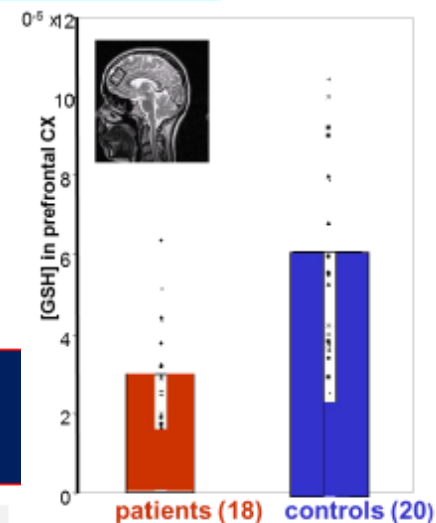
Gawryluk&al.2011; Yao &Keshavan, 2011, Flatow&al, 2013

GSH synthesis **genes associated** with SZ

Gysin &al...Do PNAS 2007; Tosic &al...Do J. Am. Hum. Gen., 2006

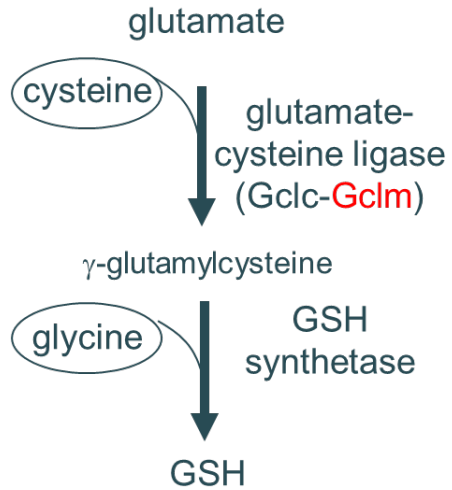
High-Risk GCLC genotypes → synthesis ↓ :
GSH ↓ levels in fibroblasts and brain

Gysin &al...Do PNAS 2007; 2011 L.Xin &al, 2014

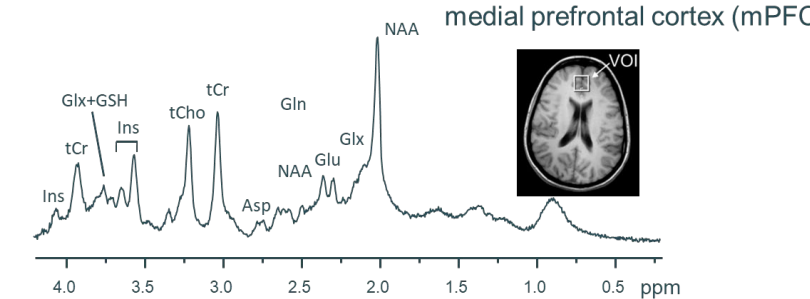


**Decreased prefrontal
GSH in SZ patients**
**Double quantum
coherence 1H-MRS**

GCLC “HIGH-RISK” GENOTYPES → GSH ↓

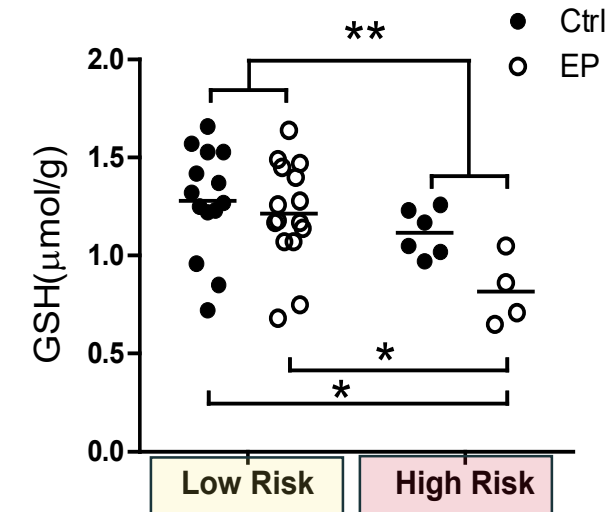
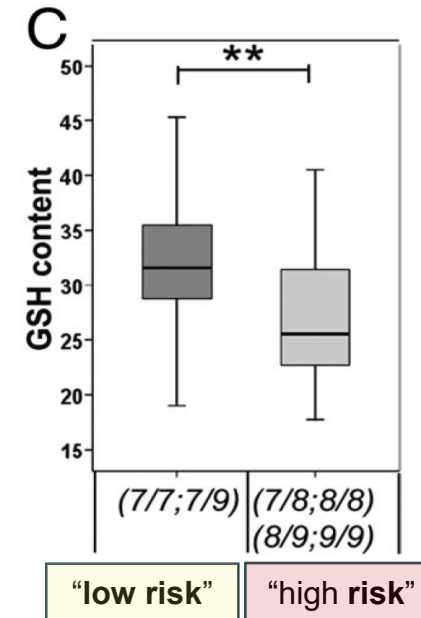
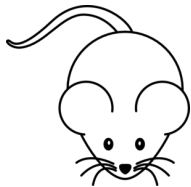


GAG trinucleotide repeat (TNR) polymorphisms in the gene coding for the catalytic (**GCLC**) subunit of GCL associated with schizophrenia



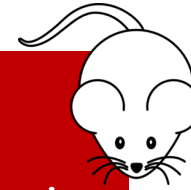
Gclm-KO mice

- low brain GSH levels (- 80-90%)
- resembles characteristic features of schizophrenia: impaired GABAergic parvalbumin-positive interneurons (PVI) in numerous brain regions, abnormal myelination, behavioral anomalies

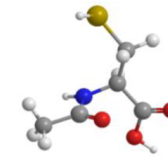


Animal model 14T MRS allows:

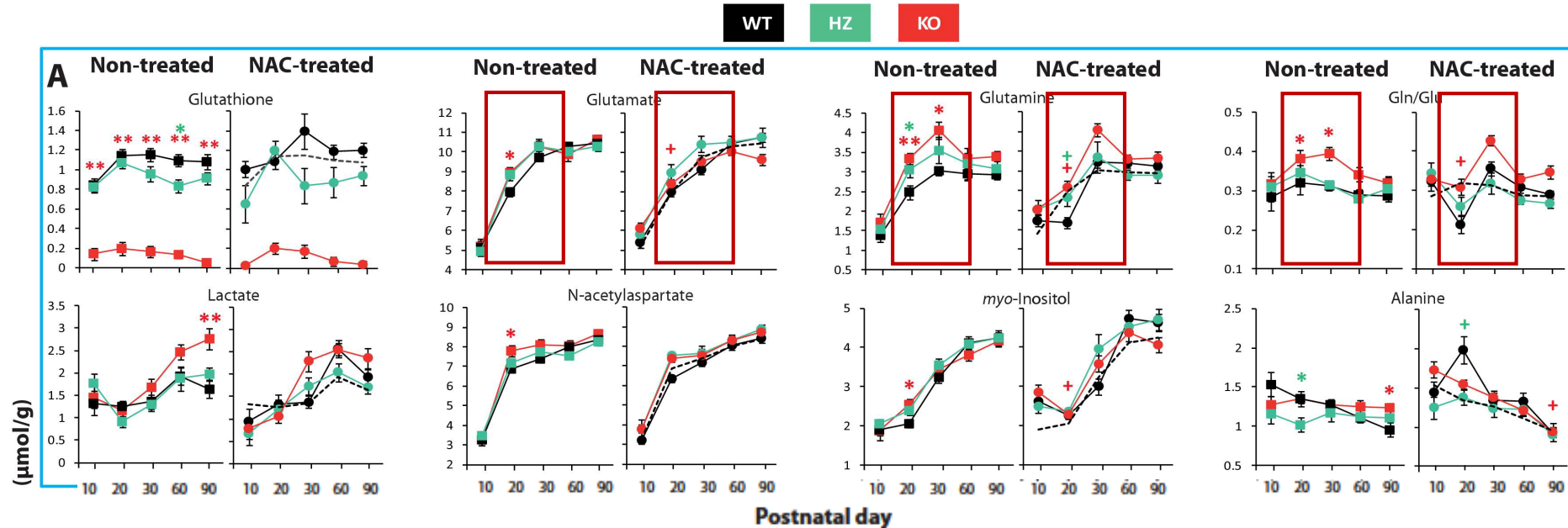
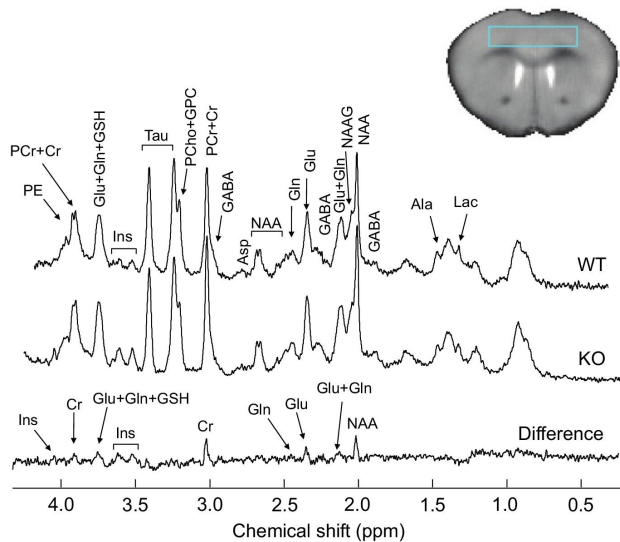
- High resolution neurochemical profile along **neurodevelopment**
- Predict potential sensitive period of vulnerability: glutamate/glutamine anomalies at **peripuberty**
- Prevention potentiality: N-Acetylcysteine normalizes neurochemical changes in the glutathione-deficient schizophrenia mouse model during development



N-Acetyl-Cysteine (NAC): a safe antidote for cysteine/glutathione deficiency



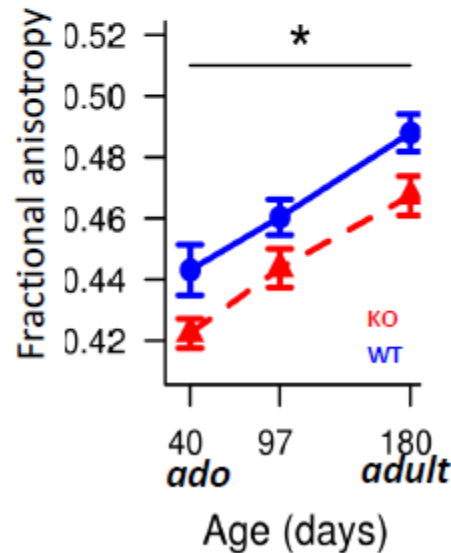
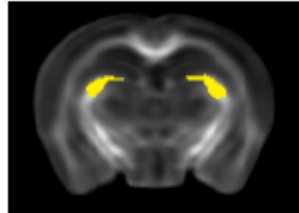
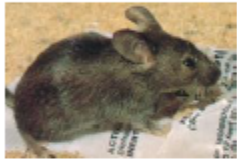
- antioxidant
- reduces disulfide bonds
- anti-inflammatory



Longitudinal DTI in GCLM-KO: Reduced WM integrity in the fornix (hippocampus) already present at peripuberty, associated with decreased conduction velocity

14T DTI of *Gclm* KO during development:
decreased fornix integrity

Electrophysiological recording:
fornix fibers conducting slower



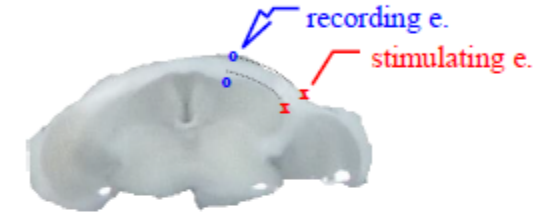
Y Van de Looij



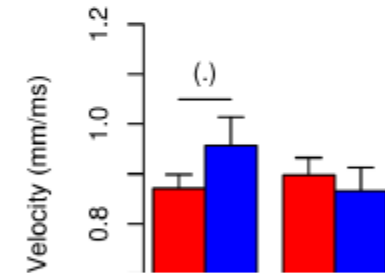
A. Corcoba

Fornix, a white matter bundle, output tract of the hippocampus, and play a key role in cognition

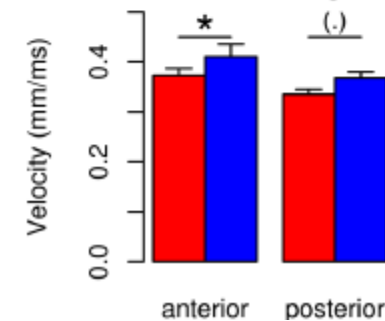
Corcoba, &al...Do IJNPP.,2015



Fast-conducting Fibers



Slow-conducting Fibers



P. Steullet

TRANSLATION TO PATIENTS: CLINICAL TRIALS

Patients

- In **chronic** patients, «proof of concept»: NAC treatment improves negative symptoms & MNN and local synchronization Berk 2008 Biol.Psy; Lavoie 2008 Neuropsychopharm, Carmeli 2012 PlosOne
- In **early psychosis**, 6 months clinical trial with **NAC** leading to biomarker guided treatment :

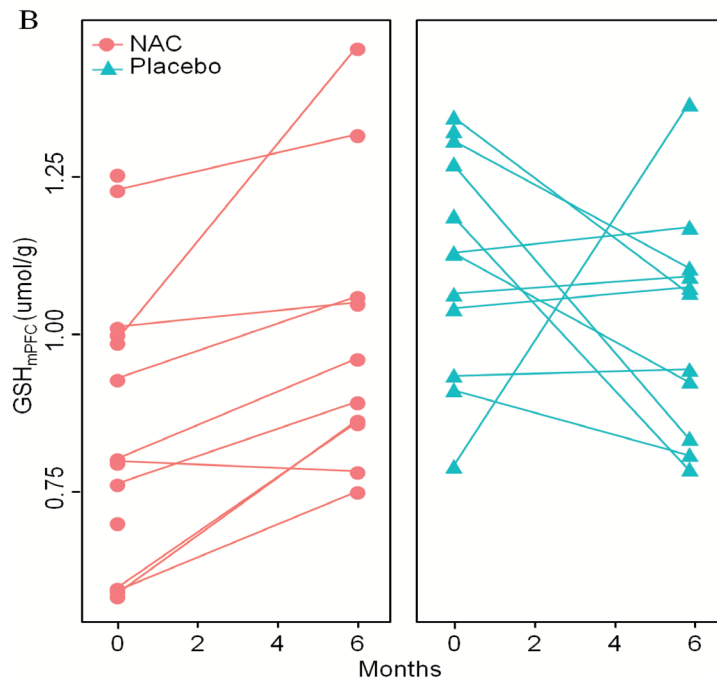
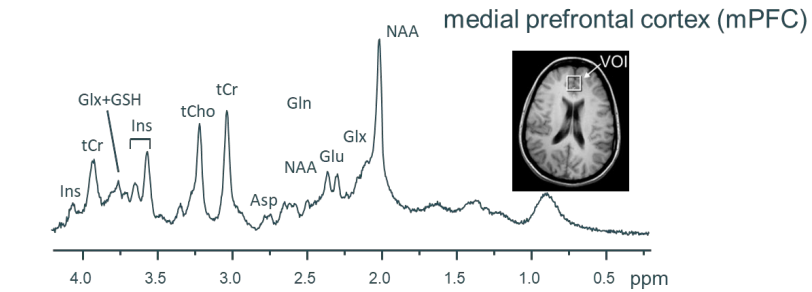
N-Acetylcysteine (NAC),
a precursor of intracellular cysteine and *GSH*

Animal models

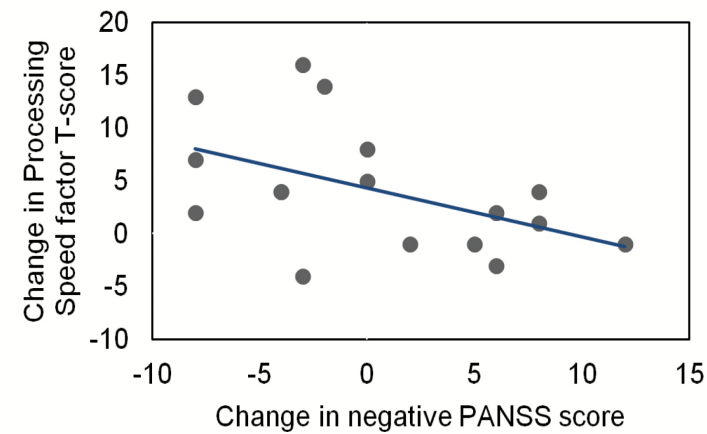
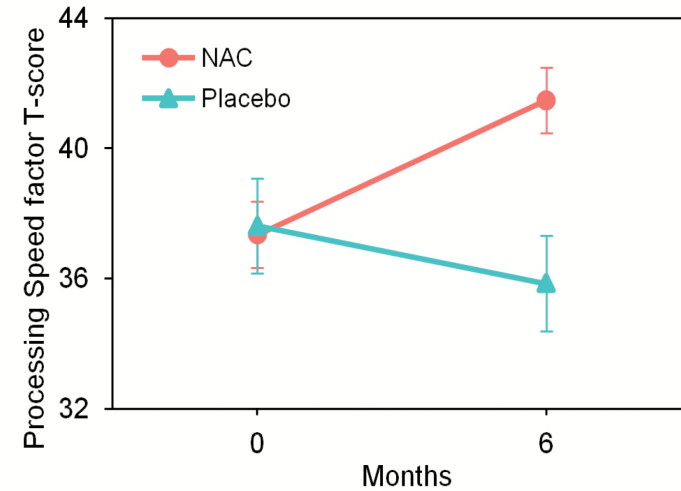
Deficits prevented by
antioxidants
GCLM-KO: Cabungcal 2013
Biological Psy.
Developmental NVHL: Cabungcal
2014 Neuron (neonatal ventral hippocampal lesion)
Convergence of various models:
Steullet 2017 Mo.Psy.



Target engagement: NAC increases prefrontal GSH levels

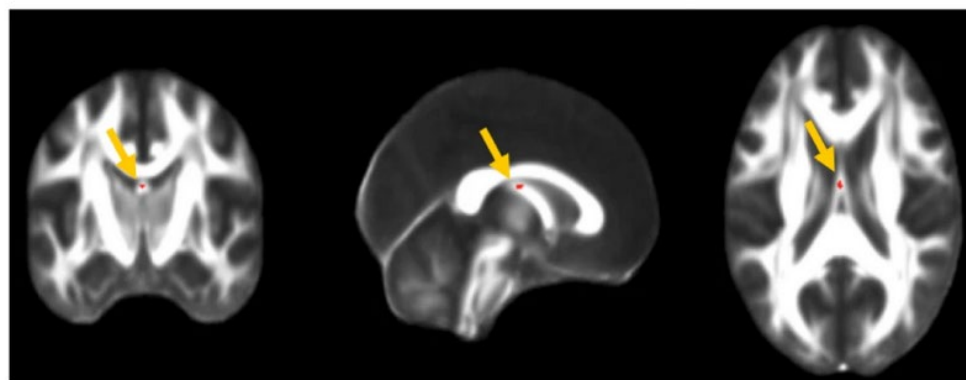


NAC improved neuro-cognition in association with negative symptoms

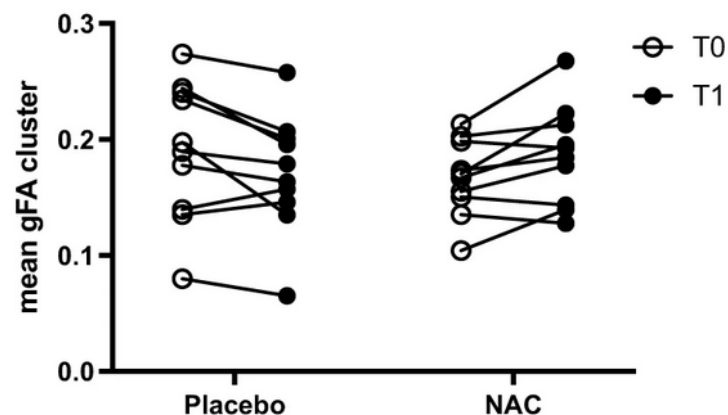


NAC IMPROVED FORNIX INTEGRITY

↑ GSH → Fornix FA ↑

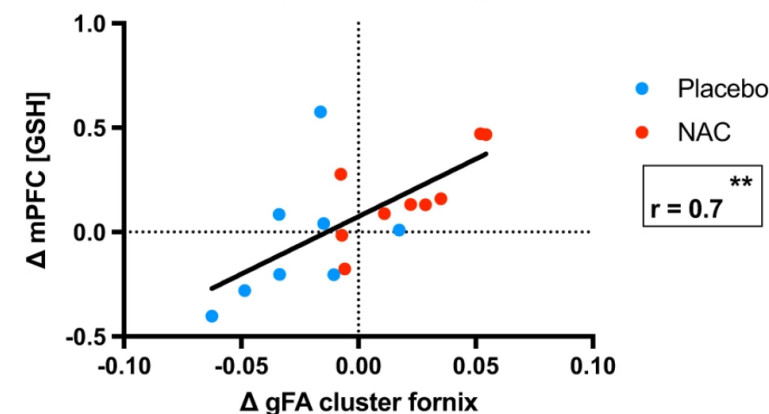


Cluster VBA ROI fornix

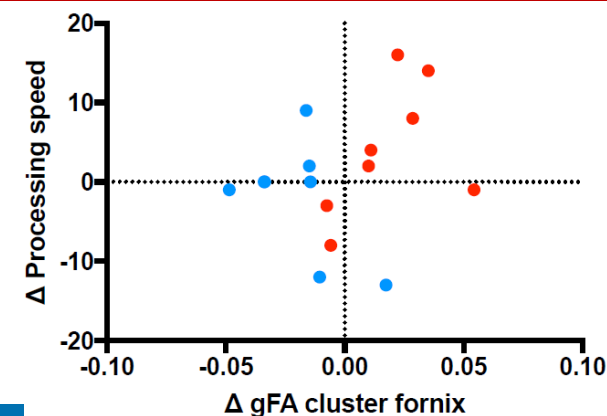


NAC → Fornix FA ↑

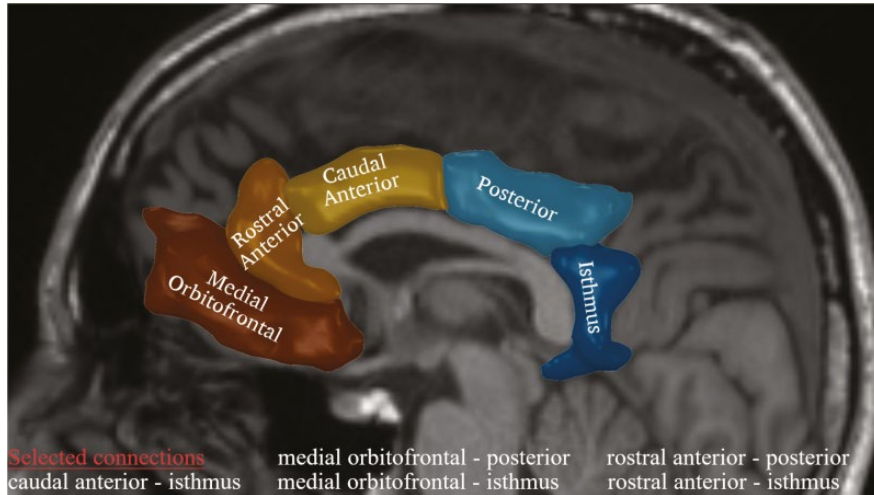
6-month longitudinal changes n = 17



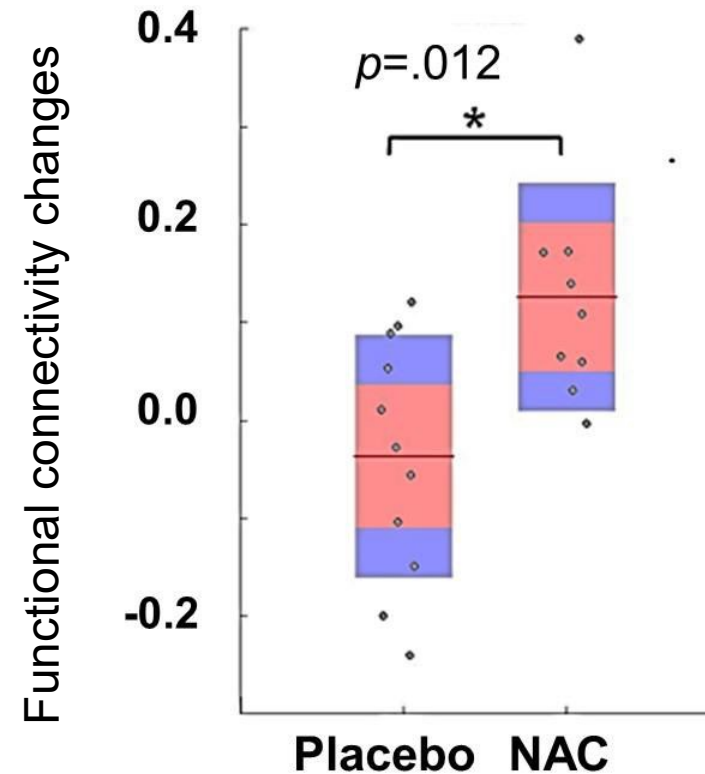
↑ Fornix FA → cognition ↑



NAC IMPROVES FUNCTIONAL CONNECTIVITY



NAC → functional connectivity between **anterior** and **posterior cingulate** ↑



EFFECTS OF NAC TREATMENT IN PSYCHOSIS

➤ NAC

- elevates the brain glutathione

Conus & al., 2018 Schizo.Bull.

- improves positive symptoms (patients with blood marker of high oxidative status)

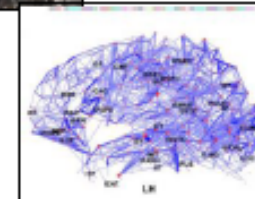
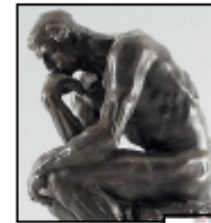
Conus & al., 2018 Schizo.Bull.

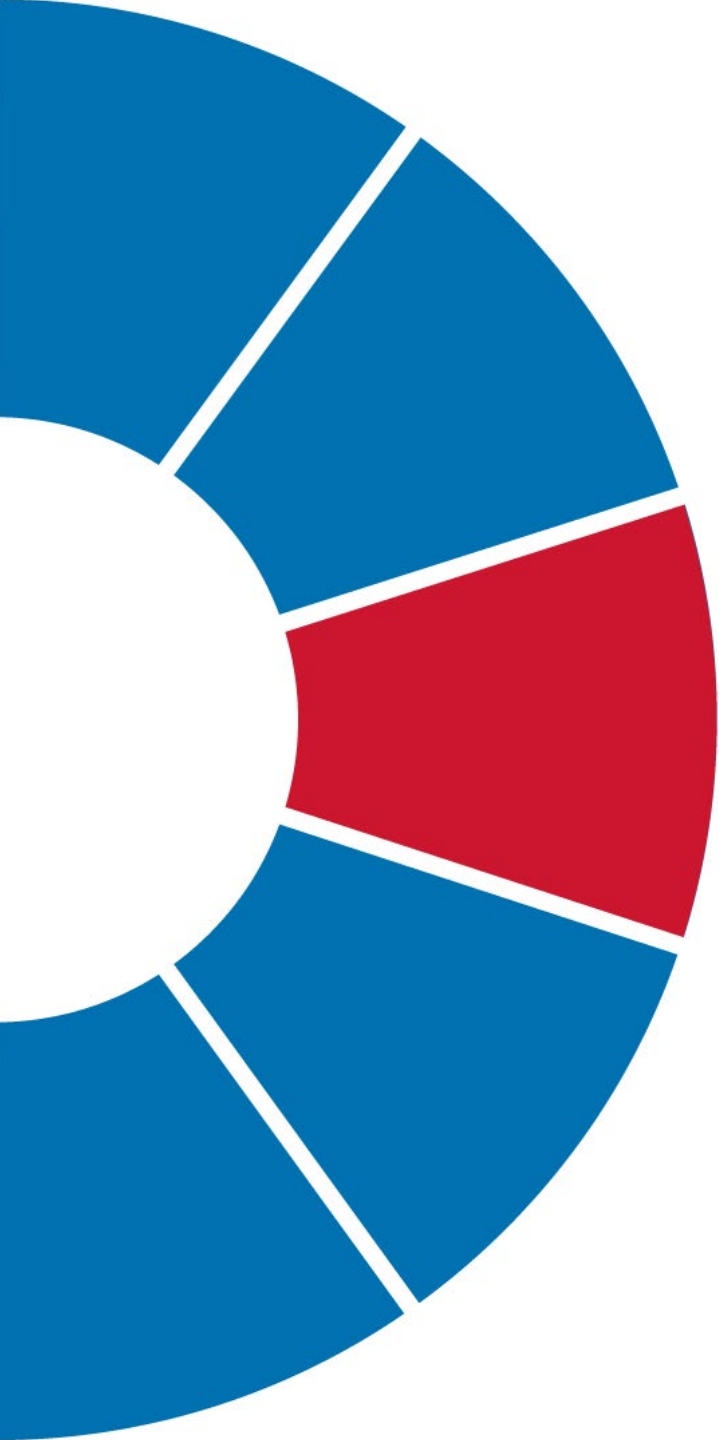
- improves the cognition

Conus & al., 2018 Schizo.Bull.

- improves the connectivity of nerve fibers (macrocircuits)

Klauser & al 2018; Mullier & al 2019





MRI PROCEDURE & SAFETY

CONTRAINDICATIONS TO MRI

- Metal implants (pacemakers, cochlear implants, aneurysm clips, metal plates or screws) can interfere with MRI and harm the patient.
- Pregnancy: unknown effects on the fetus.
- Claustrophobia
- Severe kidney disease may prevent the patient from tolerating the contrast dye used in some MRI exams.
- Weight limits that prevent larger patients from undergoing the procedure.
- Allergic reactions or kidney disease: no contrast agents



MRI PRE-EXPERIMENTAL PROCEDURE

- Ask your participants/patients: empty pockets & remove all metallic objects
- Fill in MRI safety form
- Explain the experimental procedure and consent form
- Check once more: every metallic objects are removed



MRI ACCIDENTS



<http://www.mrisafety.com>

IMPORTANT BUTTONS

- **Quench button:** use it only if there is an immediate risk to life



- **Emergency electricity button:** only be used in emergency situations

- Power failure
- Fire
- Patient emergency



MAGNET SAFETY

- Magnets are always « **ON** » even during a power failure
- In case of quenching, open the doors, there is a risk of low oxygen level
- Don't touch the cold pipes
- Report to the responsible staff ASAP, there are some procedures to follow



Emergency call: 115



THANK YOU FOR YOUR ATTENTION



C I B M . C H